Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Am J Otolaryngol 41 (2020) 102344

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Echinacea can help with Azithromycin in prevention of recurrent tonsillitis in children

Osama G. Abdel-Naby Awad

Otolaryngology, Head and Neck Department, Minia University Hospital, 122 Kornish El-Neel Street, Minia City, Minia, Egypt

ARTICLE INFO

Keywords:
Recurrent tonsillitis
Azithromycin
Echinacea
Sore throat

ABSTRACT

Purpose: Recurrent tonsillitis in children is a common disease affecting children quality of life and extends to their families. The aim of this study was to assess the effect of combined use of oral Azithromycin (AZT) plus Echinacea compared to exclusive use of AZT in children with recurrent tonsillitis.

Material and methods: A prospective comparative study including three groups of children with recurrent tonsillitis. Group 1: (100 patients) had no prophylactic treatment. Group 2 (100 patients) received [60 mg/kg] prophylactic dose of AZT divided as (10 mg/kg/day) over 6 consecutive days every month for 6 consecutive months. Group 3 (100 patients) received AZT as in group 2 plus commercially available Echinacea in a dose of 5 ml oral suspension; 3 times daily for 10 consecutive days every month for 6 consecutive months. Number of tonsillitis attacks and severity of tonsillitis symptoms were assessed and compared in different groups.

Results: Group 2 and group 3 had significant less number of tonsillitis attacks and severity of assessed symptoms during 6 months of prophylactic treatment with significant better results in group 3 (i.e. AZT plus Echinacea) compared to group 2 (I.e. AZT alone). However; there was no significant difference in patients with any prophylaxis.

Conclusion: The combined use of Echinacea with Azithromycin produced favorable outcome than Azithromycin alone in pediatric patients with recurrent tonsillitis.

1. Introduction

Upper respiratory tract infections (URTIs) include rhinitis, nasopharyngitis, tonsillitis and otitis media [1]. Cause of URTIs is mostly viral (e.g. rhinovirus, parainfluenza, respiratory syncytial virus, influenza, adenovirus and corona virus). Children are more susceptible to URTIs because their immune system is not fully mature with increased exposure to viral infections and other social and environmental factors [2].

Tonsillitis is an inflammation of the pharyngeal tonsils. The inflammation usually reaches the adenoid and the lingual tonsils; so the term tonsillopharyngitis is usually used [3]. Recurrent tonsillitis is defined as repeated attacks of acute tonsillitis with periods with only very few, or without any symptoms [4]. Recurrent tonsillitis has some sequelae and complications including: severe lower tract infections and the need for surgery with high impact on families' daily life and healthcare costs. Owing to the high morbidity, mortality and healthcare costs, effective prevention and treatment are needed [5,6].

Tonsillectomy is usually indicated when a patient had 6 or more acute tonsillitis attacks during last 12 months and not recommended if a patient had < 3 attacks [3]. Tonsillectomy is associated with significant risk of primary and secondary hemorrhage, in addition it is painful procedure [7]. Also, tonsillectomy may affect patient's immune system through the significant decrease of interleukin and immunoglobulins levels postoperatively [8]. Recent studies recommend more randomized controlled trials with adequate long-term follow-up to clarify the benefits of tonsillectomy versus non-surgical treatment in patients with recurrent tonsillitis [9]. Drugs such as penicillin and Azithromycin (AZT) are widely used to control recurrent tonsillitis. Sirimanna et al. [10] reported the usefulness of long-acting penicillin in recurrent tonsillitis prevention. However; long-term use of penicillin may result in hypersensitivity reactions, irritative responses, anaphylaxis, severe local pain and gluteal abscesses [11].

AZT is an azalide, a subclass of macrolide antibiotics. It is rapidly absorbed and widely distributed throughout the body, with higher concentrations in infected tissues and its therapeutic levels in tonsil tissue occurs during weekly medication with minimal side effects [12]. Gopal et al. [13] reported that use of 500 mg once weekly oral AZT was effective in prevention of streptococcal throat infection compared to oral penicillin therapy.

American Indians were the first to use Echinacea, a plant found in central and southwestern America for many different conditions

E-mail address: Usama.abdelnabi@mu.edu.eg.

https://doi.org/10.1016/j.amjoto.2019.102344
Received 13 September 2019

including cough, sore throat and tonsillitis. Different species of Echinacea exist: *Echinacea purpurea*, *Echinacea pallida* and *Echinacea angustifolia* are regularly used to treat the common cold [14]. Echinacea use in North America peaked in the early 1900s, but its use sharply declined with the advent of antibiotics and after it was denounced in well-respected medical journals [15]. With the recent surge in the use of herbal remedies, spending on Echinacea in the United States has risen to 1$300 million a year [16].

The aim of this study was to assess the effect of combined use of oral AZT plus Echinacea compared to exclusive use of AZT in children with recurrent tonsillitis regarding rate of tonsillitis attacks and severity of tonsillitis symptoms.

2. Materials and methods

This prospective randomized clinical trial was conducted during the period from March 2015 to March 2018 and was approved by the Committee for Medical Research Ethics in Egypt under registration number 2015NBA5732814. All patients' parents signed a written consent prior to inclusion in the study. No pharmaceutical companies funded the study or contributed to the study design, outcome evaluation or writing of this study.

2.1. Design, setting, and participants

A total of 300 pediatric patients were eligible and enrolled in this study. Children attending the ENT outpatient clinic with recurrent tonsillitis and indicated for tonsillectomy (defined as having at least 7 episodes of acute tonsillitis in previous year, 5 or more such episodes in each of the previous two years or 3 or more such episodes in each of the preceding 3 years before inclusion in the study) were included. Clinically significant sore throat is defined as acute tonsillitis with one or more of the following features: [17] 1- temperature > 38.3 degrees C, 2- cervical lymphadenopathy (tender cervical lymph nodes or nodes > 2 cm), 3- tonsillar exudate or 4- A positive culture for group A B-hemolytic streptococcus (GABHS). Both sexes (age range 5–16 years) were included.

Blocked randomization scheme using computer-generated random numbers was performed to divide children into 3 groups: Group 1: (100 patients) didn't receive any prophylactic treatment. Group 2 (100 patients) received prophylactic dose of AZT (60 mg/kg) administered as (10 mg/kg/day). AZT was administered as an oral suspension (200 mg/5 ml) for young children and 250 mg tablets for older children (with the maximum adult daily dose of 500 mg) taken as a single daily dose (2 h before or after meal) for 6 consecutive days every month for 6 consecutive months. Group 3 (100 patients) received AZT as in group 2 plus commercially available Echinacea in a dose of 5 ml oral suspension; 3 times daily for 10 consecutive days every month for 6 consecutive months, (Each 5 ml contains: 250 mg of Echinacea root powder extract standardized as NLT 4% total phenols). All patients in group 3 received the same commercially available Echinacea product. Compliance was assessed both with patient diary card and on the basis of the calculated amount of drug consumed.

We excluded from the study patients with the following: 1- rheumatic heart disease, 2- patients receiving long-acting penicillin, 3- diabetes mellitus, 4- autoimmune diseases, 5- patients who take immunosuppressant drugs or who did organ transplantation, 6- patients suffering from hepatic or renal disorders and 7- patients with history of obstructive sleep apnea.

2.2. Study plan

All children underwent complete oral and nasal examinations. We assessed complete medical history of all patients including number of tonsillitis attacks and severity of recorded tonsillitis symptoms 6 months before enrollment in the study compared to 6 months of study duration. Relevant questionnaire completed by patients' parents of younger children and by older children themselves assessing their recurrent tonsillitis symptoms (e.g. number of school absence days, dysphagia, fever, body ache and arthralgia) using a visual analogue score (VAS) to assess subjective symptoms (0 = no symptoms and 10 = severe and/or constant symptoms). Any side effects of used drugs were recorded and compared.

2.3. Statistical analysis

The Statistical Package of Social Science version 15.0 (SPSS, Chicago, Illinois, USA) was used for data analysis. The quantitative data were presented by mean and standard deviation. Mann-Whitney non-parametric test and *t*-test were applied to compare the groups with respect to different variables. Fisher's exact test was used to determine differences in the level of compliance. The probability of < 0.05 was used as a cut-off point for all significant tests.

3. Results

A total of 300 children with recurrent tonsillitis 140 (47%) males and 160 (53%) females, aged between 5 and 16 years (mean age 10.4 years) were randomly divided into 3 groups and assessed for the efficacy of new adopted prophylactic treatment regimen as follow: Group 1 (n = 100 children) had no prophylactic treatment, whereas Group 2 (n = 100 children) received oral AZT and group 3 (100 children) received oral AZT plus oral Echinacea. On enrolment; patients of the 3 groups had no statistically significant difference with respect to age, gender and weight (Table I). The mean intensity of tonsillitis symptoms according to VAS before treatment among the 3 groups was summarized in Table II with no statistically significant difference between different groups.

3.1. Difference in number of tonsillitis attacks (Tables III, IV)

In group 1: Patients had no statistically significant difference regarding number of tonsillitis attacks during study duration compared to pre-study duration ($P = .82$).

In group 2: Patients had significant less number of tonsillitis attacks during study duration compared to pre-study duration ($P = .02$).

In group 3: Patients had significant less number of tonsillitis attacks during study duration compared to pre-study duration ($P = .31$).

Patients of group 3 had significant less number of tonsillitis attacks during study duration compared to patients in group II ($P = .42$).

3.2. Difference in severity of tonsillitis symptoms

Mean intensity of different tonsillitis symptoms according to VAS before treatment in study groups were summarized in Table II. Six months from starting study (Table III): **In group 1**: patients had no statistically significant difference regarding change of severity of assessed tonsillitis symptoms compared to pre-study duration. **In group 2**: Patients had significant less severity of assessed tonsillitis symptoms compared to pre-study duration. **In group 3**: Patients had also significant less severity of assessed tonsillitis symptoms compared to pre-study duration. However; **patients of group 3** had significant less severity of assessed tonsillitis symptoms during study duration compared

Table I
Demographic characteristics of patients in 3 study groups.

	Group 1	Group 2	Group 3
Male: female	45%:55%	40%:60%	48%:52%
Age [years]: mean [SD; range]	9 ± 21	10 ± 23	11 ± 30
Weight (kg): mean (SD; range)	35 ± 21	40 ± 40	38 ± 32

Table II
Mean number of tonsillitis attacks and degree of different tonsillitis symptoms in 3 groups before treatment.

Clinical variables (Mean ± SD)	Group 1	Group 2	Group 3	*P* value
Tonsillitis attacks	5 ± 1.1	6 ± 1.1	5 ± 1.12	0.763
Number of school absence days	13 ± 2.2	15 ± 2.3	12 ± 1.6	0.534
Dysphagia	8 ± 1.3	8 ± 1.2	9 ± 1.2	0.342
Fever	9 ± 1.4	7 ± 1.3	8 ± 1.1	0.654
Body ache	8 ± 1.3	9 ± 0.7	8 ± 1.2	0.324
Arthralgia	7 ± 1.1	8 ± 0.9	7 ± 1.1	0.643

Data presented as mean ± standard deviation. *Student's t*-test for paired samples: Insignificant $p > .05$.

Table IV
Mean number of tonsillitis attacks and degree of different tonsillitis symptoms in group 2 vs. group 3 comparing post-treatment values.

Clinical variables (Mean ± SD)	Group 2	Group 3	P-value
Tonsillitis attacks	4 ± 1.3	2 ± 0.3	0.04*
Number of school absence days	10 ± 1.3	6 ± 0.6	0.02*
Dysphagia	5 ± 0.7	3 ± 0.2	0.01*
Fever	4 ± 0.6	2 ± 0.2	0.01*
Body ache	4 ± 0.7	2 ± 0.1	< 0.0001*
Arthralgia	4 ± 08	1 ± 0.1	< 0.0001*

Data presented as mean ± standard deviation. *$P < .05$ (*Student's t*-test for paired samples): represents significant difference.

to patients in group II (Table IV).

3.3. Compliance

95 children in group 2 and 97 children in group 3 received > 80% of the prescribed treatment with no significant difference ($P = .317$).

3.4. Side effects

No significant side effects were recorded in either group. 3 children in group 2 had gastrointestinal symptoms that resolved spontaneously after 24 to 48 h without a change in treatment regimen and 4 patients in group 3 had also mild gastrointestinal symptoms and loose stool that resolved spontaneously.

4. Discussion

Recurrent tonsillitis is one of the common primary care visits to physicians. The treatment of tonsillitis in children focuses on symptoms reduction, avoiding complications, decreasing the number of disease-related school absences and improving quality of life (QOL). Tonsillectomy is the most common pediatric operations; however, its effectiveness, safety, and the net benefit of tonsillectomy are unclear. Tonsillectomy morbidity has high impact on the QOL of patients such as socioeconomic factors and increased burden to parents from the suffering of the child [18]. Tonsillectomy should not be the only solution as there is a possibility of immunological deficit as the function of tonsils in the immune system is not completely clear as an important constituent of the upper respiratory tract defense system [19]. On the other hand, patients who undergo tonsillectomy are at high risk of developing bronchial asthma [20] and Crohn's disease [21].

AZT penetrates to the cell membranes and concentrates within the lysosomal compartment. It is widely distributed in the whole body, achieving higher concentrations in tissues and thus serum delivery to infected tissue is further enhanced by inflammatory processes [22]. AZT used for rheumatic fever prevention for a long time before. In our study; we adopted a new regimen for prevention of recurrent tonsillitis in pediatrics; patients received (60 mg/kg) prophylactic dose of AZT divided on 6 consecutive days every month for 6 consecutive months. Patients received AZT alone had significant less tonsillitis attacks and less severe symptoms than patients who didn't receive any prophylaxis during the same period of the study. El Hennawi et al. [18] in their study concluded that AZT is effective in prophylaxis against recurrent tonsillitis with a great benefit for better QOL compared to patients who had tonsillectomy, however; they used the prophylactic regimen of rheumatic fever prevention (once weekly AZT) [23] and they didn't include a control group in their study. Casey and Pichichero [24] reported that AZT treatment for GABHS tonsillopharyngitis in children and adults is more effective than other treatment regimens in providing clinical cure of tonsillopharyngitis. Snider et al. [25] demonstrated AZT efficacy as a prophylaxis in decreasing streptococcal infections and rheumatic activity.

Gray et al. [26] reported superiority of weekly oral AZT in the prevention of upper respiratory infection over penicillin when used as prophylaxis in 1016 US marine trainees at high risk of respiratory disease, however; 30 patients in AZT group had persistent recurrent tonsillitis in spite of AZT usage. Gopal et al. [13] reported that 15.4% of their patients with established rheumatic heart disease had recurrent tonsillitis with once weekly AZT dose. In our study; patients still had tonsillitis attacks with AZT use. Why AZT failed to prevent tonsillitis completely is not very clear. One possibility is that drug dosage was too widely spaced. Though AZT has a long half-life, drug concentration might not have been adequate. AZT when administered at 60 mg/kg per course (i.e. 20 mg/kg for 3 days, 12 mg/kg for 5 days or 10 mg/kg for 6 days) in children was superior to the 10-day course of penicillin, however; 3-days AZT regimen was inferior to 5 and 6-day regimens, also 30 mg/kg per course was inferior to the 10-day courses of penicillin [24]. AZT treatment may be required in higher doses and for longer duration to be effective in recurrent tonsillitis prevention, so we used 60 mg/kg prophylactic dose divided on 6-days.

Other possibilities of AZT failure may be due to: poor patient compliance, failure of the drug to reach adequate concentration in the mucosa, microbial tolerance to AZT, recurrent exposure of patients to virulent strains of GABHS, suppression of natural immunity and

Table III
Mean number of tonsillitis attacks and degree of different tonsillitis symptoms in 3 groups comparing pre-treatment and post-treatment values.

Clinical variables (Mean ± SD)	Group 1			Group 2			Group 3		
	Pre	Post	*P*-value	Pre	Post	P-value	Pre	Post	P-value
Tonsillitis attacks	5 ± 1.1	5 ± 1.2	0.823	6 ± 1.1	4 ± 1.3	0.02*	5 ± 1.2	2 ± 0.3	0.03*
Number of school absence days	13 ± 2.2	12 ± 2.1	0.912	15 ± 2.3	10 ± 1.3	0.01*	12 ± 1.6	6 ± 0.6	< 0.0001*
Dysphagia	8 ± 1.3	8 ± 1.8	0.856	8 ± 1.2	5 ± 0.7	0.03*	9 ± 1.2	3 ± 0.2	< 0.0001*
Fever	9 ± 1.4	8 ± 1.2	0.976	7 ± 1.3	4 ± 0.6	0.03*	8 ± 1.1	2 ± 0.2	< 0.0001*
Body ache	8 ± 1.3	8 ± 0.9	0.865	9 ± 0.7	4 ± 0.7	0.04*	8 ± 1.2	2 ± 0.1	< 0.0001*
Arthralgia	7 ± 1.1	7 ± 1.0	0.765	8 ± 0.9	4 ± 08	0.03*	7 ± 1.1	1 ± 0.1	< 0.0001*

Data presented as mean ± standard deviation. *$P < .05$ (*Student's t*-test for paired samples): represents significant difference.

disturbance of normal flora of throat [13]. AZT inhibits growth of alpha streptococci that are normal defenders of pharyngeal mucosa against pathogens at lower MIC [27]. Intracellular accumulation of macrolides have been shown in leucocytes but not in epithelial cells, which are probably the principal cells targeted by GABHS. In leucocytes; AZT accumulates predominantly in lysosomes, whereas intracellular GABHS is found in phagosomes and cytosol [28]. In a recent study we reported that adult patients with recurrent tonsillitis may have higher incidence of humoral antibody deficiency compared to their age and sex-matched controls [29]. From this point; we used Echinacea as an adjunct to AZT in a trial to enhance patients' immunity.

Echinacea, also known as the purple coneflower, it is one of the most popular herbal medicines with an estimated 1–4% of the general population using the herb in a given year. The medicinal properties of Echinacea were first recognized in the eighteenth century by Native American tribes who used the plant to treat snake and insect bites, coughs, colds and typhoid fever. Echinacea has numerous claimed medicinal properties including: anti-viral, anti-bacterial, anti-fungal, anti-oxidant, anti-carcinogenic, anti-inflammatory and wound healing properties. It has immune stimulating properties and can reduce the severity of symptoms and duration of the common cold and flu, especially if used in the early stages of infection [30].

There are no data in the previous literature (up to our knowledge) on combined use of AZT and Echinacea in recurrent tonsillitis prophylaxis. In this study; patients with combined AZT plus Echinacea had significant better results compared to patients with AZT alone. This effect of Echinacea can be attributed to several major constituents of Echinacea identified and reported to be biologically active: Caffeic acid derivatives thought to contribute to the claimed antioxidant and anti-inflammatory properties of Echinacea, Alkamides thought to have stimulatory effects on the cells of the immune system and Polysaccharides reported to act on the immune system to boost its effects. The active constituents of Echinacea may strengthen the immune response by interacting with various cells of the specific and non-specific immune system and through activation of macrophages, natural killer cells and polymorphonuclear leukocytes [31]. On the basis of this limited information, we suggest the possible value of Echinacea added to documented value of AZT in preventing tonsillitis in children.

One factor affecting the validity of studies is the quality of the Echinacea material used in clinical trials. Echinacea's immune stimulating properties are dependent on the presence of certain active constituents. Research into the quality of herbal products revealed that only 28% of Echinacea products tested contained the same amounts and types of constituents as listed on the label. This could explain why Echinacea is effective in some trials but not in others [32,33].

Patients in AZT group didn't report any significant side effects with good tolerability. O'Doherty [34] reported that AZT treatment is safe, well tolerated, and effective, given the longer duration of action, better side effect profile and lack of P450 interaction, greater stability in the presence of acid, better absorption and without gastroparesis action. Echinacea also appears to be well tolerated; few patients in this study had mild GIT symptoms and loose stool. It has been estimated that 1–4% of the general population uses Echinacea in a given year with no deaths and few significant adverse reactions have been reported [35]. Investigations into the toxic effects of Echinacea have failed to find a lethal dose. Those with a known allergy to the Asteraceae (daisy) family should avoid Echinacea as few cases of Echinacea induced anaphylaxis, asthma attack; urticaria and contact dermatitis have been reported. Echinacea can interfere with drugs metabolized by an enzyme family known as the cytochrome *p*450 system and thus prolong their action [36]. When AZT was combined to Echinacea in this study; no interactions reported and efficacy of both drugs were maintained. The development of resistant bacteria with prolonged antibiotic use is well established. Xavier et al. [37] studied the Long-term AZT therapy in patients with severe chronic obstructive pulmonary disease (COPD) and repeated exacerbations, they reported that long-term intermittent AZT therapy, administered three times a week at a dosage of 500 mg, is well tolerated and associated with significant reductions in acute exacerbations of COPD, number of hospitalizations and days of hospital stay with no development of resistant bacteria.

This study designed to determine effects of the prophylactic regimen for a finite period focusing on the potential value of adding Echinacea to AZT. Limitations of the study; that there is no data about consequences of discontinuation or continuation of prophylactic courses. Patients with GABHS tonsillopharyngitis experience clinical improvement over time with or without antibiotic therapy. Therefore, measurement of clinical response during treatment is largely meaningless in antibiotic trials. After completion of therapy, some patients experience relapse or recurrence with symptoms and signs of tonsillopharyngitis and with recovery of GABHS on culture of a throat swab sample [24,38]. However; with 60-mg/kg AZT dose, clinical cure and bacterial eradication rates in children compared with 10-day penicillin regimen were superior after discontinuation of AZT courses [24]. The study opens a new era for more research to illustrate possible consequences of more prolonged therapy, infectious course once prophylaxis is discontinued, the possible long lasting benefits and if multiple prophylactic courses need to administered. The main strengths of this study; that it is a prospective study with a control group and there is a difference in the clinical characteristics of those used the prophylactic regimen.

5. Conclusion

The combined use of Echinacea with Azithromycin produced favorable outcome than Azithromycin alone in pediatric patients with recurrent tonsillitis. Addition of Echinacea could decrease number of tonsillitis attacks and may also decrease severity of tonsillitis symptoms in these patients.

References

[1] Pichichero ME, Disney FA, Talpey WB. Adverse and beneficial effects of immediate treatment of Group A Beta haemolytic streptococcal pharyngitis with penicillin. Pediatr Infect Dis J 1987;6:635–43.
[2] Wald E. Sinusitis in children. N Engl J Med 1992;326:319–32.
[3] Bathala S, Eccles R. A review on the mechanism of sore throat in tonsillitis. J Laryngol Otol 2013;127:227–32.
[4] Salatino S, Gray A. Integrative management of pediatric tonsillopharyngitis: an international survey. Complement Ther Clin Pract 2016;22:29–32.
[5] Georgalas CC, Tolley NS, Narula PA. Tonsillitis. BMJ Clin Evid 2014;22:2104.
[6] Burton MJ, Glasziou PP, Chong LY, Venekamp RP. Tonsillectomy or adenotonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. Cochrane Database Syst Rev 2014;19:11.
[7] Georgalas C, Tolley N, Narula P. Tonsillitis. BMJ Clin Evid 2009;26:2009.
[8] Kaygusuz I, Gödekmerdan A, Karlidag T, et al. Early stage impacts of tonsillectomy on immune functions of children. Int J Pediatr Otorhinolaryngol 2003;67:1311–5.
[9] Feleszko W, Marengo R, Vieira AS, Ratajczak K, Mayorga Butrón JL. Immunity-targeted approaches to the management of chronic and recurrent upper respiratory tract disorders in children. Clin Otolaryngol 2019;44:502–10.
[10] Sirimanna KS, Madden GJ, Miles SM. The use of long-acting penicillin in the prophylaxis of recurrent tonsillitis. J Otolaryngol 1990;19:343–4.
[11] William A. Petri Jr. Penicillin, cephalosporin and other beta lactam inhibitor antibiotics. In: Goodman and Gilman's pharmacological basis of therapeutics, eds Brunton LL, Chabner BA, Knollman BC, McGraw-Hill, New York, pp. 730–752.
[12] Lister PJ, Balechandran T, Ridgway GL, Robinson AJ. Comparison of azithromycin and doxycycline in the treatment of non-gonococcal urethritis in men. J Antimicrob Chemother 1993;31:185–92.
[13] Gopal R, Harikrishnan S, Sivasankaran S, Ajithkumar VK, Titus T, Tharakan JM. Once weekly azithromycin in secondary prevention of rheumatic fever. Indian Heart J 2012;64:12–5.
[14] O'Hara MA, Kiefer D, Farrell K, Kemper K. A review of the 12 commonly used medicinal herbs. Arch Fam Med 1998;7:523–36.
[15] Puckner WA. Echinacea considered valueless: report of the council on pharmacy and chemistry. JAMA 1909;27:1836.
[16] Canedy D. Real medicine or medicine show? Growth of herbal sales raises issues about value. New York times. 1998. 23 July.
[17] Windfuhr JP. Indications for tonsillectomy stratified by the level of evidence. GMS Curr Top Otorhinolaryngol Head Neck Surg 2016;15:15.
[18] El Hennawi DE, Rifaat Ahmed M. Quality of life after tonsillectomy versus azithromycin. Interv Med Appl Sci 2016;8:141–6.
[19] Brandtzaeg P. Immunology of tonsils and adenoids: everything the ENT surgeon

needs to know. Int J Pediatr Otorhinolaryngol 2003;67:S69:S76.
[20] Nalan Y, St Sadan, Zeynep C, Dilsad M, Kenan Kose S, Zeynep M. Is adenoidectomy and/or tonsillectomy a risk factor for allergic diseases and asthma in adulthood? Eurasian J Med 2018;50:152–5.
[21] Sun W, Han X, Wu S, Yang C. Tonsillectomy and the risk of inflammatory bowel disease: a systematic review and meta-analysis. J Gastroenterol Hepatol 2016;31:1085–94.
[22] Gašparić M, Penezić A, Kolumbić-Lakoš A, Kovačić D, Kukuruzović MM, Baršić B. Safety and effectiveness of azithromycin in the treatment of respiratory infections in children. Curr Med Res Opin 2012;28:155–62.
[23] Rakesh G, Harikrishnan S, Sivasankaran S, Ajithkumar VK, Titus T, Tharakan JM. Once weekly azithromycin in secondary prevention of rheumatic fever. Indian Heart J 2012;212:12–5.
[24] Casey JR, Pichichero ME. Higher dosages of azithromycin are more effective in treatment of group A streptococcal tonsillopharyngitis. Clin Infect Dis 2005;40:1748–55.
[25] Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry 2005;57:788–92.
[26] Gray GC, Witucki PJ, Gould MT, et al. Randomized, placebocontrolled clinical trial of oral azithromycin prophylaxis against respiratory infections in a high-risk, young adult population. Clin Infect Dis 2001;33:983–9.
[27] Podbielski A, Kreikemeyer B. Persistence of group A streptococci in eukaryotic cells—a safe place? Lancet 2001;358:3–4.
[28] Harold C. Neu clinical microbiology of azithromycin. Am J Med 1991;91:S12–8.
[29] Abdel-Naby Awad OG. Prevalence of humoral immunodeficiency in adult patients with recurrent tonsillitis. Am J Otolaryngol 2019 Aug 13;40:603–10. [Epub ahead of print].
[30] Barrett B. Medicinal properties of Echinacea: a critical review. Phytomedicine 2003;10:66–86.
[31] Rininger JA, Kickner S, Chigurupati, Mclean A, Franck Z. Immunopharmacological activity of Echinacea preparations following simulated digestion on murine macrophages and human peripheral blood mononuclear cells. J Leukoc Biol 2000;68:503–10.
[32] Miller SC. Echinacea the genus Echinacea. New York, USA: CRC press; 2004.
[33] Miller SC. Echinacea: a miracle herb against ageing and cancer? Evidence in vivo. Evidence based complementary and alternative medicine 2005;2:309–14.
[34] O'Doherty B. Azithromycin versus penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/tonsillitis. Paediatric azithromycin study group. Eur J Clin Microbiol Infect Dis 1996;15:718–24.
[35] Scaglione F, Lund B. Efficacy in the treatment of the common cold of a preparation containing an Echinacea extract. Int J Immunopharmacol 1995;11:163–6.
[36] Melchart D, Linde K, Worku F, Bauer R, Wagner H. Immunomodulation with Echinacea: a systematic review of controlled trials. Phytomedicine 1994;1:245–54.
[37] Xavier P, Concepción M, Mateu E, Jordi C, Eduard M, Miguel G. Long-term azithromycin therapy in patients with severe COPD and repeated exacerbations. Int J Chron Obstruct Pulmon Dis 2011;6:449–56.
[38] Lee LH, Ayoub E, Pichichero ME. Fewer symptoms occur in sameserotype recurrent streptococcal tonsillopharyngitis. Arch Otolaryngol Head Neck Surg 2000;126:1359–62.