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# Effectiveness and safety of azithromycin in the treatment of upper respiratory tract infections

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**Key words**

*azithromycin*
*effectiveness*
*safety*
*acute pharyngitis*
*acute sinusitis*
*acute otitis media*

**Ključne riječi**

*azitromicin*
*učinkovitost*
*sigurnost*
*akutni faringitis*
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Scientific paper

The aim of the study was to describe clinical effectiveness of azithromycin in the management of upper respiratory tract infections, to examine the duration of symptoms after beginning of therapy and to mark possible adverse events of azithromycin treatment. The overall intention-to-treat (ITT) study population included 422 patients: 184 with diagnosis of acute pharyngitis (AP), 156 with acute sinusitis (AS) and 82 with acute otitis media (AOM). Clinical effectiveness was based on the results of clinical improvement and cure after three day treatment with azithromycin, calculating the clinical score for each diagnosis before treatment (at the inclusion), at the 4$^{th}$ day (end of the therapy) and at the 12$^{th}$ (end of the study). In this study azithromycin led to the relief of symptoms after three days in the 93.6 % of patients. Antibiotics were prescribed within one year before inclusion in 56.6 % of patients and 20.5 % were previously treated with macrolides. Clinical effectiveness in ITT population was 95.6 % and there were 4.4 % failures. Overall, 38 (9.1 %) patients reported 48 adverse events. The most common were: abdominal pain reported in 14 (1.1 %) patients, diarrhea in 12 (0.9 %), nausea in 5 (0.4 %), vomiting in 5 (0.4 %). The therapy was withdrawn because of an adverse event in one patient. The results of our study show that azithromycin in the treatment of upper respiratory tract infections has a high clinical effectiveness and small number of adverse events. Azithromycin is a reliable antibiotic treatment in upper respiratory tract infections, giving fast resolution of symptoms with little adverse events in patients with presumed bacterial infections.

**Učinkovitost i sigurnost azitromicina u liječenju infekcija gornjeg dijela dišnog sustava**

Znanstveni rad

Cilj studije bio je opisati kliničku učinkovitost azitromicina u liječenju infekcija gornjeg dijela dišnog sustava, ispitati duljinu simptoma nakon početka terapije i pokazati moguće nuspojave liječenja azitromicinom. U studiju je uključno 422 ispitanika: 184 s dijagnozom akutnog faringitisa, 156 s dijagnozom akutnog sinuitisa, te 82 bolesnika s akutnom upalom srednjeg uha. Klinička učinkovitost nakon tri dana liječenja azitromicinom temeljila se na poboljšanju kliničke slike i izlječenju bolesnika. Za svaku dijegnozu je izračunat klinički zbroj prije početka liječenja, te četvrti i dvanaesti dan nakon početka liječenja. Studija je pokazala kako je trodnevno liječenje azitromicinom dovelo do smanjenja simptoma u 93,6 % bolesnika. Godinu dana prije uključenja u studiju antibiotici su bili prethodno propisivani u 56,6 % bolesnika, a 20,5 % bolesnika je bilo liječeno makrolidima. Klinička učinkovitost je bila pozitivna u 95,6 % bolesnika, a neuspjeh liječenja zabilježen je u 4,4 % bolesnika. Prijavljeno je 48 nuspojava kod 38 (9,1 %) bolesnika. Najčešće nuspojave bile su: bol u trbuhu zabilježena kod 14 (1,1 %) bolesnika, proljev kod 12 (0,9 %), mučnina kod 5 (0,4 %), te povraćanje kod 5 (0,4 %) bolesnika. Prekid terapije zbog nuspojava zabilježen je kod jednog bolesnika. Rezultati studije pokazuju da u liječenju infekcija gornjeg dišnog sustava azitromicinom ima visoku učinkovitost i mali broj nuspojava. Azitromicin je pouzdan lijek izbora u liječenju infekcija gornjeg dijela dišnog sustava, s brzim povlačenjem simptoma infektivne bolesti i relativno malim brojem nuspojava.

## Introduction

Upper-respiratory tract infections such as acute pharyngitis/tonsillitis (AP), acute sinusitis (AS) and acute otitis media (AOM) are common in children and adults. These infections are usually mild, allowing treatment on outpatient basis [1–3]. Although viruses account for most of these infections, bacterial primary infection or superinfection may require antibiotic treatment. Most common bacterial causes include group A beta-hemolytic streptococcus, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* [1–3]. AOM is the most common in earlier childhood. By 3 years of age more than two thirds of children have had one or more episodes of acute otitis media, and one third have had three or more episodes [2]. AP is usually disease of children and young adults, with approximately 50 % of cases diagnosed in patients between 5 and 24 years of age [1].

Azithromycin is a macrolide antibiotic structurally modified from erythromycin with an expanded spectrum of activity and improved tissue pharmacokinetic characteristics relative to erythromycin [4]. It has expanded and enhanced antibacterial activity: it is particularly active against gram-negative pathogens, such as *H. influenzae* and *M. catarrhalis* [4, 5]. Azithromycin is also active against atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, which can also be a cause of acute pharyngitis. In the last 20 years resistance of bacteria causing respiratory tract infections increased, especially strains of *S. pneumoniae*, but reports on how that affects the results of the treatment are scarce and controversial [4–6]. Azithromycin also achieves prolonged and higher tissue concentrations and has a low incidence of gastrointestinal side effects compared to similar antibiotics [4, 7, 8]. Competitive advantages of azithromycin over other known antibiotics are its short dosing period and low potential for adverse drug reactions [4, 7, 9]. In clinical trials azithromycin showed to be either better or equally well tolerated, compared to other antibiotics [9–20].

The present study describes clinical effectiveness of azithromycin in management of upper respiratory tract infections, examines duration of symptoms after beginning the therapy and possible adverse events of treatment with azithromycin.

## Patients and Methods

This was international, multicenter, non-comparative study, which was conducted in centers in Croatia, Bosnia and Herzegovina and Macedonia. Outpatients were enrolled in this study by primary care physicians during the period of 19 months (first patient was enrolled in June 2008 and the last in November 2009). Last patient finished the study in December 2009.

The study protocol was reviewed and approved by Ethics Committees (EC) in Croatia, Bosnia and Herzegovina and Macedonia. Each patient or patient's parent/legal guardian signed Informed Consent Form before inclusion. Only patients with clinical signs and symptoms of acute pharyngitis/tonsilitis, acute sinusitis and acute otitis media to whom azithromycin would be prescribed regardless of their participation in this study were considered for inclusion. Inclusion criteria for acute pharyngitis, acute sinusitis and acute otitis media are listed in Table 1. Patients with any of the above diagnoses were treated with azithromycin 500 mg tablets or oral suspension for 3 days. Children weight less than 50 kg received 10 mg/kg/day for 3 days in oral suspension.

Azithromycin 500 mg tablets or oral suspension for children for the purpose of the study was provided by Study Sponsor.

At Visit 1 full medical history and clinical examination of patients with AP, AS and AOM were done. Optionally hematological tests and throat swabs were collected. Each patient received Patient's Diary in which they had to record time of azithromycin administration over 3 days, body temperature (twice daily), any adverse events, time when they felt relief of signs and symptoms (after one day, two days, or after more than three days). Follow up visits were at days 4 and 12. They were asked to bring filled diaries at visit 2.

Patients were clinically examined. General and specific clinical signs and symptoms were recorded, as well as adverse events. Clinical score was calculated for each diagnosis as presented in Table 2. The sum of all scores gave a total clinical score (TCS) which was considered as a measure for clinical findings at each visit. Maximum score for AP was 19 and for AS and AOM was 15.

Clinical response to therapy was evaluated as cure (complete disappearance of signs and symptoms present at Visit 1), improvement (deffervescence with substantial reduction in the intensity of signs and symptoms present at Visit 1; no need for additional antimicrobial therapy), failure (progression or recurrence of signs and symptoms and introduction of other antimicrobial therapy) or not-evaluable.

Adverse events (AE) were recorded at all post-baseline visits in patient's case report form (CRF). AE is any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not it is related. AE-report period began upon subject's entry into the study, defined as the time at which the informed consent was obtained, and ended at the final visit. All serious adverse events (SAEs) were reported in accordance with the local regulatory requirements. The outcome of an AE was also recorded.

**Table 1.** Inclusion and exclusion criteria
**Tablica 1.** Uključni i isključni kriteriji

| |
|---|
| **ACUTE PHARYNGITIS/TONSILLITIS (AP)** |
| – **inclusion criteria** |
| – Male or female out-patients;<br>– Acute onset of disease indicated by presence of fever (>37° C)<br>– Presence of at least 2 specific clinical signs and symptoms such as: sore throat, pharyngeal erythema, tonsillar enlargement, tonsillopharyngeal exudates and painful cervical lymphadenopathy;<br>– Signed informed consent (for minors, parent or legal guardian written consent needs to be obtained). |
| **ACUTE SINUSITIS (AS)** |
| – **inclusion criteria** |
| – Male or female out-patients;<br>– Presence of at least 2 specific clinical signs and symptoms such as: nasal discharge, nasal congestion and facial tenderness;<br>– Presence of signs and symptoms for at least 7 days, but less than 28 days (mild to moderate cases);<br>– Signed informed consent (for minors, parent or legal guardian written consent needs to be obtained). |
| **ACUTE OTITIS MEDIA (AOM)** |
| – **inclusion criteria** |
| – Male or female out-patients;<br>– Acute onset of disease indicated by presence of fever (>37° C)<br>– Presence of middle ear effusion (MEE) indicated by any of the following: bulging of the tympanic membrane, limited or absent mobility of the tympanic membrane, air-fluid level behind the tympanic membrane, otorrhea<br>– Signs and symptoms of middle ear inflammation as indicated by either: distinct erythema of the tympanic membrane or, distinct otalgia or irritability (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep)<br>– Signed informed consent (for minors, parent or legal guardian written consent needs to be obtained). |
| – **exclusion criteria** |
| – "No" as answer to any of inclusion criteria<br>– Hypersensitivity to macrolides<br>– Treatment with any antibiotic within 14 days prior to enrollment<br>– Participation in any clinical study within 4 weeks prior to enrollment<br>– Prior enrollment in this study<br>– Tachypnea (> 20 breaths/min for adults, or more than two standard deviations appropriate for the age of the child)<br>**+ FOR AOM:**<br>– Signs and symptoms of any complication of AOM<br>– Tympanostomy tubes present<br>– Otitis externa |

## Statistics

Categorical data were expressed in frequencies and relevant percentage. The significance of the observed differences in frequencies between relevant subgroups was tested with chi-square test or Fisher's exact test when appropriate. For continuous variables we calculated mean values with standard deviations. Differences between subgroups of interest were tested with Wilcoxon rank-sum test. The primary outcome variable were effectiveness and tolerability expressed as the number (percentage) of cured patients and number (percentage) of patients with adverse drug reactions (ADR). Secondary outcome variable was regression of symptoms assessed by changes of total clinical score. Missing values of longitudinal variables which describe treatment effectiveness (presence or absence of symptoms or accompanying scores) were imputed following the last observation carried forward (LOCF) to avoid the bias of false positive results and preserve the power of the study. Generalized linear mixed effects model was used to assess factors independently influencing regression of clinical score. Effectiveness analysis was carried out on ITT population (patients who have taken at least one dose of azithromycin and were present at least at one post-baseline visit). Safety data were analyzed on the safety population (confirmed taking of at least one azithromycin dose). All analyses were performed using SAS for Windows, version 9.2. SAS Institute Inc.

**Table 2.** Clinical score used in the assessment of treatment effectiveness
**Tablica 2.** Klinički zbroj korišten za procjenu učinkovitosti liječenja

| | | | | |
|---|---|---|---|---|
| **GENERAL CLINICAL SIGNS AND SYMPTOMS** | | | | |
| Fever (daily peak) | 0-Absent | 1 – (37,1–38° C) | 2 – (38,1–39° C) | 3 – (>39°C) |
| Chills | 0 – Absent | | 1 – Present | |
| Headache | 0 – Absent | | 1 – Present | |
| Cough | 0 – Absent | | 1 – Present | |
| Rhinitis (Except for AS) | 0 – Absent | | 1 – Present | |
| Vomiting | 0 – Absent | | 1 – Present | |
| Inappetence | 0 – Absent | | 1 – Present | |
| **SPECIFIC CLINICAL SIGNS AND SYMPTOMS** | | | | |
| **ACUTE PHARYNGITIS** | | | | |
| Sore throat | 0 – Absent | | 2 – Present | |
| Pharyngeal erythema | 0 – Absent | | 2 – Present | |
| Tonsillar enlargement | 0 – Absent | | 2 – Present | |
| Tonsillopharyngeal exudates | 0 – Absent | | 2 – Present | |
| Painful cervical lymphadenopathy | 0 – Absent | | 2 – Present | |
| **ACUTE SINUSITIS** | | | | |
| Nasal discharge | 0 – Absent | 1 – Serous | 2 – Seromucous | 3 – Mucopurulent |
| Nasal congestion | 0 – Absent | | 2 – Present | |
| Facial tenderness | 0 – Absent | | 2 – Present | |
| **ACUTE OTITIS** | | | | |
| Bulging of tympanic membrane | 0 – Absent | | 1 – Present | |
| Limited or absent mobility of tympanic membrane | 0 – Absent | | 1 – Present | |
| Otalgia or irritability | 0 – Absent | | 1 – Present | |
| Purulent otorrhea | 0 – Absent | | 1 – Present | |
| Air-fluid level behind the tympanic membrane | 0 – Absent | | 1 – Present | |
| Erythema of the tympanic membrane | 0 – Absent | | 1 – Present | |

## Results

Overall 422 ITT patients with URTI were included into the study (184 acute pharyngitis, 156 acute sinusitis, 82 acute otitis media).

### *Acute Pharyngitis*

Of 187 patients with acute pharyngitis, 184 satisfied criteria for ITT analysis. Demographic clinical and baseline data are presented in Table 3.

Pharyngeal swab was taken in only 52 (32.6 %) patients. Group A beta-hemolytic streptococcus (GABHS) was isolated in only 12/52 patients. Nevertheless, our data enable us to evaluate presence of four Centor criteria suggesting streptococcal pharyngitis or at least require microbiological confirmation of streptococcal disease (fever >38 °C, painful angular lymphadenopathy, presence of tonsillar/pharyngeal exudates and absence of cough). From 184 patients 25.5 % had positive all four Centor criteria, 33.6 % had 3 positive criteria, 28.2 % had two and 12.5 % had only one positive Centor criteria.

Total clinical score based on the intensity of symptoms and signs of acute pharyngitis were calculated for each patient. The score ranged betwee n 5 and 17, median 12. In 75 % of patients it was bellow or equal 14 suggesting overall moderate intensity of symptoms.

Antibiotics within one year before inclusion were taken by 99 (53.8 %) patients. Median time of taking antibiotics before inclusion was 4.5 months. Macrolides were taken by 37 (20.1 %) patients. Median time of taking any macrolide was 7.0 months.

**Table 3.** Demographic and baseline data
**Tablica 3.** Demografski i osnovni podaci

| | Acute pharyngitis | Acute sinusitis | Acute otitis media |
|---|---|---|---|
| Overall patients (number) | 184 | 156 | 82 |
| **COUNTRIES** | | | |
| Croatia | 103 (56 %) | 94 (60.3 %) | 46 (56.1 %) |
| Bosnia and Herzegovina | 24 (13 %) | 17 (10.9 %) | 7 (8.5 %) |
| Macedonia | 57 (31 %) | 45 (28.8 %) | 29 (35.4 %) |
| **AGE** (mean ± SD) | 21.4 ± 15.6 | 28.9 ± 16.2 | 21.6 ± 18.4 |
| **GENDER** – Male (%) | 83 (45.1 %) | 63 (40.4 %) | 42 (51.2 %) |
| **HEIGHT** (mean ± SD) | 151.8 ± 31.8 | 165.9 ± 16.4 | 146.5 ± 36.2 |
| **WEIGHT** (mean ± SD) | 54 ± 25.7 | 65.9 ± 18.4 | 52.9 ± 29.6 |
| **BMI** (mean ± SD) | 21.5 ± 4.8 | 23.4 ± 4.2 | 21.8 ± 5.3 |
| **OCCUPATION** | | | |
| Child | 79 (42.9 %) | 44 (28.2 %) | 39 (47.6 %) |
| Student | 26 (14.1 %) | 20 (12.8 %) | 10 (12.2 %) |
| Active | 75 (40.8 %) | 84 (53.8 %) | 30 (36.6 %) |
| Retired | 4 (2.2 %) | 7 (4.5 %) | 3 (3.7 %) |

**Table 4.** Clinical effectiveness and day of relief as reported by patients
**Tablica 4.** Klinička učinkovitost i dan izlječenja prema samoprocjeni bolesnika

| | Acute pharyngitis | Acute sinusitis | Acute otitis media |
|---|---|---|---|
| **CLINICAL EFFECTIVENESS** | | | |
| Cure | 157 (85.3 %) | 117 (75 %) | 68 (82.9 %) |
| Improvement | 18 (9.8 %) | 34 (21.8 %) | 10 (12.2 %) |
| Failure | 9 (4.9 %) | 5 (3.2 %) | 4 (4.9 %) |
| **DAY OF RELIEF AS REPORTED BY PATIENTS** | | | |
| 1 | 43 (24.2 %) | 21 (14.2 %) | 20 (25.3 %) |
| 2 | 70 (39.5 %) | 41 (27.8 %) | 27 (34.1 %) |
| 3 | 58 (32.7 %) | 68 (46.2 %) | 30 (37.9 %) |
| 4 | 6 (3.3 %) | 17 (11.5 %) | 2 (2.5 %) |

Clinical effectiveness was high with only nine failures (Table 4). From 184 patients 85.3 % (157/184) were marked as cure and 9.8 % (18/184) as an improvement, so there was 95.1 % (175/184) successfully treated patients.

A significant drop of clinical scores values occurred within three days of treatment, which can be seen in Figure 1 ($p < 0.001$). Previous use of macrolides or other antibiotic did not impact regression of signs and symptoms of the disease ($p = 0.419$ and $p = 0.123$, respectively).

Based o microbiology findings 11/12 patients with isolated GABSH at baseline were cured and there was 1 failure.

Diaries were received from 180 patients. Figure 2 presents cumulative percentage of patients reporting relief from symptoms from the day of inclusion. From 180 patients 171 had a relief of symptoms within 3 days (Table 4). Persistence of symptoms after day 3 was assessed in six patients.

Concomitant therapy was also reported for 108 (58.8 %) patients. Antipyretics (paracetamol with 44.5 % of all concomitant therapy) were the most commonly taken drugs, although fever at inclusion was not high.

### *Acute Sinusitis*

All of 156 patients with acute sinusitis satisfied criteria for ITT analysis. Demographic clinical and baseline data are presented on table 3.

Although not defined in Study protocol, the nasal swab was taken in 8 patients (5.1 %), in 3 patients culture was

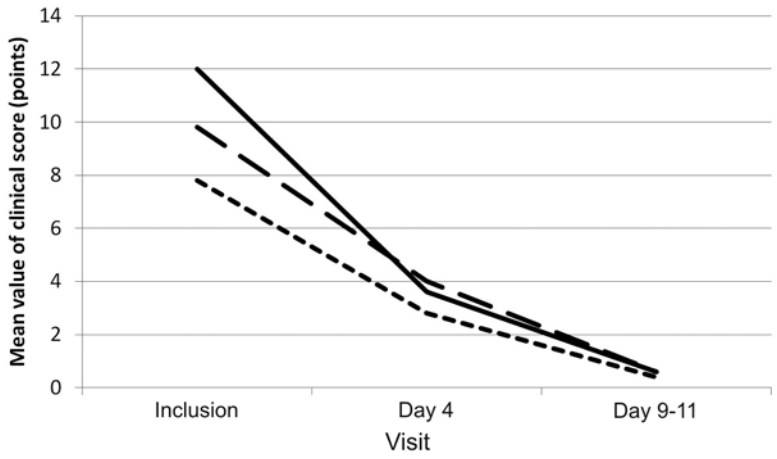


**Figure 1.** Mean values of calculated clinical score in patients on azithromycin: solid line – acute pharyngitis, dashed line – acute sinusitis and dotted line – acute otitis media

**Slika 1.** Srednje vrijednosti izračunatog kliničkog zbroja u bolesnika liječenih azitromicinom: puna crta – akutni faringitis, isprekidana crta – akutni sinusitis i točkasta crta – akutna upala srednjeg uha

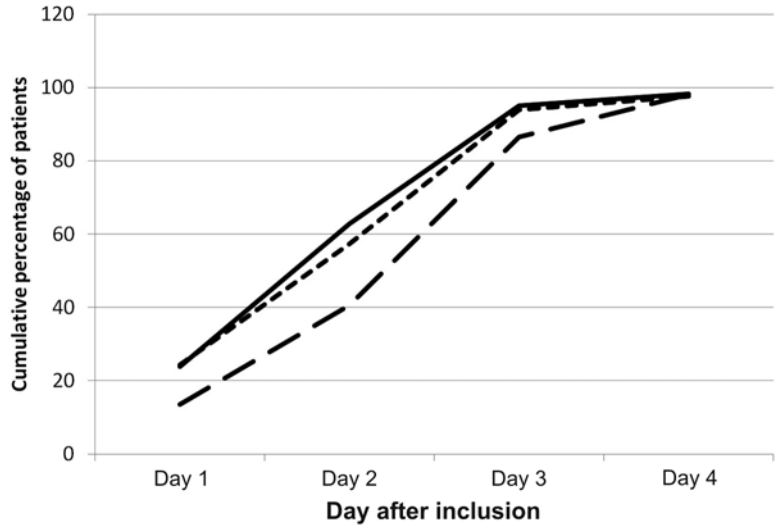


**Figure 2.** Self-reported symptom relief cumulative incidence in patients treated with azithromycin: solid line – acute pharyngitis, dashed line – acute sinusitis and dotted line – acute otitis media

**Slika 2.** Kumulativna učestalost olakšavanja simptoma prema samoprocjeni bolesnika liječenih azitromicinom: puna crta – akutni faringitis, isprekidana crta – akutni sinusitis i točkasta crta – akutna upala srednjeg uha

positive yielding isolates of *S. pneumoniae*, *H. influenzae* and *Staphylococcus aureus* in each sample.

Each symptom of acute sinusitis was present in over 90 % of patients. The total clinical score at baseline ranged between 5.0 and 14.0, median 10.0. In 75 % patients it was above or equal 11.0, suggesting moderate intensity of symptoms.

Antibiotics within one year before inclusion were taken by 84 (53.9 %) patients. Median time of taking antibiotics before inclusion was 5.0 months. Macrolides were taken by 34 (21.8 %) patients, median time of taking before inclusion was 7.0 months.

Clinical effectiveness was high 96.8 % (151/156) with only 5 failures (Table 4).

A significant drop of clinical scores mean values occurred within three days of treatment, $p < 0.001$ (Figure 1). Previous use of macrolides or other antibiotic did not impact regression of signs and symptoms of the disease ($p = 0.336$ and $p = 0.902$, respectively).

A total of 147 patients provided information on relief of symptoms in their Patient's diaries. Relief of all symptoms occurred within three days from the start of treatment in the 88.4 % (130/147) of patients (Figure 2). Persistence of symptoms after day 3 was assessed in 17 patients (Table 4).

Concomitant therapy was reported for 108 (69.2 %) patients and antipyretics were the most common concomitant therapy.

***Acute Otitis Media***

All of 82 patients with acute otitis media satisfied criteria for ITT analysis. Demographic baseline and clinical data are presented in table 3.

At the inclusion the total score ranged between 5.0 and 12.0, median 8.0. In 75 % patients it was bellow or equal 9.0 suggesting overall mild to moderate intensity of symptoms.

Antibiotics within one year before inclusion were taken by 61 (62.2 %) patients. Time of taking antibiotics before inclusion was 3.0 months. Macrolides were taken by 16 (19.5 %) patients. Median time of taking any macrolide was 7.0 months. Concomitant therapy was reported for 55 (67.0 %) patients.

Clinical cure or improvement was recorded in 95.1 % (78/82) of patients (Table 4).

A significant drop of clinical scores values occurred within three days of treatment and can be seen in Figure 1 ($p < 0.001$). Previous use of macrolides or other antibiotic did not impact regression of signs and symptoms of the disease ($p = 0.557$ and $p = 0.479$, respectively).

In 97.5 % (77/79) patients the relief of all symptoms occurred in three days (Figure 2). Two patients did not report day of relief. Persistence of symptoms after day 3 was assessed in two patients (Table 4).

***Safety***

Safety population includes 422 patients. Overall, 38 (9.1 %) of patients reported 48 adverse events. Thirty one AEs were characterized as possibly, probably or definitely related to azithromycin. The most common adverse events were abdominal pain reported in 14 (1.1 %) patients, diarrhea in 12 (0.9 %), nausea in 5 (0.4 %), vomiting in 5 (0.4 %).

## Discussion

In this study azithromycin led to relief of symptoms afte three days in the majority of patients and the clinical effect was observed apparently early. The earliest treatment effect was observed with respect to resolution of fever which in all groups occurred within 48 hours of treatment. Such fast resolution of symptoms can be explained by pharmacokinetic of azithromycin and fast achievement of high tissue concentrations (4). The patients in this study were analyzed as a group. Any division and analysis of subgroups would be inappropriate because of the low number of patients.

All patients that completed study were given full dosage (3 days of therapy). Further, we observed high compliance rate (99.5 % in AP, 98.7 % in AS and 100 % in AOM group), which might also contribute to the good effectiveness of azithromycin in our study. Other factors which could contribute to effectiveness of azithromycin might be the mild to moderate course of the disease in our patients (based on clinical score) and also possible viral etiology. However, in all groups clinical scores at the inclusion were suggesting overall moderate infection and the observed clinical effectiveness was high.

The effectiveness of azithromycin in treatment of acute pharyngitis remained in the ranges of earlier clinical studies [9, 10]. However, on contrary to earlier studies, in our study pharyngeal swab was taken in only 32.6 % (52/184) patients with AP and streptococcal infection was confirmed in 12/52 patients. Therefore, since most of acute pharyngitis were diagnosed clinically, Centor criteria were helpful in establishing the possibility of streptococcal pharyngitis (fever >38 °C, painful angular lymphadenopathy, presence of tonsillar/pharyngeal exudates and absence of cough). If three or four of Centor criteria were met, the positive predictive value is 40 to 60 % [11, 12]. In our study almost 60 % of patients had 3 or 4 positive Centor criteria. This is in accordance with the observation that more than 30 % patients in AP group had rhinitis which suggests viral infection. This can be considered as limitation of our study compared to studies where only microbiologically proven streptococcal pharyngitis was included. On the other hand, this represents reality of everyday clinical practice in which the culture diagnostic of suspected bacterial diseases is often optional [9, 10] and the therapy is given empirically.

Although the nasal swab is not adequate for confirmation of etiological diagnose it was taken in 5.1 % of patients, whereas X-ray of paranasal sinuses was performed in 10.9 % patients representing still every-day practice in diagnosing AS. Similarly, Andre et al. found that in patients with acute sinusitis who came to their general practitioner X-ray and ultrasonic investigations were performed in 1.2 % and 12.1 % of consultations, respectively [13]. These findings again confirm that most of the decisions about antibiotic treatment in every day clinical setting is grounded on clinical symptoms, despite of results of meta-analysis by Engels et al. which showed that useful information for diagnosis of sinusitis were provided by radiography and clinical evaluation, especially risk score [14]. Although some authors consider that antibiotics are overused in the treatment of AS, which may lead to higher number of adverse events and development of the resistance. Haye et al. concluded that antibiotics are beneficial because they may speed recovery in patients with moderate and severe symptoms of suspected sinusitis. Their comparative study on patients with AS have shown 93 % of clinical effectiveness in group treated with azithromycin [15] which is similar to the clinical effectiveness observed in our study. Other comparative studies have also

shown that azithromycin has clinical effectiveness equal as comparator [16].

In AOM group about two thirds of patients had signs and symptoms suggesting bacterial infection such as bulging of tympanic membrane (92.7 %) or ear discharge (41.5 %). Azithromycin is known to achieve sustained tissue concentrations in a wide range of body sites, including middle ear, this could again explain high effectiveness of azithromycin in AOM group [19, 20]. This is also in accordance with comparative studies which have shown equal effectiveness of azithromycin to amoxicillin/clavulanate for management of acute otitis media, with less adverse events in patients treated with azithromycin [19, 20]. The majority of patients were adults in whom the etiology of AOM is similar to children [21].

The dispensing of azithromycin was at the discretion of physician in patients who would be treated with azithromycin according to existing guidelines anyway[12, 13, 18, 22]. This study was non-comparative post-marketing observational study and this can be considered as its main limitation. However, this study also represents every day clinical approach to empirical antimicrobial treatment. Therefore, it provides data on 'real-life' effectiveness of azithromycin after twenty years of its clinical use.

Results of our study show azithromycin's known clinical effectiveness and favorable safety profile with small number of adverse events in treatment of upper respiratory tract infection.. Our conclusion is that azithromycin is a reliable antibiotic choice for the treatment of upper respiratory tract infections, because of adequate coverage, fast resolution of symptoms and few adverse events.

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Declaration of financial/other relationships: Dr. Baršić and Dr. Penezić received honoraria for scientific and expert's participation in the study.

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