

Why are macrolides controversial?

Some experts and clinicians believe that researching and/or using macrolides* for asthma is not worth pursuing. They argue that (1) the number of cases of asthma likely to respond to macrolides is too low, (2) the risks of macrolide treatment are too high and (3) infection may not be the explanation for macrolide benefits in asthma.

Cases of asthma likely to respond to macrolides are too low.

The number of people with asthma who will respond to macrolides is unknown. Severely uncontrolled asthma that does not respond to currently available anti-inflammatory treatments (refractory asthma) comprises an estimated 5%-15% (15 to 45 million) of the 300 million people with asthma worldwide.^{1,2} An additional 35%-45% (105 to 135 million people) with asthma worldwide remain sub optimally controlled (i.e., a total of ~150 million people with asthma worldwide have asthma that is not well controlled).³ Indirect evidence for infection is present in around half of people with asthma, and in up to 80% (36 million) of people with severely uncontrolled asthma.^{4,5} Controlled evidence from primary care settings indicates that between 50%-80% of people with severe refractory asthma may respond to azithromycin.⁶ Since the most severe 20% of asthma accounts for 80% of asthma morbidity, mortality and health care costs, macrolide benefits in a minority of people with asthma (i.e., in those with severe asthma) could have a disproportionate positive impact on disease burden.⁷

The risks of macrolide treatment are too great. Some argue that macrolide treatment will cause antibiotic resistance, sudden cardiac death, and hearing loss. These are important considerations.

Antibiotic resistance.† Exposure to any antibiotic selects for resistant organisms, but there is no evidence for any detrimental effects of macrolide resistance in those taking azithromycin. In fact, the opposite is true: azithromycin consistently shows significant clinical benefits as the only major “side effects.” For example, azithromycin exposure of entire African villages treated for trachoma (a blinding eye disease caused by *Chlamydia trachomatis*) does select for macrolide resistance in pneumonia-causing bacteria (*Streptococcus pneumoniae*) but does not result in increased resistance to penicillin that is the drug of choice for this infection.⁸ Furthermore, fewer deaths actually occurred in azithromycin-treated villages compared to non-treated villages.⁹ In the United States, daily azithromycin treatment for 12 months in severely ill COPD patients did not increase the number of macrolide resistant bacteria, but did kill off many susceptible bacteria, thus increasing the proportion (ratio) that were resistant.¹⁰ These resistant bacteria had no detectable harmful effects on the treated patients; rather, azithromycin decreased the number of COPD exacerbations and improved COPD symptoms.¹¹ In other studies, weekly azithromycin treatment for 3-12 months in adults with heart disease resulted in fewer cases of acute bronchitis and pneumonia compared to the

placebo-treated groups,^{12,13} and similar benefits for azithromycin were seen in children with recurrent lung infections.^{14,15} A concern is whether the resistant bacteria will spread to the surrounding community – this possibility should be studied in future research.

Sudden cardiac death. Azithromycin, like all macrolides (and another antibiotic class called quinolones) has a detectable but very small effect on sudden cardiac death: In individuals prone to heart disease the risk increases from 1 in 20,000 without a prescription to 1 in 10,000 with a prescription.¹⁶ This increased risk of sudden cardiac death was present only when serum levels were high (which is every day with daily azithromycin dosing compared to one day a week with weekly dosing - this is a theoretical advantage, albeit small, of weekly dosing. Future research should use a one day/once weekly dosing protocol). There are no apparent increased risks of sudden cardiac death with azithromycin in the general (average risk) population.^{17,18}

Hearing loss. An excess of 18 cases of mild hearing loss was reported out of a total of 2004 heart disease subjects treated once weekly with azithromycin for 3-12 months.¹³ Hearing test changes leading to discontinuation were detected in an excess of 32 of 1142 COPD patients treated daily with azithromycin for one year.¹¹ Daily dosing is not required to maintain high intracellular levels of azithromycin.¹⁹ Future research should use weekly dosing and monitor for hearing loss.

Infection may not be the explanation for macrolide benefits in asthma.

The underlying reason(s) for any macrolide benefits in asthma are unclear. The mechanism(s) of action for macrolides could include (i) activities against infections, (ii) direct anti-inflammatory activities or (iii) a combination of both. Interest in researching macrolides for asthma was first stimulated by evidence for *C. pneumoniae* (Cp) infections in asthma.⁴ Subsequent evidence suggested macrolides had benefits for selected people with asthma, particularly those with severe disease.^{20,21} This chain of events does not prove that the infection is the cause. Future research should **primarily** assess the benefits and harms of azithromycin in selected groups of people with asthma; and **secondarily** assess for underlying mechanisms of action. It may not be easy, or even possible, to determine underlying mechanism(s) with certainty. However, this is not valid justification for forgoing research.¹¹

* Macrolides are a class of antibiotics that have activity against a wide variety of bacteria, including *Chlamydia pneumoniae* (Cp) and *Mycoplasma pneumoniae* (Mp) that have both been associated with asthma. Azithromycin is a special type of macrolide.

† Exposure to macrolides does not *cause* resistance; antibiotics kill off the susceptible bacteria, leaving the smaller number of pre-existing resistant bacteria to multiply and potentially spread. Cp has not become macrolide resistant, likely because it is isolated within cells and is unlikely to acquire DNA (called “resistance islands”) from other bacteria. Of concern is that macrolide resistance has increased in Mp. Assuming adequate funding, Mp and its resistance pattern will also be studied in our research.

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