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Azithromycin for Recurrent Respiratory Tract Infections in Pediatric Populations

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Azithromycin for Recurrent Respiratory Tract Infections in Pediatric Populations

Abstract

Background: Severe lower respiratory tract infections in pediatric populations result in millions of hospitalizations worldwide. Some children experience recurrent symptoms and progressive episodes multiple times a year. Azithromycin has demonstrated not only antimicrobial but also potential antiviral and anti-inflammatory properties. Can azithromycin decrease disease severity or recurrence in pediatric patients with debilitating chronic respiratory tract symptoms?

Methods: Exhaustive search of available medical literature was performed using MEDLINE-Ovid, Web of Science, and CINAHL. The search terms azithromycin, respiratory tract infection, lower respiratory tract, disease progression, and recurrence were used. Studies were limited to children, age 0 to 18, and randomized control trials. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

Results: Two articles met eligibility criteria. The studies were randomized control trials evaluating azithromycin and its effect on respiratory tract infections. They both demonstrated improved outcomes in symptom severity and progression. The overall quality of both studies was moderate with room for future improvement.

Conclusion: Azithromycin is an appropriate treatment option to consider when evaluating an effective treatment plan for pediatric populations with multiple severe recurrent respiratory tract symptoms. It is important to tailor each treatment plan with patient response and judiciously utilize antibiotics. The most appropriate timeframe and dose of therapy is still to be determined.

Keywords: azithromycin, respiratory tract infection, lower respiratory tract, disease progression, recurrence

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Azithromycin for Recurrent Respiratory Tract Infections in Pediatric Populations

Mikala Pino

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Biography

[Redacted for privacy]
Abstract

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Acknowledgements

To Chris and Rayden: Thank you for your endless patience, love, and support through this busy time in our lives. We got this!

To my parents and sisters: Thank you for always believing in me, pushing me to be my best self, and supporting me in everything I do. Thank you for being you!
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List of Abbreviations

LRTI  Lower respiratory tract infection
LRT  Lower respiratory tract
NNT  Number Needed to Treat
PCP  Primary Care Provider
RTI  Respiratory tract infection
RRTI  Recurrent respiratory tract infection
Azithromycin for Recurrent Respiratory Tract Infections in Pediatric Populations

BACKGROUND

Pediatric populations are exposed to a variety of viruses and bacteria in everyday life. It is estimated that children under the age of five were admitted to the hospital for severe lower respiratory tract infections (LRTIs) 12 million times worldwide in 2010. In the United States alone 6 out of every 100 children were hospitalized for a severe LRTI. Most of these incidences are acute respiratory tract infections. Unfortunately, some children experience severe, recurrent respiratory tract symptoms throughout childhood. These recurrent symptoms can progress to severe infections and pose a significant area of concern for both patients and caregivers.

The complete etiology of recurrent respiratory tract symptoms is unclear. Most suggest that early viral infections are at fault for childhood wheezing and respiratory symptoms, while others find bacterial infections to be equally related to episodes. Regardless of etiology, morbidity and mortality exist. With recurrent symptoms children are at increased risk of respiratory issues in the future, missed school days, and subsequent sequela. Karmaus et al. furthermore demonstrated that children with recurrent LRTIs were 4 times more likely to develop asthma in the first decade of life. Recurrent symptoms also increase healthcare utilization through primary care provider, emergency room, and urgent care visits. New treatment options hold promise in addressing concerns of recurrent respiratory tract symptoms.

One treatment option of interest is the antibiotic azithromycin. While azithromycin is widely known for its coverage of atypical bacteria and respiratory concerns, current
research is also looking at it’s anti-inflammatory\textsuperscript{6,7} and antiviral\textsuperscript{8} properties as well. Azithromycin is generally well tolerated and cost effective. In pediatric populations treated with azithromycin, 6-27\% report adverse reactions. These reactions are most often gastrointestinal and include nausea, vomiting, diarrhea, and abdominal cramps. Serious concerns such as Stevens-Johnson, Schonlein-Henoch, and Churg-Strauss syndromes are rare.\textsuperscript{9} According to Tarascon,\textsuperscript{10} the average cost of treatment is $25-$49 per episode. These characteristics make azithromycin an ideal theoretical treatment option to mitigate some of the difficulties surrounding recurrent respiratory symptoms in children.

Much research has been done on azithromycin with regards to acute respiratory conditions\textsuperscript{11,12} and chronic conditions like cystic fibrosis.\textsuperscript{13} This review looks to determine what effect azithromycin can have on pediatric patients who suffer numerous episodes of progressive respiratory tract symptoms throughout the year and who are generally healthy at baseline. Ultimately, can azithromycin decrease disease severity or recurrence in pediatric patients with chronic lower respiratory tract symptoms?

**METHODS**

An exhaustive literature search using MEDLINE-Ovid, Web of Science, and CINAHL was conducted. The search terms azithromycin, respiratory tract infection, lower respiratory tract, disease progression, and recurrence were used. Studies were limited to children, age 0 to 18, and randomized control trials. Studies looking at defined recurrent respiratory tract symptoms were identified and chronic asthma was excluded. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.\textsuperscript{14}
RESULTS

The initial search was completed in MEDLINE-Ovid. This resulted in 30 articles. Web of Science resulted in another six articles and CINAHL found one. Duplicates were removed and eligibility criteria applied. Two articles\textsuperscript{15,16} were selected and included for review. Per inclusion criteria, both are randomized control trials evaluating azithromycin and recurrent respiratory tract infections. See Table I.

Bacharier et al

This most recent study\textsuperscript{15} looked at early administration of azithromycin and evaluated its ability to prevent progression to severe lower respiratory tract infections. This randomized, double blinded control trial was conducted between April 2011 and December 2014. It focused on preschool children with a history of recurrent lower respiratory tract infections. This history included severe wheezing with LRTI signs and symptoms that required one of the following: an unscheduled visit to a primary care provider (PCP), urgent care, or emergency room or systemic corticosteroids. The primary outcome was whether or not azithromycin administered early in the development of LRTI symptoms could decrease the severity of the LRTI.\textsuperscript{15}

The study's 607 participants were chosen from nine US medical facilities. All were between the ages of 12 and 71 months. Each was given an individualized action plan and parents were instructed to provide treatment at the first signs and symptoms of a LRTI. Computer generated randomization assigned 307 participants to the azithromycin treatment group and the matching placebo group had 300. The azithromycin was dosed at 12mg/kg/d for 5 days. Both groups received symptomatic care of albuterol 4 times per day during the first 48 hours and as needed after.\textsuperscript{15}
Throughout the course of the trial 443 of the participants had 937 LRTI, 473 in the azithromycin group and 464 in the placebo group. There were 164 participants who did not experience a LRTI, 84 in the azithromycin group and 80 in the placebo group. There were 433 who were treated during the first LRTI, 293 for a second, 152 for a third, and 49 for a fourth. A total of 214 participants were lost to follow-up or early termination criteria. The hazards ratio was 0.64 with a 95% confidence ratio of 0.41-0.98, P=0.04. The number need to treat was dependent on the number of recurrent LRTI experiences by the child. In patients with one LRTI the NNT was 33, with two LRTIs the NNT was 14, with three it was 10, and with four it was 7. Symptoms scores for participants treated with azithromycin during a LRTI that proceeded to severe were also less when compared to placebo. The results indicate that the azithromycin group had a decreased risk of progressing to a severe LRTI when compared to placebo and were more likely to respond to azithromycin the more recurrent their LRTI symptoms. There was no difference in time to second RTI between the two treatment groups.15 See Table II.

One major limitation of the study was the fact that the randomization period was extended from 12 to 18 months and up to four LRTIs. This was done as the result of a mild respiratory illness season the first year. Data may be different if all participants were followed for the 78 weeks. Another limitation is that a participant met exclusion criteria after one severe LRTI and was subsequently removed from the trial. Therefore, data cannot be applied to recurrent LRTI after a severe LRTI. It is also important to note that the treatment was applied during early stages of the disease progress and not once full severe LRTI symptoms were present.15

Esposito et al
The second study\textsuperscript{16} looked at recurrent respiratory tract infections (RRTIs) to determine if azithromycin could decrease disease progression and limit recurrence. They also looked to see if patients age 1-14 years had an increased incidence of Mycoplasma pneumoniae or Chlamydia pneumoniae infections. This blinded, randomized study was done between November 2000 and March 2002 at the University of Milan, Italy. A recurrent infection was defined as eight or more infections per year in children <3 years old or six or more in children \geq 3 years old.\textsuperscript{16}

In this study 352 participants with a history of recurrent RRTIs were enrolled. A computer list randomized the patients and the azithromycin group of 177 participants was given 10mg/kg/d for 3d/wk over 3 weeks. There were 175 participants in the symptom treatment group alone. Both groups received symptomatic treatment with acetaminophen, 10mg/kg/dose. Symptom reports were kept by all participants, and follow-up was recorded at 1 month and 6 months. Clinical success was determined by complete resolution of symptoms at 1 month with no recurrence of symptoms, or no more than two relapses of symptoms after the 6 month mark.\textsuperscript{16}

Of the 177 participants in the azithromycin group, 171 obtained treatment success. All of the 76 participants who tested positive for Mycoplasma pneumoniae or Chlamydia pneumoniae infections and were treated with azithromycin also obtained clinical success. In the other group 144 out of 175 participants achieved clinical success. When looking at overall clinical success the NNT was 6. RRR was 0.81 with a 95\% CI of 0.55 to 0.92. Also of importance is the 6-month clinical success. In the azithromycin group, 108 out of 170 achieved clinical success when compared to 88 out of 169 at the 6 months’ follow-up in the symptoms only group. The NNT for long term clinical success was 8.\textsuperscript{16} See Table II.
DISCUSSION

Treatment options for recurrent respiratory tract symptoms have often relied heavily on symptomatic care and the assumption of viral etiology. While treatment is highly patient response dependent, current therapy includes a combination of inhaled short acting beta2-agonists, inhaled corticosteroids, and systemic steroids. While the overall quality of these studies is moderate, clinicians can consider adding azithromycin as an option in treating pediatric patients with severe recurrent respiratory tract symptoms. As previously discussed, azithromycin is well tolerated by most pediatric patients and is generally inexpensive. This is especially true when comparing the cost of one course of antibiotics to the cost of hospitalization for a severe LRTI. Regardless, it is important to judiciously consider initiation of antibiotics and compare the risks to benefits of antibiotic therapy.

The two studies\textsuperscript{15,16} clearly demonstrate an improvement in the azithromycin treatment group. Bacharier et al\textsuperscript{15} showed that as the number of azithromycin-treated LRTIs increased, the NNT to in order to prevent a severe LRTI decreased. This demonstrates a dose-response gradient of sorts. Moreover, there was a decrease in the overall symptom score of the treatment group when compared to placebo. However, they did not demonstrate a decrease in the time or recurrence to second LRTI. While suggesting azithromycin as an option in the truly recurrent severe patient with LRT symptoms, caution about the potential for increased microbial resistance with widespread prophylactic treatment must be considered.\textsuperscript{15} In Esposito et al\textsuperscript{16} clinical success with resolution of symptoms in one month was negligible between the treatment groups. As expected there was an increased symptom resolution response in the azithromycin group
with confirmed bacterial infections. However, clinical success at the 6-month mark in the azithromycin group was increased regardless of symptom etiology.\textsuperscript{16}

When comparing the two studies\textsuperscript{15,16} it is important to consider the differences that limit their complete comparison. One big difference is the treatment dose of azithromycin. In Bacharier et al,\textsuperscript{15} they used a shorter course of therapy, 12 mg/kg/d, over five days, while Esposito et al\textsuperscript{16} chose a longer duration of treatment, 10mg/kg/d for 3 days over 3 weeks. It is difficult to suggest what an ideal azithromycin dose or course would entail. Another key difference in reviewing the studies is the duration and structure of the study itself. Bacharier et al,\textsuperscript{15} tracked and treated a cohort of patients with recurrent LRTI over 52 to 78 weeks. They recorded and addressed each episode with an emphasis on early intervention, progression to severe, and time to next recurrence. Esposito et al,\textsuperscript{16} identified pediatric patients with a history of RRTI who presented with acute respiratory tract symptoms. They treated based on treatment group regardless of current severity and tracked resolution of symptoms or clinical success at 1 and 6 months. Also, they included no placebo or blinding for the patients or caregivers. There was a wide range of RRTIs included in this study with a broad definition of clinical success.\textsuperscript{16}

Appropriate use of azithromycin in pediatric lower respiratory tract symptoms is still an evolving topic, thus continued research in this area should be pursued. The most important area is proper identification in which pediatric patients would benefit most from azithromycin initiation. This must be compared to changes in bacterial resistance and subsequent sequela. Another area includes an appropriate dose and time frame for administration of antibiotics with symptomatic care. It is also still to be determined the true mechanism of action for azithromycin effectiveness in respiratory tract infections.
CONCLUSION
Azithromycin is an appropriate treatment option to consider when treating pediatric patients with severe recurrent respiratory tract symptoms. While the benefits of azithromycin are strongly demonstrated, it is important to consider concerns regarding microbial resistance. Further research in this area is necessary before widespread prophylactic treatment of severe LRTI for the general pediatric population is recommended. When identifying the ideal patient to treat with azithromycin, it is important to note that these patients are generally healthy at baseline with multiple recurrent episodes of debilitating symptoms throughout the year. In this specific patient population early administration of azithromycin can ideally prevent the progression to severe infection. This decreases symptom severity, disease burden, and childhood morbidity.
References


### Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacharier et al(^\text{15})</td>
<td>RCT</td>
<td>Not Serious</td>
<td>Likely(^a)</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not Serious</td>
<td>Dose-Response Gradient(^b)</td>
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<td></td>
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<td>Not Serious</td>
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<td>Not Serious</td>
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</tr>
<tr>
<td>Esposito et al(^\text{16})</td>
<td>RCT</td>
<td>Serious(^c)</td>
<td>Likely(^a)</td>
<td>Low</td>
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<tr>
<td></td>
<td></td>
<td>Not Serious</td>
<td>None</td>
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<td></td>
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<td>Not Serious</td>
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</table>

\(^a\) Small number of studies  
\(^b\) NNT decreased as the doses increased  
\(^c\) Lack of blinding of patients and caregivers, no placebo

### Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Comparison</th>
<th>Patient Population</th>
<th>Study Length</th>
<th>NNT Acute</th>
<th>NNT Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacharier et al(^\text{15})</td>
<td>Azithromycin 12mg/kg/d x 5days N=307</td>
<td>Placebo N = 300</td>
<td>12 to 71 months olds with recurrent LRTI</td>
<td>12-18 month period</td>
<td>1 LRTI = 33 2 LRTI = 14 3 LRTI = 10 4 LRTI = 7(^a)</td>
<td>No change(^b)</td>
</tr>
<tr>
<td>Esposito et al(^\text{16})</td>
<td>Azithromycin 10mg/kg/d for 3 days/week for 3 weeks N=177</td>
<td>None N=175</td>
<td>1 to 14 year olds with recurrent RRTI(^c)</td>
<td>6 months</td>
<td>NNT= 6(^d)</td>
<td>NNT = 8 Clinical success at 6 months(^e)</td>
</tr>
</tbody>
</table>

\(^a\) Evaluated as did not progress to severe  
\(^b\) Author reports deference in time to second LRTI negligible, no data provided  
\(^c\) Excluded AOM, community acquired pneumonia, streptococcal pharyngitis at enrollment  
\(^d\) Symptom resolution without relapse at one-month  
\(^e\) Author defined clinical success at 6 months if ≤ 2 symptom relapses