

The Role of Macrolides in Chronic Rhinosinusitis (CRSsNP and CRSwNP)

Gretchen M. Oakley¹ · Richard J. Harvey^{2,3} · Valerie J. Lund⁴

Published online: 20 April 2017
© Springer Science+Business Media New York 2017

Abstract

Purpose of Review We assess the literature on the pharmacokinetics, indications, important considerations, and effectiveness of long-term, low-dose macrolide antibiotics in chronic rhinosinusitis (CRS).

Recent Findings The key to effective implementation of macrolide therapy in CRS is appropriate patient selection. Macrolides have demonstrated the most benefit in Th1-mediated non-eosinophilic CRS when used for durations of at least 3 months.

Summary Macrolide antibiotics have demonstrated great benefit when used for their anti-inflammatory or immunomodulatory properties, which include the blockage of pro-inflammatory cytokines, such as interleukin (IL)-8 and tumor necrosis factor- α (TNF- α). They have been used in CRS patients not responding to traditional corticosteroid-based treatment regimens, but appear to be most effective specifically in Th1-mediated non-eosinophilic CRS in long durations and low doses. Further research is needed to better identify characteristics known to correlate with macrolide response so early directed therapy can be implemented.

Keywords Macrolide · Chronic rhinosinusitis · Sinusitis · Non-eosinophilic · Medical management

Introduction

Macrolide antibiotics have gained initial popularity for their role in the treatment of chronic rhinosinusitis (CRS), based on their success in a subtype of lower airway inflammation. Erythromycin was the first in the macrolide family, discovered in a soil sample in the Philippines in the 1950s, and since then synthetic variations have been developed with better gut absorption and longer half-life [1]. The 14- or 15-membered lactone ring macrolide antibiotics (clarithromycin, erythromycin, azithromycin, and roxithromycin) inhibit bacterial protein synthesis by binding to and interfering with the assembly of the 50S large ribosomal subunit [2, 3]. However, apart from their antimicrobial effects, macrolides were found to have significant anti-inflammatory benefits in inflammatory conditions, such as diffuse panbronchiolitis (DPB), a non-eosinophilic lower airway disease common in the Japanese population, as well as demonstrating many in vitro anti-inflammatory properties, and positive effects seen at doses too low for anti-infectivity. These realizations have led to the concept of macrolide antibiotics as immunomodulatory agents rather than simply antimicrobials.

This article is part of the Topical Collection on *Rhinosinusitis*

✉ Gretchen M. Oakley
gretchen.oakley@hsc.utah.edu

¹ Division of Otolaryngology–Head and Neck Surgery, University of Utah, 50 N. Medical Dr., 3C120, Salt Lake City, UT 84132, USA

² Rhinology and Skull Base Research Group, Applied Medical Research Centre, University of New South Wales, Sydney, Australia

³ Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia

⁴ Royal National Throat, Nose and Ear Hospital, London, UK

Macrolides as Immunomodulators

The anti-inflammatory and immunomodulatory properties of macrolides that have been demonstrated involve a decrease in pro-inflammatory cytokines, including IL-6, IL-8, and tumor necrosis factor- α (TNF- α) [4–7]. Clinical studies have shown a reduction of IL-8 in nasal lavage fluid after administration of

macrolides [6, 8•, 9]. This cytokine is both a target for and product of neutrophils, with neutrophil chemoattractant properties, and is believed to be a significant mediator in the inflammatory response of certain subtypes of chronic rhinosinusitis [10]. Interestingly, this same inhibition of IL-8 by macrolides is not seen with dexamethasone or other immunosuppressants [11]. Macrolides have also been shown in vitro to inhibit neutrophil chemotaxis, oxidative burst, cell adhesion, and phagocytosis and to promote neutrophil degranulation of microbicidal molecules and neutrophil apoptosis [4, 12]. In addition, leukotriene B4 is a powerful chemoattractant of neutrophils, and erythromycin lowers the levels of both of these in bronchoalveolar lavage fluid [13].

Other effects of macrolides have been described. Mucus formation, secretion, and viscosity are known causes of morbidity, and in some cases even mortality, in chronic inflammatory airway conditions. Macrolides have been shown to decrease the burden of these [7, 14, 15], likely due to anti-inflammatory activities rather than a direct effect on mucus-producing cells. Azithromycin does not have bactericidal or bacteriostatic activity against *Pseudomonas aeruginosa*. However, it does inhibit its quorum-sensing circuitry and blocks biofilm formation, which has proven beneficial in the management of cystic fibrosis and diffuse panbronchiolitis [16, 17]. Although these other characteristics may play a role in macrolide success in DPB, they are considered a minor role and will not be discussed further.

Benefits in Lower Airway Inflammatory Conditions

The use of macrolide antibiotics for their anti-inflammatory properties first came to the attention of clinicians following their effects in diffuse panbronchiolitis (DPB). This is a chronic inflammatory airway disease common in the Japanese population, characterized by chronic recurrent bronchiolitis and peribronchiolitis with obstruction of the small airways due to formation of lymph follicles, granulomas, and scars [18]. This led to significant lower respiratory tract symptoms, as well as a high mortality rate [18]. The use of low dose erythromycin therapy improved 10-year survival from 12 to 90% [18], as well as improving clinical symptoms and radiographic findings [19]. Maximal serum and sputum levels of erythromycin were below the minimum inhibitory concentration (MIC) for clinically pathogenic *Haemophilus influenzae* and *Pseudomonas aeruginosa*, the bacteria most often identified in the sputum of DPB patients, indicating a mechanism of action other than antimicrobial [19].

Following this impressive success in DPB, macrolides were applied more broadly in the treatment of lower airway tract conditions, including cystic fibrosis (CF), non-CF bronchiectasis, chronic obstructive pulmonary disease (COPD), non-eosinophilic asthma, infectious bronchiolitis, and

bronchiolitis obliterans [20]. Similar to DPB, pulmonary neutrophil infiltration predominates in CF and non-CF bronchiectasis. Randomized controlled trials (RCTs) have shown significant benefit in using long-term, low-dose macrolides in CF patients, including improved quality of life, stabilized or improved forced expiratory volume, and fewer respiratory exacerbations [21, 22] and is a common adjunctive treatment. In non-CF bronchiectasis, studies have shown reductions in pulmonary exacerbations, sputum production, and levels of inflammatory markers in bronchoalveolar lavage fluid, such as IL-8 and neutrophil ratios [23–26]; however, increased presence of macrolide-resistant bacteria also occurred as a result of long-term, low-dose macrolide use in some cases [24]. Similarly, long-term macrolides have reduced frequency of airway exacerbations and enhanced quality of life in COPD [27]. In the case of asthma, randomized controlled trials have demonstrated improvement in bronchial hyper-responsiveness to methacholine following long-term macrolide treatment [28]. Another RCT placebo-controlled trial showed no difference in the rate of severe exacerbations or lower respiratory tract infection in patients with severe asthma taking 6 months of azithromycin versus placebo; however, there was a significant improvement in the azithromycin group when subgroup analysis of just non-eosinophilic asthma patients was performed [29], indicating its efficacy in this inflammatory airway phenotype.

Pharmacokinetics

Macrolides were initially believed to have poor pharmacokinetic properties due to early testing revealing low plasma levels of the drug. However, it was later realized that they in fact have a large volume of distribution, high tissue concentrations, and high intracellular accumulation, mainly in leukocytes, leading to efficient delivery to sites of inflammation [20]. These pharmacokinetic properties allow for less frequent dosing, which is not only more convenient for the patient, but may even be more effective. Studies have shown that azithromycin concentrations are significantly higher in sinus mucosa and sinus aspirates than in plasma. Ehnhage et al. reported a three and fivefold higher sinus fluid to plasma concentration for azithromycin immediate-release and extended-release formulations, respectively, with sinus concentrations being maintained up to 120 h [30]. Fang et al. demonstrated that exposure to azithromycin was about 28.2-fold greater in sinus tissue than in plasma at 24 h after azithromycin extended-release administration, and 21-fold greater after azithromycin immediate-release, but regardless of the formulation used, concentrations remained detectable in sinus tissue for at least 6 days [31]. The volume of distribution for azithromycin is 30 L/kg, and the plasma clearance is very high at 50 L/h [32], so low plasma concentrations are the result of

rapid blood-tissue distribution [20]. The standard plasma half-life of azithromycin is 50 h after IV and 70 h after oral administration [33]. Following a single standard dose of 500 mg of oral azithromycin, peak plasma concentrations of 0.2–0.4 mg/L were achieved, with a time to maximum concentration of 2–4 h [34]. Again, these studies have demonstrated higher concentrations of azithromycin when administered as the extended-release formulation rather than the immediate-release [30, 31, 35]. Since the use of macrolides for their anti-inflammatory rather than their antimicrobial properties for the management of CRS is in the early phase of adoption, studies have not yet indicated the sinus concentrations necessary to attain these anti-inflammatory effects.

Safety

An ongoing concern with prescribing macrolide antibiotics for the management of CRS is the fear of adverse drug effects. The most prominent of these are cardiovascular, especially prolongation of the QT interval and the arrhythmia “torsades de pointes,” gastrointestinal side effects related to increased gut motility, and sensorineural hearing loss. The concern over potential macrolide side effects and drug-drug interactions can particularly plague the rhinologist since the medications are being used to manage a condition that although often quite debilitating on a day-to-day basis is ultimately a matter of quality of life rather than life-threatening. This means it is important that risk-benefit analysis is thorough (Fig. 1).

Potential drug interactions are an important consideration when prescribing any medication. Many medications are metabolized in the liver by the cytochrome P-450 system. Macrolide antibiotics are transformed in the liver to nitrosalkanes, which can then form inactive complexes with CYP-3A4, one of the most significant of the cytochrome P-450 enzymes, inhibiting its activity [1, 37]. This mechanism accounts for most macrolide drug interactions with susceptible drugs including warfarin, cisapride, benzodiazepine, clozapine, cyclosporin, terfenadine, loratadine, and statins. Unlike the other macrolides, azithromycin does not interact with the cytochrome P-450 3A4 enzyme [20].

Macrolides are included in a list of drugs with the potential for pro-arrhythmic cardiac effects due to their interaction with one of the two important K^+ currents (delayed rectifier current, I_{Kr}) in cardiac myocytes involved in ventricular repolarization [38]. Ray et al. reported in an observational study that the risk of death from cardiac causes was twice as high among current users of oral erythromycin (10 deaths per 5305 person-years; IRR 2.01) compared to those who did not use any study antibiotics, and the risk was five times as high when erythromycin was being used concurrently with another CYP3A inhibitor (3 deaths per 194 person-years; IRR 5.35) compared to patients not using these drugs [39]. In an observational study of nearly

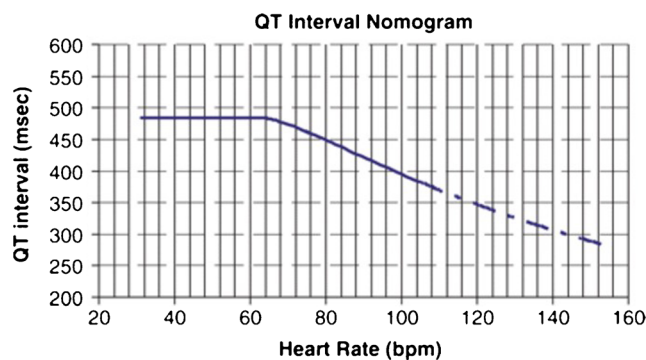


Fig. 1 A QT nomogram can be used to assess the arrhythmogenic risk of drug-induced QT prolongation. Permission granted to reproduce this figure from Chan et al., who explains it as: “QT Interval Nomogram for determining ‘at risk’ QT–HR pairs from a single 12-lead ECG. Use: The QT interval should be measured manually on a 12-lead ECG from the beginning of the Q wave until the end of the T wave in multiple leads (i.e., six leads including limb and chest leads and median QT calculated). The QT interval is plotted on the nomogram against the heart rate recorded on the ECG. If the point is above the line then the QT–HR is regarded ‘at risk’.” Reproduced with permission from Oxford University Press [36]

3000 patients with acute exacerbations of COPD and community-acquired pneumonia, clarithromycin treatment was associated with a significantly increased risk of cardiovascular events with a hazard ratio of 1.50 and 1.68, with longer courses (>7 days) being associated with more events especially in patients with pre-existing history of coronary heart disease [40]. When Svanstrom et al. compared clarithromycin, roxithromycin, and penicillin V in a Danish cohort study, the risk of cardiac death was significantly increased with clarithromycin (5.3 deaths per 1000 person-years, adjusted rate ratio 1.76) versus roxithromycin or penicillin (both 2.5 deaths per 1000 person-years), especially in women [41]. In absolute terms, 37 excess cardiac deaths occurred per 1 million courses of clarithromycin than with penicillin V. The two previously mentioned studies both show increased risk only during current use of the given macrolide, not previous use. Another population-based study also reported an increased risk of myocardial infarction, arrhythmia, and cardiac mortality in the short term during clarithromycin use [42]. However, it is important to note that this was an adjusted absolute risk difference for current use of clarithromycin versus amoxicillin of 1.90 excess myocardial infarctions per 1000 patients, 0.95 excess cardiac deaths, and 0.20 excess arrhythmia events per 1000 patients [42]. Albert et al. critically analyzes the electrophysiologic effects of macrolides, concluding that oral erythromycin does not reach peak concentrations high enough to affect cardiac repolarization and cause arrhythmias without other confounding variables at play according to in vitro electrophysiologic studies; the large majority of subjects in the literature experiencing cardiac arrhythmias on macrolides have coexisting risk factors, and without these risk factors the incidence is very low; and that the small number of deaths reported, large number of antibiotic courses, and

observational design of these studies has predisposed to an overestimation of risk for various study design reasons [43]. It is also important to keep in mind that all medications are associated with some risk and that macrolides are no exception.

However, with careful patient selection and adequate assessment of the risks and benefits on a case-by-case basis, these can be used judiciously and effectively both for their antimicrobial properties in the management of acute exacerbations of CRS and for their anti-inflammatory properties for ongoing CRS management. Of note, these studies in the literature include patient populations being treated with antimicrobial doses and durations. Intravenous administration of erythromycin 500 mg over 15 min causes a peak serum concentration of 45 mg/L at 3 min after injection [44], with slower administration leading to lower levels [45]. Oral administration achieves a peak concentration of 2–4 mg/L [46], and in vitro studies have shown no effect of erythromycin on cardiac repolarization at a concentration of 10 mg/L [47], so standard oral dosing should not lead to arrhythmias in the absence of other cardiac pre-existing conditions or confounding issues. Given that the potential cardiac risk of macrolides being reported, which is a very low absolute risk overall, is based on its peak concentrations, perhaps the use of low dose macrolides over the longer term for their anti-inflammatory properties may be even safer. However, a sensible recommendation might be that a careful cardiac and drug history is taken and an ECG is done prior to commencing treatment.

Role in Exacerbations of CRS

The use of macrolide antibiotics in the treatment of chronic rhinosinusitis (CRS) for an anti-infective purpose, in the case of acute exacerbations of CRS, would typically involve a higher dose antibiotic for a shorter duration of time. A broad range of bacteria is susceptible to macrolide antibiotics. Although penicillins are considered the treatment of choice for group-A β -hemolytic streptococcal infections, such as acute rhinosinusitis, a macrolide, mainly erythromycin, is indicated for treatment of penicillin-allergic patients. A therapeutic dose is usually administered for 10 days. One study demonstrated the MIC of erythromycin, azithromycin, and clarithromycin against *Streptococcus pneumoniae* cultures to range from 0.031 to 0.125 $\mu\text{g/mL}$ [48]. In addition to *Streptococcus pneumoniae*, macrolides also have activity against *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Staphylococcus aureus* [3, 20]. The antimicrobial spectrum for macrolides is displayed in Table 1. Given its pharmacokinetic properties previously discussed, notably the accumulation in leukocytes at inflamed sites, oral dosing either at 500 mg daily for 3 days or as a single 1–1.5 mg dose is often sufficient [20]. Of note, even when macrolides are used in the

presence of multi-drug resistant bacterial strains or below MIC, they can still lead to some clinical benefit from their immunomodulatory properties [49].

Role in eCRS/CRSwNP

Chronic rhinosinusitis is often separated out by the clinician and academician into two phenotypes, CRS with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). Given the inflammatory nature of these phenotypes, corticosteroids are commonly utilized and recommended practice for short-term [50] and postoperative settings based on evidence-based reviews [51, 52]. CRSwNP is characterized by excessive T-helper 2 (TH₂) inflammation and eosinophilic infiltration and generally responds favorably to corticosteroids. However, the effectiveness of this treatment is not uniform amongst all types of CRS. There is a subset of CRS, even CRSwNP, patients who demonstrate corticosteroid resistance and respond poorly to either oral or topical corticosteroids. These patients often fall into a recalcitrant CRS group, and research has shown that they may benefit from long-term, low-dose macrolide therapy [8, 53, 54, 55, 56, 57]. However, current understanding of the appropriate patient for macrolide therapy is poor and limits use to simply those patients who do not respond to first line anti-inflammatory therapy. Investigations into this poor corticosteroid response has shown an eosinophilic patient group responds to oral corticosteroid with significantly greater reduction in polyp size, nasal congestion, total nasal symptom scores, and nasal resistance than a neutrophilic patient group [58]. Amongst patients with nasal polyposis, 76.5% were predominantly eosinophilic, whereas the remainder were predominantly neutrophilic or were mixed. Similarly, postoperative patients using high volume corticosteroid nasal irrigations who had high tissue eosinophilia ($\geq 10/\text{HPF}$) have shown greater improvement in sinonasal outcome (SNOT-22) and endoscopy scores than those with low tissue eosinophilia ($\leq 10/\text{HPF}$) [59]. A study by Haruna et al. specifically assessed who demonstrated poor response to macrolide therapy and found that they were more likely to have polyposis, increased eosinophil infiltration in their polyps, and bronchial asthma [60].

Perhaps these differing responses according to inflammatory markers could be explained by the fact that although corticosteroids inhibit macrophages, eosinophils, basophils, and mast cells, they have much less of an effect on neutrophils [61], whereas we know that a major mechanism of action of macrolides is their anti-neutrophilic IL-8 blocking properties. Although further research is still needed, this highlights the fact that we cannot rely on simply treating CRS based on nasal polyposis phenotype, but rather must identify the underlying inflammatory process to direct our therapy. Research into the patient characteristics of those who do respond favorably to

Table 1 The spectrum of antimicrobial coverage of macrolides

Macrolide antimicrobial coverage	
Common respiratory pathogens (in ARS and CRS)	Other bacteria
<i>Streptococcus pneumoniae</i>	<i>Mycoplasma pneumoniae</i> (and <i>M. avium</i> and <i>M. intracellulare</i>)
<i>Haemophilus influenzae</i>	<i>Legionella pneumophila</i>
<i>Streptococcus pyogenes</i>	<i>Treponema pallidum</i>
<i>Staphylococcus aureus</i>	<i>Neisseria gonorrhoeae</i>
<i>Moraxella catarrhalis</i>	<i>Listeria monocytogenes</i>
	<i>Bordetella pertussis</i>
	<i>Corynebacterium diphtheria</i> (as an adjunct to antitoxin)
	<i>Campylobacter jejuni</i> (in severe or prolonged cases)
	<i>Chlamydia trachomatis</i>
	<i>Propionibacterium acnes</i>
	<i>Ureaplasma urealyticum</i>

ARS acute rhinosinusitis, CRS chronic rhinosinusitis

macrolides demonstrated an association with low serum and tissue eosinophilia [62]. More objective histopathologic analysis, such as the uniform perioperative protocol used in the prior study, may better allow the clinician to weigh the risks-benefits of long-term, low-dose-macrolide therapy and more safely and effectively guide treatment.

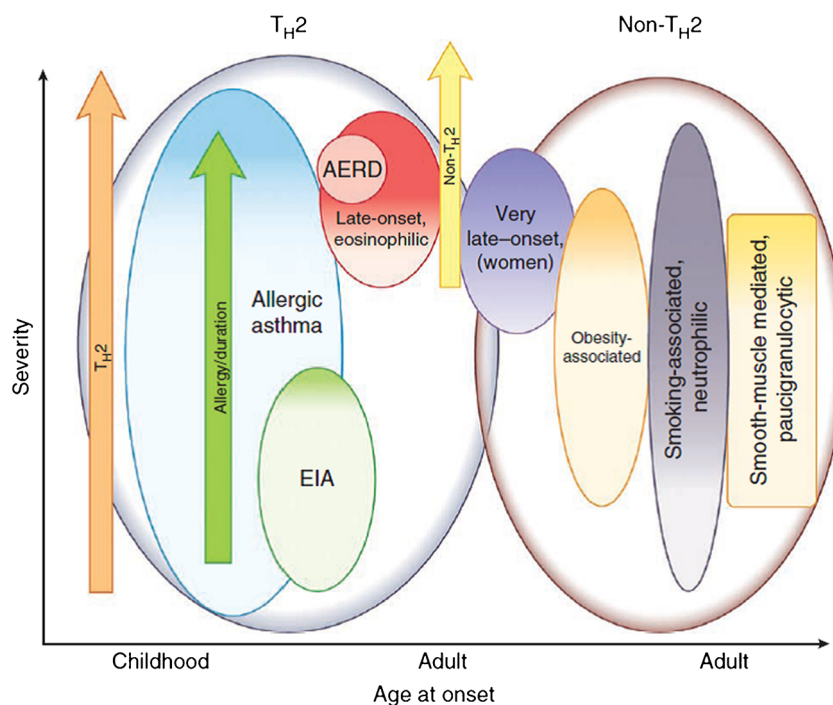
Current research demonstrates that Th2-mediated, eosinophilic CRS (eCRS) patients are unlikely to respond well to long-term, low-dose macrolide therapy, and therefore it is not

indicated in this group. If histopathologic tissue analysis is not an option, it can be assumed that CRSwNP patients will be less likely to respond since the majority of these patients demonstrate a predominantly eosinophilic CRS phenotype [58, 63].

Role in CRSsNP

CRSsNP is a phenotype that is made up of primarily three categories of inflammatory airway condition. The first is a primary or acquired mucociliary failure, including cystic fibrosis, primary ciliary dyskinesia, and bronchiectasis-related CRS. The second is CRS secondary to a broader immunodeficiency disorder, such as common variable immunodeficiency and selective IgA deficiency. Although these are understood to be largely systemic conditions, we understand that effective treatment targeted at the upper airways can benefit the entire disease process as a result of the unified airway concept [64–66]. The third and most common CRSsNP patient group consists of those patients without polyposis who do not fit into one of the categories above. This can be either a Th2-mediated eosinophilic CRS or a Th1-mediated non-eosinophilic CRS. These CRSsNP phenotypes align with those of asthma, due to the relationship between the upper and lower inflammatory airway conditions, in that there is a range of onset and severity for both types, with Th2-mediated-eosinophilic CRS being most common and typically associated with onset early in life, along with presence of allergy and atopy [67] (Fig. 2). This group demonstrates the best response to corticosteroid treatment. Th1-mediated, non-eosinophilic

Fig. 2 Depiction of the theoretical asthma phenotypes indicating the association between Th2 eosinophilic inflammation, severity, and onset. This pattern is also seen in CRS. Reproduced with permission [67]. Reprinted by permission from Macmillan Publishers Ltd.: Nat Med. 2012;18(5):716–725



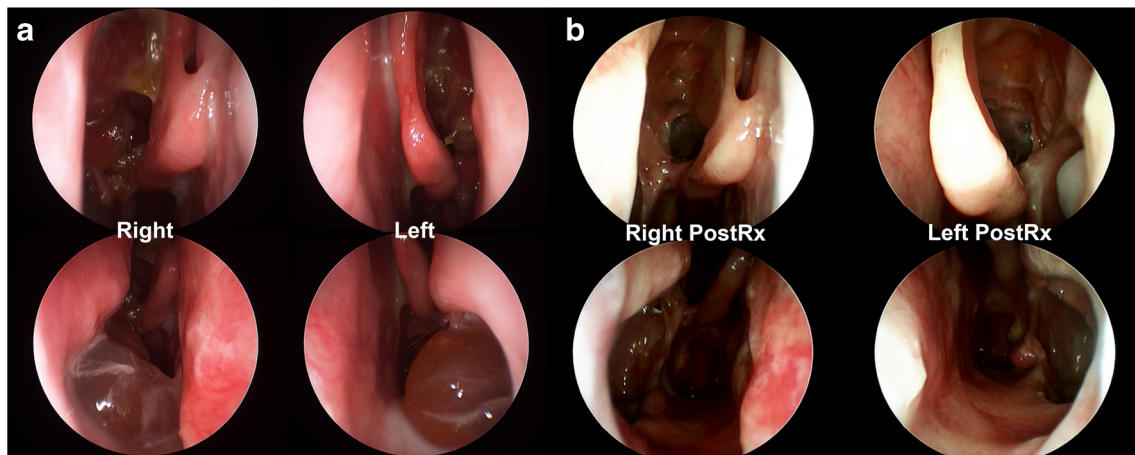


Fig. 3 This is an example of a macrolide response. This patient continues to have severe persistent disease both symptomatically and on endoscopy at 3 months following revision-endoscopic sinus surgery and

corticosteroid-based treatment (a). She was then started on long-term, low-dose macrolide therapy. After 3 months of this therapy, her endoscopic exam reveals complete normalization of mucosa (b)

Table 2 Publications within the last 5 years on macrolides in chronic rhinosinusitis. RCT = randomized controlled trial; CRSsNP = chronic rhinosinusitis without nasal polyposis; SNOT-22 = 22-item sinonasal

outcome test; ICAR = International consensus on allergy and rhinosinusitis; EPOS: European position paper on rhinosinusitis and nasal polyps

Study	Year	Number	Macrolide used	Main results	Type of study
Head et al. [70]	2016	3 studies	Multiple	Modest improvement in disease-specific quality of life in CRSsNP after 3 months of macrolide therapy	Systematic review
Orlandi et al. [55••] (ICAR)	2016	9 studies	Multiple	Macrolides are an option for CRSsNP patients; Aggregate grade of evidence: B	Systematic review
Oliveira et al. [71]	2016	32	Azithromycin	Significant improvement in SNOT-22	Case series
Amali et al. [72]	2015	66	Azithromycin	Significant improvement in SNOT-22 scores in treatment group and a higher percentage change at 3 months	RCT
Rudmik et al. [73]	2015	3 studies	Multiple	A prolonged course (>3 months) of macrolides may be considered for CRSsNP patients	Systematic review
Haxel et al. [74]	2015	58	Erythromycin	Improved postoperative nasal endoscopy in erythromycin group; No general recommendation for postoperative erythromycin in CRS.	RCT
Varvyanskaya et al. [75]	2014	66	Clarithromycin	Improved SNOT-20, rhinomanometry, saccharin transit time, nasal endoscopy, and CT findings in clarithromycin groups versus control	RCT
Maniakas et al. [76]	2014	12	Azithromycin	Macrolide therapy may help corticosteroid resistant CRS patients (sample size too small for statistical analysis)	Case series
Fan et al. [77]	2014	43	Clarithromycin	Significantly greater QOL and endoscopy improvements in high-dose, short-term versus low-dose, short-term clarithromycin therapy	RCT
Dabirmoghaddam et al. [78]	2013	40	Clarithromycin	Improvement in VAS, CT, and endoscopy findings after clarithromycin 500 mg twice daily for 8 weeks	Case series
Pynnonen et al. [79]	2013	3 studies	Multiple	Limited data to support long-term macrolides for CRS; further research needed for subgroup analysis	Systematic review
Nakamura et al. [80]	2013	39	Clarithromycin	Significantly better subjective symptom improvement at 6 months versus 3 months of postop macrolide therapy	Case series
Soler et al. [57••]	2013	17 studies	Multiple	Macrolide therapy is an option in CRS (especially in patients with low IgE); Aggregate quality of evidence: B	Systematic review
Fokkens et al. [68••] (EPOS)	2012	2 studies (RCTs)	Multiple	Level of evidence for use of macrolides in CRSsNP is Ib, strength of recommendation C.	Systematic review

RCT randomized controlled trial, CRSsNP chronic rhinosinusitis without nasal polyposis, SNOT-22 22-item sinonasal outcome test, ICAR international consensus on allergy and rhinosinusitis, EPOS European position paper on rhinosinusitis and nasal polyps, VAS visual analog scale

CRSsNP generally has a later onset in life. Current literature indicates that it is this latter group that should be targeted for most effective utilization of long-term, low-dose macrolide therapy, as it demonstrates the best response [55•, 68•].

As previously mentioned, macrolide therapy has been demonstrated to be most effective in the non-eosinophilic, non-atopic phenotype (Fig. 3). A study by the authors assessing the patient characteristics and tissue histopathology of the CRSsNP patient group with a favorable response to postoperative-long term, low-dose macrolide therapy highlighted this concept. Macrolide responders were found to have low serum and tissue eosinophilia [62, 69]. This is consistent with prior study findings. In a randomized, double-blind, placebo-controlled study by Wallwork et al., CRS patients treated with 3 months of roxithromycin therapy were found to have greater improvement in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid than those without; however, this finding was only significant in the low IgE subset [8•]. Suzuki et al. found an inverse correlation between symptom response to macrolides and eosinophil counts in peripheral blood, nasal smear, and sinus mucosa, as well as a greater symptom improvement in patients with normal rather than high IgE [69]. Assessment of serum IgE and macrolide response has not uniformly demonstrated response, however [62]. This is likely because IgE is not a reliable biomarker for eosinophilic CRS, with poor positive and negative predictive values [63]. Actual neutrophil levels in tissue has not shown a direct correlation with macrolide therapy success [62, 69], highlighting that it is not the neutrophilia of the CRS that leads directly to macrolide response, but rather its distinction from the Th2-mediated,

predominantly eosinophilic inflammatory condition. Implementing regular histopathologic analysis can add useful objective data for the clinician trying to identify patients most likely to benefit from long-term, low-dose macrolide therapy, better assess the risk-benefit ratio when using this treatment modality, and define this patient group for future research efforts.

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) reviewed several studies using macrolide therapy for CRS in varying doses, most commonly half the daily dose used to treat acute infections, with long-term therapy being defined as durations longer than 4 weeks [54•]. An evidence-based review with recommendations covering macrolide for CRS management reported a range of dosing used for all included studies to be erythromycin 400–1800 mg (4 studies), clarithromycin 150–300 mg (5 studies), roxithromycin 150–300 mg (9 studies), and azithromycin 500 mg per week (1 study) [57•]. The duration for this dosing ranged from 2 weeks to 12 months [57•]. Studies have shown that duration of low-dose macrolide therapy is an important component to its effectiveness. The recent literature on macrolides in CRS is listed in Table 2. Hashiba et al. reported improved subjective and endoscopic assessment with longer durations of macrolide therapy, from 4.7% having improvement at 2 weeks to 71% at 12 weeks [81]. Patients who respond to macrolide therapy at 3 months have also been shown to have continued improvement in symptom scores and saccharine transit time at 12 months when maintained on the medical therapy [53]. Sustained benefit beyond discontinuation of the macrolide treatment is not seen [8•]. A distinction in the efficacy of different 14- and 15-member ring macrolide

Table 3 Characteristics of chronic rhinosinusitis patients most associated with macrolide therapy success

Characteristics of macrolide appropriate CRS patient	
Lack of tissue eosinophilia	More likely to have IL8-driven inflammation
Lack of serum eosinophilia	A high serum eosinophilia has a high PPV for tissue eosinophilia
Low serum IgE	Poly-IgE production associated with nasal polyposis and macrolides demonstrate effect in subgroup within RCT
Broader lower airway disease not responsive	IL8-driven disease mostly likely occurring across entire airway. Persistent upper airway ‘only’ disease more likely to reflect local factors
Absence of squamous metaplasia	Permeant remodeling and irreversibility of mucociliary function probably not going to improve with immunomodulation.
Lack of childhood asthma	Likely allergic or IgE-mediated association
Lack of skin or conjunctival symptoms	Atopic predispositions more likely to be associated with these organs involved.
Poor systemic corticosteroid response	Suggests non-eosinophilic disease. Lack of topical response is not the equivalent as many factors contribute to poor local effectiveness.

CRS chronic rhinosinusitis, IgE immunoglobulin E, IL-8 interleukin-8, CS corticosteroids, RCT randomized controlled trial

options has not been demonstrated [60, 82]. A summary of potential characteristics of a macrolide appropriate CRS candidate is outlined in Table 3.

Conclusion

Anecdotally, rhinologists have experienced sporadic cases of dramatic macrolide responsiveness in some CRS patients. Converting this into management guidelines has been difficult, and the use of low-dose, long-term macrolides is presently the subject of large multi-centre studies in several countries. The key to effective implementation of macrolide therapy, in CRS, is patient selection. The treatment goal should be early directed therapy to patients with characteristics known to correlate with macrolide response. It may be appropriate to offer a long-term macrolide as an option to surgery in selected cases. An alternative effective practice may involve histopathologic tissue analysis and post-surgical long-term, low-dose macrolide therapy (e.g., clarithromycin 250 mg once daily) in patients with <10 eosinophils/HPF who are not responding to routine CRS care. This should be continued for at least 3 months to determine response, then may be ongoing if there is benefit. (Of note, preoperative corticosteroids affect the tissue histopathology, and intraoperative tissue biopsy needs to be performed without recent corticosteroid therapy). Decreasing the dosing frequency to three times per week is an option in some patients. If used as a carefully selected and directed therapy, macrolides have the potential to provide significant benefit to a sub-set of patients with previously-labelled recalcitrant CRS.

Compliance with Ethical Standards

Conflict of Interest Dr. Oakley declares no conflicts of interest relevant to this manuscript. Dr. Lund reports personal fees from MSD, Crucell (Johnson and Johnson), NeilMed, Vitaccess, Vifor, GSK, and Abbott. Dr. Harvey reports grants and personal fees from Olympus, Medtronic, Neilmed, and Seqiris.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular Interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Cervin A, Wallwork B. Efficacy and safety of long-term antibiotics (macrolides) for the treatment of chronic rhinosinusitis. *Curr Allergy Asthma Rep*. 2014;14(3):416.
2. Champney WS, Tober CL. Inhibition of translation and 50S ribosomal subunit formation in *Staphylococcus aureus* cells by 11 different ketolide antibiotics. *Curr Microbiol*. 1998;37(6):418–25.
3. Harvey RJ, Wallwork BD, Lund VJ. Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. *Immunol Allergy Clin N Am*. 2009;29(4):689–703.
4. Culic O, Erakovic V, Parnham MJ. Anti-inflammatory effects of macrolide antibiotics. *Eur J Pharmacol*. 2001;429(1–3):209–29.
5. Khan AA, Slifer TR, Araujo FG, Remington JS. Effect of clarithromycin and azithromycin on production of cytokines by human monocytes. *Int J Antimicrob Agents*. 1999;11(2):121–32.
6. Suzuki H, Shimomura A, Ikeda K, Furukawa M, Oshima T, Takasaka T. Inhibitory effect of macrolides on interleukin-8 secretion from cultured human nasal epithelial cells. *Laryngoscope*. 1997;107(12 Pt 1):1661–6.
7. Tamaoki J, Kadota J, Takizawa H. Clinical implications of the immunomodulatory effects of macrolides. *Am J Med*. 2004;117(Suppl 9A):5S–11S.
8. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2006;116(2):189–93. **This high quality study reported improvements in QOL scores, endoscopy, and lavage IL-8 levels in the macrolide group versus placebo, particularly highlighting benefit in a low IgE subgroup.**
9. Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. *Am J Rhinol*. 2000;14(3):143–8.
10. Bachert C, Wagenmann M, Rudack C, et al. The role of cytokines in infectious sinusitis and nasal polyposis. *Allergy*. 1998;53(1):2–13.
11. Vanaudenaerde BM, Wuyts WA, Geudens N, et al. Macrolides inhibit IL17-induced IL8 and 8-isoprostane release from human airway smooth muscle cells. *Am J Transplant*. 2007;7(1):76–82.
12. Tamaoki J, Sakai N, Tagaya E, Konno K. Macrolide antibiotics protect against endotoxin-induced vascular leakage and neutrophil accumulation in rat trachea. *Antimicrob Agents Chemother*. 1994;38(7):1641–3.
13. Oda H, Kadota J, Kohno S, Hara K. Leukotriene B4 in bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis. *Chest*. 1995;108(1):116–22.
14. Tagaya E, Tamaoki J, Kondo M, Nagai A. Effect of a short course of clarithromycin therapy on sputum production in patients with chronic airway hypersecretion. *Chest*. 2002;122(1):213–8.
15. Tamaoki J. The effects of macrolides on inflammatory cells. *Chest*. 2004;125(2 Suppl):41S–50S. **quiz 51S**
16. Hoffmann N, Lee B, Hentzer M, et al. Azithromycin blocks quorum sensing and alginate polymer formation and increases the sensitivity to serum and stationary-growth-phase killing of *Pseudomonas aeruginosa* and attenuates chronic *P. aeruginosa* lung infection in Cfr(-/-) mice. *Antimicrob Agents Chemother*. 2007;51(10):3677–87.
17. Tateda K, Comte R, Pechere JC, Kohler T, Yamaguchi K, Van Delden C. Azithromycin inhibits quorum sensing in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2001;45(6):1930–3.
18. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med*. 1998;157(6 Pt 1):1829–32.
19. Nagai H, Shishido H, Yoneda R, Yamaguchi E, Tamura A, Kurashima A. Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. *Respiration*. 1991;58(3–4):145–9.
20. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther*. 2014;143(2):225–45.

21. Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA*. 2003;290(13):1749–56.
22. Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax*. 2002;57(3):212–6.
23. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA*. 2013;309(12):1251–9.
24. Valery PC, Morris PS, Byrnes CA, et al. Long-term azithromycin for indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med*. 2013;1(8):610–20.
25. Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):660–7.
26. Yalcin E, Kiper N, Ozcelik U, et al. Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. *J Clin Pharm Ther*. 2006;31(1):49–55.
27. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689–98.
28. Kostadima E, Tsiodras S, Alexopoulos EI, et al. Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J*. 2004;23(5):714–7.
29. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax*. 2013;68(4):322–9.
30. Ehnhage A, Rautiainen M, Fang AF, Sanchez SP. Pharmacokinetics of azithromycin in serum and sinus fluid after administration of extended-release and immediate-release formulations in patients with acute bacterial sinusitis. *Int J Antimicrob Agents*. 2008;31(6):561–6.
31. Fang AF, Palmer JN, Chiu AG, et al. Pharmacokinetics of azithromycin in plasma and sinus mucosal tissue following administration of extended-release or immediate-release formulations in adult patients with chronic rhinosinusitis. *Int J Antimicrob Agents*. 2009;34(1):67–71.
32. Singlas E. Clinical pharmacokinetics of azithromycin. *Pathol Biol (Paris)*. 1995;43(6):505–11.
33. Lode H, Bomer K, Koeppe P, Schaberg T. Azithromycin—review of key chemical, pharmacokinetic and microbiological features. *J Antimicrob Chemother*. 1996;37(Suppl C):1–8.
34. Coates P, Daniel R, Houston AC, Antrobus JH, Taylor T. An open study to compare the pharmacokinetics, safety and tolerability of a multiple-dose regimen of azithromycin in young and elderly volunteers. *Eur J Clin Microbiol Infect Dis*. 1991;10(10):850–2.
35. Lucchi M, Damle B, Fang A, et al. Pharmacokinetics of azithromycin in serum, bronchial washings, alveolar macrophages and lung tissue following a single oral dose of extended or immediate release formulations of azithromycin. *J Antimicrob Chemother*. 2008;61(4):884–91.
36. Chan A, Isbister GK, Kirkpatrick CM, Dufful SB. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. *QJM*. 2007;100(10):609–15.
37. Pessayre D, Larrey D, Funck-Brentano C, Benhamou JP. Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother*. 1985;16(Suppl A):181–94.
38. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart*. 2003;89(11):1363–72.
39. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med*. 2004;351(11):1089–96.
40. Schembri S, Williamson PA, Short PM, et al. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ*. 2013;346:f1235.
41. Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. *BMJ*. 2014;349:g4930.
42. Wong AY, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ*. 2016;352:h6926.
43. Albert RK, Schuller JL, Network CCR. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med*. 2014;189(10):1173–80.
44. Houin G, Tillement JP, Lhoste F, Rapin M, Soussy CJ, Duval J. Erythromycin pharmacokinetics in man. *J Int Med Res*. 1980;8(Suppl 2):9–14.
45. Austin KL, Mather LE, Philpot CR, McDonald PJ. Intersubject and dose-related variability after intravenous administration of erythromycin. *Br J Clin Pharmacol*. 1980;10(3):273–9.
46. Nilsen OG. Comparative pharmacokinetics of macrolides. *J Antimicrob Chemother*. 1987;20(Suppl B):81–8.
47. Nattel S, Ranger S, Talajic M, Lemery R, Roy D. Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med*. 1990;89(2):235–8.
48. Blondeau JM, Shebelski SD, Hesje CK. Killing of *Streptococcus pneumoniae* by azithromycin, clarithromycin, erythromycin, telithromycin and gemifloxacin using drug minimum inhibitory concentrations and mutant prevention concentrations. *Int J Antimicrob Agents*. 2015;45(6):594–9.
49. Yamada K, Yanagihara K, Kaku N, et al. Azithromycin attenuates lung inflammation in a mouse model of ventilator-associated pneumonia by multidrug-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2013;57(8):3883–8.
50. Poetker DM, Jakubowski LA, Lal D, Hwang PH, Wright ED, Smith TL. Oral corticosteroids in the management of adult chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations. *International forum of allergy & rhinology*. 2013;3(2):104–20.
51. Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. *International forum of allergy & rhinology*. 2013;3(4):281–98.
52. Rudmik L, Soler ZM, Orlandi RR, et al. Early postoperative care following endoscopic sinus surgery: an evidence-based review with recommendations. *International forum of allergy & rhinology*. 2011;1(6):417–30.
53. Cervin A, Kalm O, Sandkull P, Lindberg S. One-year low-dose erythromycin treatment of persistent chronic sinusitis after sinus surgery: clinical outcome and effects on mucociliary parameters and nasal nitric oxide. *Otolaryngology—head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2002;126(5):481–9.
54. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl*. 2012;3(23):3 p preceding table of contents: 1–298. **A comprehensive evidence based review and treatment guidelines for CRS. This includes the use of macrolide antibiotics and concludes the level of evidence for use of macrolides in CRSnp is Ib with strength of recommendation C.**
55. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *International forum of allergy & rhinology*. 2016;6(Suppl 1):S22–209. **The most recent summary of the best available evidence and current**

- recommendations for management of the various entities of rhinosinusitis, including the evidence available for macrolide therapy in CRS. Macrolides are an option for CRSsNP patients; Aggregate grade of evidence: B.**
56. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope*. 2004;114(5):923–30. **An RCT assessing medical and surgical therapy for CRS, with the phenotypes CRSsNP and CRSwNP analyzed separately. This included the use of long term low dose macrolide therapy and demonstrated similar subjective and objective outcomes between the medical and surgical groups.**
 57. Soler ZM, Oyer SL, Kern RC, et al. Antimicrobials and chronic rhinosinusitis with or without polyposis in adults: an evidenced-based review with recommendations. *International forum of allergy & rhinology*. 2013;3(1):31–47. **A comprehensive systematic review of the use of macrolide antibiotics in CRS, concluding that the use of macrolides in CRS is an option with aggregate quality of evidence B.**
 58. Wen W, Liu W, Zhang L, et al. Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy. *J Allergy Clin Immunol*. 2012;129(6):1522–8. **e1525**
 59. Snidvongs K, Pratt E, Chin D, Sacks R, Earls TR, Harvey RJ. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. *International forum of allergy & rhinology*. 2012;2(5):415–21.
 60. Haruna S, Shimada C, Ozawa M, Fukami S, Moriyama H. A study of poor responders for long-term, low-dose macrolide administration for chronic sinusitis. *Rhinology*. 2009;47(1):66–71.
 61. Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med*. 1993;119(12):1198–208.
 62. Oakley GM, Christensen JM, Sacks R, Earls P, Harvey RJ. Characteristics of macrolide responders in persistent post-surgical rhinosinusitis. *Submitted to Rhinology in March 2017*. 2017.
 63. Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *International forum of allergy & rhinology*. 2012;2(5):376–85.
 64. Illing EA, Woodworth BA. Management of the upper airway in cystic fibrosis. *Curr Opin Pulm Med*. 2014;20(6):623–31.
 65. Lin DC, Chandra RK, Tan BK, et al. Association between severity of asthma and degree of chronic rhinosinusitis. *American journal of rhinology & allergy*. 2011;25(4):205–8.
 66. Ramakrishnan VR, Ferril GR, Suh JD, Woodson T, Green TJ, Kingdom TT. Upper and lower airways associations in patients with chronic rhinosinusitis and bronchiectasis. *International forum of allergy & rhinology*. 2013;3(11):921–7.
 67. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18(5):716–25.
 68. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50(1):1–12.
 69. Suzuki H, Ikeda K, Honma R, et al. Prognostic factors of chronic rhinosinusitis under long-term low-dose macrolide therapy. *ORL J Otorhinolaryngol Relat Spec*. 2000;62(3):121–7.
 70. Head K, Chong LY, Piromchai P, et al. Systemic and topical antibiotics for chronic rhinosinusitis. *The Cochrane database of systematic reviews*. 2016;4:CD011994.
 71. Oliveira IS, Crosara PF, Cassali GD, et al. Evaluation of the improvement of quality of life with azithromycin in the treatment of eosinophilic nasal polyposis. *Braz J Otorhinolaryngol*. 2016;82(2):198–202.
 72. Amali A, Saedi B, Rahavi-Ezabadi S, Ghazavi H, Hassanpoor N. Long-term postoperative azithromycin in patients with chronic rhinosinusitis: a randomized clinical trial. *American journal of rhinology & allergy*. 2015;29(6):421–4.
 73. Rudmik L, Soler ZM. Medical therapies for adult chronic sinusitis: a systematic review. *JAMA*. 2015;314(9):926–39.
 74. Haxel BR, Clemens M, Karauskaki N, Dippold U, Kettern L, Mann WJ. Controlled trial for long-term low-dose erythromycin after sinus surgery for chronic rhinosinusitis. *Laryngoscope*. 2015;125(5):1048–55.
 75. Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. *International forum of allergy & rhinology*. 2014;4(7):533–41.
 76. Maniakas A, Desrosiers M. Azithromycin add-on therapy in high-risk postendoscopic sinus surgery patients failing corticosteroid irrigations: a clinical practice audit. *American journal of rhinology & allergy*. 2014;28(2):151–5.
 77. Fan Y, Xu R, Hong H, et al. High and low doses of clarithromycin treatment are associated with different clinical efficacies and immunomodulatory properties in chronic rhinosinusitis. *J Laryngol Otol*. 2014;128(3):236–41.
 78. Dabirmoghaddam P, Mehdizadeh Seraj J, Bastaninejad S, Meighani A, Mokhtari Z. The efficacy of clarithromycin in patients with severe nasal polyposis. *Acta Med Iran*. 2013;51(6):359–64.
 79. Pynnonen MA, Venkatraman G, Davis GE. Macrolide therapy for chronic rhinosinusitis: a meta-analysis. *Otolaryngology-head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2013;148(3):366–73.
 80. Nakamura Y, Suzuki M, Yokota M, et al. Optimal duration of macrolide treatment for chronic sinusitis after endoscopic sinus surgery. *Auris Nasus Larynx*. 2013;40(4):366–72.
 81. Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol Suppl*. 1996;525:73–8.
 82. Kita H, Takezawa H, Isobe M, Kataura A. Long-term low dose erythromycin and roxithromycin therapy for chronic sinusitis. *Practica Otologica*. 1995;1995(Supplement 84):62–9.