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OUTCOME AFTER TONSILLECTOMY IN ADULT PATIENTS WITH RECURRENT PHARYNGITIS

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OUTCOME AFTER TONSILLECTOMY IN ADULT PATIENTS WITH RECURRENT PHARYNGITIS

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Supervised by
Professor Olli-Pekka Alho
Docent Petri Koivunen

Reviewed by
Docent Juha Seppä
Docent Petri Mattila

Opponent
Docent Karin Blomgren

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University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Recurrent pharyngitis causes doctor visits, antibiotics use and absences from school or work and thus worsens patients' quality of life (QOL). Even though tonsillectomy is often performed for recurrent pharyngitis, there is limited evidence of the tonsillectomy benefit concerning both researcher- and patient-recorded outcomes.

The intent of this work was to find out if tonsillectomy reduces numbers of pharyngitis episodes or symptom days, if tonsillectomy improves patients' QOL and if there are any clinical factors predicting QOL benefit after tonsillectomy.

Seventy adult patients with recurrent streptococcal pharyngitis (2001–2005) and 86 patients with recurrent pharyngitis of any origin (2007–2010) were enrolled for two randomised controlled trials.

Patients with recurrent pharyngitis of any origin were followed up either before (control group, n=40) or after (tonsillectomy group, n=46) tonsillectomy. At five months of follow-up, 17 (43%) patients in the control group and 2 (4%) patients in the tonsillectomy group consulted a physician for pharyngitis. Thirty-two (80%) patients in the control group and 18 (39%) patients in the tonsillectomy group experienced any kind of pharyngitis episode. Only one episode was considered severe. The numbers of days with throat pain and fever were significantly lower in the tonsillectomy group.

QOL of 142 responders measured by Glasgow Benefit Inventory (GBI) six months after tonsillectomy showed improvement: median GBI total score was +27. However, GBI total scores varied considerably between the patients (range −19 to +69). Only one patient reported declined QOL. The number of prior pharyngitis episodes, frequent throat pain, untreated dental caries and chronically infected tonsils were the best clinical factors predicting QOL improvement. The precision of these predictions was still quite low.

The results of this work suggest that tonsillectomy reduces numbers of acute pharyngitis episodes and symptoms. Although most of the episodes are not severe, tonsillectomy still generally improves patients' QOL. The distribution of QOL benefit is broad, however. Throat-related morbidity before tonsillectomy is the only clinical factor that was associated with patient satisfaction.

Keywords: adult, pharyngitis, quality of life, streptococcal infections, tonsillectomy, treatment outcome

Koskenkorva, Timo, Nielurisaleikkauksen vaikutukset toistuvia nielutulehduksia sairastavilla aikuisilla.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

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Tiivistelmä

Toistuvat nielutulehdukset aiheuttavat paljon lääkärikäyntejä, antibioottihoitoja sekä poissaoloja töistä tai opinnoista ja huonontavat potilaiden elämänlaatua. Toistuvien nielutulehdusten vuoksi päädytään usein nielurisaleikkaukseen, vaikka tutkimusnäyttö leikkauksen hyödystä on vähäistä.

Tämän väitöskirjatyön tavoitteena oli tutkia, vähentääkö nielurisaleikkaus nielutulehdusten määrää tai oireita sekä selvittää leikkauksenjälkeistä elämänlaatua ja siihen liittyviä ennustekijöitä.

Tutkimusaineisto koostui kahta eri satunnaistettua kliinistä koetta varten rekrytoiduista potilaista: 70 potilasta, joiden toistuvien nielutulehdusten aiheuttaja oli A-ryhmän streptokokki (2001–2005) ja 86 potilasta, joiden toistuvien nielutulehdusten etiologialle ei asetettu vaatimuksia (2007–2010).

Potilaat, joilla nielutulehdusten etiologia oli avoin, satunnaistettiin kahteen ryhmään: kontrolliryhmää (n=40) seurattiin ennen nielurisaleikkausta ja leikkausryhmää (n=46) sen jälkeen, molempia 5 kuukauden ajan. Seurannassa 17 (43 %) kontrolliryhmän potilasta ja 2 (4 %) leikkausryhmän potilasta hakeutui lääkäriin nielutulehduksen vuoksi. Kontrolliryhmän potilaista 32 (80 %) ja leikkausryhmän potilaista 18 (39 %) sairasti nielutulehduksen vähintään kerran. Vain yksi episodi luokiteltiin vaikeaksi. Nielukipu- ja kuumepäiviä oli merkittävästi vähemmän leikkausryhmässä.

Nielurisaleikkauksen vaikutusta elämänlaatuun tutkittiin Glasgow Benefit Inventory (GBI) -kyselyllä kuusi kuukautta leikkauksen jälkeen. Yhteensä 142 potilasta vastasi kyselyyn. GBI:n mediaanitulos +27 osoitti leikkauksen parantavan elämänlaatua. GBI-tulokset kuitenkin vaihtelivat huomattavasti potilaiden välillä (−19 – +67), vaikkakin vain yksi potilas raportoi elämänlaatunsa heikentyneen.

Aiempien nielutulehdusten määrä, usein toistuva nielukipu, hoitamaton karies ja kroonisesti tulehtuneet nielurisat ennustivat parhaiten potilastyytyväisyyttä leikkauksen jälkeen, mutta näidenkin tekijöiden ennustearvo oli melko heikko.

Tulosten perusteella nielurisaleikkaus vähentää akuutteja nielutulehduksia sekä oirepäiviä. Vaikka sairastamisjaksot ovat harvoin vaikeaoireisia, leikkaus parantaa useimmiten elämänlaatua, mutta hyödyn määrä vaihtelee merkittävästi potilaiden välillä. Ainoastaan leikkausta edeltävä nielun oireilun määrä ennustaa leikkaushyötyä jossain määrin.

Asiasanat: aikuinen, elämänlaatu, hoitovaste, nielurisaleikkaus, nielutulehdus, streptokokkitulehdukset

To my children, Maisa, Aatu and Milja

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Oulu, March 2015 Timo Koskenkorva

Abbreviations

AIC_c	Akaike information criterion
ARS	acute retroviral syndrome
CI	confidence interval
CMV	cytomegalovirus
CRP	C-reactive protein
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ENT	ear, nose and throat
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
FDA	US Food and Drug Administration
GAS	group A streptococcus
GBI	Glasgow Benefit Inventory
HIV1	human immunodeficiency virus 1
HR	hazard ratio
HSV	herpes simplex virus
IQR	interquartile range
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
non-GAS	non-group A streptococci
OECD	Organisation for Economic Cooperation and Development
OR	odds ratio
PCT	procalcitonin
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PFAPA	periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PONV	postoperative nausea and vomiting
PROM	patient-recorded outcome measure
QOL	quality of life
RADT	rapid antigen detection test
RCT	randomised controlled trial
RR	risk ratio
SD	standard deviation
TAHSI	Tonsil and Adenoid Health Status Instrument
U.K.	United Kingdom
U.S.	United States

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Koskenkorva T, Koivunen P, Penna T, Teppo H, Alho OP (2009). Factors affecting quality-of-life impact of adult tonsillectomy. J Laryngol Otol 123(9):1010-4.

II Koskenkorva T, Koivunen P, Koskela M, Niemela O, Kristo A, Alho OP (2013). Short-term outcomes of tonsillectomy in adult patients with recurrent pharyngitis: a randomized controlled trial. CMAJ 185(8):E331-6.

III Koskenkorva T, Koivunen P, Läärä E, Alho OP (2014). Predictive factors for quality of life after tonsillectomy among adults with recurrent pharyngitis: a prospective cohort study. Clin Otolaryngol 39(4):216-23.

IV Koskenkorva T, Koivunen P, Alho OP (2015). Predictive factors for medical consultation for sore throat in adults with recurrent pharyngitis. Manuscript.

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1 Introduction

A sore throat often accompanies normal flu caused by viral infection. Sore throat symptoms with or without other symptoms of respiratory infection are also one of the most common reasons for seeking medical attention (Linder & Stafford 2001). Naturally, even greater number of people never go to the doctor because of sore throat symptoms (Little & Williamson 1994). Acute pharyngitis is a sudden inflammation or infection of the pharynx, usually causing a sore throat and it is most commonly caused by upper respiratory tract infection (Mosby 2008). In acute pharyngitis, pharyngeal lymphatic tissue, including the palatine tonsils, is partially or entirely infected. Acute tonsillitis, on the other hand, is a sudden infection or inflammation of one or both of the palatine tonsils, associated with catarrhal exudate over the tonsil (Mosby 2008). Therefore, acute tonsillitis can be considered as a subgroup of acute pharyngitis. If the pharyngeal inflammation or infection includes tonsillitis, it may also be called pharyngotonsillitis (Rafei & Lichenstein 2006). These terms are somewhat overlapping and are often used synonymously, but in this present work the term acute pharyngitis is used to describe all acute pharyngeal infections that cause a sore throat, also including acute tonsillitis. This classification is practical in the present work since we have studied patients' acute pharyngeal infections both before and after the removal of the palatine tonsils.

Pharyngitis is a significant economic burden, as it causes high numbers of visits to a doctor, absences from school or work and antibiotic treatments. Total annual expenditures for adult pharyngitis in the United States (U.S.) are estimated to be $372 million (Salkind & Wright 2008). Another study estimated that the total cost of group A streptococcal pharyngitis among children in the U.S. ranges from $224 to $539 million per year (Pfoh *et al.* 2008). Annual self-reported costs per patient with recurrent or chronic pharyngitis before tonsillectomy due to medical appointments, sick leaves and medications were estimated to amount to €3644 in Finland (Wiksten *et al.* 2013). It is also notable that pharyngitis—especially recurrent or chronic—reduces patients' quality of life (Wiksten *et al.* 2013).

There are various recommendations for treating a single pharyngitis episode (Chiappini *et al.* 2011). Basically, a physician has to decide whether a patient needs antibiotic treatment or not. Depending on the treatment guidelines followed, this decision is mainly based on symptoms, verification of group A streptococcus (GAS) as a causative pathogen or both. As a result, the information recorded about a single pharyngitis episode usually includes symptoms, clinical findings as well as microbial findings and some blood test results if testing is carried out. However, according to

previous literature, we don't know if these data are of value in making a decision about tonsillectomy for recurrent pharyngitis or not. In this thesis work, factors that would predict the benefit of tonsillectomy in adults with recurrent pharyngitis were sought broadly.

Ear, nose and throat (ENT) specialists usually meet pharyngitis patients who have namely recurrent or chronic pharyngitis, which traditionally have been the most common indications for adult tonsillectomy. There is a deficiency of data in current literature on the benefit of tonsillectomy, especially in adults with recurrent pharyngitis, in terms of both the amount of postoperative throat infections and symptoms as well as postoperative quality of life (Alakärppä & Alho 2012, Burton & Glasziou 2009). The intent of this work was to investigate if tonsillectomy is a beneficial intervention for adult patients with recurrent pharyngitis episodes.

2 Review of the literature

2.1 Pharyngeal lymphatic tissue

A circular band of lymphatic tissue, known as Waldeyer's ring, guards the openings into the respiratory and digestive tracts. The anterior part of this ring is formed by the lingual tonsil, which consists of submucous lymphoid tissue located on the posterior part of the tongue. The lateral portions of the Waldeyer's ring consist of the palatine tonsils and lymphoid tissue in the proximity of the auditory tubes. The pharyngeal tonsil on the posterior part of the nasopharynx completes the ring in the back. Smaller amounts of lymphoid tissue are also found between these main tonsillar regions. (Hellings *et al.* 2000)

Waldeyer's ring tissue serves as a defence against infection and plays an important role in the development of the immune system, comprising the first organs in the lymphatic system that analyse and react to airborne and alimentary antigenic stimulation (Bogaerts *et al.* 2012). The palatine and pharyngeal tonsils contain different lymphoid compartments, which all participate in the immune response. The generation of B cells in the germinal centres is the most essential function (Brandtzaeg 2010).

2.2 Occurrence of acute pharyngitis

A sore throat is one of the most common symptoms and acute pharyngitis is one of the most common diseases for which patients visit primary care physicians (Linder & Stafford 2001). There are only a few studies about the prevalence and incidence of acute pharyngitis.

In Australia, 202 randomly selected families were followed up for 16 months. Throat cultures were taken whenever the participants had throat symptoms and also routinely every 3–4 months. In children, the annual incidences of acute pharyngitis, group A streptococcal swab-positive pharyngitis and serologically confirmed group A streptococcal pharyngitis were 33%, 13% and 8%, respectively. The corresponding incidences in adults were 14%, 5% and 3%, respectively. The incidence of acute pharyngitis varied during the year, being higher in cold seasons. (Danchin *et al.* 2007)

According to a survey that assessed the incidence of ear, nose and throat symptoms experienced by people living in Scotland, 31% of respondents had experienced at least one episode of severe sore throat or pharyngitis during the

previous year (Hannaford *et al.* 2005). Another state-wide household survey in Australia collected data on non-specific health symptoms and found the incidence of sore throat to be 22% (Heyworth & McCaul 2001). Upper respiratory infections, including acute pharyngitis, were responsible for 200 visits to a physician per 1000 persons annually in the U.S., and according to the U.S. National Ambulatory Medical Care Survey, there were an estimated 6.7 million annual visits to a physician by adults with a sore throat between 1989 and 1999 in the United States (Armstrong & Pinner 1999, Linder & Stafford 2001). A sore throat is estimated to account for approximately nine consultations for every 100 patients in general practice in the United Kingdom (U.K.) (Gulliford *et al*. 2009).

2.2.1 Normal microbial flora of the oropharynx

There are relatively few studies on the normal microbial flora of the oropharynx of healthy individuals. Hable *et al*. (1971) published a much-cited study more than 40 years ago examining the pharyngeal flora of two groups of children: one group with acute upper respiratory tract infections and another group of healthy controls. The bacterial findings of the study are summarised in Table 1. According to the study, only group A streptococcus (GAS) was isolated more frequently from the sick than from the healthy children. In other words, it is notable that most of the bacteria that cause acute pharyngitis symptoms were also present in the pharyngeal region during infection-free periods. (Hable *et al.* 1971) Similar results showing that patients with or without tonsillar disease have similar microbial flora on the tonsillar surface have been published by Van Staaji *et al*. (2003) and by Stjernkvist-Desatnik & Holst (1999). The bacteria detected in these two more recent studies are mainly similar to those in the study by Hable *et al* (1971).

Table 1. Bacteria isolated from two groups of children. Modified table presenting the results of the study by Hable *et al*. (1971).

Bacteria	Ill children		Controls	
	No.	%	No.	%
Streptococcus pyogenes (group A, beta-haemolytic)	188	38.4	13	2.7
Streptococcus species (beta-haemolytic, not group A)	33	6.7	31	6.3
Streptococcus species (group D)	38	7.8	40	8.2
Streptococci, viridans group	472	96.3	466	95.1
Haemophilus influenza	47	9.6	52	10.6
Haemophilus parainfluenzae	66	13.5	61	12.4
Haemophilus parahemolyticus	76	15.5	97	19.8
Haemophilus haemolyticus	3	0.6	3	0.6
Staphylococcus aureus	57	11.6	109	22.2
Staphylococcus epidermidis	375	76.5	340	69.4
Diplococcus pneumonia	39	8.0	32	6.5
Neisseria species	478	97.5	460	93.9
Corynebacterium species	39	8.0	36	7.4
Klebsiella species	5	1.0	3	0.6
Enterobacter species	5	1.0	3	0.6
Escherichia coli	14	2.9	17	3.5
Pseudomonas aeruginosa	4	0.8	2	0.4
Herellea vaginicola	3	0.6	0	0

490 children in both groups

2.2.2 Viral pharyngitis

Viruses are the most common cause of pharyngitis in both adult and pediatric populations. The viral etiology of acute pharyngitis varies according to the time of the year, location and local epidemiological situation.(Bisno 2001) Viral findings and their comparison between studies also critically depend on the viral detection methods. Furthermore, reported viral etiology depends on the definition and diagnostic criteria of pharyngitis. Since most viruses cause mainly common cold symptoms and represent non-specific sore throat symptoms, it may be hard to determine between viruses that cause only flu and viruses that cause flu with pharyngitis. These reasons may alter the proportions of causative viruses between different reports. Moreover, viral testing is usually not warranted to identify the specific viral etiology of pharyngitis in clinical practice.

According to the Finnish national guideline for acute pharyngitis treatment, adenovirus is the most common virus and the second most common overall microbe after GAS that causes acute pharyngitis, being most common in children under the age of five years. Epstein-Barr virus (EBV) is estimated to cause 2–9% of acute pharyngitis episodes. The Finnish guideline classifies other common viruses like rhinoviruses into pathogens that mostly cause other upper respiratory infections, and mentions them only as differential diagnostic pathogens of pharyngitis. (Sore throat: Current Care Guidelines 2013)

However, according to some foreign studies, rhinoviruses are classified into pathogens behind pharyngitis. Rhinoviruses are estimated to cause 20% of acute pharyngitis episodes in patients of all ages. Some other common viruses are estimated to cause acute pharyngitis as follows: coronavirus 5%, adenovirus 5%, herpes simplex virus (types 1 and 2) 4%, parainfluenza virus 2% and influenza virus (types A and B) 2% of all episodes. Other viruses cause less than 1% of acute pharyngitis episodes. (Bourbeau 2003, Carroll & Reimer 1996) The proportions presented by Gwaltney & Bisno (2000) are summarised in Table 2.

Some viruses produce distinctive clinical features and syndromes. Adenovirus is a common cause of self-limited childhood respiratory tract infections but is often more aggressive among adult patients and may be accompanied by a fever, cervical lymphadenopathy and conjunctivitis, causing the classic syndrome of pharyngoconjunctival fever (Hurt & Tammaro 2007).

Infectious mononucleosis is caused by Epstein-Barr virus. This disease is characterised by severe throat pain, exudative enlarged tonsils, erythematous pharynx, high intermittent fever and lymphadenopathy. (Luzuriaga & Sullivan 2010) In addition to the most evident cervical lymphadenopathy, also the axillary and inguinal lymph nodes are frequently enlarged, 50% of patients have splenomegaly, 10% to 15% have hepatomegaly and 5% have jaundice (Bourbeau 2003, Hurt & Tammaro 2007). Adolescents usually have the most clinically apparent cases. After an episode of mononucleosis, patients achieve immunity and this infection does not recur (Bisno 2001, Ebell 2004). Approximately 10% of mononucleosis-like patients are not infected with EBV and many of these patients have their symptoms attributed to cytomegalovirus (CMV) infection (Bravender 2010).

Acute retroviral syndrome (ARS) is a manifestation of primary infection with human immunodeficiency virus 1 (HIV1). After the incubation period—normally lasting three to six weeks—90% of patients develop symptoms including a fever, non-exudative pharyngitis, lymphadenopathy and systemic symptoms such as arthralgia, myalgia, lethargy and maculopapular rash (Hurt & Tammaro 2007). Coxsackie

viruses are the most frequent causes of hand-foot-and-mouth disease and herpangina (Bourbeau 2003). Primary infection with herpes simplex virus (HSV) may be indistinguishable from infections due to other viruses or bacteria, but sometimes they produce vesicles and shallow ulcers on the palate and cervical lymphadenopathy may continue for several weeks (Bourbeau 2003, Hurt & Tammaro 2007).

2.2.3 Bacterial pharyngitis

Bacteria that cause acute pharyngitis according to Gwaltney & Bisno (2000) are shown in Table 2. However, the reported bacterial etiology of acute pharyngitis varies between reports, depending on the time of year, location, local epidemiological situation and definition and diagnostic criteria of acute pharyngitis (Bisno 2001, Smeesters *et al.* 2006).

Table 2. Microbial causes of acute pharyngitis. Modified table presenting findings by Gwaltney & Bisno (2000).

Pathogen	Estimated percentage of cases
Viral	
Rhinovirus	20
Coronavirus	≥5
Adenovirus	5
Herpes simplex virus	4
Parainfluenza virus	2
Influenza virus	2
Coxsackie virus A	<1
Epstein-Barr virus	<1
Cytomegalovirus	<1
HIV type 1	<1
Bacterial	
Group A beta-haemolytic streptococci	15–30
Group C beta-haemolytic streptococci	5
Neisseria gonorrhoeae	<1
Corynebacterium diphtheria	<1
Arcanobacterium haemolyticum	<1
Mycoplasma pneumonia	<1
Chlamydia pneumonia	not determined

The list is not exhaustive. Estimated percentage of pharyngitis cases due to the indicated organism in persons of all ages

Group A streptococcus (GAS) is the most common bacterium causing acute pharyngitis, being more frequent among children than adults. It is uncommon with children under three years of age. The clinical features of GAS pharyngitis are severe throat pain, exudative and enlarged tonsils and cervical lymphadenopathy. These symptoms may be accompanied by varying non-specific symptoms like sneezing, runny nose, headache, cough, fatigue, body aches, chills and fever. (Bourbeau 2003, Komaroff *et al.* 1986).

There are many studies concerning the proportion of pharyngitis episodes caused by GAS, namely in children, and this percentage has usually been reported as 15–30% (Linder & Stafford 2001). According to a recent meta-analysis that includes 29 studies, the proportion of GAS behind a pharyngitis episode among children under 18 years of age presenting with a sore throat was 37% (95% confidence interval (CI): 32% to 43%), furthermore being 24% (95% CI: 21% to 26%) in children under five years of age. The prevalence of GAS carriage among children with no signs or symptoms of pharyngitis was 12% (95% CI: 9% to 14%). However, there is significant heterogeneity between studies reporting the proportion of GAS among children with a sore throat. (Shaikh *et al.* 2010)

The proportion of GAS behind pharyngitis episodes in adults is somewhat lower. According to most studies, GAS is reported to cause 5–23% of pharyngitis symptoms in adults (Al-Charrakh *et al.* 2011, Batty & Wren 2005, Dagnelie *et al.* 1993, Fine *et al.* 2012, Komaroff *et al.* 1986, Linder & Stafford 2001).

The role of non-group A streptococci (non-GAS) as pathogens for symptomatic acute pharyngitis is controversial. There is limited and controversial evidence in the literature on whether these bacteria are true pathogens causing acute pharyngitis episodes or not. Since non-GAS are often commensals of the upper respiratory tract, it is quite difficult to differentiate colonisation from infection. (Tiemstra & Miranda 2009) In their study, Hayden *et al*. (1989) compared children with acute pharyngitis symptoms with asymptomatic controls and found that non-GAS were isolated at similar frequencies from the ill and control children (17% vs 21%, respectively), whereas GAS was detected significantly more often among the ill children than among the controls (39% vs 16%, respectively). However, some studies suggest that streptococci C and G may cause pharyngitis that mimics GAS pharyngitis (Bisno 2001, Fretzayas *et al.* 2009), and according to some studies group C and G streptococci are estimated to cause approximately 5–14% and 4–9% of pharyngitis episodes, respectively (Al-Charrakh *et al.* 2011, Bourbeau 2003, Dagnelie *et al.* 1993, Little *et al.* 2012, Turner *et al.* 1997). In clinical practice in Finland, however, non-GAS infections are not routinely screened during a single pharyngitis episode,

epidemics being exceptions (Sore throat: Current Care Guidelines 2013). Other types of streptococci are not often associated with pharyngitis (Bisno 2001, Little *et al.* 2012).

In their study, Batty & Wren (2005) found that among throat swabs cultured for acute sore throat symptoms, 11% were positive for GAS, 1% were positive for streptococcus group C, 2% were positive for streptococcus group G and 10% were positive for Fucobacterium necrophorum. They suggest that Fucobacterium necrophorum may be as significant a cause of pharyngitis as GAS. (Batty & Wren 2005) Some other recent studies propose that Haemophilus influenzae and Staphylococcus aureus might be more common findings in pharyngeal cultures among symptomatic persons compared with asymptomatic carriers, suggesting that contrary to earlier knowledge, these bacteria may act as significant etiological agents that also cause acute pharyngitis, and they should be covered if antimicrobial therapy is used (Gul *et al.* 2007, Gunnarsson *et al.* 2001, Hotomi *et al.* 2010, Jeong *et al.* 2007, van der Veen *et al.* 2006). Although some researchers propose that some bacteria other than streptococci may act as causative pathogens behind pharyngitis episodes, these bacteria are still not routinely screened in clinical practice in Finland (Sore throat: Current Care Guidelines 2013).

Other bacteria that are traditionally reported to be responsible for less than 1% of acute pharyngitis episodes include Neisseria gonorrhoeae, Corynebacterium dipthteriae, Arcanobacterium haemolyticum, Clamydia pneumonia and Mycoplasma pneumoniae (Bourbeau 2003). Arcanobacterium haemolyticum, formerly known as Corynebacterium haemolyticum, causes pharyngitis particularly in teens and young adults and has been associated with scarlatiniform rash (Miller *et al.* 1986). Colonisation of the pharynx with Neisseria gonorrhoeae is usually asymptomatic, but clinically apparent pharyngitis may develop, and pharyngeal colonisation may be associated with disseminated disease (Bisno 2001, Brown *et al.* 1989). Pharyngeal diphtheria caused by Corynebacterium dipthteriae is nowadays extremely rare in Western countries; it occurs primarily among poorly immunised members of socioeconomically disadvantaged groups. The most evident finding is a greyish brown diphtheritic pseudomembrane, which may involve one or both tonsils or may extend widely to involve the nares, uvula, soft palate, pharynx, larynx and tracheobronchial tree, sometimes causing life-threatening respiratory obstruction. Soft-tissue oedema and prominent cervical and submental adenopathy may create a bull-neck appearance. The potent toxin elaborated by Corynebacterium diphtheriae may produce cardiac toxicity and neurotoxicity. (Adler *et al.* 2013).

According to current knowledge, Chlamydia pneumoniae and Mycoplasma pneumoniae are rarely the cause of simple pharyngitis (Bourbeau 2003).

2.2.4 Rare causes of pharyngitis

Toxoplasmosis is the main protozoal cause of acute pharyngitis. Immunocompetent patients with primary Toxoplasma gondii infection are often asymptomatic, but pharyngitis, non-tender cervical or occipital lymphadenopathy, maculopapular rashes, and hepatosplenomegaly can also occur. (Montoya & Liesenfeld 2004) Fungi, for example Candidas, can cause pharyngitis in immunocompromised individuals. Unlike other Candida species, Candida albicans has the ability to colonise the oral cavity. Superficial invasion of the mucous membranes by Candida albicans produces a white, cheesy, usually painless plaque that loosely adheres to the mucosal surface. Specific infections of the pharynx caused by other fungi are extremely rare. (Pienaar *et al.* 2010) Other rare causes of pharyngitis include, for example, gastroesofagel reflux, chemical irritation, allergies and tumours.

From here on this literature review is restricted to only pharyngitis episodes caused by common viruses or bacteria.

2.3 Complications of acute pharyngitis

Acute pharyngitis is able to cause suppurative complications like peritonsillar abscess, septicemia, acute otitis media, acute rhinosinusitis or even some invasive infections (e.g. deep neck abscesses, mastoiditis, Lemierre's syndrome, intracranial infections) (Little *et al.* 2013b). It has also been reported to be able to cause non-suppurative complications like rheumatic fever or glomerulonephritis (Spinks *et al.* 2013). However, the current rate of non-suppurative complications in developed countries is extremely low (Bisno 2001).

2.3.1 Suppurative complications

Peritonsillar abscess is the most common suppurative complication of acute pharyngitis (Spinks *et al.* 2013). The incidence of peritonsillar abscess in Sweden was recently estimated to be only 37/100 000 persons per year (Risberg *et al.* 2008). A Cochrane review reported that quinsy has become more uncommon than before, and many of the studies included in the review reported no cases at all (Spinks *et al.* 2013). Dunn *et al*. (2007) also performed a register study including 198 000 patients

from the U.K. General Practice Research Database. They found that there were 606 recorded cases of patients with peritonsillar abscess between years 1995-1997, but only 192 (31%) of these patients were presented following initially uncomplicated pharyngitis. Further, a majority of the abscesses occurred rapidly in 2–3 days, suggesting that antibiotic therapy wouldn't have been able to prevent them anyways. (Dunn *et al.* 2007).

In clinical practice, ENT specialists usually perceive acute otitis media and acute rhinosinusitis as comorbidities of pharyngitis. However, some researchers have considered these diseases as complications of pharyngitis. Many studies have reported very low or even zero incidence of acute otitis media and acute purulent rhinosinusitis after an acute pharyngitis episode (Dagnelie *et al.* 1996, Howe *et al.* 1997, Little *et al.* 1997, Zwart *et al.* 2000).

A recent Cochrane review of antibiotic selection in acute pharyngitis did not find any suppurative complications of acute pharyngitis among the 5352 pharyngitis patients included (van Driel *et al.* 2013). Little *et al*. (2013b) reported recently that the rate of any suppurative complications was only 1% (177/13 445) in patients with an acute sore throat.

Other rare but possible suppurative complications include deep neck region abscesses (i.e., parapharyngeal, retropharyngeal), mastoiditis, Lemierre's syndrome, Horner's syndrome, mediastinitits and epidural abscess, to mention a few (Little *et al.* 2013b). These are not elaborated on in this work.

2.3.2 Non-suppurative complications

GAS pharyngitis is reported to be able to lead to non-suppurative post-infectious disorders of acute rheumatic fever with or without carditis, as well as to poststreptococcal glomerulonephritis. These are autoimmune diseases mediated by immune responses following untreated GAS infection (Rodriguez-Iturbe & Musser 2008). A recent Cochrane review found that out of 8135 cases of acute GAS pharyngitis in children, only six cases with short-duration antibiotic treatment versus eight with standard-duration treatment developed long-term complications of glomerulonephritis or acute rheumatic fever (Altamimi *et al.* 2012). Adam *et al*. (2000) compared short- and long-term antibiotic therapies of 4782 children with culture-proven GAS pharyngitis. During five years of follow-up only three rheumatic fever and two glomerulonephritis episodes were diagnosed, but further investigations revealed that none of these particular episodes were probably caused by GAS pharyngitis. (Adam *et al.* 2000)

Rheumatic fever is the most common cause of acquired pediatric heart disease globally (Lennon *et al.* 2009). The incidence of acute rheumatic fever has declined remarkably in developed countries during the last decades (Spinks *et al.* 2013). Although acute rheumatic fever is now uncommon in most developed countries, it continues to be the leading cause of acquired heart disease in children in low economic areas (Carapetis *et al.* 2005). There are many RCTs on the effect of antibiotic therapy on prevention of complications, and in these trials rheumatic fever was not found at all in either antibiotic or placebo groups (Dagnelie *et al.* 1996, Leelarasamee *et al.* 2000, Little *et al.* 1997, Zwart *et al.* 2000). Furthermore, the majority of rheumatic fever episodes occur without preceding GAS infection (Veasy *et al.* 1987).

Kuroki *et al*. (2013) compared antibiotic treatment of different durations of 97 children and even conducted urianalyses 1–2 weeks after treatment to check for glomerulonephritis. They did not find any cases of glomerulonephritis. (Kuroki *et al.* 2013) Also, a Cochrane review of antibiotic benefit in protecting patients against glomerulonephritis found too few cases to draw any conclusions (Spinks *et al.* 2013).

Toxins of streptococcus A are able to cause some very rare non-suppurative complications. Rash in scarlet fever results from erythrogenic toxin of streptococcus (Wannamaker 1983). Sporadic toxic shock-like syndrome cases are suggested to be due to GAS pharyngitis episodes and proposed to be transmitted by toxins (Chapnick *et al.* 1992, Wannamaker 1983).

2.4 Diagnostic methods for acute pharyngitis

The basic issue in acute pharyngitis management has traditionally been to find out if the pharyngitis is caused by group A streptococcus, since namely GAS has been reported to have the capability to cause complications noticeably more often than viruses or other bacteria. Furthermore, antibiotic treatment has been warranted mainly for treating only GAS pharyngitis. (Chiappini *et al.* 2011, Del Mar *et al.* 2006). As a result, diagnostic methods also concentrate on differentiating GAS infections from other throat infections. Finnish current care guideline recommends diagnostic testing for GAS (Sore throat: Current Care Guidelines 2013). However, there is no consensus in clinical practice worldwide on whether the probability is high enough that clinical findings alone suffice for an antibiotic treatment decision in GAS pharyngitis or if the need for antibiotics should be ensured by further diagnostic testing (Chiappini *et al.* 2011).

2.4.1 Microbiological culture

Microbiological testing is the most accurate method for studying the etiology of pharyngitis. A throat swab culture is required for a definite bacterial diagnosis and it remains as the golden standard for documenting the presence of GAS (Mirza *et al.* 2007). Under ideal conditions, the sensitivity of a throat culture for GAS is reported to be 90% and its specificity is 99% (Hayes & Williamson, Jr. 2001).

A throat swab sample is taken by a medical professional and is obtained from the surface of the posterior pharyngeal wall and both palatine tonsils. Lilja *et al*. (1997) studied GAS attachment to epithelial cells of the pharyngeal region during GAS-positive acute tonsillitis. They found that GAS became attached namely to the epithelial cells of both the palatine tonsils and the posterior oropharyngeal wall, but not substantially to the cells of the palatoglossal arch or buccal mucosa. (Lilja *et al.* 1997) Another study reported that swab samples from the tonsils and posterior pharyngeal wall are optimal for group A streptococcus detection and superior to samples taken from the mouth (Fox *et al.* 2006). A bacteriological culture swab is usually plated on sheep blood agar and incubated at 35 °C for 18–24 hours before reading (Kellogg 1990). Cultures that are negative for GAS after 24 hours are suggested to be incubated for a second day and checked again to optimise recovery of GAS (Lauer *et al.* 1983). Even longer incubation times have been proposed (Kocoglu *et al.* 2006). So, it takes 1–3 days to get the final result of the culture. Usually a streptococcal culture that detects only group A, C and G streptococcus is considered sufficient for making an antibiotic treatment decision or for finding an asymptomatic pathogen carrier in an epidemic situation. A more inclusive bacteriological culture that detects, e.g. Arcanobacterium haemolyticum, Streptococcus pneumonia, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Neisseria meningitidis or gram negative bacteria may be essential in specific cases.

For practical reasons, pharyngeal bacterial cultures are normally obtained from the surface of the posterior pharyngeal wall and tonsils. Gul *et al*. (2007) compared tonsillar surface and tonsillar deep tissue cultures of patients who underwent tonsillectomy for recurrent tonsillitis. They found that different types of bacteria were recovered from surface cultures than from deep tissue cultures in 72% of patients from whom any pathogenic bacteria were isolated, suggesting that a surface swab does not reliably reflect the types of organisms present in the tonsil core in individual patients.(Gul *et al.* 2007) Similar results were reported by another study (Mitchelmore *et al.* 1994).

2.4.2 Streptococcus group A rapid detection tests

Even though a throat swab culture remains as the golden standard for documenting the presence of GAS, a significant disadvantage of the method is the delay of 1–3 days before results are obtained. This problem may eventually be obviated by rapid antigen detection tests (RADTs), which can confirm the presence of group A streptococcal carbohydrate antigen on a throat swab in a matter of minutes. (Leung *et al.* 2006) Numerous different rapid antigen detection methods are commercially available (Chapin *et al.* 2002, Fontes *et al.* 2007, Gerber & Shulman 2004, Schlager *et al.* 1996). All RADTs involve extraction of the group-specific carbohydrate from the cell wall of the GAS and antigen identification by an immunological reaction (Leung *et al.* 2006). There are also distinct ways and commercially available kits for performing nucleic acid testing for GAS by using either a direct non-amplified nucleic acid probe methodology or a real-time PCR method for detecting amplified GAS nucleic acid. These are called DNA probe methods. (Bourbeau 2003, Heelan *et al.* 1996) Probe tests also offer the advantage over bacterial cultures of same-day reporting of the final result, but they are somewhat slower than RADTs (Chapin *et al.* 2002).

The sensitivity and specificity of RADTs are reported by comparing the results with a simultaneously taken throat swab culture from the same individual. A large majority of the RADTs that are currently available have high specificity (i.e., 95% or greater) and sensitivity between 70% and 90% (Gerber & Shulman 2004). Due to the high specificity, positive rapid antigen detection is accepted as an adequate way to diagnose GAS pharyngitis and can be considered equivalent to a positive throat culture (Leung *et al.* 2006, Lindbaek *et al.* 2004). Conversely, it is usually recommended that negative test results should be confirmed with a throat culture, since a considerable share of patients may have false-negative rapid detection test results but positive culture findings (Gerber & Shulman 2004). For example, in their study Mirza *et al*. (2007) found that out of the 14 167 (77%) negative RADT results they found in their patients, 968 (7%) were associated with positive cultures. Chapin *et al*. (2002) reported the sensitivity, specificity, positive and negative predictive values of a DNA probe test and a rapid antigen test as follows: 95%, 100%, 100% and 97% for the probe test and 86%, 97%, 94% and 93% for the antigen test, respectively. They propose that the probe test was comparable to a culture in performance and can be used as the primary test or even as a backup for negative RADTs. (Chapin *et al.* 2002) Since many patients with negative RADT results and a simultaneously obtained positive culture have only small numbers of group A streptococcus colonies on their

culture, it has been suggested that most false-negative RADT results would occur in patients who are merely chronic streptococcal carriers and not truly infected. There are some studies for and against this issue (Gerber & Shulman 2004, Kuhn *et al.* 1999, Kurtz *et al.* 2000, Lindbaek *et al.* 2004).

2.4.3 Laboratory investigations

Blood testing of certain infection markers is occasionally performed for patients with acute infection. Usually, levels of leucocytes, C-reactive protein (CRP) or procalcitonin (PCT) or the erythrocyte sedimentation rate (ESR) in serum may be screened. In general, these infection markers may be screened in infection patients to acquire tools for differentiating between viral and bacterial infections, to look for severe infections possibly demanding oral or intravenous antibiotic therapy or to follow up the cure. Anti-streptococcal antibody titres are not recommended in routine diagnosis of acute pharyngitis, as they reflect past but not current events (Shulman *et al.* 2012).

Some studies have evaluated mean or median values of infection markers in both streptococcal and viral pharyngitis patients. Hjortdahl & Melbye (1994) reported the following mean values for streptococcal and viral pharyngitis groups, respectively: CRP 50.4 mg/l and 19.5 mg/l; blood white cell count 12.1×10^9/l and 8.8×10^9/l. Ylikoski & Karjalainen (1989) investigated 257 army conscripts 18–27 years of age. They reported mean (standard deviation, SD) CRP values of 70 (35) mg/l and 59 (7) mg/l and mean (SD) blood white cell counts of 13.3 (4.3)$\times10^9$/l and 7.9 (2.4)$\times10^9$/l in patients with group A streptococcal pharyngitis and viral pharyngitis, respectively.(Ylikoski & Karjalainen 1989) Elsammak *et al*. (2006) investigated serum PCT in children with streptococcal pharyngitis, with non-streptococcal pharyngitis and in healthy children. They found median (range) values for PCT to be 0.37 (0.11–6.50), 0.11 (0.01–0.53) and 0.02 (0.01–0.08) ng/mL, respectively. (Elsammak *et al.* 2006) According to these results, infection parameters are somewhat higher during streptococcal pharyngitis compared with viral pharyngitis.

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) wrote an updated guideline for diagnosing and treating patients with an acute sore throat and also reviewed literature concerning laboratory investigations in 2012. They found no evidence supporting the premise that clinical information combined with biomarker data could provide better prognostic information for sore throat than clinical findings only. (Pelucchi *et al.* 2012) In their recent review article Koo & Eisenhut (2011) stated that blood white cell count, CRP and PCT levels are

higher in patients with streptococcal tonsillitis than in patients with tonsillitis or pharyngitis without GAS. They conclude that further studies are required to find out which of these markers has the best test performance characteristics in pharyngitis patients.(Koo & Eisenhut 2011)

2.4.4 Symptoms and clinical findings

Diagnosis of pharyngitis is based on symptoms and clinical findings. Pharyngitis patients usually have one or more of the following features: sore throat, enlarged tonsils, exudative tonsils, fever, pharyngeal erythema, soft palatine petechiaes, anterior cervical lymphadenopathy or painful swallowing (Bisno *et al.* 2002).

According to some studies, the presence of clinical findings such as tonsillopharyngeal exudate, absence of a cough or rhinitis, a high fever or anterior cervical lymphadenopathy has been proposed to increase the statistical likelihood of the infectious agent being GAS (Chazan *et al.* 2003, Dagnelie *et al.* 1998, Kljakovic 1993, Komaroff *et al.* 1986, Vukmir 1992). Also myalgias, a positive throat culture in the preceding year and exposure to GAS infection within the previous two weeks have been suggested to increase the likelihood of GAS pharyngitis (Ebell *et al.* 2000, Komaroff *et al.* 1986).

A number of algorithms combining epidemiological and clinical factors have been devised to improve diagnostic accuracy. The most widely used clinical criteria is the Centor score, a well-validated clinical index for estimating the likelihood of GAS infection in a patient presenting with a sore throat (Centor *et al.* 1981). In the Centor score, the model for a positive guess of GAS infection consists of four variables: tonsillar exudates, swollen tender anterior cervical lymph nodes, lack of a cough and a history of fever. In their original setting, a physician made diagnoses for patients presenting with sore throat symptoms and assessed the presence of GAS using only the Centor clinical criteria. This result was compared with diagnoses proven by GAS cultures from the same individuals. They found the probabilities for a positive streptococcal culture according to Centor criteria variables to be as follows: patients with all 4 variables, 56%; 3 variables, 32%; 2 variables, 15%; 1 variable, 7% and 0 variables, 3%. (Centor *et al.* 1981)

Another popular clinical score is the McIsaac score, which is modified from the Centor score and is based on the following findings: presence of a fever, lack of a cough, tender anterior cervical adenopathy and tonsillar swelling or exudate (McIsaac *et al.* 1998). In addition to these findings, the McIsaac score also takes the patient's age into consideration (Table 3). The sensitivity of the McIsaac score (all patients,

scores ranging from 0–4 combined) for identifying GAS infection was 83%, compared with 69% for usual physician care; the specificity values of these two approaches were similar, being 92%. Among patients 3 to 14 years of age, the sensitivity of the score approach was statistically significantly higher than that of usual physician care (97% vs. 71%). (McIsaac *et al.* 1998) There are also some other published clinical scores that predict GAS etiology in pharyngitis patients, but they have not been as widely used (Dobbs 1996, McGinn *et al.* 2003, Reed *et al.* 1990).

Literature confirms that clinical findings and features alone are insufficient for differentiating the causative pathogen of acute pharyngitis episodes without any doubt; this can only be achieved by microbiological testing. According to Finnish current care guideline a positive result in GAS testing is needed for antibiotic treatment (Sore throat: Current Care Guidelines 2013). However, there is still controversy in the literature and also in clinical practice worldwide about the need for GAS testing for antibiotic prescription in acute pharyngitis (Aalbers *et al.* 2011, Fine *et al.* 2012, Little *et al.* 2013a).

Table 3. McIsaac score (modified Centor score).

Criteria	Points
Absence of a cough	1
Tonsillar exudates or swelling	1
Swollen and tender anterior cervical nodes	1
Temperature > 38°C	1
Age, years	
3–14	1
15–44	0
≥ 45	-1

Points are added up to achieve the total McIsaac score.

2.5 Medical treatment of acute pharyngitis

The majority of acute pharyngitis episodes heal by themselves in a few days. It is also known that viruses cause a majority of acute pharyngitis episodes and that there are no appropriate viral medications available for pharyngitis. GAS is the most common bacterial etiology of acute pharyngitis and also the main pathogen causing possible complications. For this reason, antibiotics are usually warranted only for GAS infection or for the cases when symptoms are particularly severe or some complication is suspected. Reducing the number of antibiotic prescriptions given for common respiratory infections has been recommended as a way to limit bacterial

resistance. The majority of patients benefit from symptomatic medical treatment. (Spinks *et al.* 2013)

2.5.1 Analgesics

There are a number of topical or systemic analgesics available for throat pain, and many of them are over-the-counter medications enabling early pain relief also by patients themselves without a medical appointment. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are the most-used medications for throat pain relief and they also have antipyretic properties that are helpful in pharyngitis. Many kinds of topical demulcents are an option for pain relief. Opioids are seldom used and warranted only for severe throat pain.

A meta-analysis of 54 RCTs that investigated pain control in general included three adult RCTs and two pediatric RCTs that studied pharyngitis specifically. The analysis showed that both ibuprofen and paracetamol are more effective than a placebo, and that 400 mg of ibuprofen was superior to 1000 mg of paracetamol in pharyngitis. The meta-analysis demonstrated no significant difference in side effects between these two drugs.(Pierce & Voss 2010) Ruperto *et al*. (2011) reported that, in children, paracetamol and ketoprofen were significantly more effective than a placebo in pain relief at one hour, and both treatments were well-tolerated. Acetylsalicylic acid (ASA) was found to be superior to a placebo in throat pain reduction without safety problems in adults and diclofenac potassium was superior to a placebo and paracetamol in adults (Eccles *et al.* 2003, Gehanno *et al.* 2003, Schachtel *et al.* 2010). Cyclooxygenase-2 (COX-2) inhibitors also seem to provide significantly greater pain relief than a placebo (Schachtel *et al.* 2007, Schachtel *et al.* 2011).
Topical demulcents with or without added anesthetics provide rapid and superior pain relief compared with a placebo, with a reported NNT of 3 (Blagden *et al.* 2002, Busch *et al.* 2010, Chrubasik *et al.* 2012, McNally *et al.* 2010, Wonnemann *et al.* 2007). A Cochrane review including seven RCTs of Chinese herbal remedies for sore throat pain found poor-quality methodology and, thus, couldn't recommend their use (Shi *et al.* 2007). A Cochrane review of zinc supplementation showed no significant improvement in pharyngitis symptoms compared with a placebo (Singh & Das 2011).

2.5.2 Antibiotics

When antimicrobial therapy is required, the safest, narrowest-spectrum and most cost-effective antibiotics should be prescribed. Considering the growing problem of

antibiotic resistance for other pathogens, this responsiveness of group A streptococci should not be endangered. (Wise *et al.* 1998) Despite agreement on these principles by expert advisory committees, data from national surveys indicate that antimicrobial agents continue to be used indiscriminately for upper respiratory infections such as acute pharyngitis. Linder & Stafford (2001) conducted a retrospective analysis in the U.S and reported that antibiotics were prescribed in 73% of visits because of a sore throat. They also found that patients treated with antibiotics were given non-recommended antibiotics in 68% of visits. (Linder & Stafford 2001) McIsaac *et al*. (2000) reported similar results. They found that, in Canada, among patients with upper respiratory infection accompanied by a sore throat, 63% of antibiotic prescriptions were given to patients with culture-negative results for group A streptococcus.(McIsaac *et al.* 2000) Gulliford *et al*. (2009) reported that the rate of prescribing antibiotics for pharyngitis remained high, with an estimated rate of 40% to 50% in U.K. consultations in 2006. Moreover, increased prescribing was reported to further increase patient attendance rates (Little *et al.* 1997).

The objectives of antibiotic therapy for GAS pharyngitis are mainly to prevent suppurative and non-suppurative complications, to some extent to decrease infectivity—enabling the patient to return to school or work—and to shorten the clinical course of the disease. The last objective can usually be accomplished only if the patient is treated early in the course of the illness (van Driel *et al.* 2013).

According to a Cochrane review, peritonsillar abscess following acute pharyngitis developed more seldom in patients treated with antibiotics than in patients treated with a placebo. Peritonsillar abscess occurred in 2 out of 1438 (0.1%) patients in the antibiotic treatment group and in 23 out of 995 (2%) patients in the placebo group (risk ratio (RR) 0.15; 95% CI: 0.05 to 0.47). The number needed to treat (NNT) with antibiotics to prevent one peritonsillar abscess was 46. However, most of the studies included in this review were done in the 1950s when peritonsillar abscesses were more common than nowadays in industrial countries. (Del Mar *et al.* 2006) Petersen *et al*. (2007) conducted a register survey in the U.K. that followed over 1 million pharyngitis episodes and reported that peritonsillar abscess occurred more rarely in patients treated with antibiotics (odds ratio (OR) 0.84; 95% CI: 0.73 to 0.97), the risk being highest in 16–64-year-old patients. However, they found a very high NNT of 4600, suggesting no benefit from routinely used antibiotics. (Petersen *et al.* 2007)

According to a Cochrane review that evaluated the need for antibiotic treatment for a sore throat, antibiotics reduced the incidence of comorbid acute otitis media

within 14 days (RR 0.30; 95% CI: 0.15 to 0.58) and the incidence of comorbid rhinosinusitis (RR 0.48; 95% CI: 0.08 to 2.76) (Spinks *et al*. 2013).

A Cochrane review reported that antibiotics reduced acute rheumatic fever by more than two-thirds within one month (RR 0.27; 95% CI 0.12 to 0.60) and about 1.7 per 100 placebo participants developed rheumatic fever. However, it is important to notice that the RCTs included in the review were further analysed and rheumatic fever occurred only in trials reported before the year 1961. The incidence of acute rheumatic fever has continued to decline noticeably in developed countries since then. (Spinks *et al.* 2013)

According to a Cochrane review, antibiotics showed a trend of being able to protect against acute glomerulonephritis, but there were too few cases for the results to reach statistical significance (Spinks *et al.* 2013). Another Cochrane review comparing the effects of traditional long-term and new generation short-term antibiotic therapies for pharyngitis in children showed that the risk for non-suppurative complications was similar between treatment groups (OR 0.53, 95% CI 0.17 to 1.64) (Altamimi *et al.* 2012).

A Cochrane review comparing antibiotics with a placebo for sore throat treatment showed an NNT value of 6 for pain resolution by day 3 from the onset of symptoms and an NNT of 21 by day 7. Antibiotics reduced pain more effectively among patients who tested positive for streptococci (RR = 0.58; 95% CI: 0.48 to 0.71) compared with patients who tested negative (RR = 0.78; 95% CI: 0.63 to 0.97). According to this Cochrane review, antibiotics offer relative benefits in pain treatment of pharyngitis but the absolute benefits are modest. (Spinks *et al.* 2013)

Beta-lactamase produced by other bacteria in the pharynx could potentially inactivate penicillin, resulting in increased treatment failures or infection relapses (Reed *et al.* 1991). Another Cochrane review was published recently comparing different antibiotic options for GAS pharyngitis (van Driel *et al.* 2013). Seventeen RCTs were included; 16 compared penicillin with another antibiotic (six with cephalosporins, six with macrolides, three with carbacephem and one with sulfonamides) and one trial compared clindamycin and ampicillin. The main result of the meta-analysis was that there was no difference in symptom resolution between cephalosporins and penicillin (OR 0.79; 95% CI: 0.55 to 1.12), but the clinical relapse rate was lower with cephalosporins (OR 0.55; 95% CI: 0.31 to 0.99); NNT 50). (van Driel *et al.* 2013) Furthermore, according to the Cochrane review and most of the studies published, there were no differences between macrolides and penicillin in symptom resolution (Bachand, Jr. 1991, Levenstein 1991, Stein *et al.* 1991, van Driel *et al.* 2013, Watkins *et al.* 1997). The authors of the Cochrane review concluded that,

based on these results and considering the low cost and absence of resistance, penicillin can still be recommended as the first choice regimen for treating acute pharyngitis (van Driel *et al.* 2013).

A Cochrane review compared short-term, late-generation antibiotics with long-term penicillin for acute streptococcal pharyngitis in children and included 20 RCTs. The majority of the studies were published between 1994 and 2004, during which period the rates of serious complications, especially acute rheumatic fever, were less common than during the dates of earlier studies. Compared with standard-duration treatment with 10 days of penicillin, the short-duration treatment with late-generation antibiotics showed lower risk of early clinical treatment failure (OR 0.80; 95% CI: 0.67 to 0.94) and no significant difference in early bacteriological treatment failure (OR 1.08; 95% CI: 0.97 to 1.20) or late clinical recurrence (OR 0.95, 95% CI: 0.83 to 1.08). However, the overall risk of late bacteriological recurrence was greater in the short-duration treatment studies (OR 1.31, 95% CI: 1.16 to 1.48), although no significant differences were found when studies of low-dose azithromycin (10 mg/kg) were eliminated (OR 1.06, 95% CI: 0.92 to 1.22). According to this Cochrane review, if antibiotics are prescribed, oral penicillin for 10 days is still recommended as the standard of care.(Altamimi *et al.* 2012)

Morbilliform rashes are common in patients with infectious mononucleosis treated with amoxicillin or ampicillin; they occur in up to 95% of patients with such drug exposure and to 40-60 % of patients with other β-lactam antibiotics. This should be taken into account when considering which antibiotic to administer in patients with possible infectious mononucleosis. (Ebell 2004, Luzuriaga & Sullivan 2010)

2.5.3 Corticosteroids

The discomfort and pain experienced by patients with pharyngitis are mainly due to inflammation of the oropharyngeal mucosa. Therefore, reducing the level of inflammation leads to fewer symptoms, being the theory behind corticosteroid treatment for pharyngitis. Corticosteroids for a sore throat have been administrated locally (by oral sprays) or systemically (by oral or parenteral administration). Corticosteroids used for a sore throat include betamethasone, dexamethasone or prednisone as a single dose or as repetitive doses for one to three days. (Hayward *et al.* 2012).

In the recent Cochrane review of corticosteroids as standalone or add-on treatment for a sore throat, eight RCTs involving 743 participants (369 children and 374 adults) were included. All of the studies in this meta-analysis were limited by the

fact that steroids were given in combination with antibiotics. In addition to the effect of antibiotics and analgesics, corticosteroids increased the likelihood of complete resolution of pain at 24 hours by more than three times (RR: 3.2, 95% CI: 2.0 to 5.1) and at 48 hours by 1.7 times. Four of the studies included in this meta-analysis showed that corticosteroids completely resolved pain at 24 hours (NNT = 3.7; 95% CI: 2.8 to 5.9), and three studies demonstrated complete pain relief at 48 hours (NNT = 3.3; 95% CI: 2.4 to 5.6). There were no differences in rates of recurrence, relapse or adverse effects compared with a placebo. The authors conclude that corticosteroids—when given in addition to antibiotics—increase the likelihood of pain resolution in patients with a sore throat, but further trials assessing their benefit without antibiotics and in children are warranted. (Hayward *et al.* 2012). The Finnish current care guideline for acute pharyngitis does not mention anything about corticosteroids (Sore throat: Current Care Guidelines 2013).

PFAPA syndrome (acronym for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) is the most common cause of periodic fever in childhood. The etiology of the syndrome is unknown, but current literature considers it as an autoinflammatory disease. (Vigo & Zulian 2012) However, the main clinical features of PFAPA include a fever higher than 39 °C lasting 3–6 days accompanied by pharyngitis and cervical lymphadenitis (Krol *et al.* 2013). Many studies have reported that treatment with single doses of corticosteroids is effective in controlling PFAPA symptoms, including a sore throat (Krol *et al.* 2013, Vigo & Zulian 2012, Yazgan *et al.* 2012).

2.6 Treatment guidelines for acute pharyngitis

The optimal management of acute pharyngitis continues to be debated. There are somewhat controversial results in the literature as well as interpretations of the results worldwide concerning diagnostic methods and medical treatment of acute pharyngitis (Chiappini *et al.* 2011, Matthys *et al.* 2007). As a result of increasing knowledge about bacterial antimicrobial resistance, requirements to avoid unnecessary antibiotic prescriptions have emerged and many national and regional treatment guidelines have been developed. However, guidelines also differ substantially in terms of the use of rapid antigen diagnostic testing or throat culture and of the indications for antibiotic treatment (Chiappini *et al.* 2011, Matthys *et al.* 2007). Although well-established guidelines for prescribing antibiotics for acute pharyngitis exist, study by Crocker *et al.* (2013) reported physicians' guideline adherence to be only 24 % in patients with pharyngitis. According to Linder *et al.* (2006) the main problem is not which

guideline to follow, since doctors usually fail to follow any guideline. They conclude that treatment should focus on issues where the guidelines agree: to avoid testing and to avoid antibiotics for patients at low risk for streptococcal pharyngitis. (Linder *et al.* 2006)

In their review article Chiappini *et al*. (2011) identified twelve national guidelines: six from European countries (France, United Kingdom, Finland, Holland, Scotland and Belgium), five from the United States and one from Canada.(Chiappini *et al.* 2011) However, the website that earlier consisted Canadian guideline provided by British Columbia Ministry of Science mentioned in the review was not accessible anymore in 2015. There is also an European regional guideline available (Pelucchi *et al.* 2012). Treatment guidelines for acute pharyngitis are presented in Table 4. The main features of each of these guidelines concerning diagnostic and treatment strategy are shown in Table 5. In summary, all the guidelines agree that narrow-spectrum penicillin is the first choice antibiotic regimen for treating GAS pharyngitis and that treatment should last for 10 days. Once-daily amoxicillin was recommended by two US guidelines as equally effective therapy. All the guidelines agree that blood tests are not recommended for diagnosis of GAS pharyngitis, RADT or culture is not needed to confirm recovery and adjunctive therapy with analgesic drugs is recommended. According to the few guidelines mentioning them, evidence concerning corticosteroids as a standalone treatment is still too scarce to allow making recommendations. (Chiappini *et al.* 2011, Pelucchi *et al.* 2012)

Table 4. Treatment guidelines for acute pharyngitis.

Country	Guideline instance
United States	American College of Physicians-American Society of Internal Medicine (ACP-ASIM) (Snow *et al.* 2001)
United States	Infectious Diseases Society of America (IDSA) (Bisno *et al.* 2002)
United States	Institute for Clinical System Improvement (ICSI) (National Guideline Clearinghouse 2013)
United States	American Heart Association (AHA) (Gerber *et al.* 2009)
United States	American Academy of Pediatrics (AAP) (American Academy of Pediatrics, Committee on Infectious Diseases 2009)
United Kingdom	National Institute for Health and Clinical Excellence (NICE) (National Institute for Health and Clinical Excellence 2008)
Scotland	Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Guidelines Network 1999)
France	Agence Francaise de Securite Sanitaire des Produits de Sante (Agence Française de Sécurité Sanitaire des Produits de Santé 2003)
Holland	Dutch College of General Practitioners (Starreveld *et al.* 2008)
Belgium	Scientific Society of Flemish General Practitioners (De Meyere & Matthys 1999)
Europe	European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (Pelucchi *et al.* 2012)
Finland	Finnish Medical Society Duodecim, Finnish Association for Central Practice, Finnish Otolaryngological Society, Infectious Diseases Society of Finland and Clinical Microbiologists Society (Sore throat: Current Care Guidelines 2013)

Table 5. Comparison of guideline recommendations for diagnosis and treatment in case of acute pharyngitis.

Guideline	Screening	Diagnosis	Throat culture if RADT is negative	When to treat with antibiotics
United States ACP-ASIM	Centor score	RADT only if Centor score is 2–3	Adults: no Children: yes	Centor score of 4 or RADT or throat culture positive
IDSA	Clinical and epidemiological parameters	Throat culture or RADT in all patients	Adults: no Children: yes	RADT or throat culture positive
ICSI	Clinical and epidemiological parameters	Throat culture or RADT in all patients	Yes	RADT or throat culture positive
AHA, AAP	Clinical and epidemiological parameters	Throat culture or RADT in all patients	Yes	RADT or throat culture positive
United Kingdom	Centor score	Clinical diagnosis if Centor score is ≥3	Not applicable	Centor score ≥3
Scotland	The Centor score should be used to assist the decision on whether to prescribe an antibiotic but cannot be relied on for a precise diagnosis	Throat swabs should not be conducted routinely. They may be used to establish etiology of recurrent severe episodes in adults when considering referral for tonsillectomy	Not applicable	Antibiotics should not be used routinely. In severe cases in which the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld
France	Clinical and epidemiological parameters	Only RADT in all patients	Adults: no, except in the presence of risk factors for acute rheumatic fever. Children: if aged >5 years	RADT or throat culture positive
Holland	Clinical and epidemiological parameters	Throat swabs should not be conducted routinely	Not applicable	Prescribing antibiotics is only recommended for patients who have an increased risk of complications

Guideline	Screening	Diagnosis	Throat culture if RADT is negative	When to treat with antibiotics
Belgium	Clinical and epidemiological parameters	RADT/throat swabs not recommended	Not applicable	Prescribing antibiotics is only recommended for patients who have an increased risk of severe complications
ESCMID	Centor score	RADT is considered if Centor score is ≥3. Throat culture should not be conducted routinely.	Not applicable	Antibiotics should be considered if RADT is positive or Centor score is ≥3
Finland	Clinical and epidemiological parameters	Throat culture or RADT if McIsaac score is ≥2	In adults and children aged >3 years: yes	RADT or throat culture positive

2.7 Recurrent pharyngitis

2.7.1 Occurrence

Published literature on the prevalence of recurrent pharyngitis is sparse. According to population-based data from Norway, the lifetime prevalence of recurrent tonsillitis was reported to be 12% (95% CI, 11.0–12.3%), with a significant predominance of female cases (Kvestad *et al.* 2005). Approximately 1% of children between the ages of 4 and 15 years had three or more GAS pharyngitis episodes per year.(St Sauver *et al.* 2006) Studies comparing the effect of corticosteroids and a placebo for acute pharyngitis have reported late recurrence rates of 7–9% in both groups (Bulloch *et al.* 2003, Kiderman *et al.* 2005). Other studies have reported late recurrence rates of 3–8% in adults after antibiotic treatment for acute pharyngitis (Adam *et al.* 2000, Carbon *et al.* 1995).

2.7.2 Natural improvement

In a majority of the controlled trials on tonsillectomy for recurrent pharyngitis, the control group (no tonsillectomy) has demonstrated a trend toward spontaneous improvement during the follow-up period, often with patients no longer meeting the original criteria for study entry. In a randomised controlled study by Paradise *et al*.

(1984), all the children met the Paradise criteria (Table 7) for tonsillectomy at enrolment. However, during the follow-up, children in the control group experienced an average of only 1.17 annual episodes of throat infection during the following year, 1.03 during the second year and 0.45 episodes during the third year. (Paradise *et al.* 1984) Results in children have been reinforced by other studies with more relaxed tonsillectomy indications (Paradise *et al.* 2002, van Staaij *et al.* 2004). A Cochrane review on the efficacy of tonsillectomy for recurrent tonsillitis concludes that some cases may resolve themselves without surgery (Burton & Glaziou 2009).

2.7.3 Microbiology and reasons for recurrence

In spite of antibiotic treatment, acute pharyngitis may recur. The reasons for recurrent pharyngitis include inappropriate antibiotic therapy, inadequate duration or dose of antibiotic therapy, re-infection, local breakdown of penicillin by beta-lactamase-producing commensals, low absorption of antibiotics, patient non-compliance, frequent exposure by family members, contaminated toothbrushes or orthodontic appliances and other unknown reasons (Holm 1994, Nseir *et al.* 2012, Pichichero & Casey 2007).

Brook *et al*. conducted microbiological studies of the tonsil core of patients with recurrent pharyngitis during three periods: 1977–1978, 1984–1985 and 1992–1993. Both the rate of recovery of beta-lactamase-producing bacteria and the number of these organisms per palatine tonsil increased over time. Specifically, beta-lactamase-producing strains were detected in 74%, 92% and 94% of tonsils, respectively.(Brook *et al.* 1995) Benzathine penicillin, cefuroxime and clindamycin may reduce the frequency of recurrent episodes (Foote, Jr. & Brook 1989, Holm *et al.* 1995, Sirimanna *et al.* 1990).

In recurrent pharyngitis, the tonsil core contains numerous aerobic and anaerobic bacteria, some of which are potentially pathogenic. Numerous studies based on the bacteriology of the palatine tonsils have been carried out. Surface swabs and tonsil core tissues differed from each other individually in approximately 30% of patients with recurrent tonsillitis, but the range of species isolated was similar in both surface and core samples (Mitchelmore *et al.* 1994). The predominant bacteria in recurrent pharyngitis are Staphylococcus aureus, Moraxella catarrhalis, alfa- and betahemolytic streptococcus species, Prevotella species, Fusobacterium species, diphteroid bacilli and Haemophilus influenza (Brook *et al.* 1995, Develioglu *et al.* 2014, Jeong *et al.* 2007, Rusan *et al.* 2009, Zautner *et al.* 2010). However, the distribution and prevalence of these bacteria vary somewhat between published

studies, and the essential bacteria in recurrent pharyngitis may have been changing over time. Jeong *et al*. (2007) observed 966 bacterial cultures from 824 patients who underwent tonsillectomy with or without adenoidectomy. They found that in recurrent tonsillitis, Staphylococcus aureus was the most common pathogen (30%), followed by Haemophilus influenzae (16%) and group A betahaemolytic Streptococcus (15%). (Jeong *et al.* 2007) Zautner *et al*. (2010) investigated tonsil specimens taken during tonsillectomy and found that intracellular residing Staphylococcus aureus was the predominant species (58%), being the most common cause of recurrent tonsillitis. They propose that Staphylococcus aureus uses this location to survive the effects of antibiotics and the host immune response. (Zautner *et al.* 2010) Some recent studies suggest that Fucobacterium necrophorum may be a far more widespread pathogen than has been previously reported and may cause especially recurrent or persistent sore throat. In their work, Rusan *et al*. (2009) studied the microbiology of upper respiratory infections requiring hospitalisation. The vast majority of the cases were throat infections, however, peritonsillar abscess was the most common diagnosis. The most frequently isolated bacteria were GAS (14%), Fucobacterium necrophorum (14%) and Staphylococcus aureus (8%). (Rusan *et al.* 2009) Batty & Wren (2005) found similar results in their study. They reported that both GAS and Fucobacterium necrophorum were responsible for 11% of positive throat cultures during acute pharyngitis. (Batty & Wren 2005) Stjernquist-Desatnik & Holst (1999) compared tonsillar core specimens of patients with recurrent pharyngitis with a control group that was operated on namely because of obstructive symptoms alone, without throat infections. They found no significant differences between the groups in terms of the mean number of bacterial isolates per patient or in the distribution of bacteria. (Stjernquist-Desatnik & Holst 1999)

There is also some literature on tonsillar bacterial biofilms as a causative agent for chronic tonsillar hypertrophy or for chronic tonsillitis, causing recurrent acute pharyngitis episodes as exacerbations. In the study by Torretta *et al*. (2013), biofilm-producing bacteria were found in 50% of 44 tonsillar specimens from children with recurrent exacerbations of chronic hyperplastic tonsillitis, and Staphylococcus aureus was the most frequent pathogen (82%). They also reported a significant relationship between the grade of tonsillar hyperplasia and the presence of tonsillar biofilm-producing bacteria. (Torretta *et al.* 2013)

2.8 Chronic pharyngitis and chronic tonsillitis

Various unspecific irritating factors like smoking, chronic rhinosinusitis, allergies, gastroesophageal reflux, poor dental hygiene and dust exposure may cause chronic pharyngitis. Usually only minor findings like hyperplasia of the lymphonoid tissue on the posterior pharyngeal wall are detectable. Elimination of the irritating factor is adequate treatment, and tonsillectomy may even worsen symptoms. (Alho 2011)

Some patients with recurrent pharyngitis develop chronic tonsillitis, and this disease is more common in adults. Patients who suffer from chronic tonsillitis usually have one or more of the following symptoms: chronic throat pain, enlarged palatine tonsils, enlarged and tender neck lymph nodes or halitosis. Some patients have cryptic tonsils and these crypts may contain intratonsillar plugs which may be a cause of bad breath. Both infection and altered immunological function have been proposed as playing a role in the development of chronic tonsillitis. Exposure to radiation also increases the risk for chronic tonsillitis. (Alho 2011)

2.9 Tonsillectomy

Tonsillectomy is one of the most common otorhinolaryngological surgical procedures. The number of tonsil operations varies over time as well as between and within different countries. (van den Akker *et al.* 2004). According to a nationwide questionnaire in Finland, 8% of the respondents younger than 30 years had undergone tonsillectomy. They also reported that the frequency of tonsillectomy operations by age was multimodal; it increased in preschool-aged children, declined thereafter and increased again in teenagers. (Mattila *et al.* 2001) According to the OECD health data 152 tonsillectomies per 100 000 inhabitants were performed in Finland in 2010. The tonsillectomy rate in 2010 in Europe was the highest in the Netherlands (241/100 000 inhabitants), the lowest in Slovenia (47/100 000 inhabitants) and was in average in European Union 128 per 100 000 population. (Lafortune *et al.* 2012)

2.9.1 Procedure and techniques

Tonsillectomy is defined as a surgical procedure that completely removes the palatine tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the pharyngeal muscular wall. Usually both tonsils are removed and adenoidectomy may be performed simultaneously. (Alho 2011)

The traditional “cold” dissection tonsillectomy technique involves removal of the tonsil by dissecting the peritonsillar space with metal instruments, with continuous haemostasis obtained through ligation of blood vessels during tonsil removal. This method is still considered a standard with which to compare the effectiveness and safety of other newer techniques. Electrosurgical dissection (i.e., diathermy) of the peritonsillar space using either mono- or bipolar diathermy is another common tonsillectomy technique—the most common “hot” tonsillectomy technique. Mono- or bipolar diathermy is also often used for haemostasis during “cold” tonsillectomy, and this kind of mixed technique is popular. Many of the newer “hot” or powered instrument techniques (e.g. radiofrequency, coblation, harmonic scalpel) have been introduced to reduce postoperative morbidity and risk of haemorrhage. The heat produced by these techniques produces haemostasis during the procedure. (McClelland & Jones 2005) Numerous randomised clinical trials have assessed and compared the different tonsillectomy techniques, but they are not covered in this work.

Tonsillotomy, intracapsular surgery or other partial tonsil removal techniques have gained popularity, especially when treating children with sleep-disordered breathing. However, they are not being generally indicated for recurrent pharyngitis because of the relatively sparse high-quality published evidence on these techniques and on their long-term follow-up, particularly concerning recurrent tonsillitis.(Baugh *et al.* 2011) These techniques are not elaborated on in this work.

2.9.2 Perioperative care, postoperative care and complications

Tonsillectomy is a surgical procedure with associated morbidity, including the disadvantages of prolonged postoperative throat pain, postoperative nausea and vomiting (PONV), delayed feeding, possible hospitalisation, risks of anesthesia and financial costs. According to a national audit in the U.K., about 1% of tonsillectomy patients experienced delayed discharge during their initial hospital stay, and up to 4% had secondary complications requiring readmission after tonsillectomy. The primary reasons for readmission or prolonged initial stay included pain, PONV, fever and tonsillar haemorrhage. (Royal College of Surgeons 2005) According to a Finnish study, 44% of patients contacted healthcare professionals postoperatively after their hospital discharge. The leading reason for a telephone contact was pain and for a personal visit haemorrhage.(Valtonen *et al.* 2004) A recent population-based register analysis in the U.S. reported an adult tonsillectomy complication rate of 1% (Chen *et al.* 2014).

The main adverse effect of tonsillectomy is frequent postoperative pain. Occasionally, significant oropharyngeal pain may result in decreased oral intake, dysphagia, dehydration and weight loss (Randall & Hoffer 1998, Salonen *et al.* 2002). Some RCTs have provided data on postoperative pain levels in adults (Atallah *et al.* 2000, McKean *et al.* 2006). Some studies have also directly addressed the question of postoperative pain over the time following adult tonsillectomy (Salonen *et al.* 2002, Warnock & Lander 1998). According to these studies, in most cases pain lessens during the first few days after tonsillectomy but is likely to increase at day 4 or 5 before finally tailing off from day 6 onwards. The reason for this increase in pain is not known, but it is not thought to be due to infection. The mean duration of post-tonsillectomy pain in adults is reported to be 12 days (Salonen *et al.* 2002).

In some settings, intraoperative local anaesthetic regimen injections into the tonsillar fossae have been found to reduce throat pain. A Cochrane review on the effects of local anaesthesia for pain reduction following tonsillectomy found no evidence to support the use of either local anaesthetic infiltration or topical application (Hollis *et al.* 2000). Three more recently published RCTs also found no benefit from local anaesthetics (El-Hakim *et al.* 2000, Nikandish *et al.* 2008, Vasan *et al.* 2002). Some recent RCTs have reported that honey—when used in addition to analgesics and antibiotics—reduces postoperative pain and analgesic requirements in children after tonsillectomy (Boroumand *et al.* 2013, Mohebbi *et al.* 2014, Ozlugedik *et al.* 2006).

Analgesics used most frequently after tonsillectomy are paracetamol and NSAIDs, and their effect on pain relief is proven by several studies (Antila *et al.* 2006, Romsing & Walther-Larsen 1997, Thorneman & Akervall 2000). Paracetamol with codeine is also often prescribed and is effective in post-tonsillectomy pain (Sutters *et al.* 2010). Although paracetamol with codeine is widely used, according to some studies it doesn't provide superior pain control compared with paracetamol alone after tonsillectomy (Moir *et al.* 2000). There is also literature reporting serious adverse effects and even deaths caused by codeine after tonsillectomy, namely in patients with obstructive sleep apnea and especially in children. Therefore, the US Food and Drug Administration (FDA) stated in 2013 that codeine is contraindicated after tonsillectomy in children. (Kuehn 2013) Occasionally also opioids are prescribed or added later on if other analgesics turn out to be insufficient for pain control (Antila *et al.* 2006). A recent review concluded that NSAIDs do not cause a statistically significant increase in postoperative bleeding requiring operative treatment (Riggin *et al.* 2013). The results of the effect of pre-emptive analgesics are controversial (El-Fattah & Ramzy 2013, Salonen *et al.* 2002).

One of the major morbidities associated with tonsillectomy is postoperative nausea and vomiting (PONV), which occurs independently of the tonsillectomy technique and in more than 70% of children who did not receive prophylactic antiemetics (Hanasono *et al.* 2004, Carlisle & Stevenson 2006). Interventions considered for PONV prevention include anti-emetic drugs, single-dose dexamethasone, acupuncture and preoperative fasting. According to a Cochrane review that included 737 studies, anti-emetics tested were effective when compared with a placebo in preventing PONV, with few side effects (Carlisle & Stevenson 2006). Another review and meta-analysis of perioperative dexamethasone in adults concluded that dexamethasone significantly reduces PONV (Diakos *et al.* 2011). Dexamethasone is also reported to decrease throat pain and postoperative bleeding after tonsillectomy (Afman *et al.* 2006, Diakos *et al.* 2011).

According to a Cochrane review of NSAIDs in pediatric tonsillectomy, there was less PONV when NSAIDs were used as part of the analgesic regimen, compared to when NSAIDs were not used (Cardwell *et al.* 2005). Another Cochrane review concluded that stimulation of the P6 acupuncture point is also effective in reducing PONV (Lee & Fan 2009). There are no studies about the effectiveness of fasting for PONV prevention in adults. A Cochrane review about preoperative fasting in children concluded that there is insufficient evidence to make a recommendation on fasting prior to tonsillectomy for the prevention of PONV (Brady *et al.* 2005).

Primary haemorrhage is defined as bleeding that occurs within the first 24 hours after tonsillectomy and is usually due to the surgical technique and reopening of a blood vessel. Secondary haemorrhage occurs more than 24 hours after the procedure, usually between the fifth and tenth postoperative days, and is often caused by sloughing of the primary eschar of the tonsillar fossa produced by the healing process. The rates of primary haemorrhage range from 0.2% to 2% and the rates of secondary haemorrhage range from 0.1% to 3%. (Windfuhr *et al.* 2005) The audit in the U.K. reported that the risk of postoperative bleeding was higher with older patients, with male gender and with a history of recurrent tonsillitis (4%) or previous peritonsillar abscess (5%) (Royal College of Surgeons 2005). According to most of the recent review articles there is no difference in haemorrhage rates after tonsillectomy between the different tonsillectomy techniques (Burton & Doree 2007, Neumann *et al.* 2007, Pinder & Hilton 2001). Postoperative haemorrhage may result in readmission leading only to observation, local anesthesia diathermy coagulation treatment or even general anesthesia surgery to control bleeding.

According to a Cochrane review, antibiotics had no impact on rates of secondary haemorrhage (Dhiwakar *et al.* 2012). Another Cochrane review found that NSAIDs

did not significantly alter pediatric postoperative bleeding rates compared with a placebo or other analgesics (Cardwell *et al.* 2005). Another meta-analysis demonstrated an increased risk of post-tonsillectomy haemorrhage with the use of aspirin after tonsillectomy, but not with NSAIDs (Krishna *et al.* 2003). The post-tonsillectomy haemorrhage rate with ketorolac is higher, ranging from 4% to 18%, suggesting that ketorolac use should be avoided after tonsillectomy (Bailey *et al.* 1997, Judkins *et al.* 1996).

Other complications of tonsillectomy are diverse. Perioperative complications include, for instance, trauma to the teeth, larynx, pharyngeal wall or soft palate; laryngospasm; laryngeal oedema; aspiration; respiratory compromise; endotracheal tube ignition; and cardiac arrest. Injuries to nearby structures have also been reported, including lip burn, eye injury and fracture of the mandibular condyle. Postoperative complications include, for example, referred otalgia, post-obstructive pulmonary oedema, velopharyngeal insufficiency, nasopharyngeal stenosis and voice changes.(Johnson *et al.* 2002) Many other rare complications of tonsillectomy have also been described. Among these are reports of vascular injury, subcutaneous emphysema, jugular vein thrombosis, atlantoaxial subluxation (Grisel syndrome), taste disorders (hypogeusia, dysgeusia and phantogeusia) and persistent neck pain (Eagle syndrome). (Leong *et al.* 2007) Complications are more common in patients with craniofacial disorders, Down's syndrome, cerebral palsy, major heart disease or bleeding diatheses and in children younger than three years of age with obstructive sleep apnea (Johnson *et al.* 2002).

Mortality rates of tonsillectomy have been estimated to be between 1 in 35 000 to 1 in 16 000 patients, based on data from the 1970s (Pratt & Gallagher 1979). A recent prospective national audit reported only one postoperative death after 33 921 tonsillectomies in England and Northern Ireland (Royal College of Surgeons 2005). A recent population-based report in the U.S. reported a 30-day mortality rate of 0.03% after tonsillectomy (Chen *et al.* 2014). About one-third of the deaths are attributable to bleeding, while the remainder are related to aspiration, cardiopulmonary failure, electrolyte imbalance or anesthetic complications (Randall & Hoffer 1998).

In the past, peri- and postoperative antibiotics were widely prescribed for tonsillectomy patients to prevent morbidity. There are, however, no randomised studies to support this practice. A Cochrane review of 10 RCTs found that antibiotics did not have a consistent or clinically important impact in reducing the main morbid outcomes after tonsillectomy (Dhiwakar *et al.* 2012).

The proportion of outpatient versus inpatient tonsillectomies has increased significantly since the 1990s (Stalfors *et al.* 2012) In Finland, about two thirds of the

tonsillectomies were performed as day surgeries in 2010 (Lafortune *et al.* 2012). However, outpatient tonsillectomy rates vary considerably worldwide. (Hanss *et al.* 2011) Several reports have shown that outpatient tonsillectomy is a safe and cost-effective procedure when patient selection is done properly (Hanss *et al.* 2011, Stalfors *et al.* 2012). The main reasons which have enabled same-day treatment operations are improved analgesia and perioperative anesthetic treatment and an extremely low rate of complications between 8 to 24 hours after tonsillectomy (Hanss *et al.* 2011).

2.10 Measuring tonsillectomy outcomes

2.10.1 Researcher-measured outcomes

Traditionally, the efficacy of treatment in non-fatal diseases has been measured by diagnoses, symptoms or some other clinical features which can be objectively measured by a researcher. There are various researcher-measured outcomes that have been used for reporting the effect of tonsillectomy namely on recurrent pharyngeal infections. These include, e.g., blood test results, medication usage, number of culture- or RADT-proven streptococcal pharyngitis episodes, number of pharyngitis episodes requiring medical visits, school or work absence, weight or height measurements and presence of cervical lymphadenopathy. (Alakärppä & Alho 2012)

2.10.2 Patient-recorded outcome measures (PROMs)

There are many studies reporting the effect of tonsillectomy in recurrent pharyngeal infections that use subjective patient-recorded outcome measures. Measurements in which the study subjects report their view of health by addressing symptoms, health status or quality of life are called patient-recorded outcome measures (PROMs). PROMs have often been collected as patient-kept diary data or as parent-kept diary data in studies concerning children. PROMs that have been used in previous studies on the effect of tonsillectomy on recurrent pharyngitis include, e.g., number of days with a sore throat or other related symptoms, number of any pharyngitis episodes, number of days of school or work absence or medication use reported by patients. PROMs can be divided into single or focused patient-reported measurements of symptoms or actual QOL scales. (Alakärppä & Alho 2012)

2.10.3 Quality of life (QOL)

Quality of life (QOL) measurements can be classified as a subtype of PROMs and it provides an additional subjective point of view on treatment efficacy. QOL is defined as individuals' perceptions of their position in life in the context of the culture and value systems, put forth by the World Health Organization (WHO). QOL scales seek to quantify a subjective sense of well-being as objectively as possible so that comparisons between different treatments or symptoms can be made over time.

Measuring QOL is based on structured questionnaires that measure an individual's perception of his/her subjective ability to function physically, mentally and socially. This measured subjective ability to function and life satisfaction are presented through different dimensions or domains. QOL instruments can be generic, disease-, site- or dimension-specific (Fitzpatrick *et al.* 1998). However, QOL instruments can give misleading results if they are not properly designed and validated.

Generic QOL instruments enable their use and comparison across different specialties or populations. Generic QOL measures are multi-domain instruments and therefore complex. As a result, a single response can distort general scoring, which leads to a danger of misinterpreting the results if improvement in only a single domain is reported as a general improvement of QOL. (Alakärppä & Alho 2012) Non-specific generic QOL instruments can also decrease sensitivity to detect the effects of interventions if the applied instrument does not contain relevant domains (Fitzpatrick *et al.* 1998). Disease- and site-specific questionnaires are more sensitive in discovering effects of interventions, but their sensitivity in detecting broader aspects of health are poor. QOL instruments have been available since the 1990s in otorhinolaryngology.

Most studies on QOL after adult tonsillectomy have used the Glasgow Benefit Inventory (GBI) questionnaire for QOL measurement (Andreou *et al.* 2013). The GBI is a generic QOL instrument developed especially for otorhinolaryngological interventions and it assesses QOL postoperatively. The GBI questionnaire includes 18 questions about change in QOL after an intervention. In scoring the GBI, the responses to all 18 questions are averaged to have equal weight. The average score is then transposed onto a continual benefit scale ranging from -100 to +100. A score of -100 means maximal negative benefit, a score of 0 no benefit at all and a score of +100 maximal positive benefit to QOL. A combined total GBI score for change in QOL after tonsillectomy can then be counted. To achieve more accurate information about QOL, the GBI subscale scores for general benefit, social support and physical benefit

can also be calculated. (Robinson *et al.* 1996) Some other occasionally used instruments for measuring QOL after tonsillectomy in chronic or recurrent tonsillitis are, e.g., the disease-specific Tonsil and Adenoid Health Status Instrument (TAHSI) and the Specific Benefits from Tonsillectomy Inventory (SBTI) and generic 17D, 16D and 15D questionnaires (Baumann *et al.* 2006, Nokso-Koivisto *et al.* 2014, Wiksten *et al.* 2013, Witsell *et al.* 2008).

2.11 Tonsillectomy outcomes in recurrent pharyngitis in adults

2.11.1 Researcher-measured outcomes

A recent Cochrane review compared tonsillectomy with non-surgical treatment for recurrent pharyngitis and included trials that used reductions in the number and severity of pharyngitis episodes as main outcome measures. This review found limited evidence of tonsillectomy benefit in adults with recurrent pharyngitis as only one RCT concerning adults was included (Burton & Glasziou 2009). In adults with proven recurrent GAS pharyngitis, tonsillectomy significantly reduced the incidence of GAS episodes in the 90-day postoperative period, with a NNT of 5 (Alho *et al.* 2007). Apart from adults with proven recurrent GAS pharyngitis, there is no evidence on which adults will objectively benefit from tonsillectomy. The same Cochrane review included four trials assessing tonsillectomy benefit in children (Burton & Glasziou 2009). The review concluded that (adeno)tonsillectomy is effective in reducing the number of episodes and days with a sore throat in children. However, according to the analysis the benefit is more marked with severely affected children, who will avoid three episodes of sore throat in the next year.(Burton & Glasziou 2009) Currently, there are no RCTs reporting the efficacy of tonsillectomy for patients experiencing recurrent pharyngitis that has lasted less than 12 months (Baugh *et al.* 2011). According to Cochrane review the control group also showed a significant spontaneous reduction in recurrent pharyngitis rates (Burton & Glasziou 2009).

Most of the published clinical trials investigating the efficacy of tonsillectomy have a high risk of bias because of poorly defined inclusion criteria, non-randomised selection of operated patients, exclusion of patients with severe symptoms, or reliance on caregivers for postoperative data collection (Burton & Glasziou 2009, van Staaij *et al.* 2004).

2.11.2 Patient-recorded outcomes (PROMs)

Some studies have reported that tonsillectomy decreases patient-reported numbers of antibiotics treatments, missed workdays and medical appointments for pharyngitis in adults (Akgun *et al.* 2009, Bhattacharyya & Kepnes 2002, Mui *et al.* 1998, Senska *et al.* 2010). Wiksten *et al*. (2013) studied the patient-reported costs of chronic or recurrent tonsillitis in adults in Finland. Costs related to primary healthcare services, previous hospital treatment, laboratory services and sick leaves were included in their analysis. The annual mean self-reported costs of chronic or recurrent tonsillitis in adults were estimated to be €3644 and they diminished to €500 after the operation. Diminished costs were most evident in self-reported sick leaves. The mean total cost of the tonsillectomy operation, perioperative care and postoperative care was estimated to be €2500. (Wiksten *et al.* 2013) Self-reported healthcare service costs and the number of days of sick leave diminished significantly also in children and in adolescents (Nokso-Koivisto *et al.* 2014). Some other studies have also evaluated the economic benefit of tonsillectomy in recurrent pharyngitis based on retrospective patient surveys, and they suggest that tonsillectomy is a cost-effective treatment method (Bhattacharyya & Kepnes 2002, Fujihara *et al.* 2006).

Also some register-based studies have been conducted. Stalfors *et al*. (2012) published an article based on data collected in the National Tonsil Surgery Register in Sweden between 1997 and 2008 and found that 97% of patients who were operated on for recurrent pharyngitis reported having experienced moderate to clear benefit six months after surgery.(Stalfors *et al.* 2012)

2.11.3 Quality of life after tonsillectomy

In their systematic review article Alakärppä & Alho (2012) concluded that although the use of QOL instruments has gradually increased, validated QOL instruments have been used very seldom in RCTs concerning otorhinolaryngological interventions.

Senska *et al*. (2010) conducted a prospective controlled study on QOL benefit of tonsillectomy in adults with recurrent pharyngitis by using the GBI 14 months after tonsillectomy. They reported improved mean GBI scores: total +19, general subscale +18, social subscale 0 and physical subscale +39. (Senska *et al.* 2010) Powell *et al*. (2012) also reported improved QOL after tonsillectomy in adults with recurrent tonsillitis in their prospective study by using the SF-36 and HRQOL generic QOL instruments. Another prospective cohort study by Wiksten *et al*. (2013) reported QOL improvement after adult tonsillectomy by using the generic 15D QOL instrument.

Most of the patients were operated on for chronic or recurrent tonsillitis. They found that the most significant QOL benefit occurred in the dimensions of discomfort and symptoms as well as sleeping. (Wiksten *et al.* 2013) Another prospective study in Finland found similar QOL improvement after tonsillectomy in children and adolescents by using generic 16D and 17D QOL questionnaires. However, indications for tonsillectomy were broader: 51% of patients had recurrent or chronic tonsillitis, 40% had tonsillar hypertrophy alone and 9% had both. (Nokso-Koivisto *et al.* 2014) The prospective studies mentioned above were published after study I of this thesis. The first large-scale prospective national QOL study was published in the U.K. by Swan *et al* (2012). They assessed the effect of otolaryngological management on the QOL of adult patients and proposed that only patients who were treated surgically or who were given a hearing aid reported a significant improvement in their QOL after treatment in the field of otolaryngology. However, the effect of tonsillectomy alone on recurrent pharyngitis was not studied in detail in that report (Swan *et al.* 2012).

There are a few uncontrolled retrospective observational studies suggesting a significant improvement in QOL, measured by the GBI, after tonsillectomy in adults with recurrent or chronic pharyngitis. Those studies have reported mean total GBI values ranging from +12 to +35, and QOL benefit has been most evident in the physical subscale in a majority of the studies. (Bhattacharyya *et al.* 2001, Richards *et al.* 2007, Schwentner *et al.* 2007) Studies reporting QOL measured by the GBI after adult tonsillectomy are presented in Table 6. Witsell *et al*. (2008) reported significant QOL benefit of tonsillectomy in adults with recurrent or chronic pharyngitis using the Tonsil and Adenoid Health Status Instrument (TAHSI) and the SF-12 Health Survey. However, all these uncontrolled studies had numerous methodological flaws, such as inclusion of patients with chronic tonsillitis without definition based on signs and symptoms, absence of a control group, low response rates with potential selection bias and poor follow-up. A systematic review assessing QOL after adult tonsillectomy in patients with chronic or recurrent pharyngitis included eight studies and concluded that tonsillectomy is likely to improve overall QOL especially in the aspect of physical and general health. However, the social benefits of tonsillectomy appear to be non-significant. (Andreou *et al.* 2013)

There are only limited data and no prospective studies about the factors that predict high QOL after tonsillectomy in recurrent pharyngitis. Baumann *et al*. (2006) reported that younger adult patients with chronic tonsillitis achieved higher postoperative GBI scores than older patients. Schwentner *et al*. (2007) found that adult patients with chronic tonsillitis having concomitant chronic diseases such as

diabetes, bronchial asthma or metabolic syndrome are likely to have lower postoperative GBI scores.

Table 6. Other studies reporting QOL measured by the Glasgow Benefit Inventory (GBI) after tonsillectomy for chronic or/and recurrent tonsillitis in adults.

Study	n	Response rate	Age group (years)	Design	Indication	Entry criteria	GBI evaluation time after tonsillectomy	Mean total GBI
Bhattacharyya *et al*. 2001	65	26%	>16	retrospective survey	chronic tonsillitis	not defined	≥1 year	+27
Baumann *et al*. 2006	109	42%	>18	retrospective survey	chronic tonsillitis	not defined	≥2 years	+17
Richards *et al*. 2007	47	39%	15-25	retrospective survey	recurrent or chronic tonsillitis	not defined	≥1 year	+35
Schwentner *et al*. 2007	227	38%	>16	retrospective survey	recurrent or chronic tonsillitis	not defined	1 to 6 years	+16 (CT)[1] +12 (HT)[2]
Senska *et al*. 2010	97	85%	≥18	prospective cohort study	recurrent tonsillitis	≥3 episodes in 12 months	14 months	+19

[1] CT = cold tonsillectomy; tonsillectomy with cold instruments, [2] HT = hot tonsillectomy; tonsillectomy with diathermy

2.12 Tonsillectomy indications and guidelines for recurrent pharyngitis

Wide variations in tonsillectomy rates have been reported around the world (van den Akker *et al.* 2004, Lafortune *et al.* 2012). Such variations are usually assumed to be due to heterogeneity in clinical practice and training rather than due to differences in clinical need (Capper & Canter 2001). The literature on tonsillectomy for recurrent pharyngitis is limited and most of the studies published refer to the pediatric population. The widely used Paradise criteria for tonsillectomy in recurrent pharyngitis are seven episodes of pharyngitis in the preceding year, five episodes in each of the preceding two years or three episodes in each of the preceding three years. These episodes also have to include, in addition to a sore throat, at least one of the following features: temperature > 38.3 °C, cervical adenopathy, positive GAS culture or tonsillar exudate (Table 7). (Paradise *et al.* 1984) However, these criteria have been arrived at somewhat arbitrarily and they do not take into account whether the pharyngitis rate is improving or worsening and make no distinction between adults and children, in whom this disease may behave in different ways.

Table 7. Paradise criteria for tonsillectomy.

Criterion	Definition
Minimum frequency of sore throat episodes	≥7 episodes in the preceding year OR ≥5 episodes in each of the preceding 2 years OR ≥3 episodes in each of the preceding 3 years
Clinical features (sore throat plus the presence of one or more qualifies as a counting episode)	Temperature > 38.3°C OR Tonsillar exudate OR Cervical lymphadenopathy (tender lymph nodes or > 2 cm) OR Positive culture for GAS

Concerning recurrent pharyngitis, there are no other widely accepted premises behind tonsillectomy indications in addition to the rate of acute episodes. Neither are there any known clinical factors that predict tonsillectomy benefit. Some studies have suggested that their own prediction rules—tonsillitis indexes—could serve as an indicator for beneficial tonsillectomy in adults, but clinical studies validating these indexes are lacking. These indexes are generated based on a combination of the frequency of pharyngitis episodes and the length of the morbidity period. (Fujihara *et al.* 2005, Kasenomm *et al.* 2005) Currently used

serum biomarkers have shown no role in clinical practice in predicting the outcome of tonsillectomy for chronic tonsillitis (Bohne *et al.* 2013).

So, there is controversy in the literature concerning tonsillectomy indications for recurrent pharyngitis. The current lack of consensus on surgical indications and perioperative management further supports the need for evidence-based clinical practice guidelines that highlight best practices. Seven recently published national guidelines concerning tonsillectomy indications in recurrent pharyngitis were identified. However, they differ from each other in some aspects. Three of them are combined guidelines including also recommendations for acute pharyngitis, and they are also mentioned in chapter 2.6. In summary, all the guidelines recommend watchful waiting and conservative treatment before tonsillectomy. Most of the guidelines recommend indications based on Paradise criteria (Paradise *et al.* 1984). A summary of the guidelines is presented in Table 8.

Table 8. Comparison of different guidelines recommending indications for tonsillectomy in recurrent pharyngitis.

Guideline	Indications
United States (IDSA)[1]	Tonsillectomy is not recommended solely for recurrent pharyngitis.
(Shulman *et al*. 2012)	Tonsillectomy may be considered in the rare patient whose symptomatic episodes do not diminish in frequency over time and for whom no alternative explanation for recurrent GAS pharyngitis is evident.
United States (AAO-HNS)[2]	Paradise criteria
(Randel 2011)	
United Kingdom (ENT UK)	- 5 or more episodes in the past year and symptoms at least for a year
(ENT UK 2009)	or
	- 8 or more episodes within a year
Scotland (SIGN)	Paradise criteria
(Scottish Intercollegiate Guidelines Network 1999)	
France	- 5 or more episodes per year in the past 2 years or
(Lescanne *et al*. 2012)	- 3 or more episodes per year in the past 3 years
Italy	- 5 or more episodes per year lasting at least 18 months
(Materia *et al*. 2005)	
Finland	- 4 or more episodes in the past year or
(Sore throat: Current Care Guidelines 2013)	- 3 or more episodes in the past 6 moths

[1] IDSA = Infectious Diseases Society of America

[2] AAO-HNS = American Academy of Otolaryngology – Head and Neck Surgery

There are also some other indications for tonsillectomy that are not the subject of this current thesis and are not elaborated on, but only mentioned here. Other indications are somewhat discretionary and include sleep-disordered breathing, PFAPA, peritonsillar abscess, halitosis, febrile seizures, malocclusion, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), muffled speech, tonsillar hypertrophy, chronic carriage of GAS and chronic tonsillitis (Baugh *et al.* 2011).

2.13 Other treatment options for recurrent pharyngitis

Three RCTs examined whether prophylactically used antibiotics are capable of reducing the incidence of recurrent pharyngitis in children. One of these three studies showed no effect and two studies showed modest but statistically significant prophylactic effect. However, natural resolving of recurrent pharyngitis over time was evident in all these studies. In addition to increased prescribing costs, general use of prophylactically used antibiotics involves the risks of development of resistant bacteria, adverse effects including allergic reactions and promotion of Candida infections. These possible hazards of antibiotics must be weighed against their efficacy. Prophylactic antibiotic therapy may be considered as an alternative to surgery in those in whom surgery is contraindicated. (Aksit *et al.* 1998, Lildholdt *et al.* 2003, Mora *et al.* 2003)

As mentioned earlier and as concluded by the Cochrane review, some cases of recurrent pharyngitis may resolve themselves without surgery as a result of natural improvement of the disease (Burton *et al.* 2009). Sometimes surgery may be an alternative to watchful waiting, and this aspect is taken into account in many treatment guidelines.

3 Purpose of the study

The purpose of the present study was:

1. To find out if tonsillectomy reduces the number of specifically defined severe acute pharyngitis episodes, the overall number of acute pharyngitis episodes or the number of acute pharyngitis episodes leading to medical consultations in adults with recurrent pharyngitis.
2. To find out if tonsillectomy diminishes the number of days with pharyngitis symptoms and days off from school or work in adults with recurrent pharyngitis.
3. To assess the quality of life of adult patients with recurrent pharyngitis after tonsillectomy.
4. To determine predictive factors for patient satisfaction after tonsillectomy in adult patients with recurrent pharyngitis.
5. To find out the patient- or episode-related factors that predict primary care medical consultation for acute pharyngitis in adults.

4 Patients and methods

4.1 Quality of life and factors affecting it after tonsillectomy for recurrent streptococcal pharyngitis (I)

A total of 70 consecutive adult patients with recurrent streptococcal pharyngitis episodes, referred to a tertiary care ear, nose and throat (ENT) department from October 2001 to May 2005 and fulfilled the entry criteria, were enrolled for this prospective cohort study. This population was originally collected for another randomised controlled study (Alho *et al.* 2007). The study inclusion criteria included three or more pharyngitis episodes in the preceding six months or at least four episodes in the preceding 12 months. These episodes had to be severe enough for the patient to seek medical attention and at least one of the episodes had to be GAS infection proven by RADT or by culture. The exclusion criteria were: on-going antibiotic treatment for another reason; any possibility that recurrence was due to non-compliance with treatment; history of peritonsillar abscess; major airway or heart disorder or bleeding diathesis making same-day surgery unfeasible; age under 15 years; and residence outside the city of Oulu or the neighbouring eight communities at the time.

All the patients were examined at assignment by an ENT doctor and background data on patient characteristics, risk factors and pharyngitis history were obtained. All the patients underwent tonsillectomy under general anesthesia as outpatient surgery. The tonsillectomies were performed by several ENT doctors using blunt or diathermy dissection and details of the procedures and recovery periods were recorded. Changes in QOL were assessed six months after tonsillectomy by using the Glasgow Benefit Inventory (GBI) questionnaire. In scoring the GBI questionnaire, we averaged the responses to all 18 questions to give each question equal weight. We then transposed the average score onto a continual benefit scale ranging from -100 to +100; a score of -100 meant maximal harm, a score of 0 meant no change and a score of +100 suggested maximal benefit of QOL. In addition to the total GBI score, GBI subscale scores for general benefit, social support and physical benefit were also calculated. (Robinson *et al.* 1996) The GBI instrument was validated in Finnish by forward translation, reconciliation, back translation and pilot testing as suggested by Wild *et al*. (2005). The questions in Finnish are presented in Appendix 1.

To obtain more accurate data on the patients' pharyngitis symptoms before and after tonsillectomy, diary data on symptoms were also collected. Patients were asked

to record their acute symptoms (throat pain, fever, rhinitis and cough), pharyngitis episodes and doctor visits either before or after tonsillectomy. Of the 70 patients, 34 randomly selected patients were asked to collect this diary data on symptoms before their tonsillectomy during their waiting list time. The other randomly selected 36 patients were advised to collect the same diary data for six months after their tonsillectomy. Simple randomisation was used and the allocation sequence was concealed from the investigators using sequentially numbered, opaque, sealed envelopes.

The objective of this study was to determine the influence of tonsillectomy on the QOL of adult patients suffering from recurrent streptococcal tonsillitis, and to determine any factors that predict patient satisfaction.

4.2 Number of pharyngitis episodes and symptom days after tonsillectomy in recurrent pharyngitis of any origin (II)

Participants for this randomised controlled trial were recruited from consecutive patients referred to a tertiary care ENT centre from October 2007 to December 2010 for tonsillectomy because of recurrent pharyngitis. A total of 86 patients volunteered to participate and fulfilled the study criteria. The clinical criterion for entry to the study was three or more pharyngitis episodes within the previous 12 months. These episodes had to be disabling, prevent normal functioning, be severe enough for the patient to seek medical attention and be thought to involve the palatine tonsils. It was not necessary for any of the episodes to be proven GAS infection. The exclusion criteria were age less than 13 years, history of peritonsillar abscess, chronic tonsillitis, on-going use of antibiotic agents, residence outside of the Oulu region, pregnancy or previous illness making outpatient surgery unfeasible.

All the patients were examined by an ENT doctor and background data on patient characteristics, risk factors and pharyngitis history were obtained at the beginning of the study. Patients were assigned to the control group or the tonsillectomy group by using simple randomisation. The allocation sequence was concealed from the investigators by using sequentially numbered, opaque, sealed envelopes. The patients in the control group were placed on a waiting list for tonsillectomy to undergo surgery after 5 to 6 months (watchful waiting) and they were followed up before the tonsillectomy. The patients in the tonsillectomy group underwent surgery as soon as possible—taking practical matters into account—and they were followed up at least five months after the tonsillectomy. The tonsillectomies were performed under

general anesthesia as day surgery by several ENT surgeons using blunt or diathermy dissection.

The patients were advised to visit the study physician primarily or their general practitioner secondarily whenever they had acute symptoms suggestive of pharyngitis during their follow-up period. The patients were particularly advised that it was important to seek medical advice for their symptoms during the trial exactly as they had done before. At the acute visit, the patients underwent a thorough clinical examination including a throat swab and a blood test to measure serum levels of C-reactive protein (CRP). The CRP test was repeated three days later. All laboratory and microbiological analyses were performed by staff blinded to the clinical data. A study notebook provided to the patients included information about the study and written instructions for their general practitioners, including information on examining and recording ear, throat and nose status and taking blood samples and throat cultures during the acute appointment for the study purpose. The patients received treatment as prescribed by a physician (the study physician, if available), who recorded the date, location, diagnosis and treatment of acute episodes in the notebook. The study notebook also included a GBI questionnaire to be answered six months after surgery.

During their follow-up period the patients used a symptom diary to record the presence and severity (1 = mild, 2 = moderate or 3 = severe) of the following acute symptoms: throat pain, cough and rhinitis. They also recorded days with a fever and absence days from school or work. Symptoms lasting more than 30 days were considered chronic and were not included in our analysis.

The primary outcome was the difference in the proportion of patients who had a severe pharyngitis episode within five months before or after tonsillectomy. To be considered severe, an episode had to involve medical consultation registered in the study notebook and the patient needed to have acute throat pain and signs suggesting that the symptoms originated in the pharynx. In addition, the serum level of CRP, either on the day of the acute appointment or three days later, had to be higher than 40 mg/L. If a blood sample was mistakenly not collected, the result of a throat culture had to show other than normal flora and the patient had to grade the throat pain as severe (grade 3) in the symptom diary. Secondary outcomes were between-group differences in proportions of patients with any episode of pharyngitis (sore throat lasting $\geq$ 2 days) and in proportions of patients with an episode leading to medical consultation during the five-month follow-up. Other secondary outcomes were between-group differences in time to the next pharyngitis episodes, in the mean rate of episodes, in the mean number of days absent from school or work and in the mean number of symptomatic days during the whole follow-up time.

4.3 Quality of life and factors affecting it after tonsillectomy for recurrent pharyngitis of any origin (III)

In this prospective cohort study, the populations of study I and study II were combined and altogether 156 patients were enrolled. The participants were screened from consecutive adult patients referred for tonsillectomy as described in chapters 4.1 and 4.2. The clinical criterion for the study entry was three or more episodes of pharyngitis of any origin within the previous 12 months. Exclusion criteria were: age less than 13 years, history of peritonsillar abscess, chronic tonsillitis, on-going use of antibiotic agents, residence outside of the Oulu region, pregnancy or previous illness.

At the initial visit, the patients were examined by an ENT doctor and their tonsils were classified as normal, enlarged, chronically infected or scarred. The patients also answered a self-administered questionnaire where information on patient characteristics, prior pharyngeal symptoms and pharyngitis episodes was collected. The background information gathered included age, gender, allergy, tobacco use and risk factors for pharyngitis (number of people in the family, similar infections in the family, dental caries and use of the same toothbrush over three months). Furthermore, we collected data on the number of previous episodes of acute pharyngitis diagnosed by a physician during the past 12 months and whether the patient had experienced GAS pharyngitis diagnosed by a physician during the past six months. These data were collected by either asking the patients or checking medical records. We also asked if the patients had experienced recurrent respiratory infections or frequent throat pain. All the patients underwent tonsillectomy. The details and adverse effects of the tonsillectomy were recorded.

We allocated half of the participants to keep a diary on acute symptoms before tonsillectomy by using simple randomisation that was done earlier for study I and study II. The diary-based data on symptoms after tonsillectomy were not used in this study III. In this study the randomly selected subgroup who kept a diary while being on the waiting list for tonsillectomy was called the diary-keepers group. They were given symptom diaries in which they recorded the presence of the following acute symptoms they had before tonsillectomy: throat pain, fever, cough and rhinitis. In addition, medical consultations for pharyngeal symptoms were recorded.

4.4 Predictive factors for medical consultation for sore throat in adults with recurrent pharyngitis (IV)

This study is a secondary analysis of data from two randomised trials. The populations of study I and study II were combined and altogether 156 patients were analysed. The methods used in these trials are described in chapters 4.1 and 4.2.

The patients used a symptom diary to record the presence of the following acute symptoms: throat pain, cough, rhinitis and fever. Also the severity (mild, moderate or severe) of the throat pain was recorded in the pharyngitis of any origin material (86 patients). (II) We collected the study notebooks at the follow-up visit and checked missing or illegible information by telephone. Two patients lost their symptom diaries: it was assumed in the analysis that they had no symptoms during the study period. We considered at least two consecutive days with a sore throat as an episode. The patients recorded altogether 208 such episodes of acute pharyngitis.

In this study, we sought patient- and episode-related factors possibly explaining whether or not the patient made a medical visit for an acute sore throat either before or after tonsillectomy.

4.5 Statistical analysis

4.5.1 Study I

Descriptive data were given as means with standard deviations (SDs) or as medians with ranges. The chi-square test was used to compare categorical variables and the Mann–Whitney U test was used to compare continuous variables. The group of patients who were least pleased six months after their tonsillectomy was determined on the basis of the total GBI score. A cut-off point of +18 was used. A total GBI score of less than +18 represented the worst 30th percentile of patients considering their postoperative QOL. Survival curves were constructed according to the Kaplan–Meier method, starting from the date of the first follow-up day and the differences between the groups were tested with the log rank test.

4.5.2 Study II

To achieve statistical power of 80% to detect an absolute difference of 25% in the recurrence rates of severe pharyngitis episodes, it was estimated that 70 patients needed to be enrolled in the study. This estimate using a five-month recurrence rate of

25% in the control group and 0% in the tonsillectomy group was based on the results of the previous trial (Alho *et al.* 2007). All of the participants were analysed on an intention-to-treat basis according to a pre-established plan.

For descriptive data, means with standard deviations (SDs) or medians with interquartile ranges (IQRs) were calculated. The Mann–Whitney U test was used to compare continuous variables. Survival curves were constructed by using the Kaplan–Meier method, starting from the date of randomisation in the control group and from the date of surgery in the tonsillectomy group. Differences between the groups were tested by using the log-rank test. The absolute differences and the 95% confidence intervals (CIs) in the proportions of recurrence between the groups at five months were calculated. The numbers of all pharyngitis episodes, symptomatic days and absences from school or work per person-year were determined by using follow-up data. In the tonsillectomy group, the individual recovery times immediately after tonsillectomy during which the patient had continuous throat pain, (mean 17 (SD 6) days) were excluded from the risk time.

4.5.3 Study III

For descriptive data, means with SDs or medians with ranges or IQRs were calculated. Linear regression modelling was applied to assess the predictive value of various items of patient data in predicting the GBI total score. First, models were fitted for all subjects for whom pertinent data were available, in which the prognostic factors included routinely recorded history and clinical characteristics. The small-sample corrected Akaike information criterion (AIC_c) was used to select the optimal subset of predictors. Second, for those patients for whom all diary data were also available, models including these factors upon the most predictive clinical characteristics were fitted, and an optimal model was again sought by AIC_c. The computations were performed using functions *lm* and *glmulti* in an R environment for statistical computing. The results of regression models with the GBI total score as the outcome variable were reported as estimated regression coefficients and their 95% confidence intervals of the factors selected for the final model. The correlation coefficient, r, between observed and fitted scores was calculated.

4.5.4 Study IV

For descriptive data, we calculated means with SDs or ranges. To explore patient-related variables and medical consultations, we constructed survival curves for

altogether 156 patients according to the Kaplan-Meier method, starting from the date of the randomisation. The primary end point was the first visit to a physician because of a sore throat. We calculated the cumulative incidence of medical consultations during up to five months of follow-up using life-table analysis. We used a Cox proportional-hazards regression model to explore associations between various patient-related factors and medical consultations for a sore throat. The cumulative risk of visiting a physician was calculated as an adjusted hazard ratio (HR) with 95% confidence intervals (CI). The model included the following variables: age (≤ 20 or > 30 years *vs.* 21–30 years); gender (male *vs.* female); tobacco use (no *vs.* yes); prior streptococcal pharyngitis (no *vs.* yes); number of episodes of pharyngitis in the prior six months (≤ 3 *vs.* > 3) and chronically infected tonsils found at enrolment (no *vs.* yes). The associations between patient-related factors and medical consultations were similar in the episodes before and after tonsillectomy, so these two data sets were combined.

To study episode-related factors and medical consultations, we similarly constructed Kaplan-Meier curves of altogether 208 episodes of acute pharyngitis the 156 patients had, starting from symptom onset. The primary end point was the first visit to a physician because of a sore throat during the first seven days. We calculated the cumulative incidence of medical consultations up to the first week of symptoms using life-table analysis. We used a Cox proportional-hazards regression model to explore the associations between various episode-related factors and medical consultations. The cumulative risk of visiting a physician was calculated as an adjusted HR with 95% CIs. The model included the following variables: maximum throat pain during the episode (mild *vs*. moderate *vs*. severe); fever (no *vs.* yes); other respiratory symptoms (no *vs.* yes) and pre- *vs.* postoperative episode.

4.6 Ethical aspects

All the study protocols were approved by the ethical committee of Oulu University Hospital. Informed consent was obtained from all the participants. All of the patients were treated according to Finnish guidelines concerning tonsillectomy for recurrent pharyngitis and only generally used microbiological and laboratory investigations were carried out. Patients assigned to a waiting list were operated on according to our hospital's normal waiting list time for tonsillectomy and none of the study patients had to wait longer than normally for the operation because of the present study. This waiting time is restricted by Finnish law to no longer than six months. Because of randomisation, some of the study patients were operated on sooner and some

according to our normal waiting list time. However, this possibility was told to all of the participants before randomisation and they approved it.

5 Results

5.1 Background characteristics of the patients in studies I–IV

Altogether 156 adult patients attended studies I–IV. At assignment, 82 of them were randomised to have tonsillectomy as soon as possible, taking practical matters into account. Seventy-four of the patients were placed on a waiting list for tonsillectomy and were operated on according to our hospital's normal waiting time. Details of the baseline characteristics of all the patients are shown in Table 9.

Table 9. Distribution of characteristics obtained by history and preoperative clinical examination in a prospective cohort of 156 adults recruited to studies I–IV.[1]

Characteristic	Immediate tonsillectomy (n=82)	Tonsillectomy after waiting time (n=74)
History		
Median (range) age, years	25 (14–44)	27 (14–65)
Female sex	56 (68)	48 (65)
Median (IQR)[2] number of all pharyngitis episodes per year	5 (4–6)	4 (4–5)
Streptococcal pharyngitis during prior six months	68 (83)	56 (76)
Frequent throat pain	35 (43)	19 (26)
Allergy	29 (35)	21 (28)
Tobacco use	34 (42)	26 (36)
Risk factors for pharyngitis		
Family size over four	22 (27)	13 (18)
Similar infections in the family	12 (15)	11 (15)
Untreated dental caries	13 (16)	7 (10)
Use of same toothbrush over three months	18 (22)	18 (25)
Clinical examination[3]		
Large tonsils	26 (32)	22 (30)
Scarred tonsils	55 (67)	49 (66)
Chronically infected tonsils	8 (10)	10 (14)

[1] Numbers are numbers of patients (percentages) unless otherwise indicated

[2] IQR, interquartile range

[3] More than one feature possible with the same patient

5.2 Effect of tonsillectomy on pharyngitis episodes (II)

Of 260 patients referred for tonsillectomy because of recurrent pharyngitis, 86 fulfilled the study criteria and were recruited. Forty patients were randomly allocated to the control group and 46 patients to the tonsillectomy group. The mean length of the follow-up period was 5.7 (SD 0.7) months for the control group and 6.2 (SD 0.5) months for the tonsillectomy group. At five months of follow-up only one patient in the control group and no patients in the tonsillectomy group had experienced an episode of severe pharyngitis (difference 3%; 95% CI −2% to 7%). Even though severe episodes were rare, tonsillectomy seemed to decrease the overall number of pharyngitis episodes. Seventeen (43%) patients in the control group and two (4%) patients in the tonsillectomy group had consulted a physician for pharyngitis (difference 38%, 95% CI 22% to 55%). Thirty-two (80%) patients in the control group and 18 (39%) patients in the tonsillectomy group had experienced any kind of acute pharyngitis episode (difference 41%, 95% CI 22% to 60%). (Table 10) During the whole follow-up the mean number of pharyngitis episodes was significantly lower in the tonsillectomy group than in the control group. (Table 11)

Table 10. Proportions of adults with recurrent pharyngitis who had experienced an acute pharyngitis episode of various severity at five months. Patients were randomised to watchful waiting (control) or immediate tonsillectomy. Figures are numbers (percentages) of patients.

Outcome	Intention to treat analysis (n=86)		
	Control (n = 40)	Tonsillectomy (n = 46)	%difference (95% CI)[1]
Researcher-recorded			
Experienced a severe pharyngitis episode[2]	1 (3)	0 (0)	3 (-2 to 7)
Experienced an acute pharyngitis episode with medical consultation[3]	17 (43)	2 (4)	38 (22 to 55)
Patient-recorded			
Experienced acute pharyngitis of any kind[4]	32 (80)	18 (39)	41 (22 to 60)

[1] CI = confidence interval, [2] Acute sore throat and signs that suggested pharyngeal and/or tonsillar origin of symptoms (oedema, erythema, exudative tonsillitis, anterior cervical lymphadenitis) and additionally C-reactive protein level higher than 40 mg/L either on the appointment day or three days later,
[3] Acute sore throat and signs that suggested pharyngeal and/or tonsillar origin of symptoms (oedema, erythema, exudative tonsillitis, anterior cervical lymphadenitis), [4] Two consecutive days of throat pain recorded in the symptom diary

5.3 Effect of tonsillectomy on pharyngitis symptoms (II)

Tonsillectomy also diminished pharyngitis symptoms. During the whole follow-up period, the number of days with throat pain, fever, rhinitis and cough were significantly lower in the tonsillectomy group than in the control group. The difference in days with throat pain was considerable even when throat pain during immediate postoperative recovery period (mean 17 (SD 6) days) was noticed. (Table 11) The patients graded their throat pain according to its severity (1 = mild, 2 = moderate, 3 = severe), and in both groups most of the throat pain days were graded as mild. (Fig. 1)

Table 11. Diary data outcomes at the end of the whole follow-up period[1] in adults with recurrent pharyngitis randomised to watchful waiting (control) or immediate tonsillectomy groups. Figures are means (SDs)[2] calculated as events per year.

Outcome	Intention to treat analysis (n = 86)		
	Control (n = 40)	Tonsillectomy (n = 46)	P value[3]
Subjective			
All sore throat episodes	7.4 (5.8)	1.5 (2.4)	<0.05
Days with throat pain	40.2 (60.5)	5.1 (8.7)	<0.05
Days with a fever (>37.5 °C)	7.8 (10.1)	2.2 (5.2)	<0.05
Days with rhinitis	26.3 (28.4)	10.2 (14.3)	<0.05
Days with a cough	16.0 (17.7)	7.0 (14.8)	<0.05
Objective			
Medical consultations for pharyngitis episodes	1.0 (1.4)[4]	0.1 (0.5)	<0.05
Days of school or work absence	6.6 (11.8)	3.3 (10.0)	<0.05

[1] Mean length of follow-up: 5.7 months (SD 0.7) in the control group and 6.2 months (SD 0.5) in the tonsillectomy group. The patients in the tonsillectomy group had a mean number of 17 days (SD 6) of throat pain and a mean number of 14 days (SD 6) of school or work absence during the immediate postoperative period. These are not included in the days presented in the table.

[2] SD = standard deviation, [3] Mann-Whitney U test, [4] Only one episode was due to group A streptococci

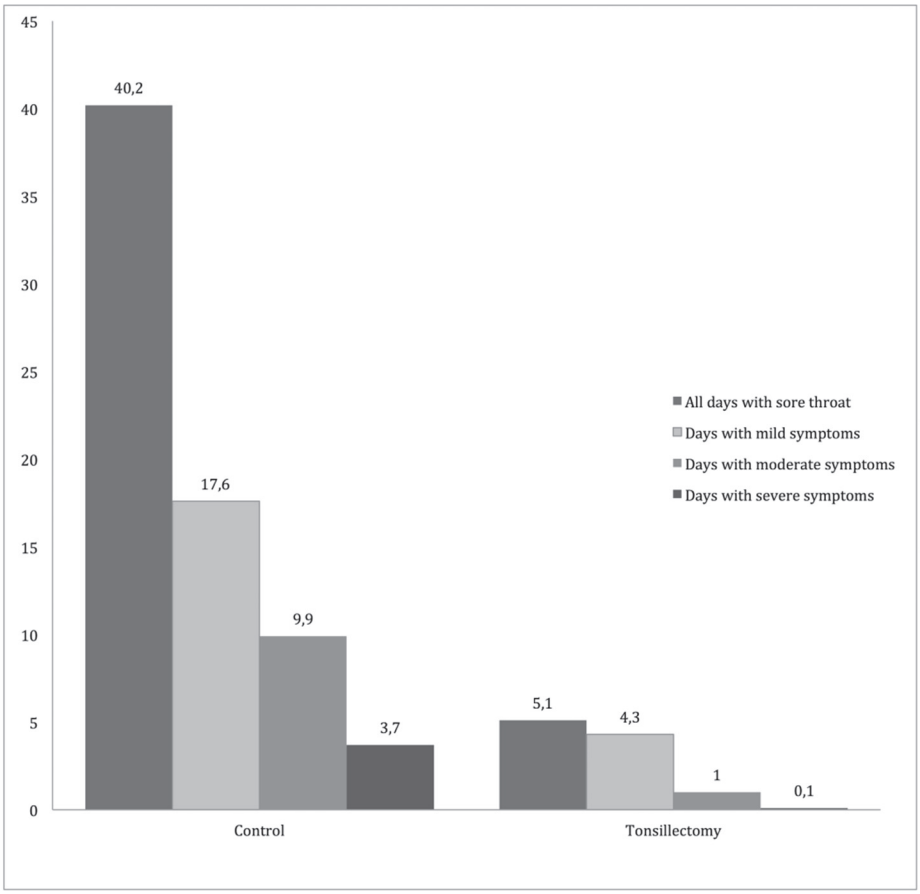

Fig. 1. All the sore throat days and days with severe, moderate or mild sore throat symptoms graded by the patients during the follow-up[*] in adults with recurrent pharyngitis randomised to watchful waiting (control) or immediate tonsillectomy groups. Figures are means (SDs)[†] calculated as events per year. [*)] Mean length of follow-up was 5.7 months (SD 0.7) in the control group and 6.2 months (SD 0.5) in the tonsillectomy group. The patients in the tonsillectomy group had a mean number of 17 days (SD 6) of throat pain and a mean number of 14 days (SD 6) of school or work absence during the immediate postoperative period. These immediate recovery times are not included in days presented in the table. [†)] SD = standard deviation. The data are not exhaustive; some patients marked the symptom days in their diaries without grading.

5.4 Effect of tonsillectomy on quality of life (I,III)

5.4.1 Study I

The GBI questionnaire assessing change in postoperative quality of life was sent to 70 adults who had had their tonsils removed because of recurrent pharyngitis caused by GAS. In all, 62 (89%) patients returned the questionnaire. Of these patients, 40 (65%) were female, their mean age was 26 years (range 15–46 years) and the mean length of the follow-up period was 166 (SD 49) days. The mean total GBI score after tonsillectomy was +26 (SD 14) for adult patients with recurrent streptococcal pharyngitis. The mean scores for GBI subscales were as follows: general health +25 (SD 18); social functioning +5 (SD 14); and physical functioning +55 (SD 23).

5.4.2 Study III

Postoperative quality of life after tonsillectomy for adult patients with recurrent pharyngitis caused by any or unknown etiological agent was assessed by using the GBI for the larger population in study III. Of the 156 enrolled patients, 153 underwent tonsillectomy and 142 (93%) returned the GBI questionnaire. Of the respondents, 94 (66%) were female and their median age was 27 years (range 14–65 years). About 17% of the patients had experienced more than 6 episodes during the previous year. The mean follow-up time was 5.6 (SD 1.2) months. The total GBI score and subscale scores between the patients varied considerably. The range in the total GBI score was −19 to +69, but only one patient reported a negative score. However, on average the patients showed improvement in their QOL: the median total GBI score, physical subscore, social subscore and general subscore were +27 (IQR 18–36), +83 (IQR 50–100), 0 (IQR 0–0) and +19 (IQR 8–30), respectively. The distribution of the GBI scores was broad and is shown in Figure 2.

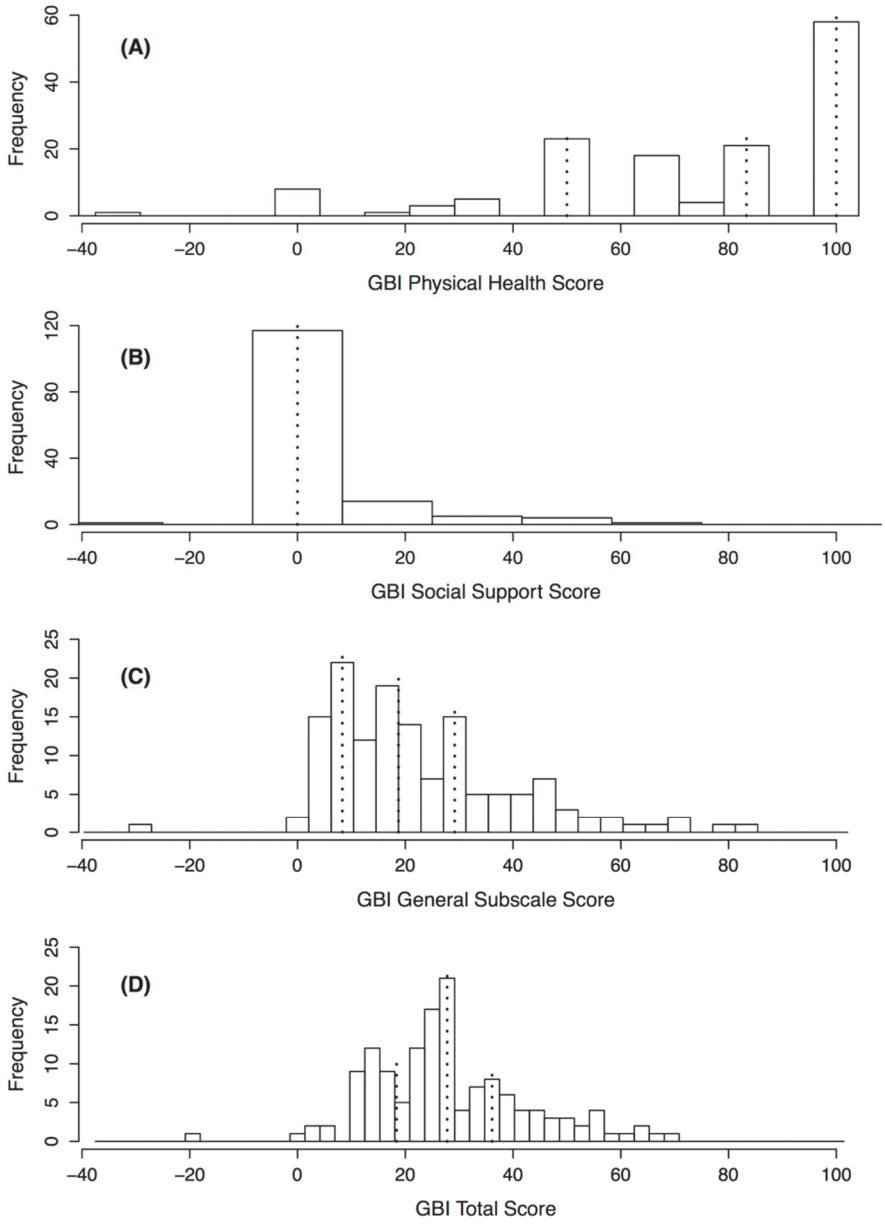

Fig. 2. Histograms describing the frequency distribution of patients (n = 142) by Glasgow Benefit Inventory (GBI) Physical Health Score (panel A), GBI Social Support Score (B), GBI General Subscale Score (C) and Total GBI Score (D).

5.5 Factors predicting improvement in quality of life after tonsillectomy (I, III)

5.5.1 Study I

Factors possibly affecting the postoperative QOL of patients with recurrent streptococcal pharyngitis were screened in study I. Of the 62 GBI respondents, 34 patients were randomised to keep a post-tonsillectomy diary and 28 patients a pre-tonsillectomy diary. The mean length of the diary-based follow-up period was 171 days (SD 11) among the post-tonsillectomy patients and 160 days (SD 69) among the pre-tonsillectomy patients. Thirty per cent of the least pleased patients in terms of the GBI total score (GBI < +18) were compared with the others. There were no differences in the baseline characteristics or pharyngitis risk factors between the least pleased and the others. Similarly, the number of previous pharyngitis episodes reported by the patients at enrolment did not differ between these two groups. There were also no significant differences between the least pleased and the other patients concerning the appearance of the palatine tonsils at the preoperative evaluation, tonsillectomy technique, time in the operating theatre, amount of blood loss, complication rate or perioperative findings.

During the pre-tonsillectomy follow-up period the least pleased patients recorded significantly fewer pharyngitis episodes and days with a fever in their diaries than did the others (Table 12). This difference between the two groups was also evident in the time to the first tonsillitis episode during the follow-up period. Similarly, the number of medical consultations for tonsillitis and the number of days with a sore throat and a cough all tended to be lower among the least pleased patients. After tonsillectomy, however, according to the diary data, the number of pharyngitis episodes and days with a sore throat and a fever declined similarly in both groups (Table 12). Also, the time to the first pharyngitis episode after tonsillectomy was similar between the least pleased patients and the others.

Table 12. Diary data on morbidity before and after tonsillectomy[1] according to postoperative quality of life in 62 adults who had tonsillectomy for recurrent streptococcal pharyngitis. The figures are means (SDs).

Morbidity	Least pleased[2] (n = 19)	Others (n = 43)	p[3]
Before tonsillectomy			
All episodes of pharyngitis	1.4 (1.8)	2.5 (1.9)	0.04
Medical consultations for pharyngitis episodes	0.5 (1.1)	1.0 (1.0)	0.09
Days with a sore throat	9.1 (15.4)	14.1 (12.1)	0.07
Days with a fever	1.0 (3.2)	3.3 (3.0)	0.01
Days with rhinitis	9.1 (12.9)	8.1 (13.0)	0.88
Days with a cough	0.3 (0.9)	3.8 (6.5)	0.08
After tonsillectomy			
All episodes of pharyngitis	0.8 (1.3)	0.6 (0.8)	0.71
Medical consultations for pharyngitis episodes	0.1 (0.3)	0.2 (0.4)	0.66
Days with a sore throat	4.2 (6.4)	3.2 (5.1)	0.69
Days with a fever	0.6 (1.7)	0.7 (1.6)	0.39
Days with rhinitis	7.8 (10.6)	6.3 (5.6)	0.57
Days with a cough	3.1 (4.2)	2.6 (3.1)	0.95

[1] Mean length of diary-based follow-up: 160 days (SD 69) before tonsillectomy and 171 days (SD 11) after tonsillectomy, [2] Glasgow Benefit Inventory score <18 six months after tonsillectomy, representing the worst 30th percentile of the patients in terms of postoperative quality of life, [3] Mann-Whitney U test

5.5.2 Study III

Clinical factors that predict change in QOL after tonsillectomy in patients with recurrent pharyngitis with any or unknown origin were sought in study III by using multivariate analysis. Of the 142 GBI respondents, 63 patients were randomised to keep a diary on the symptoms they had prior to tonsillectomy (diary-keepers subgroup) and 56 (89%) returned it completely filled. A linear regression model was used to predict the total GBI score for all patients (n = 136) for whom data on routinely recorded anamnestic and clinical characteristics were available. Initially, preoperative characteristics obtained by patient history and clinical examination were analysed. The analysis resulted in a model with the following four predictors: number of pharyngitis episodes during the preceding year, frequent throat pain, untreated dental caries and presence of chronic infection in the tonsils. The estimation results of this model are displayed in Table 13(A). The predictive ability of this model was quite modest, though, as can be observed in the scatterplot of the fitted total GBI score

based on this model plotted against the observed score (Fig. 3A), and from the correlation coefficient $r = 0.39$ between the observed and fitted scores.

Models including the previously selected four factors as well as pertinent items from the patient diaries were then fitted to the subgroup of diary-keepers (n = 56) with complete data on all these variables. According to the regression analysis, the lowest value for this criterion was achieved with a model including only the following two diary items: days of fever and number of throat episodes during the previous few months (Table 13(B)). The predictive ability of this model appeared somewhat better than above (Fig. 3B), yet remained rather modest, the correlation coefficient now being $r = 0.55$ between the observed and fitted values.

Table 13. Results of regression models with the total GBI score as the outcome variable. The entries are estimated regression coefficients and their 95% confidence intervals (CI) of the factors selected for the final model using the corrected Akaike information criterion (AIC_c) in two settings (A) and (B) as to the number of patients and predictive factors available.

Predictive factor	Coefficient	95% CI
(A) All patients (n = 136); routinely collected history and clinical characteristics		
Intercept	20.18	14.09 to 26.26
Pharyngitis episodes per year	1.37	0.25 to 2.49
Frequent throat pain	5.56	0.80 to 10.32
Untreated dental caries	-6.34	-12.69 to 0.01
Chronic infection in tonsils	6.61	-0.62 to 13.84
(B) Subgroup of patients (n = 56); diary items in addition to the above		
Intercept	18.86	13.29 to 24.42
Days with a fever per year	0.59	0.19 to 0.99
Episodes of throat pain per year	0.89	0.18 to 1.60

Correlation coefficients (*r*) between the observed and fitted scores of the selected models:
(A) 0.39, (B) 0.55

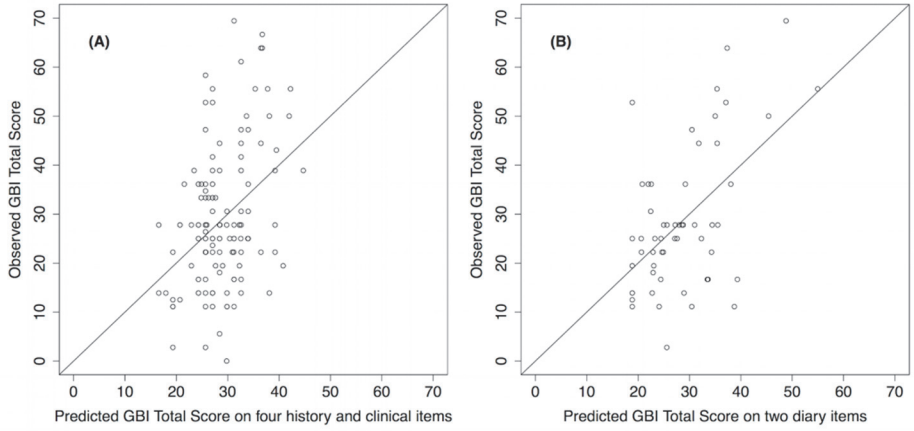

Fig. 3. Scatterplots of observed values against predicted values of the Glasgow Benefit Inventory total score based on (A) a model including four history and clinical items fitted on 136 patients (see Table 13(A)), and (B) a model including two diary items fitted on 56 patients providing these data (see Table 13(B)).

5.6 Predictive factors for medical consultation for sore throat in adults with recurrent pharyngitis (IV)

Of the 156 patients, 104 (67%) were female and 52 (33%) male, and their mean age was 26 years (range 14–65 years). Sixty (38%) patients smoked. The patients had experienced an average of 3.3 (SD 1.3) episodes of pharyngitis during the prior six months and 130 (83%) had had a group A streptococcal infection in the past. At enrolment, 18 (12%) patients had chronically infected tonsils found in the clinical examination. The mean length of the follow-up period was 5.9 months (SD 1.2).

Among the 156 analysed patients, the proportion who visited a physician for an acute sore throat during the whole follow-up period was 25% (40 patients). In the multivariate analysis, female gender (HR 3.3, 95% CI 1.4–8.0) and a finding of chronically infected tonsils at the clinical examination (HR 2.7, 95% CI 1.2–6.1) were factors that were associated significantly with medical consultation during a pharyngitis episode (Table 14). Age, tobacco use, prior streptococcal infection and having experienced frequent prior pharyngitis episodes did not affect the consultation rate.

Table 14. Association between various patient- and episode-related factors and having a medical consultation during an episode of acute pharyngitis in material based on two randomised trials in Finland.

Characteristic	Classification	Hazard ratio[1]	95% CI[1]	p
Patient-related				
(n=156 patients)				
Age	≤20 or >30 years	1.0		0.40
	21–30 years	0.7	0.4–1.5	
Sex	Male	1.0		<0.01
	Female	3.3	1.4–8.0	
Tobacco use	No	1.0		0.17
	Yes	0.6	0.3–1.2	
Prior streptococcal pharyngitis	No	1.0		0.51
	Yes	1.3	0.6–3.3	
Frequent pharyngitis episodes[2]	No	1,0		0.59
	Yes	1.2	0.6–2.3	
Chronically infected tonsils[3]	No	1.0		0.01
	Yes	2.7	1.2–6.1	
Episode-related				
(n=208 acute pharyngitis episodes)				
Postoperative episode		1.0		0.62
Preoperative episode		1.5	0.3–6.7	
Maximum throat pain[4]	Mild	1.0		
	Moderate	1.6	0.5–5.8	0.44
	Severe	4.3	1.0–18.6	0.05
Fever	No	1.0		0.62
	Yes	0.7	0.2–2.3	
Other respiratory symptoms	No	1.0		0.83
	Yes	1.1	0.4–3.1	

[1] Cox regression model, [2] >3 episodes in six months, [3] found during clinical examination at enrolment, [4] calculated among those episodes, from which data on severity of throat pain was available (n=135), CI = confidence interval

Seventy-eight patients had altogether 208 acute pharyngitis episodes, the mean duration being 6.2 days (SD 4.5). Of these episodes, 161 (77%) were preoperative and 47 (23%) were postoperative. Besides throat pain, 115 (55%) episodes involved other respiratory symptoms and 61 (29%) involved a fever. Data on throat pain severity was available for 135 acute episodes: maximum throat pain recorded in the patient diaries during the episode was mild in 54 (40%), moderate in 60 (44%) and severe in 21 (16%) episodes.

Of the 208 episodes, 36 (17%) led to a medical consultation during the first seven days of symptoms for 27 patients. Of these 36 episodes, 9 (25%) were caused by group A streptococci according to a throat culture or rapid antigen test. In 16 (44%) cases the patients received antimicrobial treatment. The mean duration of acute symptoms before the medical visit was 4.1 days (SD 3.6). According to the Cox regression model, only the fact that the patient had had severe throat pain during these first seven days correlated significantly with the medical consultation (HR 4.3, 95% CI 1.0–18.5) (Table 14). In contrast, having had moderate throat pain, fever, the presence of other respiratory symptoms and whether the episode was pre- or postoperative was not associated with the medical consultation.

5.7 Operative details and adverse effects of tonsillectomy (I–IV)

Among all of the 153 operated patients in these studies (I–IV), tonsillectomy led to a median of 5 ml (range 0–200 ml, IQR 3–20 ml) of blood loss and a median of 14 days (range 4–37, IQR 13–17 days) of immediate throat pain. Severe throat pain (grade 3) lasted for a median of 4 days (range 0–14, IQR 2–7 days) after tonsillectomy. Median time in the operating room was 55 minutes (IQR 45–65 minutes). Five per cent of the patients were readmitted to hospital because of secondary bleeding and 3% because of postoperative pain. There were no serious adverse effects related to tonsillectomy in these studies.

6 Discussion

6.1 Severity of recurrent pharyngitis episodes

We explored the acute pharyngitis episodes of adults who suffered from recurrent pharyngitis. We found that the acute pharyngitis episodes either before or after tonsillectomy, both lasted less than one week, on average. More than half of the episodes were accompanied by other respiratory symptoms (rhinitis, cough) and less than one-third involved a fever. According to our findings, a vast majority of the pharyngitis episodes were mild or moderate. We found that after five months of follow-up only one patient waiting for tonsillectomy and none of the already operated patients had a severe pharyngitis episode as determined by the presence of patient-reported severe symptoms and serum levels of CRP. Furthermore, recent literature shows that complications caused by pharyngitis are extremely rare in Western countries and the effect of antibiotic treatment has only modest influence on recovery time and symptom relief (Bisno 2001, Little *et al.* 2013b, Spinks *et al.* 2013, van Driel *et al.* 2013). We also know that pharyngitis places a great burden on primary care health services due to the high amount of doctor appointments and antibiotics use (Salkind & Wright 2008, Wiksten *et al.* 2013). Our results suggest that most pharyngitis episodes and symptoms could be managed without medical care services.

Some national guidelines, the Finnish one for example, recommend that streptococcal pharyngitis should be diagnosed by rapid antigen testing or by culture, and should be treated with antibiotics (Sore throat: Current Care Guidelines 2013). We mainly recruited patients with recurrent pharyngitis regardless of the microbiological etiology of their pharyngitis episodes. However, according to the background characteristics of our participants, 80% of them had experienced at least one proven streptococcal pharyngitis episode during the previous six months. This proposes that also streptococcal pharyngitis episodes are very rarely severe and the value of streptococcal testing and treating a single pharyngitis episode with antibiotics is questionable.

6.2 Effect of tonsillectomy on the numbers of episodes and symptoms

The recent Cochrane review (Burton & Glasziou 2009) on the effect of tonsillectomy on recurrent tonsillitis found only a single previous randomised controlled trial

involving adults—namely done by our research team—which included adults who were severely affected by recurrent group A streptococcal pharyngitis.(Alho *et al.* 2007) According to that study tonsillectomy reduces the number of acute pharyngitis episodes and days with pharyngitis symptoms in a short follow-up period in recurrent streptococcal pharyngitis. In study II we conducted a randomised controlled trial and enrolled adults with recurrent pharyngitis of any origin. Sixty-three per cent of them became exposed and experienced at least one streptococcal episode in the six months before randomisation.

Patients showed similar benefit from tonsillectomy in both of these RCTs. In the previous trial, Alho *et al*. (2007) found an absolute difference of 30% in the proportion of patients who had pharyngitis with medical consultation and 25% in the proportion of patients who had pharyngitis of any kind between the surgical and control groups after a three-month follow-up. In the present trial (study II), these differences were 38% and 41%, respectively, after the five-month follow-up period. The results are remarkably similar, considering the difference in the observation periods. Adult patients with recurrent pharyngitis seem to benefit from tonsillectomy similarly in terms of recurrence rate, regardless of the etiology of the episodes. However, patients who did undergo surgery had fewer episodes of pharyngitis overall even though the episodes were mainly mild or moderate.

According to Alho *et al*. (2007), tonsillectomy also significantly reduced days with sore throat and days with a fever in adult patients with recurrent streptococcal pharyngitis. In our study II we found similar results when patients had recurrent pharyngitis of any origin. During six months of follow-up, the number of days with throat pain, fever, rhinitis and cough were significantly lower in the group of patients who had undergone tonsillectomy compared with the control group. The difference in days with throat pain was notable even when the unavoidable immediate postoperative throat pain days (mean 17, SD 6 days) were taken into account. Also the days of absence from school or work were significantly fewer.

We showed that the effect of tonsillectomy on both objective outcomes (rate of episodes with medical consultation, absences from school or work) and subjective outcomes (data from patient-recorded diaries) is clear. The benefit is evident regardless of the etiology of the pharyngitis episodes, and results like this have not been published earlier as controlled trials. Some uncontrolled studies have also reported similar results, suggesting that tonsillectomy reduces pharyngitis incidence, medical consultations, antibiotics use and absences from school or work (Bhattacharyya & Kepnes 2002, Hsu *et al.* 2007, Mui *et al.* 1998).

6.3 Quality of life after tonsillectomy

We have shown that tonsillectomy significantly reduces pharyngitis episodes and symptom days. On the other hand, we have shown that a vast majority of pharyngitis episodes are not severe, suggesting that medical consultation may not be as valuable as recommended by some guidelines. Since objective findings are somehow two-fold, it is important to determine whether or not patients experience benefit from tonsillectomy by studying the QOL effect of tonsillectomy.

We found that patients' QOL improved remarkably after tonsillectomy when the GBI questionnaire was used for assessment. The benefit was evident—in addition to the total GBI score—also in all of the GBI subscales and regardless of the etiology of the recurrent pharyngitis. There are only a few previous observational studies reporting that tonsillectomy has improved the QOL of patients with chronic or recurrent tonsillitis (Baumann *et al.* 2006, Bhattacharyya *et al.* 2001, Richards *et al.* 2007, Schwentner *et al.* 2007, Senska *et al.* 2010, Witsell 2008) (Table 6). However, these reports have been primarily retrospective with rather low response rates, implying a high risk of substantial information bias and selection bias. Furthermore, in most of these studies the patient material is inevitably heterogeneous, as no pre-specified entry criteria are given. Still, these studies seem to be broadly in agreement with our results and also suggest that, on average, patients experience QOL improvement after tonsillectomy

Furthermore, the change in the median total GBI score or the median scores of different GBI subscales was not uniform. The distribution of the change in QOL has been poorly reported earlier. Although we found the average total GBI score after tonsillectomy to be fairly high, the individual total GBI scores varied. A majority of the patients had distinctly high total GBI scores, confirming QOL improvement. On the other hand, there were a few patients who reported low total GBI scores, suggesting insignificant QOL improvement after tonsillectomy. One patient in fact even scored a negative total GBI value.

QOL improvement was generally highest in the GBI physical health subscale, but practically no change was observed in the GBI social subscale in study III. This suggests, and also supports experience from practical clinical work, that the QOL of patients with recurrent pharyngitis is mostly impaired because of disturbing symptoms, medical visits and absences from work. The GBI physical subscale questions measure especially these features. Most of the previous studies have also reported higher GBI scores in the physical subscale compared with other subscales

(Baumann *et al.* 2006, Richards *et al.* 2007, Schwentner *et al.* 2007, Senska *et al.* 2010).

6.4 Preoperative factors predicting patient satisfaction after tonsillectomy

We have shown that a majority of adult patients with recurrent pharyngitis experience QOL improvement after tonsillectomy. Nevertheless, there are some patients who are not satisfied with their operation. It would be very useful to recognise these unsatisfied patients before tonsillectomy, and for this reason we searched for preoperative factors predicting patient satisfaction. There is only limited previous data addressing factors that predict improved QOL after tonsillectomy. Baumann *et al*. (2006) reported that younger adult patients with chronic tonsillitis had better postoperative GBI scores than older patients. Schwentner *et al*. (2007) found that adult patients with chronic tonsillitis who have concomitant chronic diseases such as diabetes, bronchial asthma or metabolic syndrome are likely to benefit less from tonsillectomy according to the postoperative GBI.

In study I we screened predictive factors for patient satisfaction by comparing anamnestic information of pharyngitis history and risk factors, preoperative clinical findings, perioperative details and the number of diary-recorded preoperative symptoms between the least pleased and other patients. We found that anamnestic preoperative information from the patients was not accurate enough to predict postoperative improvement in QOL, and diary data were superior to it. The only factors that were associated with low patient satisfaction were a small number of tonsillitis episodes and days with a fever before tonsillectomy reported in the diaries. The results of study I can be regarded as preliminary results. Factors that predict tonsillectomy benefit were examined more extensively in study III and the population of study I was also included in study III.

In study III we examined possible predictive factors for QOL improvement with a larger population by using multivariate analysis. We sought factors that predict QOL change by prospectively recorded preoperative history, clinical examination and diary-based data on preoperative acute symptoms. We were not able to find such predictive factors that would have accurately identified those patients who would benefit most from tonsillectomy. Prior throat-related morbidity (number of prior pharyngitis episodes, frequent throat pain and chronically infected tonsils) did predict the total postoperative GBI score best as far as routinely collected medical history and physical examination data were concerned. However, the overall predictive ability of

all these factors remained fairly weak even after the more accurate diary-based data on the numbers of days with throat pain and a fever were included. Thus, the clinical variables seemed to explain change in QOL after tonsillectomy rather poorly.

It seems like other individual and environmental characteristics like personality, motivation, social, psychological and economic support and value preferences, which were not measured in our studies, may also be responsible for the varying QOL changes related to tonsillectomy. This emphasizes the fact that a physician should carefully discuss with a patient and inform a patient about probable results and adverse effects of tonsillectomy before a decision is made about the operation. However, we found that the rate of preoperative symptoms may be somewhat useful in predicting patient satisfaction. The number of prior pharyngitis episodes and frequent throat pain in the patient's history and the clinical finding of chronically infected tonsils predict patient benefit after tonsillectomy to some extent. At least in the case of uncertain indications for surgery, a period of watchful waiting of at least six months may be suggested, during which the patient can record the number, duration and severity of the episodes. According to the present results it would be most useful to record the number of days with throat pain and a fever, which predicted patient satisfaction most accurately.

6.5 Predictive factors for medical consultation for sore throat in adults with recurrent pharyngitis

Acute pharyngitis episodes experienced by adult patients both before and after tonsillectomy lasted less than a week on average, and in the overwhelming majority of cases involved at most only mild or moderate throat pain. Also, less than one-third involved a fever. Thus, it was not surprising that only one of every six episodes led to medical consultation. Severe throat pain during the acute pharyngitis episode was related to a medical visit, suggesting that patients who feel themselves more ill seek medical attention more eagerly. This finding probably means that patients are mainly looking for pain relief when they consult a physician. It also suggests that patients are aware that milder episodes usually heal by themselves without medical care. According to the literature, most pharyngitis episodes heal spontaneously (van Driel *et al.* 2013). The fact that chronically infected tonsils found at enrolment increased the consultation rate may indicate that these patients had a more severe underlying chronic tonsillar infection.

According to our findings, the medical appointment rate for acute pharyngitis was higher in women than in men. A higher consultation rate probably leads to an

increased amount of recurrent pharyngitis diagnoses, and may further increase referrals to specialist care for tonsillectomy, namely among women. In fact, two-thirds of the patients in our study population who were referred to an ENT specialist were female, supporting this assumption. This suggestion may also be supported by earlier literature reporting that women also have higher consultation rates with specialists for consideration of paranasal surgery due to recurrent acute rhinosinusitis (Bhattacharyya *et al.* 2012, Bugten *et al.* 2008, Cutler *et al.* 2013). The Finnish guideline for acute pharyngitis treatment recommends streptococcal testing and antibiotic treatment for streptococcal infection (Sore throat: Current Care Guidelines 2013). Most Finnish patients have learned this policy during their earlier medical contacts and therefore pretty conscientiously visit the doctor when they have pharyngeal symptoms. It may be hypothesized that women in general may be more obedient to healthcare advice and may seek medical attention more often for this reason. In contrast, such patient- and episode-related factors as age, tobacco use, history of streptococcal pharyngitis, fever and whether the episode occurred before or after tonsillectomy did not correlate with a medical visit.

6.6 Strengths and weaknesses

As we used an open trial design, the placebo effect may explain part of the subjective benefit after surgery. That may explain the slight beneficial effect of tonsillectomy on cough and rhinitis in study II. The follow-up time in all the studies was relatively short for practical reasons: the waiting list time for elective tonsillectomy is restricted by Finnish law and it can't last over six months. However, it is assumable that the short-term effect of tonsillectomy reflects its overall usefulness. Any improvement in the pharyngitis rate during the waiting list time was likely due to the natural course of the disease and it is unlikely that the patients reported negatively biased data in their diaries during the waiting list time. So, the difference between groups was likely due to the benefit of tonsillectomy rather than to any negative effect of remaining on the waiting list.

The use of the waiting list time also offered some advantages. Patients placed on the waiting list knew they would be operated on later, and due to that a majority of them agreed to participate and only three patients asked for the possibility to undergo a tonsillectomy earlier due to severe subjective symptoms. The waiting list controls and the prospective study design enabled us to collect diary data on preoperative symptoms, and this diary data was found to be important, as it seemed to more

accurately predict the patients' QOL improvement than data based only on the patients' memory.

The response rate of the GBI questionnaire was considerably high and the non-respondents did not differ significantly from the respondents in their baseline characteristics and severity of symptoms before tonsillectomy, making the possibility of selection bias unlikely. We investigated the patients' QOL changes six months after the tonsillectomy, which may cause some recall bias. However, according to a previous study, QOL assessment after an intervention appears to provide information that is more highly correlated with patient satisfaction and more sensitive than serial change data (Fischer *et al.* 1999). We used the Glasgow Benefit Inventory score to measure QOL alterations. The GBI has been demonstrated to be quite sensitive to the impact of ear, throat and nose interventions.(Robinson *et al.* 1996)

We studied referral patients who suffered from recurrent pharyngitis episodes. However, even among these selected participants, the symptoms were usually mild. To minimise the effect of participating in a trial, we emphasized to the patients that it was important to seek medical advice for their symptoms during the trial in exactly the same way they had done before. Since we collected self-reported data on symptoms, some episodes may have gone undetected. These results can only be generalised to countries where national guidelines suggest that tests should be done for β-haemolytic Streptococcus A when treating acute pharyngitis.

Our entry criterion was at least three disabling clinically significant episodes of pharyngitis per year. This threshold for tonsillectomy is a bit lower than the criteria presented in certain guidelines. In our experience, those criteria are too strict for adult patients who opt for surgery earlier. However, decisions to perform tonsillectomy with so few episodes were exceptions in cases when the episodes were prolonged or more disabling than usually. Most of the patients had about five episodes during the previous year.

The use of several surgeons increases the generalizability of our results. As we recruited only patients who suffered from recurrent pharyngitis episodes, our results are not generalizable to patients whose tonsillar disease encompassed merely halitosis, bad taste in the mouth, tonsillar debris or obstructive symptoms.

6.7 Clinical implications

According to the findings of this study, adult patients with recurrent pharyngitis generally benefit subjectively from tonsillectomy in terms of QOL. This QOL increase is evident among patients who have had three or more acute pharyngitis

episodes during the previous 12 months. The tonsillectomy criteria (Paradise criteria) traditionally used in many countries seem to be somewhat too strict according to our findings, and some patients with fewer episodes also clearly benefited from tonsillectomy (Paradise *et al.* 1984). However, there is a wide distribution in QOL improvement, and preoperative clinical factors that predict tonsillectomy benefit seem to explain change in QOL rather weakly. This emphasizes the fact that the ENT doctor should carefully discuss with the patient and explain the possible benefits, disadvantages and risks of tonsillectomy before a treatment decision is made. The rate of preoperative throat symptoms is the only thing that modestly predicts tonsillectomy benefit and may be used, even with a diary of symptoms, when the decision about tonsillectomy is controversial.

It is also notable that acute pharyngitis episodes are mainly mild or moderate and complications of acute pharyngitis are rare. During acute pharyngitis, rapid antigen tests or cultures that detect group A streptococcus are recommended and carried out in many countries, also in Finland. This study doesn't elaborate on whether streptococcal testing is appropriate for treating single cases of acute pharyngitis. However, according to our findings, adult patients with recurrent pharyngitis benefit from tonsillectomy regardless of the etiology of single episodes, and knowledge of the origin of previous acute episodes is not essential when making a decision about tonsillectomy or when referring a patient to an ENT doctor.

7 Conclusions

Based on the results of this study, the following conclusions can be made.

1. Adult patients who have pharyngitis involving the palatine tonsils more than three times per year benefit from tonsillectomy. Tonsillectomy reduces the overall number of acute pharyngitis episodes and the number of acute episodes leading to medical consultation. However, pharyngitis and sore throats prevented by surgery are usually mild.
2. After tonsillectomy adult patients with recurrent pharyngitis have fewer days with a sore throat, days with fever and absences from school or work.
3. Carefully selected adult patients who have recurrent pharyngitis episodes that involve the palatine tonsils and prevent normal functioning have substantial postoperative improvement in QOL after tonsillectomy, on average. QOL benefit is achieved regardless of the etiology of the pharyngitis episodes. However, the distribution of QOL benefit is wide.
4. The only clinical factor that predicts QOL benefit and patient satisfaction after tonsillectomy is throat-related morbidity before tonsillectomy. Still, even when diary-based data on symptoms are used, clinical factors can rather modestly predict which patients will benefit most from the operation.
5. Among adult patients who suffer from recurrent pharyngitis episodes, the great majority of acute pharyngitis episodes are mild and only a few lead to a medical consultation. Female gender, chronically infected tonsils and having severe throat pain increase the consultation rate among these patients.

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Appendix

Appendix 1. Glasgow Benefit Inventory questionnaire in Finnish.

Toistuvat nieluinfektioepisodit ja tonsillektomia

Elämänlaatukysely tutkittavalle

Olette osallistuneet nielurisaleikkaustutkimukseemme ja Teille on tehty nielurisaleikkaus kuusi kuukautta aikaisemmin. Tutkimukseen kuuluen tiedustelemme, onko nielurisaleikkauksella ollut vaikutusta elämänlaatuunne. Pyydämme Teitä ympyröimään jokaisen kysymyksen kohdalta tilanteeseenne parhaiten sopivan vaihtoehdon.

Onko leikkaushoito vaikuttanut tekemiisi asioihin?	teen paljon vähemmän	teen vähemmän	ei vaikutusta	teen enemmän	teen paljon enemmän
	1	2	3	4	5
Onko leikkaushoito kaikkiaan parantanut vai huonontanut elämääsi?	huonontanut paljon	huonontanut vähän	ei vaikutusta	parantanut vähän	parantanut paljon
	1	2	3	4	5
Oletko ollut enemmän vai vähemmän optimistinen tulevaisuuden suhteen leikkauksen jälkeen?	paljon pessimistisempi	vähän pessimistisempi	ei vaikutusta	vähän optimistisempi	paljon optimistisempi
	1	2	3	4	5
Onko sinulla vähemmän vai enemmän itseluottamusta leikkauksen jälkeen?	paljon vähemmän	vähemmän	ei vaikutusta	enemmän	paljon enemmän
	1	2	3	4	5
Oletko tyytymättömämpi vai tyytyväisempi itseesi leikkauksen jälkeen?	paljon tyytymättömämpi	vähän tyytymättömämpi	ei vaikutusta	vähän tyytyväisempi	paljon tyytyväisempi
	1	2	3	4	5
Onko sinun vaikeampi vai helpompi olla ihmisten seurassa leikkauksen jälkeen?	paljon vaikeampi	vähän vaikeampi	ei vaikutusta	vähän helpompi	paljon helpompi
	1	2	3	4	5
Onko luottamuksesi työsi suhteen vähentynyt vai lisääntynyt leikkauksen jälkeen?	vähentynyt paljon	vähentynyt hiukan	ei vaikutusta	lisääntynyt vähän	lisääntynyt paljon
	1	2	3	4	5

Oletko enemmän vai vähemmän vaivautunut ihmisten parissa leikkauksen jälkeen?	paljon enemmän vaivautunut	hiukan enemmän vaivautunut	ei vaikutusta	hiukan vähemmän vaivautunut	paljon vähemmän vaivautunut
	1	2	3	4	5
Onko itsetuntosi kohentunut vai vähentynyt leikkauksen jälkeen?	vähentynyt paljon	vähentynyt vähän	ei vaikutusta	kohentunut vähän	kohentunut paljon
	1	2	3	4	5
Oletko enemmän vai vähemmän kiusaantunut ongelmastasi leikkauksen jälkeen?	paljon enemmän kiusaantunut	vähän enemmän kiusaantunut	ei vaikutusta	vähän vähemmän kiusaantunut	paljon vähemmän kiusaantunut
	1	2	3	4	5
Oletko osallistunut vähemmän vai enemmän sosiaalisiin tapahtumiin leikkauksen jälkeen?	paljon vähemmän	vähän vähemmän	ei vaikutusta	vähän enemmän	paljon enemmän
	1	2	3	4	5
Oletko enemmän vetäytyvä vai osallistuva sosiaalisissa tilanteissa leikkauksen jälkeen	paljon vetäytyvämpi	vähän vetäytyvämpi	ei vaikutusta	vähän osallistuvampi	paljon osallistuvampi
	1	2	3	4	5
Tuntuuko sinusta, että saat vähemmän vai enemmän tukea ystäviltäsi leikkauksen jälkeen?	paljon vähemmän	vähän vähemmän	ei vaikutusta	vähän enemmän	paljon enemmän
	1	2	3	4	5
Tuntuuko sinusta, että saat vähemmän vai enemmän tukea perheeltäsi leikkauksen jälkeen?	paljon vähemmän	vähän vähemmän	ei vaikutusta	vähän enemmän	paljon enemmän
	1	2	3	4	5
Tuntuuko sinusta, että on harvempia vai useampia ihmisiä jotka todella välittävät sinusta leikkauksen jälkeen?	paljon harvempia	vähän harvempia	ei vaikutusta	vähän useampia	paljon useampia
	1	2	3	4	5
Oletko joutunut käymään vähemmän vai enemmän lääkärin vastaanotolla leikkauksen jälkeen?	paljon enemmän	vähän enemmän	ei vaikutusta	vähän vähemmän	paljon vähemmän
	1	2	3	4	5
Oletko leikkauksesi jälkeen sairastunut flunssaan tai muihin hengitystieinfektioihin aiempaa harvemmin?	paljon useammin	vähän useammin	ei vaikutusta	vähän harvemmin	paljon harvemmin
	1	2	3	4	5

Oletko joutunut käyttämään lääkkeitä vähemmän vai enemmän leikkauksen jälkeen?	paljon enemmän	vähän enemmän	ei vaikutusta	vähän vähemmän	paljon vähemmän
	1	2	3	4	5

Kiitos vastauksista.

Original publications

I Koskenkorva T, Koivunen P, Penna T, Teppo H, Alho OP (2009). Factors affecting quality-of- life impact of adult tonsillectomy. J Laryngol Otol 123(9):1010-4.

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IV Koskenkorva T, Koivunen P, Alho OP (2015). Predictive factors for medical consultation for sore throat in adults with recurrent pharyngitis. Manuscript.

Original publications are not included in the electronic version of the dissertation.

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