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When guideline treatment of asthma fails, consider a macrolide antibiotic

This class of drugs has the potential to benefit patients with persistent, poorly controlled asthma and those with new-onset disease as an adjunct to first-line therapy.

PRACTICE RECOMMENDATIONS

› Consider a trial of azithromycin for patients who have poorly controlled persistent asthma and are not responding to guideline treatment with the combination of an inhaled corticosteroid and either a long-acting bronchodilator or long-acting muscarinic antagonist. **B**

› Consider a trial of azithromycin in addition to first-line guideline therapy for patients who have new-onset asthma. **C**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

In vitro laboratory and in vivo animal models support the biologic plausibility that chronic infection is a potential cause of asthma.^{1,2} Arising from that hypothesis, macrolide antibiotics have been the subject of clinical trials and other studies to determine whether these drugs are efficacious in the long-term management of asthma in adults and children. Macrolides might also have immunomodulatory and antiviral properties that can benefit patients with asthma.³

This article looks at the evidence and clinical scenarios for the use of macrolides in asthma, provides proposed dosing schedules, and reviews associated concerns, including adverse effects, risk of bacterial resistance, and cost.

3 cases to consider

CASE 1 ▶ Paul D developed severe, refractory asthma at 30 years of age after an acute respiratory illness. At age 40, he was treated with 14 weekly doses of azithromycin. His asthma resolved slowly over 12 months.

Outcome. Mr. D has remained free of symptoms of asthma for more than 20 years.

CASE 2 ▶ Casey K developed severe wheezing at 18 months of age after an acute respiratory illness. Refractory asthma symptoms persisted until 6 years of age, at which time he was given 12 weekly doses of azithromycin. Asthma symptoms gradually resolved.

Outcome. Casey was able to resume normal physical activities, including competitive swimming.

CASE 3 ▶ Amy S, who had no history of respiratory problems, presented at 30 years of age with a 3-month history of wheezing and dyspnea after an acute respiratory illness. She was treated



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symptomatically with bronchodilators; wheezing failed to resolve. After 6 months of persistent wheezing that significantly affected her exercise capacity, Ms. S was given a diagnosis of persistent asthma and received 12 weekly doses of azithromycin.

■ **Outcome.** Ms. S's symptoms resolved completely within months.

Evidence of benefit of macrolides in asthma

These 3 cases, taken from my practice (but with names changed), demonstrate the therapeutic potential of macrolide antibiotics for patients with asthma under specific clinical circumstances. The cases are referenced again in the following examination of the literature on macrolides for asthma.

■ **Meta-analysis.** Reiter et al⁴ performed a meta-analysis of 12 randomized clinical trials of macrolides for long-term management of asthma in children and adults. Prolonged treatment was defined as > 3 weeks of continuous administration of a macrolide. The pooled effect of macrolides on forced expiratory volume in 1 second (FEV₁) was not significant; however, a significant effect on peak expiratory flow, symptom scores, quality of life, and airway hyperreactivity was observed.

Comment: The study's authors concluded: "Macrolides may therefore be beneficial as adjunct asthma therapy. Future trials, focusing on long-term safety and effectiveness, should use standardized outcomes and procedures."

■ **Cochrane meta-analysis.** Kew et al⁵ performed a meta-analysis of 23 studies of macrolides for managing chronic asthma for the Cochrane Database of Systematic Reviews. In their review, they reported

- no significant effects of macrolides on asthma exacerbations, asthma control, quality of life, and rescue medication use; and
- significant effects of macrolides for asthma symptoms and FEV₁.

Two within-study subgroup analyses showed a possible benefit of macrolides for non-eosinophilic asthma, defined by a predominance of neutrophils in a bronchoalveolar lavage specimen. Kew et al⁵ noted that (1) most of the evidence examined in the review was of low quality and (2) inclusion criteria, interventions, and outcomes were highly variable.

Comment: The validity of a meta-analysis depends on the validity and similarity of underlying trials. Both meta-analyses just de-



INSTANT POLL

Have you ever used a macrolide antibiotic to help control symptoms in a patient with asthma?

- Yes
 No

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Some patients with asthma who respond to azithromycin experience persistent improvement after antibiotic treatment.

scribed were characterized by (1) grouping trials of older and newer macrolides and (2) significant selection bias in the underlying trials.

Selection bias is prevalent in asthma research and is a major contributor to uncertainty: Randomized controlled trials upon which guideline treatments are based have systematically excluded > 90% of people with asthma.⁶ Exclusions include past or current smoking, the asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome, severe asthma, and acute respiratory illness; these exclusion criteria have also been applied to studies of macrolides. Importantly, patients in the excluded groups are probably those most likely to respond to a macrolide.² Pragmatic effectiveness studies (broad eligibility criteria, adequate duration of azithromycin treatment, a posttreatment observation period, and pre-specified biomarker subgroup analyses) have been recommended to address the hypothesis of what has been termed *infectious asthma*.²

Inconsistent evidence, the generally poor quality of underlying studies, and uncertainty about which subgroup(s) of asthma patients might benefit all contribute to a strength of recommendation of “B” for treating asthma with macrolides. Two recent randomized trials^{7,8} that were not included in the cited meta-analyses, along with other evidence,² point to 2 groups of patients who are candidates for a trial of azithromycin: those with severe refractory asthma and those with new-onset asthma.

■ **Clinical trial in adults.** Gibson et al⁷ conducted a randomized, double-blind, placebo-controlled trial of azithromycin 500 mg 3 times a week or placebo for 1 year in 420 adults who had uncontrolled persistent asthma despite taking medium-to-high doses of an inhaled corticosteroid (ICS) plus a long-acting β agonist (LABA) (the AMAZES [Asthma and Macrolides: The Azithromycin Efficacy and Safety] trial; Level 1 study). The mean baseline asthma control questionnaire score was 1.5, equivalent to an Asthma Control Test (ACT) score* of 15.⁹

Azithromycin reduced the frequency of asthma exacerbations (to 1.07 per patient-year for azithromycin, compared with 1.86 per patient-year for placebo [incidence rate ratio = 0.59; 95% confidence interval (CI), 0.47-0.74]). The percentage of patients experiencing at least 1 exacerbation was reduced with azithromycin treatment (61% of patients in the placebo group experienced ≥ 1 exacerbation, compared with 44% in the azithromycin group [$P < .0001$; number needed to treat = 6]). Asthma quality of life was also improved by azithromycin ($P = .001$).

There was no significant difference between azithromycin and placebo in the overall rate of serious adverse events. Diarrhea that did not require treatment discontinuation was more common in patients treated with azithromycin (34%) than in the placebo group (19%). There was no posttreatment observation period to assess whether these azithromycin benefits waned or persisted after treatment was stopped.

Other evidence¹⁰ indicates that at least some patients who respond to azithromycin will experience persistent improvement after antibiotic treatment is completed (see **CASE 1**).

■ **Pediatric clinical trial.** Stokholm et al⁸ performed a randomized, double-blind, placebo-controlled trial of azithromycin in children 1 to 3 years of age who had been given a diagnosis of recurrent asthma-like symptoms (Level 1 study). Treatment was a 3-day course of azithromycin oral solution, 10 mg/kg/d, or placebo. Random allocation was performed for 158 asthma-like episodes in 72 children.

Azithromycin reduced the wheezing episode to a mean duration of 3.4 days, compared with 7.7 days for placebo (risk reduction = 63.3%; 95% CI, 56%-69.3% [$P < .0001$]). Effect size increased with early initiation of treatment: ie, an 83% reduction in episode duration was seen when treatment was initiated *before* Day 6 of the episode, compared with a 36% reduction if treatment was initiated *on or after* Day 6 ($P < .0001$).

No differences between the randomized groups were observed in clinical adverse effects.

*The ACT score is generated by tallying numerical responses to 5 questions (7 questions for pediatric patients [the c-ACT]), from 1 (worst control) to 5 (best control). A simple working definition of severe refractory asthma is an ACT score of ≤ 15 in a patient taking a combination ICS and LABA inhaler. The ACT and the c-ACT are available at www.asthmacontroltest.com (© GSK group of companies).

Comment: The brief course of azithromycin provided to patients in this trial did not have a significant impact on time to next episode of troublesome lung symptoms in individual children. Previous clinical observations have suggested that a longer duration of treatment (3-6 months) might be required to achieve lasting improvement or remission in selected patients with asthma (see **CASE 2**).^{10,11} The short-term benefit of azithromycin for acute wheezing is limited to children: Two comparable acute dosing trials in adults have shown little¹² or no¹³ short-term benefit; however, these negative findings have been hypothesized to be the result of selection bias.¹⁴

Other evidence is worth examining

Other studies not included in the meta-analyses of randomized controlled trials provide additional evidence to support a recommendation of a trial of azithromycin in patients with severe, refractory, or new-onset asthma.

■ Nonrandomized controlled evidence. AZMATICs (AZithroMycin/Asthma Trial in Community Settings)¹⁵ is the sole randomized, double-blind, placebo-controlled trial of long-term azithromycin that included a 9-month posttreatment observation period. Seventy-five participants were randomized to receive a loading dose of 600 mg of azithromycin or placebo once daily for 3 days in Week 1. They then received either azithromycin 600 mg or placebo once weekly for 11 weeks. Posttreatment observation was performed until 48 weeks after randomization.

However, many eligible subjects, whom the principal investigator believed were ideal candidates for randomization, declined randomization because they did not want to risk receiving placebo. To accommodate those patients, the protocol was amended to include an open-label (OL) azithromycin arm, in which each participant's personal physician prescribed azithromycin 750 mg for 11 weeks after a loading dose¹⁶ (OL cohort only, Level 2 study: controlled, nonrandomized, nonblinded). The OL group had (1) a higher baseline prevalence of severe, persistent asthma (32%) than the randomized group (8%)

($P = .012$); and (2) worse asthma quality of life than the randomized patients ($P = .023$). The OL group represented selection bias attributable to patient preference.

The less severely affected randomized group of the trial did not exhibit significant effects attributable to azithromycin. The more severely affected OL cohort demonstrated significant, and large, azithromycin treatment effects for asthma symptoms, asthma quality of life, and asthma control ($P < .05$ for both groups; number needed to treat [NNT] = 3) that persisted during the posttreatment observation period.

Comment: The authors concluded: "Pending further randomized trials and given the relative safety of azithromycin and the significant disease burden from severe, refractory asthma, prescribing prolonged azithromycin therapy to patients with uncontrolled asthma may be considered by managing clinicians, particularly for patients who have failed to respond to conventional treatment and as an alternative to instituting immunomodulatory agents."¹⁵

■ Before-and-after trial. Forty-six patients with moderate or severe chronic, persistent, stable asthma were selected as a cohort unlikely to experience spontaneous remission (ie, patients in exacerbation were excluded) (Level 2 study: prospective cohort).¹⁷ Subjects were treated for a median of 4 weeks (range, 3 to 9 weeks) with oral doxycycline, 100 mg bid; azithromycin, 1000 mg, once weekly; or erythromycin, 1000 mg/d in divided doses. Average duration of posttreatment follow-up was 6 months. All subjects were positive for antibodies to *Chlamydia pneumoniae*.

Four patients with diagnosed acute *C pneumoniae* respiratory infection developed chronic asthma, which disappeared in each case after treatment. Of the other 42 seroreactive patients who were treated a mean of 6 years after they developed chronic asthma, 21 had either complete remission of asthma symptoms ($n = 3$) or major persistent clinical improvement ($n = 18$). Clinical improvement was more likely to occur in patients with early disease ($P = .01$) and before development of fixed airway obstruction ($P < .01$).

These results are consistent with the hy-



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>
 Rather than increasing the risk of asthma by disrupting the “healthy” microbiome, azithromycin might be helpful in treating an “unhealthy” microbiome.

pothesis that chronic infection of the lower respiratory tract contributes to the development and progression of asthma.¹⁷ Although clinical improvement was more likely in early asthma compared with asthma with fixed airway obstruction, improvement was nevertheless noted in the latter group.

Physicians should also note the landmark trial of azithromycin in severe, smoking-associated COPD, which found a clinically significant benefit in reducing exacerbations and improving quality of life (NNT = 3, to prevent 1 exacerbation).¹⁸

■ Case series. In a prospective case series (Level 2 study: prospective cohort), 163 primary care outpatients (adolescents and adults) who had acute wheezing illnesses or chronic asthma were evaluated for *C pneumoniae* infection by serologic testing.¹⁹ A subgroup of this cohort also had nasopharyngeal cultures tested for *C pneumoniae*.

Twenty patients (12%) were given a diagnosis of *C pneumoniae* infection defined by serology (n = 15), culture isolation (n = 3), or both (n = 2). Of the 20, 10 wheezed for the first time—6 of whom subsequently developed chronic asthma (n = 5) or chronic bronchitis (n = 1), with a serologic profile suggesting chronic infection. The other 10 patients who had a diagnosis of *C pneumoniae* infection already had a diagnosis of chronic asthma. In patients with established chronic asthma, initial serologic findings suggested chronic, rather than acute, *C pneumoniae* infection.

**Tx recommendations:
 When to consider azithromycin**

Randomized⁷ and nonrandomized¹⁵ evidence supports treating severely uncontrolled or refractory asthma (strength of recommendation [SOR], **B**); no comparable randomized trials of azithromycin have been conducted for new-onset asthma (SOR, **C**). Consider prescribing empiric azithromycin for patients with new-onset asthma in the context of shared decision making about potential benefits, harms, and consequences of chronic asthma (SOR, **C**).

It is important to note that wheezing is frequently associated with uncomplicated

acute bronchitis that resolves spontaneously without antibiotic treatment.¹¹ Azithromycin treatment for new-onset asthma should therefore be reserved for patients in whom apparent uncomplicated acute bronchitis fails to resolve after 3 to 6 months, and whose illness is diagnosable as asthma (see **CASE 3**).¹⁰

Do biomarkers predict response?

Confirming *C pneumoniae* infection by bronchoscopy before beginning treatment has been recommended²⁰ but might be impractical; also, diagnostic testing for *C pneumoniae* is limited in availability and has potentially low sensitivity for diagnosing chronic deep lung infection.

So should you test for *C pneumoniae* biomarkers (or for biomarkers of *Mycoplasma pneumoniae*, another atypical infection implicated in the pathogenesis of asthma²¹) before initiating treatment? Azithromycin has antimicrobial, immunomodulatory, and potential antiviral properties.³ The body of evidence reviewed here indicates that the effects of macrolides on asthma might be, at least in part, antimicrobial. However, there is no direct evidence that the benefit of azithromycin in asthma is limited to patients who have positive infection biomarkers.²² Therefore, infection biomarker testing as a decision aid cannot be recommended at this time (although future research might alter this recommendation).

Acute bronchitis and asthma-onset associated with an acute lower respiratory tract infection have been statistically associated with biomarkers of *C pneumoniae* infection.²³ However, *C pneumoniae* biomarkers are also prevalent in patients who have asthma that is not associated with an infectious onset.²³ Several other matters are worth noting:

- *C pneumoniae*-specific IgA²³ and IgE²⁴ are promising biomarkers that deserve further investigation.
- *M pneumoniae* infection has also been associated with asthma and a response to antibiotic therapy.^{21,25}
- Noneosinophilic severe asthma is another potential predictive characteristic.²⁶ The applicability of this biomarker to primary care practice is limited, how-

➤ Physicians who prescribe long-term azithromycin should instruct patients to report any hearing loss.

ever, by the invasive nature of bronchoscopy and by the uncertain validity of the diagnostic concept: There is no guarantee that dynamic inflammatory infiltrates remain stable over a lifetime. Furthermore, the AMAZES Trial⁷ reported that azithromycin benefit was comparable in eosinophilic and noneosinophilic asthma.

Potential for harm with long-term macrolide use?

Controversies about the role of macrolides in asthma involve uncertainty about who might benefit from treatment and the potential harms of macrolides use (TABLE 1^{27,28} and discussed below).²⁹

■ **Adverse effects.** The newer macrolides azithromycin and clarithromycin offer favorable safety and tolerability profiles, compared with those of older agents.³⁰ In clinical trials of azithromycin, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea) were usually mild or moderate and rarely (< 2% of subjects) required discontinuation of study medication.^{31,32} *Clostridium difficile* diarrhea has not been reported in any of the large clinical trials, in which thousands of patients received azithromycin for 3 to 12 months.^{31,32} The major clinical “side effects” attributable to azithromycin are a significant reduction, compared to placebo, in acute respiratory illness, bronchitis, pneumonia, and sinusitis.^{31,32}

■ **Antibiotic resistance.** Exposure of populations to macrolides can increase the percentage of macrolide-resistant bacterial respiratory pathogens³³; policies aimed at decreasing inappropriate macrolide prescribing can significantly lower that percentage.³⁴ There is no evidence, however, of any detrimental effects of macrolide resistance in individual patients receiving azithromycin.³³

In trials of azithromycin for the treatment of trachoma in Africa, significantly fewer deaths occurred in villages where subjects were treated with azithromycin than in villages where azithromycin therapy was not provided.³⁵ In the United States, weekly azithromycin treatment for 3 to 12 months in adults with heart disease resulted in fewer cases of acute bronchitis and pneumonia, compared with

the placebo-treated groups^{31,32}; similar benefit for azithromycin was seen in children who had recurrent lung infection.^{8,36}

Nevertheless, concern over the spread of macrolide-resistant bacteria to the surrounding community is a concern and a possibility—and should be the subject of future research.

■ **Sudden cardiac death.** In a Medicaid population, the risk of sudden cardiac death from taking a macrolide among patients at high risk of cardiovascular disease was 1 in every 4000 administrations.²⁷ Compare that level of risk with the 1 in 167 risk of an acute cardiovascular event in patients with COPD who start taking a LABA.³⁷ There is no detectable increase in the risk of sudden cardiac death when taking azithromycin in the general (ie, average cardiovascular risk) population^{38,39} or when azithromycin is coadministered with a LABA.³

■ **Hearing loss.** An excess of 18 (< 1%) patients affected by hearing loss, 7 of whom sought medical attention, was reported among 2004 patients who had stable coronary artery disease and had been treated once weekly with azithromycin for 12 months ($P = .02$, compared with placebo).³² In another study, hearing test changes leading to discontinuation of azithromycin were detected in an excess of 32 (2.8%) of 1142 patients with COPD treated daily for 1 year.¹⁸

Physicians who prescribe long-term azithromycin should instruct patients to report any hearing loss.

■ **Drug–drug interactions.** Azithromycin is free of the drug–drug interactions characteristic of conventional macrolides, such as clarithromycin.⁴⁰ Nevertheless:

- Caution is advised when giving azithromycin in conjunction with coumadin or theophylline.
- Giving azithromycin with antacids that contain aluminum or magnesium salts can reduce the rate, although not the extent, of the absorption of azithromycin.
- The serum concentration of azithromycin is markedly increased when it is given with nelfinavir.⁴⁰

■ **Microbiome effects.** The host microbiome can have a significant effect on the

TABLE 1

What are the potential harms of long-term macrolide dosing?^{27,28}

Harm	Comment
Adverse effects	Gastrointestinal effects (usually mild) Loose bowel movements associated with azithromycin are due to promotility effects
Antibiotic resistance	Documented with all antibiotics, including macrolides No evidence of harm in any patient taking a macrolide Spread of resistance to the larger community after asthma treatment has not been documented; further research is required
Sudden cardiac death	Not documented in average-risk people Azithromycin: Among high-risk patients, 1 death for every 4000 administrations, thought to result from a prolonged QT interval; risk might be mitigated by weekly dosing ²⁷ Clarithromycin: Among high-risk patients, 1 death for every 115 administrations ²⁸
Hearing loss	Rare and reversible; risk might be mitigated by time-limited weekly azithromycin dosing Counsel patients taking a prolonged macrolide to report hearing loss
Drug–drug interactions	Minimal with azithromycin More common with clarithromycin Exercise caution when co-administering with coumadin, theophylline, or nelfinavir
Microbiome effects	One hypothesis is that macrolides treat a “bad” microbiome associated with asthma A single randomized trial in children found that azithromycin had no long-term (4 years post-randomization) effects on gut microbiome
Cost	A limited course of a macrolide is less expensive than chronic use of an inhaled corticosteroid or a long-acting β agonist inhaler (or combination formulations of these agents)

risk of asthma.² A cross-sectional study indicated that lower respiratory bacterial burden is greater in patients with asthma, compared with that of healthy control subjects, and correlates with bronchial hyperresponsiveness.⁴¹ Early colonization of the infant nasopharynx, particularly with *Streptococcus* spp, is a predictor of asthma risk.^{42,43} Bacterial pathogens in the nasopharyngeal biome at the time of upper respiratory viral infection are significant determinants of risk for the spread of infection to the lower airways, suggesting that these microorganisms contribute to the risk of persistent asthma.⁴¹

Investigators have speculated that, rather than increasing the risk of asthma by disrupting the “healthy” microbiome, azithromycin

might be helpful in treating an “unhealthy” microbiome.^{42,43} Recently, it was shown in a randomized trial that azithromycin induced a perturbation in the gut microbiota of children 14 days after randomization, although the drug did not have a long-lasting effect on the composition of gut microbiota.⁴⁴

What about cost?

Inhaled corticosteroids and combination formulations of an ICS and a LABA are expensive and must be taken for the long term. A 3-month course of generic azithromycin—comparable to what was used in the OL subgroup of AZMATICs¹⁵—costs about as much as 1 ICS and LABA combination inhaler. Using published results,^{15,45} a pilot cost-effectiveness

> In the long run, azithromycin was 10 to 20 times as cost effective as the other 3 therapeutic options for improving asthma quality-of-life outcomes.

➤ Consider a trial of azithromycin for patients who have new-onset asthma.

TABLE 2

Long-term (≥ 3 months) macrolide dosing schedules for treating asthma in adults and children^{7,15}

Drug	Dosage, schedule, and duration
Azithromycin (adults)	Loading dose: 1 500-mg tablet daily for 3 d 1 wk later, start 1 500-mg tablet 3 times weekly ⁷ for 11 wk Total: 36 500-mg tablets or Loading dose: 2 250-mg tablets daily for 3 d Then, 3 250-mg tablets once weekly ^a for 11 wk. ¹⁵ (Can give 1 tablet on each of 3 d of the week if adverse effects develop—eg, 1 tablet on Monday, 1 on Wednesday, and 1 on Friday) Total: 39 250-mg tablets
Azithromycin (children < 110 lb)	Loading dose: 10 mg/kg in suspension, daily for 3 d Then, 20 mg/kg once weekly ^a for 11 wk
Clarithromycin (adults)	1 500-mg tablet bid for 12 wk Total: 168 500-mg tablets
Clarithromycin (children)	7.5 mg/kg in suspension bid for 12 wk

^aProlonged (> 1 week) intracellular half-life for azithromycin allows once-weekly dosing.

analysis in patients with persistent asthma compared doubling the ICS dosage, adding salmeterol, adding tiotropium, or prescribing 3 months of azithromycin. In the long run, azithromycin was 10 to 20 times as cost-effective as the other 3 therapeutic options for improving asthma quality-of-life outcomes.* However, reliable cost-effectiveness analyses require more, and better, evidence.

Recommendations to reflect on for your practice

TABLE 2^{7,15} outlines selected long-term (≥ 3 months) macrolide dosing schedules in the management of asthma. Consider a trial of azithromycin for your patients

- whose asthma is refractory (poorly controlled persistent asthma), despite treatment with either an ICS and LABA combination or an ICS and long-acting muscarinic antagonist combination; and
- who have new-onset asthma.

*Data available from the author upon request. See "Correspondence," at end of article.

Last, there is no evidence for or against prescribing azithromycin for patients who have chronic asthma that is not refractory but is uncontrolled because they are not being treated according to guidelines. **JFP**

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➤ At press time, the *European Respiratory Journal* published a patient-level meta-analysis that demonstrates that maintenance use of azithromycin decreases exacerbations in adults with asthma. To learn more, go to <https://erj.ersjournals.com/content/54/5/1901381>.

Macrolides for Asthma: Registry of Clinical Experience

More information is needed about the “real world” effectiveness of antibiotic treatment for severe refractory and new-onset asthma. If you are a prescribing clinician who cares for patients with asthma and you are considering prescribing antibiotics for asthma, you are invited to document your outcomes by entering prospective, de-identified patient data into a human subjects committee-approved online registry. To gain access to the registry, and for more information, contact the author at dlhahn@wisc.edu or visit <https://www.fammed.wisc.edu/wren/resources/macrolides-for-asthma/>.