Prophylactic azithromycin in pre-schoolers with chronic respiratory symptoms: a longitudinal survey

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Abstract

Objectives: Long-term prophylactic azithromycin (AZM) is used in daily practice in children with chronic respiratory symptoms because of its immunomodulatory and anti-inflammatory properties. No substantial scientific evidence is available for the population without underlying condition. The objective of this study is to test if prophylactic azithromycin has an effect on respiratory outcomes in preschool non-cystic fibrosis (CF) children with chronic respiratory symptoms. As secondary outcomes the evolution of body mass index Z-scores, as a measure of overall health, and respiratory tract cultures were studied.

Study design: Non-CF-children between one and six years old with chronic respiratory symptoms, treated with prophylactic AZM were included in this retrospective analysis. The number of respiratory exacerbations and body mass index Z-scores one year before and one year after the start of AZM were compared. The nature of the respiratory disease, reason for discontinuing AZM and respiratory microbiological profiles were studied.

Results: 35 children were included. A significant reduction in the number of exacerbations was observed, both in the entire population (p=0.00004) and in the subgroup of children (n=14) without an underlying condition (p=0.002). No significant difference in body mass index Z-scores and respiratory microbiological profiles was seen. However, a non-significant increase (p=0.188) in macrolide-resistant bacterial infections was observed.

Conclusion: Prophylactic AZM may decrease the number of exacerbations in non-CF pre-schoolers with chronic respiratory symptoms. However, the increased bacterial macrolide-resistance requires further evaluation.

Introduction

The management of chronic respiratory symptoms, especially in young children, remains a challenge. Symptoms are often difficult to control and response to treatment varies from child to child. Chronic respiratory symptoms include recurrent wheeze and persistent productive and non-productive cough. They can occur after a single lower respiratory tract infection, after multiple viral infections, or present as result of an underlying asthma, Protracted Bacterial Bronchitis (PBB) or other chronic lung diseases such as cystic fibrosis (CF), primary ciliary dyskinesia (PCD) or immune deficiencies (1,2). If not treated properly, chronic inflammation and obstruction of the lower airways can cause destruction of the airway wall, resulting in irreversible dilated bronchi, better known as bronchiectasis (3). Conditions as CF, PCD, immune deficiency, but also recurrent PBB increase the risk of bronchiectasis in children (2).

In recent years, macrolides have been used, not only for their antimicrobial effects but also for their anti-inflammatory and immunomodulatory properties. Macrolides reduce airway mucus secretion and viscosity, downregulate the inflammatory cascade and reduce pro-inflammatory cytokine production (4,5). In vitro, broad-spectrum anti-viral properties have been demonstrated. Azithromycin (AZM) in particular shows promising results for clinical efficacy (5).

The purpose of this survey is to investigate if prophylactic AZM in preschool children with chronic respiratory symptoms has an effect on: the number of respiratory exacerbations, the body mass index (BMI) Z-score (standard deviation scores) which is an indicator of the general health status of the child, and the microbiological profile of the respiratory cultures.

Methods

Study design

This retrospective, longitudinal, single-centre, observational cohort study was conducted in the KidZ Health Castle of the UZ Brussel. Approval of the ethics committee of our institution was obtained on the 8th of November 2017 (reference number 2017-321).

Study population

Children from one to six years old treated for minimal 3 months with prophylactic AZM for chronic respiratory symptoms (between January 2011 and November 2016) were included in the analysis. These children were followed at the paediatric pulmonology department at least every three months and more frequently if needed.

Chronic respiratory symptoms were defined as wheezing, dyspnoea, cough or bronchorrhea over a period of minimum three months in one year, despite maximal conventional therapy (inhaled corticosteroids, bronchodilators, antibiotic courses, physiotherapy) (6). Prophylactic AZM treatment was defined as the administration of AZM during at least a period of three entire months with a dosage of 10mg/kg/day three consecutive days a week.

Exclusion criteria were: AZM treatment with the intention to cure an acute infection such as whooping cough or Mycoplasma infections and children with CF or an immunodeficiency in whom treatment with IV or SC immunoglobulins was started during the year before or the year after the start of prophylactic AZM therapy.

Children without CF but with an underlying condition such as PCD, bronchopulmonary dysplasia, significant anatomical abnormalities, immune deficiencies or with proven structural lung damage as for example non-CF bronchiectasis were not excluded from analysis.

Patients who met the inclusion criteria were identified by electronic and manual searches in the electronic medical records of the years 2011 until 2016. They were divided in two groups: children with chronic respiratory symptoms/unremitting wheeze without a known underlying aetiology and children with a known underlying condition as described earlier.

The duration of the AZM treatment and the reason for discontinuing AZM were included in the analysis. Analysis occurred for a one-year period before and a one-year period after prophylactic AZM therapy.

As primary outcome, the number of respiratory exacerbations during the year before (Y-1) and the year after (Y+1) the start of AZM were determined.

An exacerbation was defined as an increase in signs and symptoms (wheezing, dyspnoea, cough, bronchorrhea) with, according to the treating physician, need for oral antibiotics or need for hospitalisation.

As secondary outcome, the BMI Z-score was recorded just before and one year after the start of AZM. BMI Z-scores were calculated using the software WHO Anthro and WHO Anthro Plus (7,8).

Fungal and bacterial cultures of respiratory tract secretions were performed on an occasional basis: cough swab performed by the physiotherapist (9), sputum if possible and bronchoalveolar lavage (BAL) in case a bronchoscopy was required for diagnostic or therapeutic purpose (atelectasis). The microbiological profile from the respiratory cultures were compared between Y-1 and Y+1.

Statistical analyses were performed using IBM SPSS Statistics version 23. The number of respiratory exacerbations were analysed using a Wilcoxon signed rank test. Fisher's exact test was applied for the results of cultures for respiratory tract secretions. BMI Z-scores were analysed using a paired t-test. A p-value <0.05 was accepted as statistically significant.

Results

Study population (Table 1)

Thirty-five patients (54% males mean age: four years) met the inclusion criteria. Of these, 14 (40%) had chronic respiratory symptoms or unremitting wheeze without an underlying condition whereas 21 (60%) had a known underlying condition (bronchiectasis 6/21, PCD 7/21, immune deficiency 6/21, bronchopulmonary dysplasia 1/21, anatomical abnormality 1/21).

Treatment duration with prophylactic AZM varies between three months and 12 months, with an The main reason for discontinuing AZM was a favourable clinical course (12/35; 34%). AZM was discontinued during the summer period in 6/35 patients (17%) and was not restarted after the summer or because the summer period concurred with the 12 month follow-up after the start of AZM. In 2/35 (6%) patients AZM was stopped because of insufficient clinical benefit. Only one patient had therapy related adverse events (gastrointestinal complaints), requiring discontinuation of AZM. In one patient, AZM was stopped because of refusal by the child (taste problem). (Table 2)

Respiratory exacerbations (Table 3, Figure 1, Figure 2)

In Y-1, the cohort had a median of three respiratory exacerbations (p25=2; p75=5). Of the 124 respiratory exacerbations for the whole group, 82 (66%) were treated at home with antibiotics and 42 (34%) required hospitalization.

In Y+1, a median of one respiratory exacerbation (p25=0; p75=2) was found. Of the 53 respiratory exacerbations found, 36 (68%) were treated at home with antibiotics and 17 (32%) required hospitalization.

In Y+1 significantly fewer respiratory exacerbations were observed (p=0.00004) compared to Y-1, with a median difference of two exacerbations. In Y+1, 26 patients (74%) had fewer respiratory exacerbations than in Y-1. In five patients (14%) the number of respiratory exacerbations did not change and in four patients (11%) more respiratory exacerbations were noted in Y+1 compared to Y-1.

A significant decrease (p=0.007) in de number of hospitalisations was noted with a median of one hospitalization in Y-1 compared to a median of zero hospitalizations in Y+1.

In the subgroup without an underlying condition (n:14) a decrease in the median number of exacerbations (p=0.002) was seen, with a median of 3.5 exacerbations in Y-1 and a median of 0.5 exacerbations in Y+1. The number of hospitalizations in this subgroup decreased by approximately one hospitalization a year (p=0.007).

In the subgroup with a known underlying condition (n:21), a significant decrease in the total number of exacerbations was seen (from median 3 exacerbations per year to two exacerbations per year, p=0.007). However, no difference in the number of hospitalizations (p=0.231) was noted. (Table 3)

BMI Z-scores

Before the start of AZM, the average BMI Z-score was 0.38. One year later, the average BMI Z-score remained unchanged (0.40)(p=0.873).

Respiratory microbiological profile (Figure 3)

Twenty patients (54%) had cultures from respiratory tract secretions taken the year before as well as during the year after the start of AZM. Only these patients were used for further analyses. The number of cultures taken in Y-1 (n=80) did not significantly differ from Y+1 (n=71) (p=0.450).

The most common pathogen in Y-1 was Haemophilus influenzae, which was found in 26 of the 80 cultures (32.5%). In Y+1, H. influenzae was cultured 16 times (22.5%) (p = 0.205). Moraxella catarrhalis was isolated in Y-1 in 5% of the cultures. In Y+1, M. catarrhalis was no longer found (p = 0.123). No significant difference was found in any of the other most frequent respiratory (bacterial et fungal) pathogens.

In the total study population, only one macrolide resistant bacterium (Streptococcus pneumonia) was cultured in Y-1. In Y+1, an increase in macrolide resistance to four isolates was observed, two macrolide-resistant Staphylococcus aureus and two macrolide-resistant S. pneumoniae strains, however these are considered non-significant (p = 0.188).

Discussion

This longitudinal retrospective analysis shows that prophylactic AZM in non-CF preschool children with chronic respiratory symptoms results in a significant reduction of respiratory exacerbations. Our data also show a significant decrease in the number of hospitalizations after prophylactic AZM.

Similar results on pulmonary exacerbations in different patient populations were reported.

One randomized controlled trial (RCT) on long-term AZM use in preschool children with non-CF bronchiectasis, aged one to eight years old, showed a decrease of exacerbations in the AZM group compared to placebo (10). Comparable results were seen in adults with bronchiectasis (11, 12).

Long-term AZM use in patients, aged 7 to 50 years old, with PCD showed a 50% reduction in pulmonary exacerbations (13). Also in CF patients prophylactic AZM use demonstrated a decrease in pulmonary exacerbations (14-16).

Abovementioned studies report all similar findings regarding pulmonary exacerbations. It is important to notice that these studies only included patients with an underlying condition. Our analysis is therefore unique as it also includes preschool children without an underlying condition. Subanalysis of our data showed that in otherwise healthy children, AZM could also reduce the number of hospitalisations. Earlier studies did not support this finding. A possible explanation for this discrepancy is that children with an underlying disease may be hospitalised more frequently as a preventive measure.

Long-term AZM therapy is in most of the cases well tolerated, which is in line with previous publications (10, 11, 16, 17).

Despite its positive effect on pulmonary exacerbations, no change in BMI Z-scores was observed before and during/after AZM treatment. Importantly, mean BMI Z-scores before treatment were not so poor in our cohort. Only a study in CF-children could demonstrate an increase in weight and BMI in the AZM group compared to placebo (16).

Respiratory microbiological profiles showed no difference in the respiratory pathogens nor in the number of positive cultures before and after prophylactic AZM use. An increase, though non-significant, in macrolide-resistant S. aureus and S. pneumoniae isolates was seen. Isolation of an increased number of macrolide-resistant strains, especially S. aureus, has also been observed in CF-children under prophylactic AZM. (14,18)

In areas where prophylactic AZM is widely used, such as East Asia, bacterial resistance is dramatically high (19). This possible risk of antibiotic resistance shows that long-term prophylactic AZM use is not without risks and needs to be limited. New non-antibiotic macrolides, with immunomod-

Table 1: Clinical characteristics before the start of azithromycin

	Patients (n=35)
Age (mean ± SD) (years)	3.95 ± 1.73
Male (n, %)	19 (54%)
Female (n, %)	16 (46%)
Nature of the respiratory condition (n, %)	
1. Chronic respiratory symptoms/unremitting wheeze	14 (40%)
2. Known underlying condition	21 (60%)
BMI Z-score (mean ± SD)	0.38 ± 1.18
Median number of exacerbations the previous year	3

Abbreviations: SD: standard deviation; BMI: body mass index

Table 2: Duration and reason for discontinuing azithromycin

Duration of azithromycin (mean ± SD) (months)	9 ± 2.9
Reason for discontinuing azithromycin (n, %)	
No discontinuation within 12 months	13 (37%)
Favorable evolution	12 (34%)
Summer months	6 (17%)
Insufficient effect	2 (6%)
Refusal by child	1 (3%)
Side effects	1 (3%)

Abbreviations: SD: standard deviation

Table 3: Exacerbations (median, [p25;p75])

	Y-1	Y+1	p-value
Total study population (n=35)			
Total number of exacerbations	3 [2;5]	1 [0;2]	0.00004
At home oral antibiotics	2 [1;3]	1 [0;1]	0.0003
Hospitalization intravenous antibiotics	1 [0;1]	0 [0;0]	0.008
Hospitalization oral antibiotics	0 [0;0]	0 [0;0]	0.317
Hospitalization without antibiotics	0 [0;0]	0 [0;0]	0.595
Total number of hospitalizations	1 [0;2]	0 [0;1]	0.007
Chronic respiratory symptoms (n=14)			
Total number of exacerbations	3.5 [2.75;5.25]	0.5 [0;1]	0.002
At home oral antibiotics	2 [1;4.25]	0 [0;1]	0.012
Hospitalization intravenous antibiotics	1 [0;2]	0 [0;0.25]	0.030
Hospitalization oral antibiotics	0 [0;0]	0 [0;0]	1.000
Hospitalization without antibiotics	0 [0;0]	0 [0;0]	0.157
Total number of hospitalizations	1 [0.75;2]	0 [0;0.25]	0.007
Known underlying condition (n=21)			
Total number of exacerbations	3 [1;5]	2 [0.5;2.5]	0.007
At home oral antibiotics	2 [1;3]	1 [0;2]	0.011
Hospitalization intravenous antibiotics	1 [0;1]	0 [0;0.5]	0.128
Hospitalization oral antibiotics	0 [0;0]	0 [0;0]	0.317
Hospitalization without antibiotics	0 [0;0]	0 [0;0]	1.000
Total number of hospitalizations	1 [0;1]	0 [0;1]	0.231

Figure 1: Respiratory exacerbations in total study population
Boxplot with median, p25, p75 and outliners of the total number of exacerbations, the total number of hospitalizations and the exacerbations treated by oral antibiotics at home, Y-1 compared to Y+1. A significant reduction in the total number of exacerbations (p=0.00004), in the total number of hospitalizations (p=0.007) and in the exacerbations treated at home with oral antibiotics (p=0.0003) is seen.

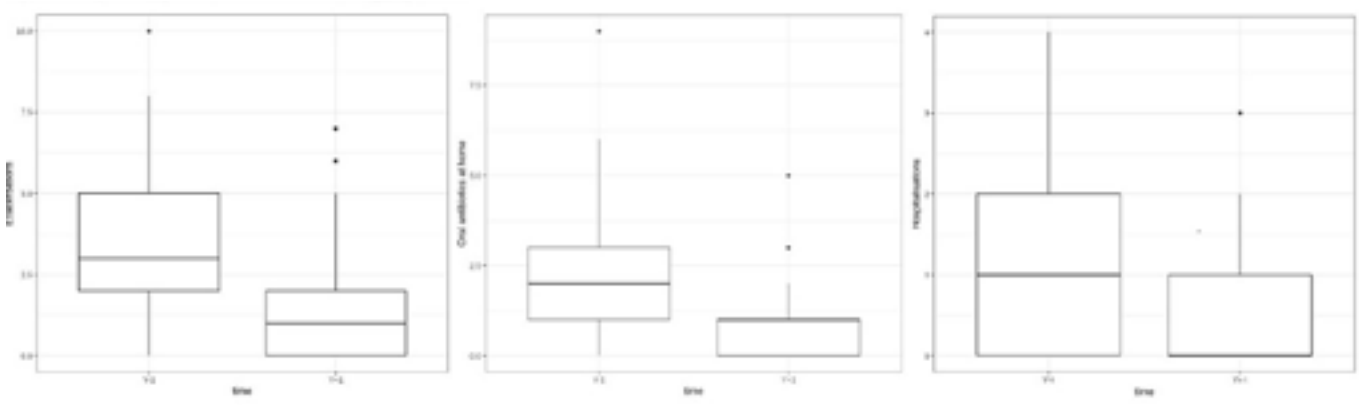


Figure 2: Exacerbations per subject
Difference in the number of exacerbations per subject, Y-1 (begin of arrow) compared to Y+1 (end of arrow).

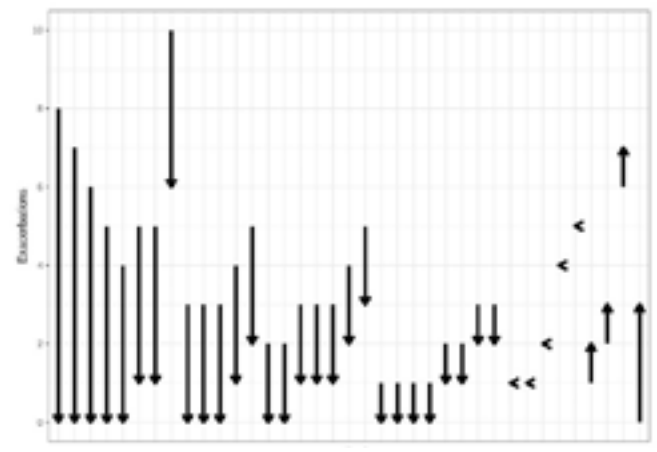
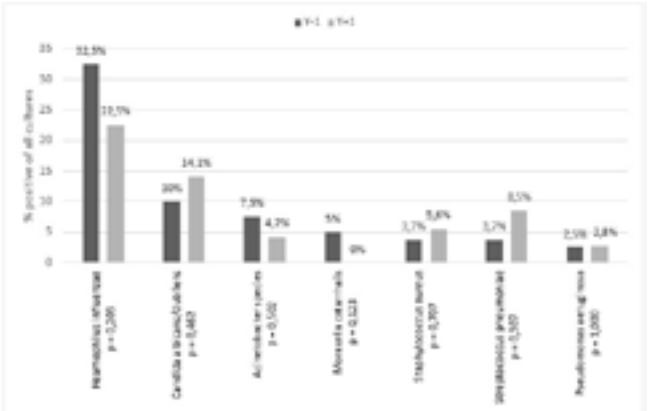


Figure 3: Respiratory microbiological profile
Respiratory microbiological profile of the study population, Y-1 compared to Y+1. The percentage of positive cultures of the total number of respiratory cultures is shown for the most frequent pathogens.



ulatory and anti-inflammatory properties, but without antibacterial activity are likely to gain more attention in the future (20). Studies to determine whether these non-antibiotic macrolides have an equal benefit as prophylactic AZM for chronic respiratory symptoms have not yet been undertaken.

Despite some original findings, limitations of our analysis must be quoted as the study design (retrospective study), the small study population and the age category of the population. As we did not perform a case-control study we could not demonstrate that the reduction in the number of exacerbations is not related to the normal evolution of respiratory infections in the child at this age. This is particularly important in children with persistent wheezing, since it is a condition characterized by a spontaneous resolution with age. Another bias due to the unstandardized (retrospective) follow-up of the patients may have had an effect on the results. Also due to the retrospective nature of our study, the effect of AZM on daily chronic symptoms and quality of life could not be investigated.

Additionally, we could not use a better outcome measure than 'respiratory exacerbation'. The age group of the study population limits the use of more objective parameters like spirometry. In preschool children with CF the use of lung clearance index (LCI) has shown to be a good parameter to measure exacerbations and its effect on treatment (21). However, LCI measurements are not routinely performed in this age group. A prospective double-blind RCT using LCI as an outcome could overcome some limitations in this report.

Conclusion

We demonstrate a beneficial effect of the prophylactic use of AZM in preschool children with chronic respiratory symptoms irresponsive to conventional treatment. A clinically relevant and significant decrease in the number of respiratory exacerbations is observed, as well as a reduction in the hospitalizations related to these exacerbations. This finding may be of interest for paediatricians who are facing therapeutic dilemma's in treating pre-schoolers with recurrent respiratory symptoms. However, the increased bacterial macrolide-resistance requires further evaluation. Before concluding that long-term AZM in children with recurrent respiratory symptoms should become a standard of care, larger and placebo-controlled studies will have to be conducted. Meanwhile, starting prophylactic AZM in a child with chronic respiratory symptoms should be a well-considered decision, after a thorough evaluation including diagnostics for underlying conditions and taking in account possible side effects.

Disclosure

The authors declare that there is no conflict of interest.

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