Comparative Study of Oral Daily Amoxicillin, Long Acting Intramuscular Penicillin, and Tonsillectomy in Prevention of Recurrent Pharyngitis

Amira S Ahmed[1], Engy A Wahsh[2], Essam Eldin G. Ahmed[3]

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Beni Suef University, Egypt

[2] Faculty of Pharmacy, Nahda University, Beni Suef, Egypt

[3] Department of Pediatrics, Faculty of Medicine, Fayoum University, Fayoum, Egypt

Abstract

Pediatric recurrent pharyngitis represents a huge global health burden causing much morbidity and mortality in children. The aim of the study was to compare the efficacy of oral daily amoxicillin, intramuscular penicillin, and tonsillectomy in reducing the incidence of recurrent pharyngitis Between July 2012 and June 2013, a total of 100 paediatric patients (56 males and 44 females) diagnosed with recurrent pharyngitis were enrolled in the study. The clinical criterion for study entry was three or more episodes of pharyngitis in six months. The selected patients' clinical data were recorded and a throat swab was obtained. Patients were divided randomly into three groups A, B, and C. Group A received a monthly ten days course of oral amoxicillin suspension (25mg/kg/day) for six months, group B received a single dose of intramuscular benzathine penicillin G every 3 weeks for 6 months and group C included patients who undergo tonsillectomy. All patients were scheduled for a monthly follow-up visit, during which they the number of recurrent pharyngitis episodes, compliance, adverse events and drug tolerability were assessed. All treatment regimens significantly decreased recurrences. While oral amoxicillin and IM penicillin efficacy were comparable, tonsillectomy was similarly effective to IM penicillin treatment and more effective than oral amoxicillin therapy. The once daily oral amoxicillin is a safe, effective and convenient alternative to IM penicillin in reducing the incidence of recurrent pharyngitis. Tonsillectomy is also a suitable alternative, however its possible related morbidity and mortality should be considered.

Keywords: Recurrent pharyngitis, prevention, amoxicillin, intramuscular benzathine penicillin G

(Rec.Date: Sep 29, 2014 Accept Date: Oct 16, 2014)

Corresponding Author*:* D Amira S. Ahmed, Lecturer Department of Clinical Pharmacy Faculty of Pharmacy, Beni Suef University, Egypt
E-mail: amirashaban19@yahoo.com

Introduction

Recurrent pharyngitis is a very common complaint in the pediatric population. It is a persistent clinical problem that causes repeated use of antibiotics and a significant burden on both families (absences from school or work) and societies (health care costs) [1]. Although the disease appears to be self-limited in most cases, the risk for suppurative and non-suppurative complications is still a worrying issue [2]. Even without these complications, the disease still adds a heavy socioeconomic burden. Estimated economic costs of pediatric pharyngitis in the United States range from $224 million to $539 million per year, including indirect costs related to parental work losses [3]. This problem appears to be even worse in developing countries where it is not only more prevalent but also more severe causing over 2 million deaths per year [4-7].

While recurrent pharyngitis often begins as viral infections, bacterial infections is observed in 60% of patients with upper respiratory tract symptoms lasting at least 10 days [8,9]. Several bacterial etiological agents have been identified and frequently isolated from the tonsillar core including; Streptococcus pyogenes, Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus. influenzae [10-12]. Group A beta-hemolytic streptococcus (GABHS) is the most important pathogenic bacterial etiology and has been the focus of diagnostic and therapeutic efforts aimed at reducing its risk of both suppurative (quinsy, acute otitis media, acute sinusitis) and nonsuppurative complications (e.g. acute rheumatic fever, acute glomerulonephritis) if left untreated [2].

Unfortunately, the lack of an effective immunization, the persistence or recurrences of an infection despite an optimal treatment have made secondary prevention by continuous antimicrobial prophylaxis, the only means of protecting at risk individuals [13-15].

Several antibiotics have been shown to be effective, including penicillin and its congeners (such as ampicillin and amoxicillin), as well as numerous cephalosporins, macrolides and clindamycin [16]. However, issues such as, efficacy, safety, antimicrobial spectrum, dosing schedules, compliance, and cost, should be considered in selecting the most optimal therapy [17].

The American Heart Association (AHA), the American Academy of Pediatrics (AAP) [14,18], and the Infectious Diseases Society of America (IDSA) [19] have always

recommended either a monthly ten days course of oral penicillin V (2 to 4 times a day) or a monthly single intramuscular injection of benzathine benzyl penicillin (IM BPG) as the mainstay therapy in patients without penicillin allergy. This is simply due to its cost effectiveness, narrow spectrum of activity and long standing proven efficacy in elimination of GABHS and prevention of rheumatic fever [20]. Furthermore, according to a recent systematic review, to date, no penicillin-resistance has been documented [21].

However, the monthly IM injection of benzathine penicillin has not gained wide acceptance, largely because of frequent prolonged pain at the site of injection and increased risk of side effects, which led some individuals to discontinue prophylaxis. For this reason in clinical practice, most physicians viewed oral therapy to be more advantageous over parenteral treatment by reducing patient discomfort, needle-associated complications, providing shorter exposure to the medication, and less severe allergic reactions [14,22,23].

However, poor patient compliance to the multiply dosed oral penicillin V (2 to 3 times daily for 10 days each month) jeopardized the whole treatment success where most failures occurred in non-adherent patients [14]. Furthermore, several attempts to use a once daily oral dose of penicillin V to effectively treat pharyngitis have failed [24].

Recently many comparative clinical trials have proven that once daily oral amoxicillin therapy was as efficacious for recurrent pharyngitis as oral penicillin V (2 to 3 times daily) [25-27]. Therefore, no doubt that this equally cheap, effective globally available, well tolerated, more palatable and once daily dosed amoxicillin presents a cost-effective and convenient alternative to oral or injectable penicillin [28].

In addition, although tonsillectomy has been used traditionally to prevent recurrent throat infections mostly as a second choice post drug therapy failure, its clinical relevance is still poor. However, it has been reported that tonsillectomy modestly reduces the number of episodes and days with sore throat in both children [29] and adults [30]. Aim of work to compare the efficacy of a monthly ten days course of oral amoxicillin, single intramuscular injection of long acting penicillin every 3 weeks for six months, and the effect of tonsillectomy in reducing the incidence of recurrent pharyngitis

Patients and Methods

Between July 2012 and June 2013, a total of 100 pediatrics patients (56 males and 44 females) referred to the hospital for being diagnosed with recurrent pharyngitis (between the ages of 2 and 10 years) were enrolled in the study. The clinical criterion for study entry was three or more episodes of pharyngitis in six months. The symptoms and signs during the episodes had to be severe enough for the patient to seek medical attention. Participation was voluntary, and written informed consent was obtained from the parents or guardians of all the children. The study was approved by the Ethics Committee of Fayoum University teaching Hospital.

Patients were excluded from the study if they met one or more of the following criteria; Pharyngitis most probably due to viral etiology from the clinical view and physical examination (e.g. presence of oral ulcers, characteristic viral upper respiratory tract infection), Children with a known hypersensitivity to penicillin or likely to require treatment with other antimicrobials during the study period, had a history of rheumatic fever or rheumatic heart disease, immunodifficient patients either (e.g. patients under chemotherapy, prolonged steroid use or nephrotic syndrome), had renal or hepatic dysfunction, or required hospitalization for any reason at the time of enrollment.

Study design

On admission, the selected patients were subjected to a complete and detailed medical history, physical and clinical examination. Informed consent was obtained from all individual participants included in the study. All their baseline demographic and clinical data were recorded and a throat swab was simultaneously obtained for standard throat culture. Study treatment details were summarized in figure 1. Patients were divided randomly into three groups A, B, and C. Group A received a monthly ten days course of a single daily dose of 25mg/kg/day of oral amoxicillin suspension (Delpedox® 400mg/5ml; Deltapharma, Egypt) for six months, group B received (Retarpen® 1.2 million units; Sandoz Pharma, Egypt) a single dose of intramuscularly administered benzathine penicillin G (IM BPG; 600 000 units if body weight <27 kg; 1.2 million units if body weight ≥27 kg) every 3 weeks for 6 months and group C included patients who undergo tonsillectomy. Parents/guardians of children in the amoxicillin group were instructed and stressed to administer the antibiotic at the same time every day for 10 days each month. All patients were scheduled for a monthly follow-up visit, during which they were required to assess the number of recurrent pharyngitis episodes.

Compliance, adverse events and drug tolerability were also assessed by parental report during this visit.

Statistical Analysis

SPSS V17.0 (SPSS Inc, Chicago, USA) was used for statistical calculations. Comparison of recurrence and absence from school before and after treatment was accomplished using Paired-samples T test. Comparison of recurrence and absence from school between the three treatment groups was accomplished using one-way Anova test. The calculated P-value is considered significant if ≤ 0.05.

At the end of study, the animals were euthanized with CO2 inhalation. Histological studies of seminiferous tubules were performed on formaldehyde-fixed and paraffin embedded testicular samples with thickness of 6-7 micrometer stained with Hematoxylin and eosin method. Tissue sections were studied at ×200 magnification. The histological study of tissue samples was performed on the images obtained with digital camera (Olympus DP70, Olympus Europe, Hamburg, Germany). For each tissue sample, the numbers of twenty tubules were studied in different microscopic fields.

Results

Baseline demographic characteristics

The baseline demographic and clinical characteristics of patients were presented in table 1. A total of 100 patients with recurrent pharyngitis were recruited in the study, patients were randomly assigned into three groups. Group A of 40 patients (28 males and 12 females) with mean ± SD age and weight of 4.09 ± 1.596, and 16.52± 7.11, respectively. Group B of 40 patients (22 males and 18 females) with mean ± SD age and weight of 5.59 ± 2.17, 18.8 ± 5.02, respectively. Group C of 20 patients (6 males and 14 females) with mean ± SD age and weight of 5.6 ± 2.01, and 17.2 ± 3.29, respectively. During the study 10 patients from group A and the same from group B withdrew and did not complete the study period which is 6 months, and their data were not included in the results. The incidence of joint symptoms in the study patients varied from 6 (20%), 14 (46.6%), and 12 (60%), for groups A, B, and C respectively.

As shown in table 2, when examining throat swab results of all study patients with recurrent pharyngitis, the most prevalent pathogenic bacterial species was Staphylococcus aureus (34

patients; 34%; p=0.000). The next prevalent pathogenic organism was GABHS (22 patients; 22%). Normal flora was identified in (26 patient; 26%).

The incidence of recurrent pharyngitis was not significantly changed with either the presence of joint symptoms or vaginal delivery, however breast fed study patient were found to significantly decrease recurrence at p=0.003 compared to non-breast fed ones. The results were illustrated in table 3.

As it is evident from table 4, a highly statistically significant improvement in mean ± SD recurrence of pharyngitis of (13.5 ± 5.6 vs. 1.4 ± 1.1, p=0.001), (9.9 ± 5.8 vs. 1.0 ± 0.8, p=0.001), and (6.5 ± 5 vs. 0.5 ± 0.4, p=0.003) was observed post treatment for groups A, B and C respectively. Similarly, the mean ± SD absence of children from school showed a marked significant decrease post treatment from (20.3 ± 6.6 vs. 3.0 ± 2.3, p=0.001), (16.4 ± 8.6 vs. 2.3 ± 1.6, p=0.001), and (11.3 ± 6.4 vs. 1.1 ± 1.0, p=0.001) for groups A, B, and C, respectively.

According to results shown in table 5, the six months treatment period of a monthly ten days course of oral amoxicillin® (25mg/kg/day) were comparable to IM penicillin treatment every 3 weeks regarding recurrence and school absence. The mean ± SD recurrence and school absence were 1.4 ± 1.1, 3.0 ± 2.3, and 1.0 ± 0.8, 2.3 ± 1.6, for the oral amoxicillin and the IM penicillin groups, respectively. However, regarding the tonsillectomy patients group, the mean ± SD recurrence and school absence was significantly decreased to 0.5 ± 0.4 (p = 0.021) and 1.1 ± 1 (p = 0.032) when compared to the oral treatment group. On the other hand, no significant difference was observed between the parenteral therapy group and the tonsillectomy patients group.

Adverse effects

All treatments were well tolerated. As shown in table 6, minor side effects were reported by 20% (6/30) patients in the oral amoxicillin group including; mouth ulcers 13.3% (4/30) and stomach pain 6.7% (2/30). However, 87% (26/30) patients reported discomfort at site of injection In IM penicillin group. There was no significant difference among the treatment groups with respect to the incidence or severity of adverse events. None of the adverse events required hospitalization, stopping the treatment regimen, medical attention, or withdrawal from the trial. There were no serious adverse effects related to tonsillectomy.

Compliance

During the six months treatment period, 96.6% of subjects consumed >95% of their medication in group A. There was no significant difference (p>0.64) between the oral (96.6%), and parenteral (100%) treatment groups

Discussion

Recurrent acute pharyngitis remains a common illness in children and young adults and can lead to serious complications if not treated [31]. Secondary prevention of recurrent pharyngitis is particularly important since even an asymptomatic or an optimally treated throat infection can still trigger recurrence [4].

Recently, the once daily oral amoxicillin has been appreciated to be an attractive and convenient alternative to either the multiply dosed oral or injectable penicillin [25,27] and have been endorsed by the more recently published AHA guidelines as first-¬line therapy [5]. In addition, tonsillectomy has been the most common surgical procedure performed on children suffering from recurrent pharyngitis [32] in the United Kingdom and the United States [29].

Our study was designed to compare the effectiveness and safety of prophylactic treatment of oral amoxicillin, the long-standing recommended therapy of IM BPG, and tonsillectomy in reducing the episodes of recurrent pharyngitis. On admission, a throat swab was simultaneously obtained for standard throat culture from selected patients, in order to illustrate the distribution of the potentially pathogenic microorganisms causing recurrent pharyngitis.

In our study we used recurrence of symptoms not bacterial eradication (as confirmed by throat cultures) as the primary outcome to compare between different studies treatments. Because persistent positive throat cultures with the absence of symptoms could mean nothing but a carrier state [5].

The results illustrated in table 2 showed the significant prevalence of the pathogenic bacterial species of Staphylococcus aureus (17 patients; 34%; p<0.001) compared to other species. This is in harmony with a previous study by Zautner et al who demonstrated that staphylococcus aureus is the major bacterial pathogen causing recurrent pharyngitis and it uses this location to survive the effects of antibiotics and the host immune response [33].

The results of table 3 clearly showed the significant (p=0.003) superiority of breast-fed children in having lower episodes of recurrent pharyngitis compared to non-breast fed ones. Since, the incidence of recurrent pharyngitis has been strongly correlated with limited, immature or even defected immune systems [34,35]. Our results adds further evidence to the importance of breast feeding that was previously reported to enhance the child immune systems and hence decreasing infections [36,37].

Although it has been first debated whether it is worthwhile offering antibiotic for treatment and prevention of acute recurrent pharyngitis since it is simply self-limiting in most cases [5], several studies have confirmed the effectiveness of these prophylactic antibiotic treatment in reducing symptoms, recurrence, socioeconomic burden [38,39] and the risk of complications [22]. Without treatment, pharyngitis may be associated with persistent positive throat cultures for up to 6 weeks in 50% of patients [40].

Apparently, our results in table 4 confirmed the beneficial effect of either the prophylactic treatment with both oral amoxicillin and IM BPG, in significantly reducing recurrences by 89.65%, 89.86% and school absence by 85.21%, 86.16% respectively. This was consistent with a previous study by Sirimanna et al who demonstrated a significant reduction in the number of attacks of pharyngitis experienced by the long acting penicillin treated group, especially those aged 5 to 11, resulting in a drop in the number requiring tonsillectomy [41].

Moreover, several other studies confirmed the beneficial effects of IM penicillin in significantly reducing recurrence, ameliorating symptoms compared to a placebo group [5], reducing the incidence of otitis media, peritonsillar abscess [42], and acute rheumatic fever by more than 80% when compared with no antibiotic treatment [22].

However, so far the preferable therapy whether oral or parenteral is still controversial. Although strong evidence from literature suggests the superiority of parenteral penicillin in decreasing recurrences compared to oral treatment, this evidence has been estimated to be poor [43]. Simply, these studies varied considerably in penicillin doses, and schedules [44-46]. Noteworthy that some of these studies used a different penicillin formulation (potassium penicillin) [44-46], whereas the oral penicillin V used today is more consistently absorbed showing higher blood levels, and has been shown to decrease recurrences compared to benzathine penicillin [47].

Recently, oral amoxicillin has been appreciated and even endorsed by American Heart Association (AHA) guidelines as first-¬line therapy [5]. Several studies have confirmed the equal efficacy of oral amoxicillin to oral penicillin in treating and preventing recurrent pharyngitis [25-27]. Another previous study by Cohen et al showed similarity of efficacy and safety of amoxicillin (50 mg/kg/day) for 6 days and penicillin (45 mg/kg/d three times a day) for 10 days in the treatment of GAS tonsillopharyngitis [48].

Noteworthy, oral amoxicillin is not only a mere convenient alternative to oral penicillin but may be even a superior one due to its expected better compliance with less dosing (once daily dosing Vs. two to three times).

The results of our study showed the comparable safety and effectiveness of both the IM penicillin and the once daily oral amoxicillin therapy in reducing recurrences and school absences.

A previous study by Rimoin et al (2011) found that oral amoxicillin treatment was inferior to IM penicillin treatment in Egyptian children with poor compliance of (30.1%), and of comparable efficacy in Croatian children of good compliance (84.4%), suggesting IM BPG should be preferred where compliance is a major concern [49]. However in our study, compliance was not an issue with treatment regimens, as parents/guardians of children in the amoxicillin group were strongly stressed on the importance of administering the antibiotic at the same time every day for 10 days each month. This highlights the importance of compliance as the major driving force in improving success rates with oral amoxicillin treatment.

Although, long years of experience with IM penicillin have rarely reported severe toxic reactions, the discomfort of intramuscular injections decreased both patient and physician acceptability [19,22] for this dosage form in favor of oral treatment. However, even if the oral therapy seems to be the preferable choice, the major driver of its success remains proper compliance, where several studies have correlated treatment failures to non-adherent patients [49].

Regarding tonsillectomy, our results showed that it decreased recurrence and school absence comparably to the parenteral therapy and more significantly than the oral treatment. This was consistent with a recent Cochrane review that reported that tonsillectomy significantly reduced pharyngitis episodes, especially with more severely affected children [50]. Other

studies have found it to be an effective alternative for both children [29] and adults [30] with a documented history of recurrent episodes of pharyngitis.

Moreover, a study by Koskenkorva et al, showed a significantly lower rate of pharyngitis number of symptomatic days (throat pain, fever, rhinitis, cough), fewer days absence from school or work in the tonsillectomy group than in the control group [51].

Yet, it is still unknown how tonsillectomy should benefit streptococcal pharyngitis, as other pharyngeal lymphoid and soft tissues are often also infected [52,55]. Furthermore, despite the probable beneficial effect of tonsillectomy, it is still a surgical procedure with an associated morbidity that includes possible hospitalization, risks of anesthesia, prolonged throat pain, and financial costs. Several surgical related complications including; throat pain, postoperative nausea and vomiting, delayed feeding, voice changes, hemorrhage, and rarely death have been reported and must be considered [54,55]

Although this strategy of prophylactic treatment of all patients with recurrent pharyngitis might be debated to expose patients to unnecessary side effects and increased antibiotics resistance [56,57], however several studies have found this to be the most cost-effective strategy with the greatest reduction for potential complications and death [58-60]. It has been reported that the health benefits gained from reducing complications and socioeconomic burden much outweighs the minimal risk of antibiotic treatment. Moreover, even the concern for development of antibiotic resistance is not justified since despite the large-scale use of penicillin, to date no resistant strains has yet developed [21], and even the minimum inhibitory concentrations have not changed in >70 years [60]. No doubt, that recurrent pharyngitis is a problem that requires an appropriate prophylactic antibiotic treatment, not only for its possible sequela if untreated but also for its marked global socioeconomic and health care burden. Our study showed that the once daily oral amoxicillin was a safe, effective and convenient alternative to IM penicillin in reducing recurrences and school absence provided that proper compliance is stressed. Thus it is more preferable to avoid the painful and psychic impact on children from IM PBG unless compliance is an issue. Moreover, tonsillectomy is a suitable alternative to antimicrobial treatment; however it should be reserved for severe cases not responding to treatment due to its related morbidity and possible complications.

Conflict of interests

The authors declare that they have no conflict of interest and no competing financial interests.

Acknowledgments

Special thanks to staff of Fayoum University Teaching Hospital for their support and help.

References

1. Koskenkorva T, Koivunen P, Koskela M, Niemela O, Kristo A, Alho OP. Short-term outcomes of tonsillectomy in adult patients with recurrent pharyngitis: a randomized controlled trial. CMAJ. 2013;185(8):331-6.
2. Sarrell EM, Giveon SM. Streptococcal pharyngitis: a prospective study of compliance and complications. ISRN Pediatrics. 2012;2012:796389.
3. Pfoh E, Wessels M, Goldmann D, Lee G. Burden and economic cost of group A streptococcal pharyngitis. Pediatrics. 2008;121:229-34.
4. Manyemba J and BMM. Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever--a systematic review. SAMJ. 2003;93(3):212–8.
5. Wessels MR. Streptococcal pharyngitis. NEJM. 2011;364(7):648-55.
6. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86(5):408-16.
7. Wardlaw T, Salama P, Johansson E, Mason E. Pneumonia:the leading killer of children,. Lancet. 2006;368:1048-50.
8. Kowalska M, Kowalska H, Zawadzka-Glos L, Debska M, Szersszen E, Chmielik M, Wąsik M. Dysfunction of peripheral blood granulocyte oxidative metabolism in children with recurrent upper respiratory tract infections. Int J Pediatr Otorhinolaryngol. 2003;67:365-71.
9. Angelo S, Massimo D, Barbara C, Francesco, Luca G, Barbara J, Renzo M. Sulphurous water inhalations in the prophylaxis of recurrent upper respiratory tract infections. Int J Pediatr Otorhinolaryngol. 2008;72:1717-22.
10. Klug T, Henriksen J, Fuursted K, Ovesen T. Similar recovery rates of fusobacterium necrophorum from recurrently infected and non-infected tonsils. Dan Med Bull. 2011;58:A4295.
11. Gul M, Okur E, Ciragil P, Yildirim I, Aral M, Kilic MA. The comparison of tonsillar surface and core cultures in recurrent tonsillitis. Am J Otolaryngol. 2007;28:173-6.
12. Stjernquist-Desatnik A, Prellner K, Schalen C. Colonization by Haemophilus influenzae and group A streptococci in recurrent acute tonsillitis and in tonsillar hypertrophy. Am J Otolaryngol. 1990;109:314-31.
13. Benedict F, Massell M, Larry M. Prevention of rheumatic fever. JAMA. 1972;221(4):410-11.

14. Gerber MA., Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, Taubert A. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease. Circulation. 2009;119(11):1541-51.
15. Mahakit P, Vicente JG, Butt DI, Angeli G, Bansal S, Zambrano D. Oral clindamycin 300 mg BID compared with oral amoxicillin/clavulanic acid 1 g BID in the outpatient treatment of acute recurrent pharyngotonsillitis caused by group a beta-hemolytic streptococci: an international multicenter randomized investigator-blinded, prospective trial in patients between the ages of 12 and 60 years. Clin Ther. 2006;28(1):99-109.
16. Diaz, MC, Symons N, Ramundo ML, Christopher NC. Effect of a standardized pharyngitis treatment protocol on use of antibiotics in a pediatric emergency department. Arch Pediatr Adolesc Med. 2004;158(10):977-81.
17. Gerber MA. Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am. 2005;52(3):729-4.
18. Armengol CE, Hendley JO. Occurrence of group A beta-hemolytic streptococcal pharyngitis in the four months after treatment of an index episode with amoxicillin once-daily or twice-daily or with cephalexin. Pediatr Infect Dis J. 2012;31(11):1124-7.
19. Shulman ST, Bisno AL, Clegg HW, Gerber MA, Kaplan EL. Clinical practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. 2012 update by the Infectious Disease Society of America; 2012. Clin Infect Dis. 2012;55(10):e86–102.
20. Schwartz B, Marcy M, Phillips W, Gerber M, Dowell S. Pharyngitis principles of judicious use of antimicrobial agents. Pediatrics. 1998;101:171-4.
21. Van Driel ML, De Sutter IM, Keber N, Habraken H, Christiaens T. Different antibiotics treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev. 2013;4 :1-73.
22. Robertson K, Volmink J, Mayosi B. Antibiotics for the primary prevention of acute rheumatic fever: a meta- analysis. BMC Cardiovasc Disord. 2005;5(1):11.
23. Baltimore R. Re-evaluation of antibiotic treatment of strep- tococcal pharyngitis. Curr Opin Pediatr. 2010;22:77–82.
24. Gerber MA and RRT. New approaches to the treatment of group A streptococcal pharyngitis. Curr Opin Pediatr. 2001;13(1):51-5.
25. Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. BMJ. 1993;306:1170-2.
26. Feder HMJ, Gerber MA, Randolph MF, Stelmach PS, Kaplan EL. Once-daily therapy for streptococcal pharyngitis with amoxicillin. Paediatrics. 1999;103:47-51.
27. Clegg HW, Ryan AG, Dallas SD, Al. E. Treatment of streptococcal pharyngitis with once-daily compared with twice-daily amoxicillin: a noninferiority trial. Pediatr Infect Dis J. 2006;25:761–7.

28. Lennon DR, Farrell E, Martin DR, Stewart JM. Once-daily amoxicillin versus twice-daily Penicillin V in group a {beta}- hemolytic Streprococcus pharyngitis. Arch Dis Child.. 2008;93(6):474-8.
29. Baugh RF, Archer SM, Mitchell RB, Richard MR, Amin R, Burns JJ, David H. Clinical practice guideline: tonsillectomy in children. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011;144(1):1–30. http://www.ncbi.nlm.nih.gov/pubmed/21493257. abstract access date 11.08.2013.
30. Burton MJ, Glasziou PP. Tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. Cochrane Database Syst Rev. 2009;1.
31. Mora R, Salami A, Mora F, Cordone MP, Ottoboni S, Passali G.C, Barbieri M. Efficacy of cefpodoxime in the prophylaxis of recurrent pharyngotonsillitis. Int J Pediatr Otorhinolaryngol. 2003;67(1):225-8.
32. Khan I, Ahmad S, Chawala JA. Original article comparison of FNA vs surface swab culture in isolating core flora in recurrent tonsillitis. J Ayub Med Coll Abbottabad. 2012;24:157-8.
33. Zautner AE, Krause M, Stropahl G, Holtfreter S, Frickman H, Maletzki C, Kreikemeyer B, Pau H.W, Podbielski A. Intracellular persisting Staphylococcus aureus is the major pathogen in recurrent tonsillitis. journal of public library of science one. 2010;5(3):e9452.
34. Schaad UB. OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review. World J Pediatr.2010;6:5–12.
35. David J, Rosen F. Deficiencies in immunoglobulins and cell- mediated immunity (CD-Rom). Chapter IX, Scientific Am Med ,New York, US, SAM-CD.; 2000.
36. Pickering LK, Granoff DM, Erickson, JR, Masor ML, Cordle CT, Schaller JP , Winship TR, Paule CL, Hilty DM. Modulation ofthe immune system by human milk and infant formula containing nucleotides. Pediatrics. 1998;101:242-9.
37. Stuebe A. The risks of not breastfeeding for mothers and infants. Reviews in obstetrics and gynecology. 2009;2(4):222-31.
38. Rober M, Bass J, Michels G. Streptococcal pharyngitis: placebocon rolled double blind evaluation of clinical response to penicillin therapy. JAMA . 1985;253:1271–74.
39. Randolph MF, Gerber MA, DeMeo KK, Wright L. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. J Pediatr. 1985;106:870–5.
40. Catanzaro FJ, Stetson CA, Morris, AJ, Chamovıtz R, Rammelkamp CH Jr, Stolzer BL, Perry WD. The role of the streptococcus in the pathogenesis of rheumatic fever. Am J Med. 1954;17:749–56.
41. Sirimanna KS, Madden GJ, Miles SM. The use of long-acting penicillin in the prophylaxis of recurrent tonsillitis. J Otolaryngol. 1990;19(5):343–344.
42. Del Mar C, Glasziou P, Spinks A. Antibiotics for sore throat. Cochrane Database Syst Rev. 2006;4:CD000023.

43. Manyemba J, Mayosi BM. Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever--a systematic review. SAMJ 2003;93(3):212–8.

44. Feinstein AR, Wood HF, Epsteın JA, Taranta A, Sımpson R, Tursky E. Acontrolled study of three methods of prophylaxis against streptococcal infection in a population of rheumatic children. NEJM. 1959;260:697–701.

45. Feinstein A, Spagnuolo M, Jonas S, Kloth H, Tursky E, Levitt M. Prophylaxis of recurrentrheumatic fever. Therapeutic-continuous oral penicillin vs monthly injections. JAMA. 1968;206:565–8.

46. Feinstein A. Prophylaxis of recurrent rheumatic fever. Ineffectiveness of intermittent therapeutic oral penicillin. JAMA. 1965;191:451–4.

47. Phair J, Carleston J, Weihl C. Penicillin phenoxymethyl. Use in rheumatic fever prophylaxis. Am J of Diseases of Children. 1973;126:48–50.

48. Cohen, R, Levy C, Dolit C, De La Rocque F, Boucherat M, Fitoussi F, Language J, Bingen E. Six-day amoxicillin vs. ten-day penicillin V therapy for group A streptococcal tonsillopharyngitis. Pediatr Infect Dis J. 1996;15(8):678–82.

49. Rimoin AW, Hoff NA, Walker CLF, Hamza H.S, Vince A, Rahman N.A, Andrasevic S, Emam S, Vukelic D, Elminawi N, Ghafar H.A, da Cunga ALA, Qazi S, Gardovska D, Steinhoff M.C Treatment of Streptococcal Pharyngitis With Once-Daily Amoxicillin Versus Intramuscular Benzathine Penicillin G in Low-Resource Settings: A Randomized Controlled Trial. Clin Pediatr. 2011;50(6):535 –42.

50. Martin J, Burton and PPG. "Tonsillectomy or adenotonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis (Review)." Cochrane Database Syst Rev. 2009;1:1–34.

51. Koskenkorva T, Koivunen P, Koskela M, Niemela O, Kristo A, Alho O-P. Short-term outcomes of tonsillectomy in adult patients.CMAJ. 2013;185(8):331–6.

52. Burton MJ, Towler B GP. Tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis. Cochrane Database Syst Rev. 2000;2:CD001802.

53. Feinstein A, Levitt M. The role of tonsils in predisposing to streptococcal infections and recurrences of rheumatic fever. N Engl J Med. 1970;282:5–91.

54. Blakley BW, Magit AE. The role of tonsillectomy in reducing recurrent pharyngitis. Otolaryngol Head Neck Surg. 2009;140:291–7.

55. Alho OP, Koivunen P, Penna T, Teppo H, Koskela M, Luotonen J. Tonsillectomy versus watchful waiting in recurrent streptococcal pharyngitis in adults: randomised controlled trial. BMJ. 2007:334:939.

56. Report of the Committee on Infectious Disease. Group A Streptococcal infections. In: Pickering L, ed. IL: AAP . 29th Editi. Elk Grove Village. 2012:668–80.

57. Dajani A, Taubert K, Ferrieri P, Peter G, Shulman S. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Hear. Pediatrics. 1995;96:758–64.

58. Lieu T, Fleisher G, Schwartz J. Cost-effectiveness of rapid latex agglutination testing and throat culture for streptococcal pharyngitis. Pediatrics. 1990;85:246–56.

59. Webb K. Does culture confirmation of high-sensitivity rapid streptococcal tests make sense? A medical decision analysis. Pediatrics. 1998;101:E2.

60. Irlam, J, Mayosi BM, Engel M, Gaziano TA. Primary prevention of acute rheumatic fever and rheumatic heart disease with penicillin in South African children with pharyngitis: a cost effectiveness analysis. Circ Cardiovasc Qual Outcome. 2013;6(3):343-51.