

ORIGINAL ARTICLE

Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study

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Abstract

Background: Asthma exacerbations are major contributors to asthma morbidity and rather difficult to treat. There is inconclusive evidence that macrolide antibiotics may have an effect on asthma exacerbations through their antibacterial and/or anti-inflammatory properties. The aim of the study was to evaluate the efficacy of clarithromycin on medium-term asthma activity when given as an add-on therapy in children with acute asthma.

Methods: This pilot, open-labeled, randomized, prospective study included 40 school-aged children, with intermittent or mild persistent asthma, presenting with an acute exacerbation. Children were randomized to receive 15 mg/kg of clarithromycin for 3 wk, in addition to their regular (GINA-guided) exacerbation treatment. The microbial trigger of exacerbations was assessed by serology and PCR. Children were followed up with diary cards for 12 wk; lung function was assessed at entry, 3, and 12 wk after the exacerbation.

Results: Children in the clarithromycin group had significantly more symptom-free days (78 ± 2 vs. 69 ± 6 days, $p < 0.00001$) and less total number of periods with loss of control (9 vs. 19, respectively, $p = 0.013$) during the follow-up period, compared to controls. Moreover, treated children presented reduced duration of the index episode (5.0 ± 1 vs. 7.5 ± 1 days, $p < 0.00001$). Lung function did not differ between groups.

Conclusions: When added to regular treatment, a 3-wk course of clarithromycin was associated with an increase in the number of symptom-free days, reductions in the number and severity of days with loss of control following index episode, and a decrease in the duration of the initial asthma exacerbation.

Acute exacerbations are major contributors to the morbidity and cost of asthma, particularly in children (1). Exacerbations are more difficult to prevent and treat in comparison with chronic asthma. There has been little change in exacerbation treatment over the last 20 yr (2). Recent studies have confirmed that high doses of inhaled steroids or montelukast given early in the course of an exacerbation can improve relevant outcomes (3), although this remains controversial (4). Nevertheless, these approaches are unlikely to come into daily practice, owing to potential untoward effects (5) and lack of superiority in comparison with long-term prophylactic treatment. Hence, improved therapeutic approaches are needed.

The majority of asthma exacerbations are triggered by an upper respiratory tract infection, most frequently associated with human rhinoviruses (RVs) (6). In a small proportion of cases, atypical bacteria such as *Mycoplasma pneumoniae* (*Mycoplasma pn*) and *Chlamydophila pneumoniae* (*Chlamydophila pn*) have been implicated (7). Macrolides are effective in the treatment for atypical bacterial infections; they also have anti-inflammatory properties (8), including *in vitro* effects on RV-induced inflammation (9). A number of studies have investigated the potential use of macrolides in asthma with inconclusive results (10, 11). The role of macrolides in asthma exacerbations remains relatively unexplored. A 2-wk clarithromycin treatment was able to reduce the

duration of symptoms in bacterial-induced asthma exacerbations in children, but also reduced relapses in non-infected children (12). Telithromycin, a ketolide, has shown efficacy when given during an acute exacerbations of asthma in adults (13). More recently, a role for macrolide trial in problematic asthma in children is reported (14); however, data on exacerbations are still scanty (15). There is therefore some promising evidence that needs to be further explored.

We hypothesized that macrolides may increase symptom-free days post-asthma exacerbation. The aim of this pilot study was to assess the efficacy of a 3-wk course of clarithromycin, as an add-on to regular treatment, on symptom-free days, and lung function during a 12-wk follow-up period, in asthmatic children experiencing an acute exacerbation.

Methods

Patients

Children 6–14 yr old, diagnosed with intermittent or mild persistent asthma, according to GINA 2005 (16), deriving from the population followed up in the Allergy Department, 2nd Pediatric Clinic of the University of Athens, were invited to participate. Historical data on severity (by means of emergency department visits, hospitalizations, need for oral steroids), control, lung function (including reversibility), and atopy were available for all invitees at a regular basis within the last 2 yr. Parents were instructed to contact the study physician in case, according to their judgement, an acute asthma exacerbation (index episode) occurred. Children with any additional chronic condition excepting allergic rhinitis and/or inability to follow the study procedures were excluded.

Exacerbations were clinically confirmed by the study physician, and the following characteristics were documented: severity of wheezing, respiratory rate, oxygen saturation, peak expiratory flow (PEF), and spirometry. Information on demographic characteristics and previous asthma activity were documented in a standardized questionnaire. A nasal wash and a blood sample were obtained for the detection of common respiratory viruses and/or atypical bacteria and microbiological analyses, respectively.

Patients received regular treatment for their exacerbation (oxygen, β_2 agonists $\pm$ anticholinergic, and systemic steroids) and were discharged or hospitalized according to clinical judgement (GINA guidelines). When released for home, parents (and children) were given diary cards, prophylactic treatment according to asthma control level (GINA) and PEF meters (mini wright) with instructions for their use at home. Subsequently, a computerized randomization table, blinded to patients and to the study physician, was used to allocate children to oral clarithromycin 15 mg/kg daily for 3 wk (clarithromycin group), or to no additional medication (controls).

The follow-up was defined as the 3 months post-exacerbation period. Follow-up visits for clinical assessment were performed at 3, 6, and 12 wk, while lung function measurements were taken at 3rd and 12th week post-randomization. In case children presented symptoms in the intervals of the schedules

visits, parents were instructed to contact the study physician and were examined in the clinic if needed. A blood sample was obtained at 6 wk for the measurement of convalescent antibodies to atypical bacteria.

Parents gave written informed consent, and the study was approved by the institutional ethics committee.

Outcome measures

The primary outcome was days without symptoms, during the subsequent 12 wk after inclusion. Predefined secondary outcomes included number and severity of periods with loss of control according to GINA 2008 (17), such as daytime symptoms (cough, wheezing, difficulty in breathing, nocturnal symptoms, and need for rescue therapy), time to loss of control, duration and severity (mild, moderate, severe according to GINA) of the index exacerbation, peak flow rate (PFR) variability (derived from daily PFR monitoring at home), and lung function during the follow-up period. Loss of control was assessed by means of symptoms according to diary cards; periods of loss of control were defined as two or more days with lower airway symptom score higher than the child's median (18). A subgroup analysis between infected and non-infected patients by atypical bacteria and between atopic and non-atopic children was also planned.

Microbiological evaluations

Reverse transcription polymerase chain reactions (RT-PCR) were performed in nasal wash samples for respiratory viruses and atypical bacteria as previously described (19, 20). IgG and IgM antibody testing against *Mycoplasma pn.* and *Chlamydia pn.* was performed in serum samples obtained upon enrollment (index episode) and 6 wk later, according to the hospital's laboratory standard procedures (ELISAs).

Spirometry

Spirometry was performed with a Jaeger MasterScope-PC spirometer (VIASYS Healthcare, Höchberg, Germany). All maneuvers were performed with the children in the standing position, using a nose clip. Results were reported only if at least two technically acceptable curves (up to how many maneuvers? per visit) according to standard criteria. Spirometry was performed before and after bronchodilation using 400 μ g salbutamol (Aerolin®; GlaxoSmithKline, Athens, Greece) by a metered-dose inhaler through a mouthpiece.

Statistical analysis

This was an open, prospective, randomized, controlled parallel interventional study. The intervention group received clarithromycin in addition to asthma medication and the control group only asthma medication. Demographic characteristics, medical history parameters, and treatment outcomes between groups were compared using Fisher's exact test for categorical data. Age was normally distributed and compared with *t* test. Logistic regression analysis was used to calculate odds

ratios (ORs) for the association between clarithromycin administration and risk of a subsequent loss of control. Linear regression was applied to assess the effect steroids had on clarithromycin administration-related outcomes of interest. The results obtained from these models are presented as *B*-coefficients. Descriptive statistics of non-normally distributed, continuous variables and categorical data are presented as median (inter-quartile range). Normally distributed continuous variables are presented as mean $\pm$ s.d. (s.d., standard deviation). All reported *p*-values are based on two-sided tests and compared with a significance level of 5%. STATA 9.1 for Windows (Stata Corp LP, College Station, TX, USA) was used for all statistical calculations and plots.

Results

Baseline characteristics

Two hundred children were invited to participate. Of these, 18 patients/parents declined or were unable to participate and 142 did not report an acute asthma exacerbation during a predefined 2-yr period.

Forty children (18 boys) presented with an acute exacerbation. Clarithromycin group (*n* = 18) and controls (*n* = 22) did not differ in any of the demographic characteristics. Although clarithromycin group presented with previous slightly more severe clinical characteristics in respect to asthma, this did not reach statistical significance (Table 1).

Symptom-free days following first asthma exacerbation

At the end of the follow-up period (12 wk after inclusion), children treated with clarithromycin presented significantly more symptom-free days compared to controls [78 (2) vs. 69 (6) days, respectively, *p* < 0.0001] (Fig. 1); this improvement appeared early, as it was also present at the 3rd [16 (1) vs. 13 (2) days respectively, *p* < 0.0001] and 6th week [36 (2) vs. 29 (3) days, respectively, *p* < 0.0001] of the follow-up.

Characteristics of periods with loss of control during the follow-up period

The clarithromycin treatment group presented less periods with loss of asthma control compared to controls [1.5 (1) vs. 2 (1), *p* = 0.014], an effect evident from the 6th week of follow-up (data not shown). The total number of periods with loss of control, post-index episode, was significantly reduced in the clarithromycin group (9 vs. 19, respectively, *p* = 0.013). The clarithromycin group was less likely to have one or more periods of lost control (OR = 6.33 CI: 1.37–29.2, *p* = 0.018) compared to non-treated children. There were no differences in asthma control in respect to gender, family history of atopy, tobacco smoke exposure, number of siblings, and previous asthma severity, except clarithromycin intake (data not shown).

None of the children required hospitalization during the study period. The *severity* according to the diary score was lower in the clarithromycin group during the first period with

Table 1 Comparison of baseline demographical data and medical history information between patients who did or did not received clarithromycin treatment

	Clarithromycin group (<i>n</i> = 18)	Controls (<i>n</i> = 22)	<i>p</i> -value
Boys, <i>n</i> (%)	9 (50%)	9 (40.9%)	0.565
Age: yr, mean (s.d.)	9.09 (2.67)	8.44 (2.47)	0.436
Atopic, <i>n</i> (%)	9 (50%)	11 (50%)	0.999
Patients with previous referrals to emergency departments	13 (72.2%)	12 (54.6%)	0.251
Patients with previous severe asthma exacerbations	8 (44.4%)	4 (18.2%)	0.093
Patients with previous admissions for asthma	4 (22.2%)	1 (4.6%)	0.093
Nocturnal awakening because of asthma	11 (61.1%)	10 (45.5%)	0.595
Patients receiving ICS	11 (61.1%)	13 (59.1%)	0.897
Patients treated for rhinitis	7 (38.9%)	6 (27.3%)	0.435
Patients with family history of atopy	5 (27.8%)	10 (45.5%)	0.251
Patients exposed to tobacco smoke	8 (44.4%)	10 (45.5%)	0.949
Current exacerbation severity index	17 (2)	15 (5)	0.092
Patients who received systemic corticosteroids for the current exacerbation	16 (88.8%)	14 (63.6%)	0.067

Fisher's exact test was used for all comparisons apart from age (*t* test).

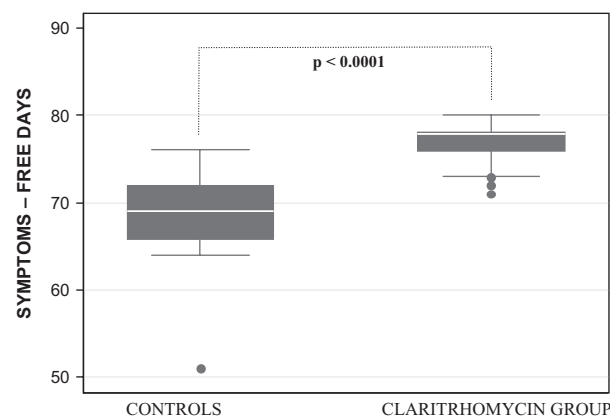


Fig 1 Symptom-free days during the follow-up period of 12 wk post-asthma exacerbation episode for each group. Children receiving clarithromycin in addition to their standard asthma treatment have significantly more symptom-free days compared to controls.

loss of control [diary card score: 14 (3) in 9 clarithromycin group vs. 18 (2) in 19 controls, *p* = 0.0002] but not during the subsequent ones [18 in one patient from clarithromycin

group vs. 17 (3) in nine controls, $p = 0.280$]. Furthermore, the total duration of periods with loss of control was also significantly shorter, respectively, [0.5 (3) vs. 7 (5) days, $p < 0.00001$] (Fig. 2). Time to first period of loss of control was prolonged in the clarithromycin group [67.5 (38) vs. 26.5 (33) days, $p = 0.003$]. However, this effect was not observed in the time interval between any second and third period [34 (36) vs. 26.5 (27) days, $p = 0.301$].

No differences were noted in respect to any of the outcomes between atopic and non-atopic children.

Duration of the index episode

In favor of an early action of clarithromycin was the finding that duration of the index episode was significantly shorter compared to control group [5 (1) vs. 7.5 (1) days, $p < 0.00001$] (Fig. 3).

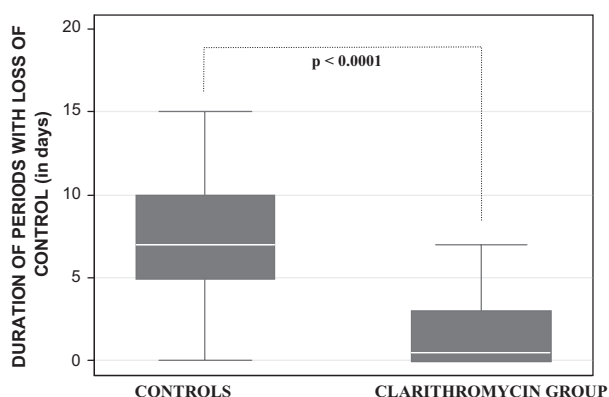


Fig 2 The total duration of periods with loss of control was shorter in the clarithromycin-treated in comparison with the control group.

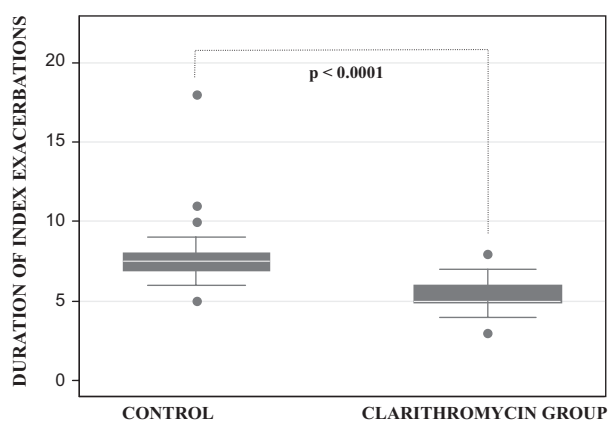


Fig 3 The duration of the index exacerbation episode was significantly shorter in the clarithromycin-treated compared to control group.

Lung function measurements

FEV₁ before bronchodilation did not significantly differ between clarithromycin group and controls on day 0, 3, and 12 wk. Statistically significant differences were noted in clarithromycin group between the index asthma exacerbation FEV₁ and FEV₁ on 6th and 12th weeks of follow-up (FEV₁: 1.91 ± 0.47 l vs. 2.03 ± 0.48 l $p < 0.004$ and 2.14 ± 0.47 l, $p < 0.001$, respectively). However, such significant differences were not recorded in controls (FEV₁: 2.15 ± 0.67 l, 6th week: 2.20 ± 0.63 , $p = 0.164$ and 12th: 2.23 ± 0.59 l, $p = 0.07$). No differences in FEV₁ measurements between atopic and non-atopic subjects at any time point were noted.

In all patients, paired data comparison between the personal best PEF measurement during the study and the minimum morning PEF during the index exacerbation and any periods with loss of control was significantly different. There was a significant difference in minimum morning PEF between clarithromycin group and controls (214.7 ± 49.1 l/min vs. 275 ± 83.7 l/min, respectively, $p = 0.032$) during the first exacerbation; however, this did not reach statistical significance during days with loss of control (Table 2).

Evaluating the impact of steroid administration on clarithromycin effect

Oral corticosteroids were used in marginally more children in the clarithromycin group than in controls (16/18 vs. 14/22, respectively, $p = 0.067$). After adjusting for steroid co-administration, clarithromycin administration resulted in 10.9 more symptom-free days in the treated group in comparison with the control group. The total duration of the loss of

Table 2 Mean daily morning peak expiratory flow (PEF) values: comparisons between clarithromycin and control group

	Mean PEF _{min} (l/min)		
	Controls (n), Min%Max*	Clarithromycin group (n), Min%Max*	p-value†
PEF _{max}	343.8 ± 87.1	305 ± 71	0.137
PEF _{min} during			
Exacerbation	275 ± 83.7 (22) 79.9 ± 11.3%	214.7 ± 49.1 (18) 71.3 ± 13.4%	0.032
p-value‡	<0.0001	<0.0001	
1st relapse	295.8 ± 87.8 (19) 79.9 ± 11.5%	240.4 ± 77.5 (9) 79.2 ± 9.4%	0.107
p-value‡	<0.0001	0.003	
2nd relapse	298.8 ± 120.4 (8) 84.3 ± 11%	290 (1) 60%	–
p-value‡	0.022	–	

*Minimum morning PEF (PEF_{min}) during each exacerbation expressed as the percent of personal best (PEF_{max}) during study period.

†Mean PEF_{min}: comparison between clarithromycin and controls.

‡Comparison (paired data) between PEF_{min} mean values at each time point vs. PEF_{max}.

control experienced in clarithromycin group was 7.9 less days compared to controls, independently of steroid co-administration. Administration of clarithromycin reduced the number of periods of loss of control by approximately one (0.9) taking into account steroid administration (Table 3).

Viral and atypical bacterial detection by RT-PCR

Overall, nasal washes were positive for a microorganism in 26/40 children (65%), including 18 RV (8/18 clarithromycin group and 10/22 controls), three adenovirus, two *Mycoplasma pn.*, two parainfluenza, and one RSV. No *Chlamydia pn.* was detected. The presence of RV did not affect any of the outcomes in either clarithromycin group or controls (data not shown).

Patients with acute mycoplasma infection were serologically confirmed and were equally distributed between clarithromycin group and controls (1 in each group, $p = 0.704$). Owing to the small number of positive cases, the planned subgroup analysis among microorganisms was not performed.

Discussion

This is the first study to show that a 3-wk course of clarithromycin, when given in addition to regular treatment, in children presenting with an acute asthma exacerbation, is effective in preventing subsequent symptoms, by means of symptom-free days, and reducing the number and severity of periods with loss of asthma control during the next 3 months. Moreover, children treated with clarithromycin presented significant less duration of the index exacerbation, with a 2.5 days reduction in duration, which is not only statistically but also highly clinically significant.

Both the findings that exacerbations were not associated with atypical bacteria, with the exception of one per group, as well as the important carryover effect of the treatment from 3 to 12 wk, support the possibility that the mechanism of action of clarithromycin was anti-inflammatory rather than antibacterial, in line with other studies (13). Of course, the latter cannot be completely excluded, as there is still a possibility that some infections with either *Mycoplasma/Chlamydia pn.* may have not been detected, although the microbiological results are in agreement with previous experience associated with acute asthma exacerbations (21,22). Nevertheless, recent data are indicative of a significant associ-

ation of bacterial infections with asthma-related symptoms, which may in part explain our observed results (23).

Macrolide anti-inflammatory properties include several pathways such as inhibition of the oxidative burst of polymorphonuclear leukocytes, protection against membrane disruption caused by bioactive phospholipids (24, 25), inhibition of T-cell cytokine secretion by mitogen-stimulated peripheral blood mononuclear cells, and more (26, 27). Their effect may also be indirect, through improving the efficacy of steroids (28). More recently, it has been shown that azithromycin has anti-viral activity through increased induction of virus-induced interferons and reduced viral replication and release, which in turn could lead to reduced inflammation as a consequence of reducing virus load (9).

Lung function measures were not different between groups. Changes in lung function are not pronounced in children with a post-viral asthma phenotype, as in adults and a considerable proportion do not have signs of bronchoconstriction in between exacerbations (29).

In all primary and secondary outcomes, the interaction between steroid and clarithromycin administration is non-significant. Co-administration does not seem to affect additively any of the outcomes of interest. Thus, the role of clarithromycin on each of the outcomes appears to be independent. The size of the study was adequate for evaluating the primary and secondary outcomes. A *post hoc* power analysis revealed that group sample sizes of 20 at each group achieved 90.23% power to detect non-inferiority and 80.45% power to detect equivalence using one-sided, two sample *t* test at a significance level (α) of 0.025. Owing to the small subgroup of infected subjects, we cannot conclude whether the effect of clarithromycin would have been the same in children infected with atypical bacteria.

The major drawback of the study is obviously its open design, which was performed owing to lack of resources necessary to perform a blinded study. Nevertheless, we considered important to proceed with evaluating this potential treatment, putting every effort to reduce open design-related biases. Patients were invited from a long-term follow-up group, in order to reduce predetermined views on the exacerbation outcome and increase acceptance of the proposed treatments. Moreover, clarithromycin is a commonly used antibiotic, and therefore, patients may not have conceived they were receiving an investigational treatment. In fact, no patient/parent dropped out of the study after randomization. The two groups were comparable in respect to several baseline

Table 3 Results of multivariate regression models evaluating the effect of steroids on clarithromycin administration-related outcomes of interest

Models/outcomes of interest	Clarithromycin		Steroid		Interaction	
	B-coefficient	p-value	B-coefficient	p-value	B-coefficient	p-value
Symptom-free days	10.9	0.003	2.3	0.242	-3.74	0.332
Number of periods with loss of control	-0.9	0.013	-0.02	0.925	0.6	0.126
Duration of index episode (days)	-10.9	0.003	-2.8	0.145	4.05	0.280
Duration of loss of control (days)	-7.9	0.005	-1.2	0.404	3.2	0.277

characteristics; in fact, the clarithromycin group presented marginally more severe asthma symptoms prior to inclusion. Such difference further supports the effectiveness of the proposed treatment, without nevertheless substituting the need for a blinded assessment. Concerns are raised in respect to the use of macrolide antibiotics as anti-inflammatory treatment for asthma, such as the induction of resistant microbial strains that may affect the usefulness of these antibiotics, possibly resulting in excess morbidity from the resistant microorganisms (30). Nevertheless, the results of our study suggest that clarithromycin may be effective early in treatment, therefore could be potentially useful for short-term exacerbation management. It is important to note that although this study provides evidence of an 'add-on' macrolide treatment on

acute asthma exacerbations, it does not propose such an intervention as a clinical guidance. Several issues have still to be solved in respect to clearly define populations who might benefit from such intervention, elucidate mechanisms of actions, and evaluate the possibility of resistance induction. To this respect, placebo-controlled and trials comparing to antibiotics with no expected action on cytokine, are needed.

In conclusion, clarithromycin at a usual dose given for 3 wk beginning at the onset of an acute asthma exacerbation, in addition to regular treatment, may reduce the duration of the exacerbation and medium-term disease burden, in asthmatic children. Further studies are needed to confirm these results, characterize responsive patient populations, and elucidate mechanisms of action.

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