respiratory MEDICINE

REVIEW

Role of long term antibiotics in chronic respiratory diseases

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Summary
Antibiotics are commonly used in the management of respiratory disorders such as cystic fibrosis (CF), non-CF bronchiectasis, asthma and COPD. In those conditions long-term antibiotics can be delivered as nebulised aerosols or administered orally. In CF, nebulised colomycin or tobramycin improve lung function, reduce number of exacerbations and improve quality of life (QoL). Oral antibiotics, such as macrolides, have acquired wide use not only as antimicrobial agents but also due to their anti-inflammatory and pro-kinetic properties. In CF, macrolides such as azithromycin have been shown to improve the lung function and reduce frequency of infective exacerbations. Similarly macrolides have been shown to have some benefits in COPD including reduction in a number of exacerbations. In asthma, macrolides have been reported to improve some subjective parameters, bronchial hyperresponsiveness and airway inflammation; however have no benefits on lung function or overall asthma control. Macrolides have also been used with beneficial effects in less common disorders such as diffuse panbronchiolitis or post-transplant bronchiolitis obliterans syndrome. In this review we describe our current knowledge the use of long-term antibiotics in conditions such as CF, non-CF bronchiectasis, asthma and COPD together with up-to-date clinical and scientific evidence to support our understanding of the use of antibiotics in those conditions.
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Introduction

Respiratory diseases are commonly associated with significant morbidity and mortality, affecting patients' quality of life (QoL) and leading to associated increased costs to the health services. Therefore therapeutic anti-bacterial and anti-inflammatory modalities that may reduce the frequency of exacerbations, the need for hospitalisation and resulting improvement in patients QOL may have important health economic implications. In recent years there has been an improvement in our understanding of managing respiratory conditions using anti-bacterial and/or anti-inflammatory agents. Control of infective exacerbations and thereby the inflammation with oral or aerosol preparations of antibiotics has been shown to have beneficial effects in many of respiratory disorders. This review aims to examine the studies on long-term antibiotic use in management of respiratory diseases, to identify evidence supporting their role and to discuss their potential clinical benefits and limitations.

Role for macrolides

Macrolide antibiotics belong to an expansive family of compounds that are characterized by the presence of a macrocyclic lactone ring.[1] They exert their effects by binding to 50 s ribosomal RNA and have a broad spectrum of activity against many organisms.[2] The immunomodulatory properties of macrolides is related to the lactone ring which is seen with the 14 (erythromycin, clarithromycin and roxithromycin) and the 15 (azithromycin) member macrolides.[3] Though the precise mechanism of action of macrolides is unknown it has been proposed that macrolides can: attenuate mucous hypersecretion; reduce production of pro-inflammatory cytokines which can lead to a reduction in accumulation and proliferation of neutrophils in the mucosal epithelium; and a suppressive effect on lymphocytic activity.[4] In human and animal models macrolides suppress the production of cytokines such as interleukin (IL)-5, IL-8, IL-6, IL-1β, IL-10, tumour necrosis factor (TNF)-α and granulocyte-monocyte colony stimulating factor (GM-CSF); inhibit neutrophil adhesion to epithelial cells; the respiratory burst of neutrophils; and the mucous secretion from airways.[5–9] Macrolides also inhibit RNA-dependent protein synthesis and binding to the bacterial ribosomal subunits. Moreover, macrolides attenuate lipopolysaccharide-induced MUC5AC gene expression and clarithromycin in particular significantly reduces the MUC5AC expression at both the mRNA and protein levels.[10] It has also been reported that in COPD patients, macrolides improve macrophage phagocytosis of apoptotic airways epithelial cells, reduce systemic inflammation and induced increased expression of macrophage mannose receptors.[11,12] Hence the dual action of enhanced clearance of apoptotic cells and bacteria may diminish the secondary necrosis and production of inflammatory mediators.

In patients infected with *Pseudomonas (P.) aeruginosa* macrolides have effects on biofilm development. Biofilm formation and virulence factors in *P. aeruginosa* are controlled by a system of bacterial intercommunication, known as quorum sensing. This system comprises genes encoding transcriptional activators, namely *lasR* and *rhlR* and macrolides inhibit the transcription of several of these genes.[13,14] Macrolides can affect bacterial adherence of pathogens like *P. aeruginosa*[15] and consequently there has been an increasing interest in the use of macrolides in patients colonised with pseudomonas. Macrolides have also been proposed to have pro-kinetic activity on the gastrointestinal tract hence reducing gastro-oesophageal reflux and micro-aspiration which are common phenomena in pulmonary conditions.[16–18] Additionally, macrolides have been reported to have anti-proliferative actions and slow both bronchial epithelial cell proliferation and fibroblast migration.[19,20]

Despite the numerous positive outcomes macrolides possess, more recently, there have been reports in murine models[21] and CF patients[22,23] that long-term macrolides may be associated with the development of non-tuberculous mycobactria (NTM) infections by blocking the autophagosomal clearance of human macrophages by preventing lysosomal acidification, hence impairing autophagic and phagosomal degradation. Hence macrolide therapy may predispose NTM infections by hampering intracellular mycobacterial killing in macrophages.

Role for nebulised antibiotics

Antibiotics delivered directly to the airways by nebulisation have been shown to be very effective in managing pulmonary complications of cystic fibrosis (CF).[24] The benefits of inhaled antibiotics are related to the local delivery of the drug to the lung resulting in much higher sputum concentrations compared with that of intravenous or oral agents. In addition, nebulised antibiotics seem to have a lower side effect profile and toxicity. In the context of inhaled antibiotics therapies, it is important to highlight, the role of the inhalation devices as they determine optimal particle size and the lung deposition of the medication.[25,26] Besides the anti-microbial features of antibiotics, their bioavailability as well as the profile of the adverse effects should also be taken into account. A potential problem associated with the long-term use of nebulised antibiotics is related to patients' adequate adherence with their medications.[27] Despite some limitations, inhaled antibiotics have been shown to be beneficial in CF patients, especially those with chronic colonisation with *P. aeruginosa*.

Asthma

There is a reasonable body of evidence indicating attenuation of corticosteroid requirements with the use of macrolides in stable corticosteroid-dependent asthma patients. It has been proposed that the anti-inflammatory mechanism of macrolides is due to the inhibition of the cytochrome P450 system (CYP3A4).[28] Erythromycin, clarithromycin and troleandomycin have been reported to reduce methyl-predinsolone clearance in asthmatics[29–32] besides independently manifesting anti-inflammatory activity to those of corticosteroids and theophyllines. Roxithromycin and azithromycin do not inhibit the cytochrome P450 system, but still are effective in reducing bronchial hyper-responsiveness (BHR).[33,34] Moreover macrolides by inhibiting IL-6 and IL-8 may possibly lead to improvements in FEV_1 in asthmatics.[35,36] Several case series' and open-labelled studies using macrolides have been conducted in asthmatic patients with positive outcomes.[6,29,30,32–34,37–39] In 2005, a Cochrane review assessed the use of macrolides in asthma.[6] Seven studies with a total of 416 asthma patients were considered based on an inclusion criteria of (summarised in Table 1): the studies being double-blind placebo-controlled (DBPC); ≥4 weeks of treatment in patients with varying severity of asthma (clarithromycin — 3 studies, roxithromycin — 2 studies; troleandomycin — 2 studies); evaluation of asthma symptoms and at least one measure of lung function (FEV_1, FVC and/or PEF).[40–46] There were no significant differences in forced expiratory volume in 1 s (FEV_1), and difference between forced vital capacity (FVC) and corticosteroid usage in the studies. However, significant improvements in favour of macrolides in symptom control, BHR, attenuation in eosinophilic inflammation and good drug tolerability. Despite the positive outcomes, caution in the interpretation is vital as the studies include small numbers, different macrolides assessed, a variety in severities of asthma and chronic infection with *Chlamydia* (C.) *pneumonia*, as well as diverse range outcome measures.

Following this review, a number of new studies have been published in the literature using clarithromycin and azithromycin. A trial on patients with severe refractory asthma[47] reported significant improvements in the clarithromycin-treated group compared to placebo in Juniper's Asthma-related Quality of Life Questionnaire (AQLQ) scores,[48] and reduction in sputum IL-8 and neutrophils, and self-reported wheezing; particularly in the subgroup of patients with non-eosinophilic (sputum) asthma but there was no improvements in FEV_1, hypertonic saline challenge or sputum eosinophil counts. Piacentini et al. conducted an 8 week trial on the efficacy of azithromycin versus placebo on lung function, BHR and airway inflammation in 16 asthmatic children[49] and reported significant reduction in hypertonic saline-induced BHR and sputum neutrophilia in favour of the azithromycin-treated children compared to placebo, but no changes in FEV_1 between both groups. In another randomised placebo-controlled, blinded, allocation-concealed parallel group clinical trial in 45 adults with stable, persistent asthma, it was observed that there were significant improvements in azithromycin-treated (compared to placebo) subjects in asthma symptoms and rescue inhaler use during treatment that persisted at 3 months after treatment, but not in the AQLQ.[50] Of note, in the azithromycin-treated subjects the overall asthma symptom improvement was higher in the subgroup of patients with high immunoglobin (Ig) A to *Chlamydia pnuemoniae* than in the lower IgA (28% vs. 12%), but not significant. Moreover, there was a positive and significant association between anti-Chlamydial IgA, but not anti-Chlamydial IgG, with asthma symptom changes at 6 months. Hence, it was proposed that the anti-Chlamydial IgA could help with 6-month asthma prognosis, as measured by an overall asthma symptom scale. From the various studies, we can see that there may be a possible role for macrolides in chronic asthma; however their routine use is not clearly justified based on current evidence.

Chronic Obstructive Pulmonary Disease (COPD)

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) impair health status, accelerate the progression of the disease and are associated with significant early mortality.[51] The frequency and severity of exacerbations is associated with long-term mortality independent of co-morbidities, FEV_1, age and body mass index (BMI).[52] Airway inflammation plays a key role in the pathogenesis of COPD and a variety of microbial organisms promote the inflammatory process precipitating an acute exacerbation. Given the role of inflammation and infections in COPD the use of long-term antibiotics may offer a distinctive benefit to control this disease.[53]

One of the earliest studies by Gomez and colleagues observed a statistically significant reduction in the number of acute infectious episodes and hospital admissions in azithromycin-treated versus placebo following a 3-day prophylactic treatment course every 21 days during the winter months.[54] The important trials are summarised in Table 2.[55–60] The first prospective study investigating the efficacy of long-term macrolide therapy in patients with

Table 1 Summary of the studies of macrolides in asthma (Modified from Richeldi et al.[6]).

Study (Reference)	Study design	Number of subjects	Duration of study	Antibiotic	Outcomes
Amayasu et al.[40]	Randomised DBPC Crossover study	17 adult subjects with mild-to-moderate atopic asthma	8 weeks	CRM	- Improvement in patients' symptoms and Methacholine PC20 in favour of CRM -No change in FEV_1 and FVC between Gps - Reduction in blood and sputum eosinophil counts, and sputum ECP - No serious adverse events
Black et al.[41]	Randomised DBPC	219 asthmatic subjects with serological evidence of *C. pneumoniae* infection as demonstrated by IgG and IgA antibody titres	6 weeks	RXM	- Improvements in morning and evening PEF in favour of RXM - No significant changes symptom scores, AQLQ or Chlamydia antibody titres between Gps - No serious adverse events
Kamada et al.[42]	Randomised DBPC Gp A: TDM + MP; Gp B: TDM + prednisolone; Gp C: placebo + MP	19 children (6−17 yrs) with OCS-dependent asthma (OCS tapering study)	12 weeks	TDM	- Improvements in all Gps in OCS reduction compared to baseline (and between Gp A and Gp C) - Significant improvement in Gp A in symptom scores - Non-significant reduction in pulmonary function in all Gps (except for significant attenuation in FEV_1 and FEF_{25-75} in Gp B) - Significant reduction in Methacholine PC20 in Gp A - No serious adverse events
Kostadima et al.[43]	Randomised DBPC of Gp A: CRM b.i.d.; Gp B: CRM t.i.d.; Gp C: placebo	75 adult subjects with mild persistent asthma	8 weeks	CRM	- Significant improvement in FEV_1 in Gp B - Significant improvement in Methacholine PD20 in Gps A and B - No changes in cortisol levels (in the 40 subjects that were assessed compared to baseline)
Kraft et al.[44]	Randomised DBPC	55 adult subjects with moderate persistent asthma (31 with evidence of *C. pneumoniae* or *M. pneumoniae* infection)	6 weeks	CRM	- No change in FEV_1 between Gps - No significant difference in IL-2, IL-4, IL-5, IL-12 and TNF-α airway biopsies and BAL between PCR + ve and PCR −ve subjects Subgroup analysis of PCR + ve and −ve for *C. pneumomiae* or *M. Pneumoniae* receiving CRM or placebo: - Significant increase in FEV_1 in PCR + ve subjects receiving CRM (not in PCR −ve or PCR + ve subjects receiving placebo)

					- Significant reduction in IL-5, IL-12 and TNF-α in BAL in PCR + ve receiving CRM and only the latter 2 mediators in PCR −ve receiving CRM Significant reduction in TNF-α in airway biopsies in PCR + ve and −ve receiving CRM
Nelson et al.[45]	Randomised DBPC of TDM + MP vs. placebo + MP	75 adult asthmatic subjects with severe persistent asthma (OCS tapering study)	52 weeks (single blind for 52 weeks for 57 subjects [TDM $n = 30$; Placebo $n = 27$]	TDM	- Significant reduction in hospitalisation, OCS for exacerbations, OCS tapering and dual- photon densitometry of lumbar spine in both Gps at 52 and 104 weeks compared to baseline (but not between Gps) - Significant increase in blood eosinophil count and 60 min stimulated cortisol levels at 52 weeks in both Gps - Significant reduction in mean IgG level in the TDM compared to placebo at 52 weeks - Significant increase in mean fasting blood sugar (at 104 weeks) and cholesterol levels (at 52 and 104 weeks) in the TDM Gp than placebo - No significant improvement in Methacholine PC20 between Gps
Shoji et al.[46]	Randomised DBPC Crossover study	14 adult subjects with aspirin-intolerant mild/moderate asthma	8 weeks	RXM	- Significant reduction in symptom score with RXM compared to placebo - No significant differences between both in pulmonary function, sulpyrine PC20 and leukotriene E4 urinary elimination. - Significant reduction with RXM in mean ECP and eosinophil count in serum and sputum compared to placebo - No serious adverse events

Abbreviations: DBPC — Double-blind, placebo-controlled study; CRM — Clarithromycin; PC20 — Provocation concentration causing a 20% reduction in FEV$_1$; Gp — Group; FEV$_1$ — Forced expiratory volume in 1 s; FVC — Forced vital capacity; ECP — Eosinophilic cationic protein; RXM — Roxithromycin; *C. pneumomiae* — *Chlamydia pneumoniae*; Ig — Immunoglobulin; flow; PEF — Peak expiratory flow; AQLQ — Asthma-related quality of life; TDM — Troleandomycin; MP — Methylprednisolone; yrs — years; OCS — Oral corticosteroids; FEF$_{25-75}$ — Forced expiratory flow 25%−75%; b.i.d — Twice daily; t.i.d. — thrice daily; PD20 — Provocation dose causing a 20% reduction in FEV$_1$; *M. pneumoniae* — *Mycoplasma pneumoniae*; IL — Interleukin; TNF-α — Tumour necrosis factor alpha; PCR — Polymerase chain reaction; +ve — Positive; −ve — Negative; vs. — versus.

Table 2 Summary of the studies of long term antibiotics in COPD.

Study	Study design	Number of subjects	Duration of study	Antibiotic	Outcomes
Albert et al.[55]	Randomised placebo control study	1577	12 months	Azithromycin250 mg daily	- Median time for first exacerbation better for azithromycin group - Reduced frequency of acute exacerbations - Reduced risk of acute exacerbations - Improved quality of life - Caused hearing decrements in a small percentage
He et al.[58]	Randomised DPBC trial	36	6 months	Erythromycin125 mg three times daily	- lower mean exacerbation rate - Delayed time for first exacerbation favouring erythromycin - Decreased sputum neutrophils and neutrophil elastase
Blasi et al.[57]	Randomised uncontrolled trial	22	6 months	Azithromycin 500 mg three times a week	- Lower cumulative number of exacerbations and hospitalisations-Reduction in the time for first exacerbation-Improved quality of life
Seemungal et al.[59]	Randomised DPBC trial	109	12 months	Erythromycin250 mg twice daily	- Reduced rate of exacerbations - Shorter duration of exacerbations - No difference in terms of stable FEV_1, serum CRP, sputum IL-6 or IL-8
Banerjee et al.[56]	Prospective Randomised DPBC trial	67	3 months	Clarithromycin 500 mg once daily	- No change in health status, exacerbation rate or sputum bacterial numbers
Sethi et al.[60]	Randomised DPBC trial	1157	48 months	6 courses of Moxifloxacin 400 mg OD for 5 days	- Reduction in the exacerbation rates - No unexpected adverse events

stable COPD was an open-label, randomized trial of erythromycin (200—400 mg/d) for 12 months in 109 patients with COPD. Thirty patients (56%) compared to six patients (11%) in the control group and erythromycin group respectively had one or more exacerbations. Although this trial was noteworthy, it was unblinded. However, not all the initial trials were supportive of a role for long-term antibiotics. Banerjee et al. examined the role of 3-months oral clarithromycin or placebo once-daily in 67 patients with moderate-to-severe COPD. The authors concluded that treatment of stable COPD with clarithromycin yielded no clinical advantage and did not improve health status, sputum bacterial numbers, or prevent infective exacerbations.[56] However, the short duration (3 months) of the antibiotic could have had a bearing on the results. Seemungal and colleagues in a randomized, DPBC study of 109 patients administered erythromycin 250 mg twice daily to patients with moderate COPD (80% of patients on inhaled corticosteroids) over 12 months.[59] They found that erythromycin treatment was associated with a significant reduction in exacerbations compared with placebo, but had no significant impact on FEV_1, sputum inflammatory markers, serum inflammatory markers or bacterial flora. The frequency of side effects was low in both arms with no differences between the two arms.

The results of the above studies suggest that macrolide therapy may be beneficial in COPD patients preventing acute exacerbations of COPD (AECOPD) and altering the natural course of the disease. Whether this is due to its antimicrobial properties or due to immunomodulation needs to be established. The balance between inflammation and immunomodulation is important in chronic airway diseases and macrolides may have a possible effect on this balance in addition to its anti-microbial effects to reduce AECOPD. That said, a randomised DBPC trial in stable COPD patients with pulsed moxifloxacin (moxifloxacin 400 mg/day) ($N = 573$) or placebo ($N = 584$) once daily for 5 days and treatment repeated every 8 weeks for a total of 6 courses found that at 48 weeks the odds ratio (OR) for suffering an exacerbation was reduced by 20% in the intention-to-treat group.[60] No changes in the overall health status, rates of hospitalization or mortality, or attenuation of lung function decline were noted. Subgroup analyses demonstrated that the reduction in exacerbations with moxifloxacin was seen in COPD of all severity categories, supporting a role for quinolones in preventing exacerbations.

Recently, Albert and colleagues conducted a multicenter randomised trial of 1142 patients at risk of AECOPD to receive 250 mg daily of azithromycin ($n = 570$) or placebo ($n = 572$) for a year in addition to usual care.[55] The primary outcome i.e. time to first exacerbation was significantly increased in the azithromycin group when compared to placebo (226 days vs. 174 days). The hazard ratio for having an acute exacerbation per patient year was 0.74 in the

azithromycin group. Although there was no significant reduction in the hospitalisation rates, urgent care visits or mortality between the two groups, azithromycin treatment improved the QoL measures and had similar frequency of serious adverse events in both groups except for hearing loss and colonisation with macrolide-resistant organisms. While there was a question on the role of long-term antibiotics in stable COPD to prevent exacerbations, the trial by Albert et al. has provided support for the long-term use of azithromycin to reduce exacerbations. It is still unclear whether this beneficial effect is due to the anti-bacterial properties or to the immunomodulatory effects of macrolides. Furthermore, the likely development of resistance to antibiotics in the long-run and the role for azithromycin on a once, twice or thrice weekly regimen, given the extremely long tissue persistence of the drug needs to be explored. Therefore, adverse effects of macrolides such as hearing loss, effects on QTc and interactions with other agents need to be taken into account and balanced against possible benefits in individual patients. In addition, patients need ongoing assessments for potential benefits of long term therapy with macrolides and at the same time be aware of potential adverse effects. Although, there have been no studies or guidelines recommended how long one should administer macrolides to assess the efficacy of macrolides, we suggest a trial of 3—6 months in the first instance, followed by regular reviews on benefit vs adverse events.

Cystic fibrosis (CF)

CF is one of the most common genetic disorders[61—63] in which the main defect relates to the malfunction in the CF trans-membrane conductance regulator (CFTR). This defect in turn results in chronic respiratory infections which remain the main cause of morbidity and mortality in CF.[64—67] In early CF, *Staphylococcus (S.) aureus* and *Haemophilus (H.) influenzae* remain the main pathogens.[24,61] However, overall the most commonly isolated pathogen in CF is *P aeruginosa*. Recently, pathogens such as *Burkholderia (B.) cepacia* and *Stenotrophomonas (S.) maltophilia* have been reported in CF with increasing frequency.[24,61]

Antibiotics in CF are used to manage exacerbations as well as to prevent, eradicate and control respiratory infections, hence potentially improving survival.[24] Flucloxacillin, which has shown to reduce the incidence of infection with *S. aureus*, has acquired long term use in young children with CF aged up to 3 years.[68] Similarly, other oral agents in particular macrolides have been shown to be beneficial in CF (Table 3).[69—77] A number of studies have shown that the long-term use of azithromycin in CF patients resulted in improved lung function, reduction in a number of infective exacerbations and the use of antibiotics.[69—79] For example, Wolter et al. reported that in adults with CF, azithromycin improved QoL, reduced both the number of respiratory exacerbations, and the rate of decline in the lung function.[70] Similar outcomes were reported by Saiman and colleagues with oral azithromycin in CF patients chronically infected with *P. aeruginosa*.[71] Although the exact mode of action of macrolides in CF is not fully

understood, the benefits are mainly observed in patients colonised with *P. aeruginosa*. However, some also reported the benefit of long-term macrolides in CF patients even prior to *P. aeruginosa* infection.[73] Chronic colonisation with *P. aeruginosa* is one of the main predictors of morbidity and mortality in CF,[80] hence the need to control this infection.

Numerous antibiotics have been tested for aerosolized use in CF, including tobramycin, colomycin, gentamicin, aztreonam and taurolidine and some of them have acquired clinical use in CF.[81—88] Nebulised antibiotics in CF have been used to manage acute respiratory exacerbations as well as chronic therapy to stabilise lung function and prevent chronic colonisation with *P. aeruginosa*. For example, studies have shown that treatment with nebulised colomycin can lead to effective eradication of colonisation of *P. aeruginosa*.[81,82] In fact, three months thrice daily regime of nebulised colistin showed that after 3.5 years only 16% of treated patients had developed chronic *P. aeruginosa* infection compared to 72% of untreated historical controls.[81] Similarly, studies revealed that in CF patients inhaled tobramycin resulted in effective eradication of early infection with *P. aeruginosa*.[89] Moreover, long-term intermittent administration of inhaled tobramycin has been well tolerated and resulted in improved lung function and decreased density of *P. aeruginosa* in the sputum as well as reducing the risk of hospitalization.[84,90] Similar observations have been reported with nebulised tobramycin and colomycin in CF patients colonised with *P. aeruginosa* by others[83]; hence both of these agents are being regularly used in clinical practice. A recent Cochrane review on long term inhaled antibiotics in CF has concluded that inhaled antibiotic treatment probably improves lung function and reduces exacerbation rate, but a pooled estimate of the level of benefit was not possible. The best evidence was for inhaled tobramycin.[91]

Amongst the new inhalation antibiotics approved for the use in CF patients with *P. aeruginosa* colonisation is a monobactam formulation, aztreonam lysinate.[87,92] The use of inhaled aztreonam in CF patients with *P. aeruginosa* colonisation resulted in reduction of bacterial burden, preservation of lung function, and improvement in symptoms associated with disease.[93—95] McCoy and colleagues observed that 28-days of nebulised aztreonam compared with the placebo in CF patients on nebulised tobramycin improved lung function, respiratory symptoms and reduced sputum density of *P. aeruginosa*.[93] Similar observations were noted in an 18-month study with nebulised aztreonam besides being well tolerated.[95] Another novel inhaled antibiotic tested in CF patients with chronic *P. aeruginosa* includes an aerosol formulation of levofloxacin (MP-376, Aeroquin).[96] This new preparation of inhaled levofloxacin resulted in improved lung function and reduction in antibiotics use. Geller et al. observed that in CF patients colonised with *P. aeruginosa* nebulised levofloxacin was well tolerated, improved FEV_1 by 8.7% and reduced sputum *P. aeruginosa* density.[96]

There have also been attempts to use nebulised antibiotics to treat CF patients colonised with *B. cepacia* as those patients have an increased morbidity and mortality. Taurolidine is an antibiotic with a broad spectrum of activity against gram negative and positive bacteria as well as being an anti-endotoxin. Ledson and colleagues assessed the

Table 3 Summary of the studies of long term antibiotics in cystic fibrosis.

Study	Study design	Number of subjects	Duration of study	Antibiotic used	Outcomes
Saiman et al.[71]	Randomised Placebo controlled	185(87 treatment group)	6 months	Azithromycin	Improved FEV_1, reduced number of exacerbations,
Wolter et al.[70]	Randomised placebo controlled	60 adult CF patients	3 months	Azithromycin	No decline in FEV_1, fewer courses of IV antibiotics, decline in C reactive protein, improvement in QOL
Kabra et al.[78]	Randomised controlled	56 children	12 months	Azithromycin low dose 5 mg/kg/day compared with high dose 15 mg/kg/day	No difference in clinical score, FEV_1 and pulmonary exacerbation rates between the two groups
Hodson et al.[83]	Randomised controlled	115	4 weeks	Nebulised colomycin compared with nebulised tobramycin	Both treatments reduced bacterial load. Nebulised tobramycin improved lung function in CF patients chronically colonised with *P. aeruginosa*
Ramsey et al.[84]	Randomised placebo controlled	520	24 weeks	Nebulised tobramycin	Improvement in pulmonary function, decrease in the density of *P. aeruginosa* in sputum, decreased risk of hospitalization
McCoy et al.[93]	Randomised controlled	211	28 days	Inhaled aztreonam solution	Improvement in pulmonary function and respiratory symptoms
Retsch-Bogart et al.[94]	Randomised placebo controlled	164	28 days	Inhaled aztreonam solution	Improvement in pulmonary function and respiratory symptoms
Oermann et al.[95]	Open label	274	18 moths	Inhaled aztreonam solution	Clinical benefits in pulmonary function, health-related quality of life, and weight
Ledson et al.[88]	Randomised double blinded cross over	20	4 weeks	Inhaled taurolidine	No change in *B. cepacia* colony count or spirometry, nor symptom score
Frederiksen et al.[81]	Comparison with historical control	48 patients compared with 43 control	44 moths	Inhalation of colistin and oral ciprofloxacin	16% of the treated patients developed chronic *P. aeruginosa* infection compared with 72% of the control patients ($P < 0.005$), improvement in lung function
Gibson et al.[89]	Randomised double blind	21	28 days	Inhaled tobramycin	Reduction in *P. aeruginosa* density
Geller et al.[96]	Randomised placebo controlled	151	28 days	Inhaled ciprofloxacin	Reduction in *P. aeruginosa* density, improvement in pulmonary function (FEV_1), reduction in need for anti-pseudomonal antibiotics

effects of inhaled taurolidine in CF patients infected with *B. cepacia*.[88] Although Taurolidine was well tolerated it did not affect the *B. cepacia* colony count or other outcomes assessed. Inhaled formulations of ciprofloxacin have shown promise in patients with non-CF bronchiectasis[97] and will be of interest to see whether similar effects will be seen in CF. Overall the use of inhaled antibiotics in CF has been widely accepted. The main role of inhaled antibiotics in CF has been in patients with chronic colonisation with *P. aeruginosa*, however there are potential new agents currently being assessed which may acquire clinical use in the future.

Non-CF bronchiectasis

Long-term antibiotics in bronchiectasis reduces exacerbations, improves symptoms and QoL by reducing bacterial load and airway inflammation.[98] The early evidence for long-term antibiotics in bronchiectasis stems from the MRC multi-centre study where 122 patients with bronchiectasis were allocated to penicillin ($n = 38$), oxytetracycline ($n = 44$) and placebo ($n = 40$). After a year, in the oxytetracycline group there was a 64% reduction in sputum volume, had fewer days off work; fewer days confined to bed and reduced episodes of fever. Unfortunately, no formal statistical analyses were performed.[99] Currie et al. in a randomised placebo controlled trial evaluated the effect of high-dose amoxicillin (3 gm twice daily) in 38 patients with bronchiectasis.[100] The frequency of exacerbations during the study treatment phase was similar in both groups, but they were less severe than before study treatment in the amoxicillin group. There was a greater reduction in purulent sputum volume between exacerbations during the study treatment in the amoxicillin group compared to placebo. Independent assessment of the overall response based on patients' diary cards showed that a higher proportion improved in the amoxicillin-treated (11 of 17) compared to placebo (4 of 19). Adverse events experienced by patients were minor and there was no change in the bacterial flora based on sputum and stool cultures. More recently a New Zealand group conducted a DBPC study to evaluate the role of azithromycin in reducing frequency of exacerbations, improvement in lung function and health-related QoL in 141 (71 azithromycin; 70 placebo) patients with non-CF bronchiectasis for 6 months.[101] They reported a significant reduction in the rate of exacerbations but no differences in the other parameters assessed.

Studies in non-CF bronchiectasis include both oral and nebulised antibiotics and are summarised in Table 4.[100,102−106] Davies and colleagues in an open-labelled prospective trial evaluated the role of azithromycin 250 mg thrice/wk for 4 months in 39 bronchiectasis patients.[102] All the patients had more than 4 documented exacerbations during the previous 12 months. There was a reduction in exacerbations warranting oral and intravenous antibiotics, and an improvement in TLCO. Yalcin and colleagues examined the effects of clarithromycin on inflammatory markers (IL-8, TNF-alpha, IL-10 levels and cell profiles in bronchoalveolar lavage (BAL) fluid, pulmonary function and sputum production in children with non-CF bronchiectasis in a randomised DBPC trial.[106] Following 3

months of treatment compared to placebo, the clarithromycin-treated subjects showed a significant decrease in IL-8 levels, total cell count, neutrophil ratios in BAL fluid and daily sputum production, but no significant differences in pulmonary function test parameters. Barker and colleagues examined the microbiological efficacy and safety of nebulised tobramycin twice daily for 4 weeks in 74 patients with bronchiectasis and *P. aeruginosa* in a randomised DBPC trial ($n = 37$ in each group).[107] At Week-4, the treatment group had a mean decrease in *P. aeruginosa* density of 4.54 $\log_{10}$ colony-forming units/g sputum ($p < 0.01$). At Week-6, *P. aeruginosa* was eradicated in 35% in the treatment group but was detected in all placebo patients. No differences in lung function were reported. This study supported a role for nebulised antibiotics in bronchiectasis, albeit for a 4-week duration.

In a trial involving 30 bronchiectatic patients with nebulised tobramycin for 6 months with[103] there was a reduction in hospital admissions and in-patient days during treatment phase and a decrease in *P. aeruginosa* density up to 3 months of stopping tobramycin. However, there was no difference in exacerbations, antibiotic use, lung function or QoL between the treatment periods. Another trial involving nebulised ceftazidime and tobramycin twice daily in patients with bronchiectasis concluded that the treatment group had less admissions and in-patient days, but there was no difference in the lung function or use of oral antibiotics use between groups.[105] More recently, a study from Edinburgh randomised sixty-five patients to either twice daily nebulised gentamicin, or 0.9% saline, for 12 months.[104] At 12 months the treatment group had reduced sputum bacterial density with 30.8% eradication in those infected with *P. aeruginosa* and 92.8% eradication in those infected with other pathogens; less sputum purulence; greater exercise capacity and fewer exacerbations with increased time to first exacerbation. No differences were seen in 24-h sputum volume and lung function parameters. Of note, *P. aeruginosa* isolates developed resistance to gentamicin. Recently, the ORBIT 1 study evaluated the efficacy, safety, and tolerability of once daily inhaled ciprofloxacin in the management of *P. aeruginosa* infections in patients with non-CF bronchiectasis.[97] The data revealed that at 28 days nebulised ciprofloxacin reduced *P. aeruginosa* density and improved QoL. Murray et al. conducted a 1-year randomised placebo controlled study assessing the efficacy of nebulised gentamicin compared to placebo in a number of sputum, objective, subjective and exacerbations parameters.[104] They reported substantial improvements sputum bacterial density with over 30% having eradicated *P. aeruginosa* and over 90% eradicating other pathogens, sputum purulence, fewer exacerbations and delay to first exacerbations, improved exercise capacity as well as improvement in subjective parameters of cough and QoL. Moreover there were no *P. aeroginosa* isolates developing resistance to gentamicin. Of note, there were no improvement sin 24-h sputum volume and various assessments of lung function.

There is consistent evidence that long-term antibiotics either oral or nebulised improves QoL, decreases exacerbation frequency and reduces the bacterial load. Unlike the CF experience, there does not seem to be an improvement of pulmonary function after treatment with nebulised

Table 4 Summary of the studies of long term antibiotics in Non-CF bronchiectasis.

Study	Study design	Number of subjects	Duration of study	Antibiotic	Outcomes
Murray et al.[104]	Randomised placebo controlled trial	65	12 months	Neb gentamicin 80 mg twice daily	- Reduction in bacterial load - Decrease in number of exacerbations - Significant prolongation for time to first exacerbation - Bronchospasm observed in 21.9% (Vs 6% in placebo)
Orriols et al.[105]	Open labelled study	17	12 months	Neb ceftazidime 1 gm bd & Neb tobramycin 100 mg bd or placebo	- Reduced number of admissions & in-patient stays - No difference in the use of oral antibiotics - No changes in lung function
Drobnic et al.[103]	Double blind placebo controlled crossover trial	30	6 months	Nebulised tobramycin 300 mg twice daily	- Reduction in the number of admissions - Reduction in hospital stays - Reduction in pseudomonas density in sputum - No difference in number of exacerbations or QOL
Yalcin et al.[106]	Randomised placebo controlled	34 (children)	3 months	Clarithromycin 15 mg/kg	- Reduction in sputum volume - Improvement in maximal mid-expiratory flow - No change in FEV_1
Davies et al.[102]	Prospective open labelled	39	10 months	Azithromycin 250 mg three times weekly	- Decreased exacerbation frequency - Decreased need for IV antibiotics - Improvement in symptoms and TLCO
Currie et al.[100]	Randomised placebo controlled	38	32 weeks	Amoxicillin 39 twice daily	- Similar frequency of exacerbations but less severe in the amoxicillin group - Greater reduction in sputum purulence - Less time confined to bed and away from work

antibiotics. In practice, the prescription of long-term antibiotics should be considered for patients exacerbating at least 3 times/yr and in patients with fewer exacerbations but with greater morbidity.[108] There may also be a lower threshold for starting long-term antibiotics in patients with primary or secondary immunodeficiency. Antibiotic choices should be based on sputum microbiology and careful monitoring needs to be in place regarding microbial resistance and adverse events.

Diffuse panbronchiolitis (DPB)

DPB is a chronic respiratory condition of unknown aetiology, almost exclusively described in the Far East (mainly Japan, but also Korea and China), characterised by chronic inflammation of the respiratory tract with progressive destruction of the lung parenchyma.[109–111] Up to the early 1980s DPB was a fatal condition, however with the use of long-term macrolides it is now a very treatable condition with its 5-year prognosis increasing from 63% in the 1970s to about 90% in the late 1990s.[112] Initially, case reports and series' using low-dose erythromycin[112,113] reported clinical and radiological improvements in patients with DPB, but recent reports have also reported similar positive findings with clarithromycin, roxithromycin and azithromycin (Table 5).[114–117] A recent Cochrane review reported that, of the many studies assessed only one was identified to have adequate quality.[4] In this study of 19 subjects with DPB, 12 were randomly assigned to receive low-dose erythromycin and rest no treatment.[118] It was observed that compared to the pre-treatment CT scan, there were marked improvements in the interval CT scan in all subjects following treatment with the erythromycin. Of note, 71.4% of the control group subjects had worsening of their interval scan. This study had a number of methodological errors with no fixed times of treatments, interval scans, and mention of adverse events besides the small cohort of subjects.

Table 5 Summary of the studies of macrolides in diffuse panbronchiolitis.

Study	Study design	Number of subjects	Duration of study	Antibiotic used	Outcomes
Akira et al.[118]	Observational RCT of efficacy of macrolide treatment	19 subjects (12 active treatment and 7 no treatment)	Not specified	Erythromycin	- CT scans showed a reduction in number and size of centrilobular and branched linear airways of high attenuation in all subjects. - No change to airway dilatation or peripheral areas of lung attenuation. In the untreated group progression of disease was noted in 71.4% of subjects.
Kudoh et al.[112]	Retrospective observational survival study based on year of diagnosis	498 subjects(Gp A: 1970−79 [only std ABx avail} [$n = 190$]; Gp B: 1980−84 [quinolones avail][$n = 221$]; Gp C: 1985−90 (Erythromycin avail} [$n = 87$])	N/A	Erythromycin	- Survival rate of Gp C was significantly higher than Gps A and B. - Of the 87 in Gp C 5/24 died in patients not receiving ERM compared to 3/63 from ERM treated. - Efficacy of ERM increased survival in older compared to younger subjects.
Yamamoto et al.[134]	Retrospective observational study comparing quinolone vs. macrolide	101 subjects	N/A	Erythromycin	Significant improvements in favour of ERM in: - Exertional dyspnoea - CXR findings, PaO_2 - ESR, titre of cold agglutination - Amount of sputum in favour of ERM
Kobayashi et al.[117]	Open-labelled study of efficacy and safety	60 subjects (efficacy data on 52 and safety data on 55)	12 weeks	Azithromycin	- Efficacy rate was 86.6% (44/52) - Sputum reduction 65.2% (30/46) - Reduction in exertional dyspnoea 50% (23/46) - Improvement in FEV_1, cold agglutination and CRP in smaller numbers of subjects. - Eradication of sputum organisms 39.5% (15/38)
Kadota et al.[115]	Prospective open-labelled study	10 subjects	4 years	Clarithromycin	- FEV_1 and FVC improved within 6 months in most subjects. - PaO_2 at rest improved in 3−6 months. - Improvement in the comprehensive improvement score in 6 months (in 9 subjects). - Negative sputum cultures in majority of subjects at 6 months. - No adverse events with the use of CRM.

Abbreviations: RCT − Randomised control trial; CT scan − Computed tomography scan; Gp − Group; std − standard; ABx − antibiotics; avail − available; n − number; N/A − Not applicable; vs. − versus; CXR − Chest X-ray; PaO_2 − Partial pressure of oxygen in arterial blood; ESR − erythrocyte sedimentation rate; FEV_1 − Forced expiratory volume in 1 s; CRP − C-reactive protein; FVC − Forced vital capacity.

Despite the lack of large RCTs to confirm the efficacy and safety of macrolides in DPB, the Ministry of Health and Welfare of Japan have implemented the use of macrolides in its treatment on diagnosis for 6-months based on the observational studies and expert opinion.

Post-transplant bronchiolitis obliterans syndrome (BOS)

Obliterative bronchiolitis (OB) is an airway inflammatory process that results in significant long-term morbidity and mortality in post-transplant patients, mainly of the lung, but also of other organs, synonymous with chronic graft rejection.[119–121] Although OB is thought to be mainly immunologically mediated and is rarely successfully managed with the use of immunosuppressive agents, significant numbers of transplant patients experience concurrent bacterial and non-bacterial infections which may worsen lung inflammation and potentially worsen the chronic rejection. Azithromycin has been examined in several small post-lung transplant studies with potential benefits, but this has been questioned. Four prospective open-labelled studies with azithromycin treatment have been described in the literature, 3 have shown significant improvements in FEV$_1$,[122–124] but 1 showing no improvement in FEV$_1$.[125] Furthermore, 2 retrospective case series' using azithromycin have been conducted, one reporting positive FEV$_1$ improvements beyond 3 months of treatment cessation in a majority of patients,[126] but the other did not.[127] In the largest prospective study of 14 lung transplant patients receiving azithromycin for 3 months, besides the mean increase in FEV$_1$, it was reported that BAL neutrophils, % neutrophils and IL-8 mRNA ratio decreased significantly but had no impact on IL-17 mRNA ratio.[124] They noted a responder group of 6 patients (increase >10% FEV$_1$) who had a marked reduction in %BAL neutrophilia, IL-8 mRNA and IL-17 mRNA. Moreover, they reported a significantly positive correlation between the initial %BAL neutrophilia and response to treatment. Of note, a BAL neutrophilia of >15% had a positive predictive value of 85% for a significant FEV$_1$ response to azithromycin, and that a BAL neutrophilia <15% had a negative predictive value of 100%.[124] Similar positive and negative predictive values have been reported by another group.[128]

The clinical benefits of azithromycin have been hypothesised to be due to: the pro-kinetic effect diminishing the gastro-oesophageal reflux[122] and enzyme inhibition, increasing the plasma concentrations of immunosupressors.[123–126] However, these have not been substantiated. The role of *C. pneumoniae* infection has been implicated in the development of BOS, with donor-recipient serology mismatch (i.e. donor positive/recipient negative) being an independent risk factor for BOS development.[129] Furthermore, it has been reported that *C. pneumoniae* infection in lung transplant patients is associated with poor outcome and increased risk of BOS.[130] From the available data, azithromycin has been associated with positive outcomes; physicians need to be cautious that this therapy is not viewed as a panacea for treatment of BOS, and that larger clinical trial with long-term follow-up are needed to determine the benefits in all and responding patients.

Opinions and conclusions

Different macrolides have variable pharmacokinetic and pharmcodynamic properties such as the long half-life of azithromycin and its higher concentration in sputum,[131,132] whereas roxithromycin with its higher anti-inflammatory activity,[133] compared to other macrolides. It is also not clear as to whether the actual mechanism of action of macrolides is due to the anti-microbial (deep-seated infection clearance), anti-reflux or anti-inflammatory, and in certain cases anti-fibrotic properties. From this it appears that macrolides may manifest their biological efficacy in a range of respiratory conditions through a number of recognised potential mechanisms or others that still yet to be established. To investigate these mechanisms needs substantial effort and collaboration between clinicians and scientists not only in translational studies, but also on the bench. From the available evidence it should be noted that guidelines recommend the use of macrolides in the management of CF (azithromycin in particular) and pan-bronchiolitis. In the former, the recommendations are based on well designed DBPC studies and meta-analyses and in the latter by consensus opinion (Japanese health authority). In the remaining conditions discussed in this review the data are not so stringently clear and hence there remains a need for well-conducted studies to establish their efficacy. Lastly, it may be that with the aid of these mechanistic and efficacy-based studies in the future, we may be in a better position to determine a disease-specific macrolide, i.e. 'tailored treatment' for the individual patients.

Aerosolised antibiotics deliver anti-microbial therapy to diseased lungs, hence providing targeted therapy with possibly limited adverse events to patients. Most of the current available data on inhaled antibiotics involve anti-pseudomonal agents which if administered early enough may help with eradication, or in the long-term reduce the risk of recurrent infections especially in CF and non-CF bronchiectasis patients.

In this review we have highlighted the various respiratory conditions in which long-term antibiotics, oral or nebulised, have been investigated. The data is more robust in CF (nebulised antibiotics and oral azithromycin) compared to non-CF bronchiectasis, panbronchiolitis and COPD, and even less so with asthma and BOOP. The CF model can serve as a foundation to investigate the role of long-term antibiotics, especially nebulised in non-CF bronchiectasis. Identification of the precise mechanism of anti-inflammatory effect of macrolides would encourage development of newer molecules with immunomodulatory effects, hence circumventing the anti-bacterial effects. There appears to be a role for long-term antibiotics, especially macrolides, in a number of chronic inflammatory airway disorders, however there is an urgent need to establish this by performing longer, macrolide-specific, DBPC and bench studies to establish their efficacy, safety and mechanisms of action.

Conflict of interest statement

Boehringer, GSK/Allen & Hanburys and Wyeth.JK has no conflict of interest.JBM has received honoraria for speaking and financial support to attend meetings/advisory boards from Wyeth, Chiesi, Pfizer, MSD, Boehringer Ingelheim, Teva, GSK/Allen & Hanburys, Napp, Almirall and Novartis.

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