Pediatric rheumatology

Efficacy of empirically prescribed amoxicillin and amoxicillin + clavulanic acid in children's reactive arthritis: A randomised trial

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Abstract

Objective

To evaluate the efficacy of early empiric prescription of amoxicillin and amoxicillin + clavulanic acid in children with reactive arthritis (ReA) when the arthritis-triggering microorganism is not identified.

Methods

138 children, ranging in age from 2 to 16 years, with ReA of up to 3 months duration were randomly assigned to 3 groups and either prescribed antibacterial treatment with amoxicillin or amoxicillin + clavulanic acid (amoxicillin-potassium clavulanate combination) or were not given antibiotics (control group). Patients in all 3 groups were prescribed the usual treatment with nonsteroidal antiinflammatory drugs. Both groups of patients under antibacterial treatment were randomised into 2 subgroups: patients given a 10- to 14-day or a 28-day-duration antibacterial course. The results of the study were evaluated after 1 and 3 months of observation by determining the percentage of patients that had no clinical or laboratory signs of disease activity.

Results

After 1 month of observation no signs of disease activity were found in 48.0% of patients who were prescribed amoxicillin, in 58.5% of patients treated with amoxicillin + clavulanic acid, and only in 13.0% of patients from the control group ($p < 0.001$ for either antibacterial treatment in comparison with the control group). After 3 months of observation no disease activity was found in 92.0% of patients who used amoxicillin, in 95.1% of those treated with amoxicillin + clavulanic acid, and in 58.7% of children from the control group ($p < 0.001$ for either antibacterial treatment in comparison with the control group). There was no significant difference in the efficacy of amoxicillin and amoxicillin + clavulanic acid. The duration of the antibacterial course showed no influence on the results of treatment.

Conclusion

Amoxicillin or amoxicillin + clavulanic acid in 10- to 14-day courses are advisable, in addition to the antirheumatic treatment, for children in the early stage of ReA when the arthritis-triggering microorganism is not identified.

Key words

Reactive arthritis, drug therapy, antibiotics, amoxicillin, amoxicillin-potassium clavulanate combination.

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Introduction

The interaction between the triggering microorganism and the host in reactive arthritis (ReA) has recently been given a new interpretation and the tem "slow bacterial infection" introduced (1). In *Chlamydia*-induced arthritis it means that despite the negative synovial culture results, different morphological forms of *Chlamydias* can persist in the joint, with the premise that *Chlamydias* undergo some kind of growth not excluding the possibility of intermittent or slow replication of the microorganism (2). Such an interpretation has encouraged trials for the evaluation of the efficacy of antibacterials.

Tetracyclines and ciprofloxacin are the most thoroughly investigated antibiotics among those used for the treatment of adult ReA. In a long-term (3-month) study applying lymecycline in arthritis triggered by *Chlamydia, Yersinia or Campylobacter,* a significant increase in the rate of recovery was found only in *Chlamydia*-induced arthritis (3). Wollenhaupt *et al.* (4) when using doxycycline for 2 weeks or 4 months of therapy for *Chlamydia*-triggered arthritis found no significant difference between the groups in the occurrence of remission. In a study of Sieper *et al.* (5), a 3-month course of ciprofloxacin when applied in ReA and undifferentiated oligoarthritis exerted a better (but not significantly) effect than a placebo only in *Chlamydia*-associated arthritis. Other authors who applied a 3-month (6) or a 12-month (7) courses of ciprofloxacin found no advantage of this antibiotic over placebo treatment in ReA.

Although data on the efficacy of antibiotics in ReA are very controversial, it can be said that *Chlamydia*-induced and post-enteric ReA differ in their response to antibiotic therapy in favour of *Chlamydia*-induced arthritis (8). Studies of the etiopathogenesis and efficacy of antibacterials in ReA are devoted mainly to sexually transmitted and enteric infections in adults. In paediatrics, the onset of ReA in more than half of all cases is associated with upper respiratory tract infections (URTIs), while infections in other localizations are less frequent (9). The results of antibacterial treatment of ReA in adults cannot be directly transferred to paediatric patients, since the use of tetracyclines and ciprofloxacin in children is limited. The results of paediatric studies show that up to 39% of patients have arthritis or extraarticular manifestations of ReA many months or years following the onset of the disease (10-12) or experience more than one occurrence (13).

Although there is suggestive evidence that ReA in children is a more self-limited disease than that observed in adults (14), it may turn out that in children after recurrent episodes it can lead to chronic arthritis and significant disability (15). In cases when chronicity develops, the clinical picture of the disease corresponds with that of one of the subgroups of juvenile idiopathic arthritis (JIA) (16). There is a growing number of arguments for such an approach (16, 17) and we share it, as even in cases of chronic arthritis the specific antibacterial treatment was suprisingly effective when we succeeded in cultivating the arthritis-triggering bacteria from faeces (*Yersinia enterocolitica, Escherichia coli 01*) (18, 19). Consequently, every effort should be exerted for the identification of causative bacteria in ReA as specific antibacterial therapy could be expected to be the most beneficial.

However, the range of descriptions of the new bacterial triggers of ReA is permanently growing. Revealing etiologic bacteria in ReA requires a large number of tests and considerable experience in their interpretation, which are often difficult in rheumatologic practice, thus allowing a child with ReA to be considered as having JIA. Empiric antibacterial therapy might be the best approach when the arthritis-triggering microorganism is not specified. Amoxicillin could be a good candidate for empiric treatment, but it doesn't show efficacy on β-lactamase-producing bacteria. Amoxicillin + clavulanic acid (amoxicillin-potassium clavulanate combination) may serve as an alternative antibacterial. It was found to be active in more than 90% of main respiratory pathogens, including β-lactamase-producing *Moraxella catarrhalis*

(20) and methicillin-resistant *Staphylo - coccus aureus* (21), the latter often being detected in children with rheumatic arthritides (22). Moreover, it is effective in a broad spectrum of ReA triggers of enteric origin and in polymicrobial genital infections, including β-lactamase-producing bacteria (23). Amoxicillin and its combination with clavulanic acid are known to exhibit good tissue-penetrating properties, to cause rare adverse reactions and to be acceptable for the treatment of children.

In the present study, we evaluated the efficacy of early empiric prescription of amoxicillin and amoxicillin + clavulanic acid in children's ReA when the arthritis-triggering microorganism is not identified.

Materials and methods

We recruited outpatients from the Consultative Polyclinic of Vilnius University Children's Hospital, who were referred to a paediatric rheumatologist for consultation from all over the country during the period January 1995 to January 1998. The inclusion criteria were: 1) age up to 16 years; 2) arthritis duration not more than 3 months; 3) clinical manifestation of infection in a 4-week period before the onset of arthritis; 4) no other causes (trauma, disease) of arthritis, except the above-mentioned infection, identified; 5) the presence of active joints during the first examination of a patient. Exclusion criteria were: 1) infection during a 4-week period before the onset of arthritis or during the arthritis period before entering the study treated with antibacterial drugs; 2) evident viral infections (such as rubella) during a 4-week period before arthritis; 3) antirheumatic medicines other than nonsteroidal anti-inflammatory drugs (corticosteroids or other) prescribed for the treatment of arthritis.

As an evidence of preceding infection, its clinical presentation during a 4-week period before the onset of arthritis was used. This criterion was approved at the International Workshop on Reactive Arthritis (24). Clinical presentation of infection was verified by the available medical documentation, from the parent's and patient's affirmation or clinical examination during enrollment of the patient into the study. Tonsillitis, maxillitis and otitis were also included in the term URTI in this work. An active joint was defined as a joint with swelling or limitation in the range of joint movement with joint pain or tenderness, which was observed during examination of the patient and was not due to primarily mechanical damage or other defined diseases.

The study was carried out according to the rules of the Helsinki Declaration 1975/83. Parents and older patients gave their informed consent to participate. All participants of the study received one of the nonsteroidal anti-inflammatory drugs during the study period. Patients in the control group were treated only with nonsteroidal antiinflammatory drugs, whereas patients in the 2 study groups were additionally prescribed either amoxicillin or amoxicillin + clavulanic acid at a dose of approximately 40 mg/kg/day *per os*, but never more than 2.0 g/day. The recommendations for antibacterial treatment were made by the author of this study, but the antibiotics were prescribed by the local physicians who had referred the patients to the paediatric rheumatologist. This was done to ensure permanent care for the participants (outpatients) of the study by their local physicians. Consequently, in 5 patients who were recommended amoxicillin + clavulanic acid the medication was changed to amoxicillin.

The state of the patients was evaluated by the author at the beginning of the study, after 1 month, and after 3 months of observation including a count of active joints. In addition, at the beginning of the study patients were seen by an otorhinolaryngologist and an ophthalmologist, and X-ray examination of the first damaged joint (and others, if needed) was performed. Analyses of blood (hemoglobin concentration, red and white blood cell count, differential leucocyte count, erythrocyte sedimentation rate) and urine were carried out during the first examination of the patient and repeated after 1 and 3 months. The results of the study were evaluated after 1 and 3 months of observation by determining the percentage of patients who had no clinical or laboratory signs of disease activity. A patient was considered as having no signs of disease activity if he had no active joints, no extra-articular signs of disease and a normal erythrocyte sedimentation rate.

This study was an open, randomised, controlled, phase II clinical trial. After the exclusion of patients who did not meet the above-mentioned inclusion criteria or who refused to participate in the study, the patients were randomly assigned to 3 groups and prescribed different antibacterial treatments: 1) amoxicillin; 2) amoxicillin + clavulanic acid (augmentin, amoxiclav); 3) no antibacterial treatment (control group). Each group of patients with antibacterial treatment was randomised into 2 subgroups and prescribed either a 10- to 14-day or a 28-day antibacterial course. A multistage randomisation, with the application of random permuted blocks was used. Permuted blocks of 3 patients were applied during the randomisation into 3 main groups and blocks of 2 patients during randomisation into subgroups, based on the duration of antibacterial treatment. Randomisation lists of consecutive treatment assignments were prepared in advance using a table of random numbers.

The sample size was calculated by a statistical method for qualitative outcomes (25) on the basis of data that up to 39% of children with ReA have long-standing disease activity (10-12). Thus, good results with no disease activity after 3 months of observation in the control group without antibacterial treatment should be expected in about 61.0% of patients. As we could not expect to collect large groups of patients, this index in the study groups was chosen to be 95%, showing a large difference from the control group. According to the calculations, a sample size of at least 32 patients in each group was required (when $p_1 = 61.0\%$; $p_2 = 95.0\%$; $\alpha = 0.02$; $\beta = 0.1$). As a 10.0% to 20.0% dropout rate could be expected, we had to increase the sample size up to 35 to 38 patients per group.

The efficacy of antibiotics was evaluated by intention-to-treat analysis for all randomised patients. The intention-to-treat analysis was carried out according to the following approach. Five children were changed from the assigned amoxicillin + clavulanic acid regimen to amoxicillin. As this change in medication was random, these patients were analysed in the amoxicillin group as having been assigned during randomisation. Eleven patients did not finish the study. One girl who was prescribed amoxicillin did not begin antibacterial treatment because several days afterwards she left the country. She was not included into any of the analyses. Patients prescribed corticosteroids were considered as having the disease activity after 1 and after 3 months of observation. Patients who showed no disease activity after 1 month and did not show up for the last visit after 3 months were evaluated as having no disease activity after 3 months either. Such an interpretation was based on the results of patients who had completed the whole 3-month study period – none of the participants from either of the 3 groups who had no disease activity after 1 month of observation changed this result after 3 months. In cases when after 1 month of observation the disease was active and the patient did not appear for the last visit after 3 months, the latter result was also evaluated as active disease.

The data were calculated by the chi square test for the comparison of proportions. When comparing the baseline demographic and clinical characteristics and the results of treatment between all 3 groups, differences were considered statistically significant at $p < 0.017$, which was calculated from $p < 0.05$ with the application of the Bonferroni adjustment for multiple comparisons (25). The differences in the efficacy of 10- to 14-day and the 28-day courses of antibacterial treatment were considered to be significant at $p < 0.05$.

Results

Out of 294 patients screened, 138 were enrolled in the study and randomly assigned to receive amoxicillin, amoxicillin + clavulanic acid or no antibacterial treatment (Fig. 1). There was no essential difference between the groups in the reasons for withdrawal, nor did the percentage of patients who withdrew during the 3-month study differ: 4 (8%) in the amoxicillin group, 3 (7.3%) in the amoxicillin + clavulanic acid group, and 4 (8.7%) in the control group.

All 3 groups had similar demographic and baseline characteristics, with no statistically significant differences between the groups (Table I). The most frequent infection before arthritis was URTI, which was found in 61.0% to 69.6% of patients in the groups studied. Some of the patients had clinical manifestations of more than one type of infection: 13 (26%) in the amoxicillin group, 9 (22.0%) in the amoxicillin + clavulanic acid group and 10 (21.7%)

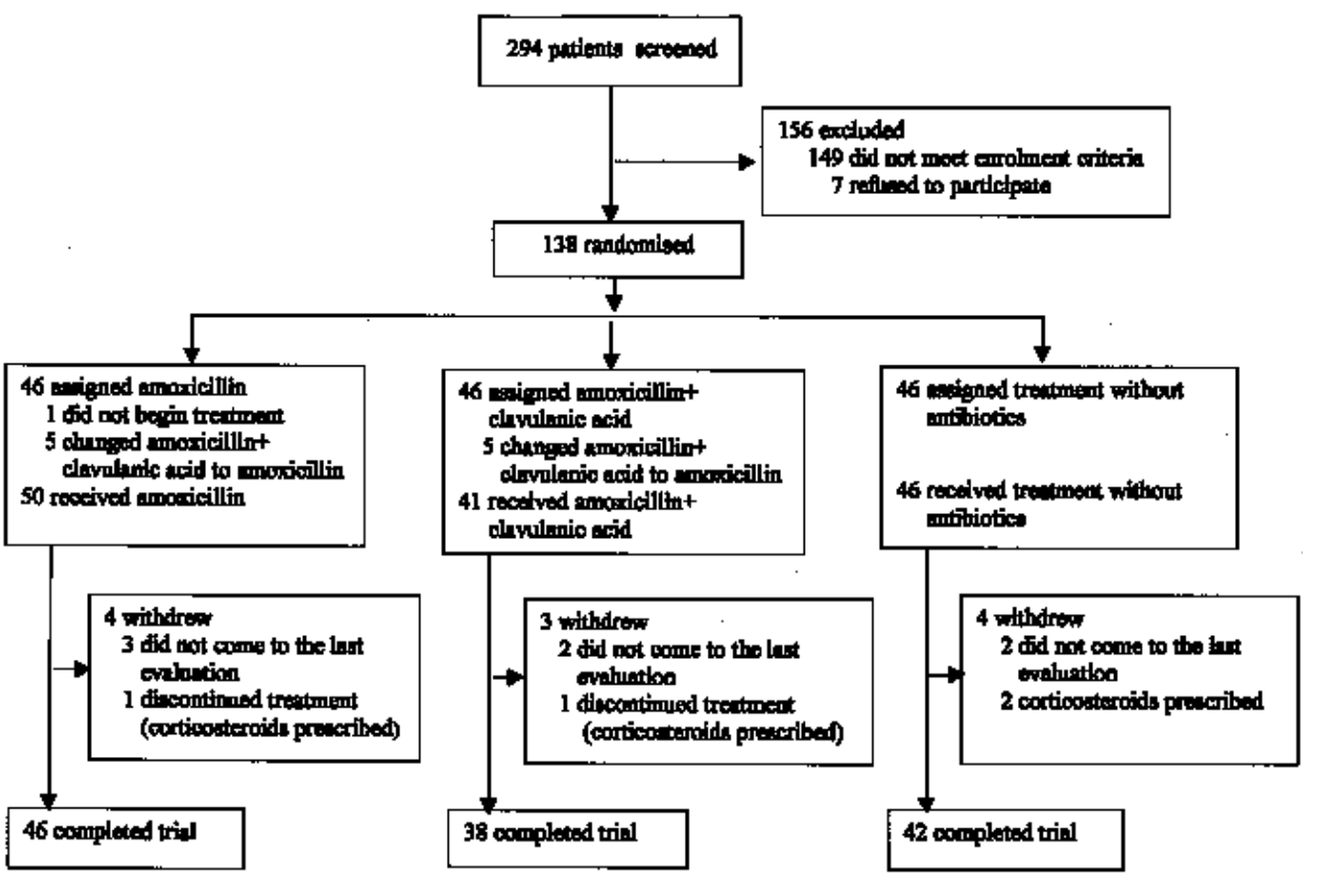

Fig. 1. The flow of participants through stages of the trial.

Table I. Baseline demographic and clinical characteristics of patients with reactive arthritis.

Characteristic		Amoxicillin n = 50	Amoxicillin + clavulanic acid n = 41	Control group without antibiotics n = 46
Sex	Boys	18 (36.0%)	16 (39.0%)	18 (39.1%)
	Girls	32 (64.0%)	25 (61.0%)	28 (60.9%)
Mean age ± SD (years)		8.5 ± 3.7	8.3 ± 3.7	8.7 ± 3.6
Duration of disease (months)	< 1	22 (44.0%)	19 (46.3%)	24 (52.2%)
	1 - 3	28 (56.0%)	22 (53.7%)	22 (47.8%)
Pattern of disease	Oligoarticular	22 (44.0%)	16 (39.0%)	19 (41.3%)
	Polyarticular	28 (56.0%)	25 (61.0%)	27 (58.7%)
Infections during the 4 weeks before the presentation of arthritis	Upper respiratory tract	34 (68.0%)	25 (61.0%)	32 (69.6%)
	Gastrointestinal	20 (40.0%)	19 (46.3%)	15 (32.6%)
	Urogenital	6 (12.0%)	5 (12.2%)	6 (13.0%)
	Skin	3 (6.0%)	1 (2.4%)	3 (6.5%)

No significant differences in any index between the amoxicillin, amoxicillin + clavulanic acid and the control groups.

Table II. Efficacy of amoxicillin and amoxicillin + clavulanic acid in the treatment of children with reactive arthritis.

Indices of evaluation		Amoxicillin n = 50	Amoxicillin + clavulanic acid n = 41	Control group without antibiotics n = 46
Patients with no signs of disease activity	After 1 month of observation	24 (48.0%) p < 0.001*	24 (58.5%) p < 0.001*	6 (13.0%)
	After 3 months of observation	46 (92.0%) p < 0.001*	39 (95.1%) p < 0.001*	27 (58.7%)
Adverse reactions		5 (10.0%)	5 (12.2%)	3 (6.5%)

* Significant differences in comparison with control group.
Differences between the amoxicillin and amoxicillin + clavulanic acid groups were not significant.

Table III. Comparison of the efficacy of 10- to 14-day and 28-day courses of antibiotics in children with reactive arthritis.

Indices of evaluation	Amoxicillin		Amoxicillin + clavulanic acid	
	10-14 d. n = 25	28 d. n = 25	10-14d. n = 21	28d. n = 20
Patients with no signs of disease activity				
After 1 month of observation	9 (36.0%)	15 (60.0%)	10 (47.6%)	14 (70.0%)
After 3 months of observation	22 (88.0%)	24 (96.0%)	20 (95.2%)	19 (95.0%)

No significant differences in the efficacy of 10- to 14-day and 28-day courses of antibiotics.

in the control group. In all groups, more than half of the patients had a polyarticular pattern of disease.

As is shown in Table II, after both 1 month and 3 months of observation, results of treatment with amoxicillin and amoxicillin + clavulanic acid were considerably better compared to the results of the control group ($p < 0.001$ in all cases). There was no significant difference between the groups of patients treated with amoxicillin or amoxicillin + clavulanic acid after one month and at the end of the observation period.

Adverse reactions manifested as rash or gastrointestinal complaints and did not require discontinuation of the treatment. They did not differ significantly in their frequency in patients treated with antibiotics and in the control group (Table II). In the amoxicillin group gastrointestinal complaints were observed in 4 (8.0%) patients (nausea 2, abdominal pain 1, diarrhoea 1) and a rash in one patient. In the amoxicillin + clavulanic acid group gastrointestinal complaints were observed in 4 (9.8 %) patients (in all cases irregular, slight diarrhoea) and a rash in one. In all 3 patients (6.5%) of the control group adverse reactions presented as abdominal pain.

The duration of the antibacterial course showed no significant influence on the results of treatment (Table III). However, the efficacy of the 28-day course tended to be better than that of the 10- to 14-day course after 1 month of observation in both groups treated with antibiotics ($p = 0.17$ in the amoxicillin group and $p = 0.26$ in the amoxicillin + clavulanic acid group).

After 1 month of observation, X-ray examination of joints was repeated in 6 patients with oligoarthritis (2 in the amoxicillin group and 4 in the control group) because of clinical and/or laboratory suspicion of an infectious process in bones or joints. The suspicion was excluded by further observation in all these patients.

Discussion

In this study, a significant effect of amoxicillin and amoxicillin + clavulanic acid was observed in children with ReA, when these drugs were prescribed in the first 3 months of the disease. They shortened the active period of the disease, but this study does not answer the question of recurrences. Patients receiving other antirheumatic treatment than nonsteroidal antiinflammatory drugs were excluded from the study. Such additional treatment at the beginning of the disease in most cases is corticosteroids, given in the more severe cases resembling a systemic subgroup of JIA. The pathogens of the upper respiratory tract, such as *Streptococcus*

pyogenes, may cause asymptomatic or too mild an infection to warrant medical attention (26). The clinical presentation of infection before arthritis served as a criterion for inclusion of patients in this study, and cases with a silent infection before arthritis were not included in this work. New studies are needed for the evaluation of empiric antibacterial treatment in the above-mentioned subgroups of patients, but from our experience in prescribing antibiotics for such patients we can speculate that the results of those studies will hardly differ from the results obtained in the current study.

Amoxicillin and amoxicillin + clavulanic acid showed no significant difference in efficacy when administered in the 10- to 14-day and 28-day courses. However, the compared groups with a different duration of antibacterial treatment were too small to enable a reliable conclusion. An enlargement of the groups might influence the results of treatment after a 1-month observation period in favour of 28-day antibacterial course, but it seems hardly probable that it would improve the final results after 3 months, where not even a trend of a higher efficacy of the 28-day course was observed. This is in agreement with the results of other studies, which showed that the prolongation of the antibacterial course had no influence on the treatment efficacy in adult ReA (4, 6, 7).

Phillips and colleagues (27) have succeeded in cultivating *Borrelia burgdorferi* from the blood in 43/47 patients with chronic Lyme disease who had undergone a 6-week to 6-month (mean approximately 3 months) treatment with intravenous third-generation cephalosporin and suffered a subsequent relapse. The authors used a method which was specifically designed for the reversion of L-forms to classic parent forms of microorganisms. Currently accepted standards for serologic diagnosis proved to be inadequate, as 91% of patients in that study would have been misdiagnosed as not having Lyme borreliosis. It has been shown in children with Lyme arthritis that the use of intra-articular steroids prior to antibiotics as well as the absence of antibacterial treatment during the first occurrence of arthritis may shift the course of the disease towards chronicity (28). Thus, from our study (only patients with a disease duration up to 3 months were enrolled) and from the data in the literature presented above, it seems that not the prolongation of the antibacterial course but rather its early prescription is decisive in the efficacy of antibiotics in ReA. Sometimes a lack of response to antibacterial treatment in ReA could be caused by the coexistence of several triggers of arthritis, and a course of another antibacterial could lead to success (29).

Haemophilus influenzae, *Moraxella catarrhalis* and *Streptococcus pneumoniae* are the most common bacterial pathogens in the upper respiratory tract, while *Streptococcus pyogenes* is the predominant bacterial pathogen in pharyngitis and tonsillitis (30). Of these *Streptococcus pyogenes* is the most often mentioned as a cause of pediatric ReA. There is growing interest in staphylococcal infection in rheumatology at present. Experimental data have shown that the superantigen produced by *Staphylococcus aureus* can reactivate arthritis in joints that have been previously exposed to *Streptococcus pyogenes* cell wall polymers (31). Thus, an arthritis-promoting, exacerbating action of staphylococcal infection can be expected. Besides, *Staphylococcus aureus* may trigger ReA itself (32). Zhang and colleagues (33) have reported that the persistence of the causative microorganism elsewhere in the body can predispose towards the chronization of arthritis. This suggestion might apply to URTIs as well, as the elimination of the chronic focus of bacterial infection by tonsillectomy can essentially improve even the aggressive course of JIA (34). Different microorganisms may be present on the tonsillar surface and in their deep tissue, the difference being most frequent in the growth of *Staphylococcus aureus*, which tends to persist in the deep tissue (35). This may result in difficulties while elucidating bacterial triggers or promoters of ReA in the upper respiratory tract. Empiric antibacterial therapy might justify itself in such cases.

A large part of URTIs are of viral etiology, but this does not rule out the need for antibacterials if arthritis develops, because the viral infection can activate bacteria residing in the upper respiratory tract (30). Therefore, the complexity of elucidation and of the role of upper respiratory tract bacterial pathogens in pediatric arthritis should be emphasized, and the significance of URTIs in ReA should not be restricted only to the detection of the presence or absence of streptococcal infection.

Our results are optimistic with respect to the empiric prescription of antibiotics in addition to antirheumatic treatment in pediatric ReA, and show it to be more beneficial than antibacterial therapy in adult ReA. Studies in adults demonstrated that *Chlamydia*-induced and post-enteric ReA differ in response to antibiotic therapy in favour of *Chlamydia*-induced arthritis (8). In the majority of patients in our study arthritis was associated with upper respiratory tract pathogens, and the positive results of antibacterial treatment could mean that arthritis of this origin responds better to antibacterials than arthritis triggered by sexually transmitted or enteric pathogens.

This study cannot answer all questions regarding antibacterial therapy in pediatric ReA, but our data show that larger studies may be called for in this field. Until these studies are performed, the results of our study could serve as an indication to prescribe amoxicillin or amoxicillin + clavulanic acid in 10- to 14-day courses, in addition to antirheumatic treatment, in the early stages of ReA in children, when the arthritis-triggering microorganism is not identified.

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