Eur Arch Otorhinolaryngol
DOI 10.1007/s00405-015-3872-6

HEAD AND NECK

Clinical practice guideline: tonsillitis I. Diagnostics and nonsurgical management

Jochen P. Windfuhr[1] · Nicole Toepfner[2] · Gregor Steffen[3] · Frank Waldfahrer[4] · Reinhard Berner[2]

Received: 15 December 2015 / Accepted: 17 December 2015

Abstract More than 120,000 patients are treated annually in Germany to resolve repeated episodes of acute tonsillitis. Therapy is aiming at symptom regression, avoidance of complications, reduction in the number of disease-related absences in school or at work, increased cost-effectiveness and improved quality of life. The purpose of this part of the guideline is to provide clinicians in any setting with a clinically focused multi-disciplinary guidance through different conservative treatment options in order to reduce inappropriate variation in clinical care, improve clinical outcome and reduce harm. Surgical management in terms of intracapsular as well as extracapsular tonsillectomy (i.e. tonsillotomy) is the subject of part II of this guideline. To estimate the probability of tonsillitis caused by β-hemolytic streptococci, a diagnostic scoring system according to Centor or McIsaac is suggested. If therapy is considered, a positive score of ≥ 3 should lead to pharyngeal swab or rapid test or culture in order to identify β-hemolytic streptococci. Routinely performed blood tests for acute tonsillitis are not indicated. After acute streptococcal tonsillitis, there is no need to repeat a pharyngeal swab or any other routine blood tests, urine examinations or cardiological diagnostics such as ECG. The determination of the antistreptolysin O-titer (ASLO titer) and other antistreptococcal antibody titers do not have any value in relation to acute tonsillitis with or without pharyngitis and should not be performed. First-line therapy of β-hemolytic streptococci consists of oral penicillin. Instead of phenoxymethylpenicillin–potassium (penicillin V potassium), also phenoxymethlpenicillin–benzathine with a clearly longer half-life can be used. Oral intake for 7 days of one of both the drugs is recommended. Alternative treatment with oral cephalosporins (e.g. cefadroxil, cefalexin) is indicated only in cases of penicillin failure, frequent recurrences, and whenever a more reliable eradication of β-hemolytic streptococci is desirable. In cases of allergy or incompatibility of penicillin, cephalosporins or macrolides (e.g. Erythromycin-estolate) are valuable alternatives.

Keywords Tonsillitis · Pharyngitis · Antibiotic therapy · McIsaac score · Tonsillectomy · Tonsillotomy

Introduction

The incidence peak of acute tonsillitis is observed in children of school age, but it may generally occur at any age. It can only be assumed that (pharyngo-)tonsillitis caused by group A β-hemolytic streptococci (GABHS) or *Streptococcus pyogenes* is responsible for about 5 % of acute medical consultations. Also for the prevalence of recurrent acute tonsillitis in Germany, no significant statistics are available. In 2010, approximately 127,000 tonsillectomies including tonsillotomies were performed in Germany on an inpatient basis [1]. Further details, not relevant for this clinical guideline, are provided in the literature [2, 3]. Histopathological examination of the tonsils alone is not capable to establish the diagnosis of tonsillitis. The diagnosis is much

✉ Jochen P. Windfuhr
Jochen.Windfuhr@mariahilf.de

[1] Department of Otorhinolaryngology, Plastic Head and Neck Surgery, Kliniken Maria Hilf, Sandradstr. 43, 41061 Mönchengladbach, Germany

[2] Department of Pediatrics, University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany

[3] Private Practice, Hermannstr.1, 51143 Cologne, Germany

[4] Department of Otolaryngology, Head and Neck Surgery, University Hospital of Erlangen, Waldstr. 1, 91054 Erlangen, Germany

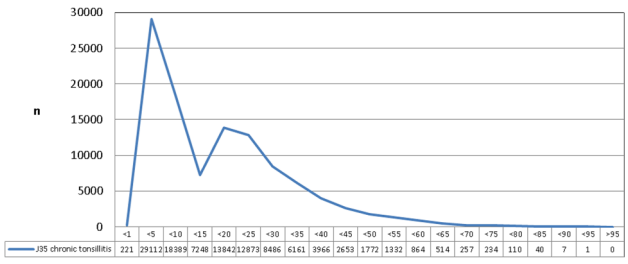
Published online: 11 January 2016

more based on the patient's history and clinical symptoms. Bathala and Eccles [4] described the mechanism of pain secondary to tonsillitis.

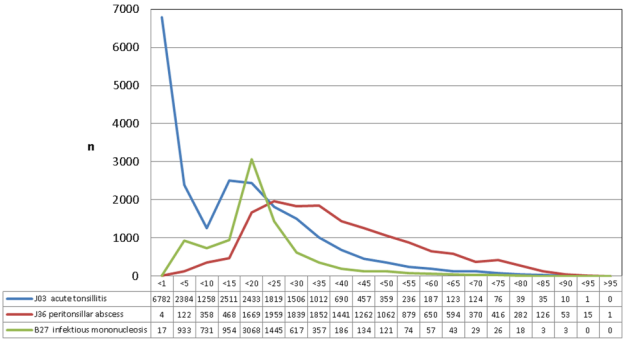
Acute tonsillitis is mainly caused by viruses, such as double-stranded DNA viruses (human adenoviruses, Epstein Barr Virus), single-stranded DNA viruses (Human Boca Virus), single-stranded RNA viruses (influenza and para-influenza viruses; rhino-viruses; entero-viruses including Coxsackie viruses; corona viruses; respiratory syncytial virus (RSV); human meta-pneumo-virus), retro-viruses [human immunodeficiency viruses (HIV)]. The most important pathogens that cause bacterial tonsillitis are GABHS, i.e. *Streptococcus pyogenes*. The disease transmission generally occurs via droplet infection transmitted by other patients with acute GABHS tonsillitis, very rarely by asymptomatic carriers [5]. However, even autoinfection via the normal flora of the mouth and the pharynx is possible. Other pathogen reservoirs may be pets, farm animals, but also articles of daily use such as tooth brushes. More rarely, other bacteria must be considered such as e.g. *Streptococci* of group C and G, *Haemophilus influenzae, Nocardia, Corynebacteria and Neisseria gonorrhoeae*. The bacterial symbiosis of *Fusobacterium nucleatum* and *Borrelia vincentii* leads to a disease known as Vincent's angina, which is characterized by a mostly unilateral, ulcerating tonsillitis with intensively putrid halitosis.

The term "recurrent acute tonsillitis (RAT)" means occurrence of repeated episodes of sore throat interrupted by intervals without or insignificant complaints. Unfortunately, this term is mixed loosely with the expression of "chronic tonsillitis" (ICD-10 Code: J35), an arbitrarily chosen and not scientifically defined term. RAT may lead to fibrosis of the tonsils and to fixation of the tonsil in its bed via the mechanism of transmitting the inflammation to the peritonsillar tissue ("peritonsillitis"), which becomes clinically obvious because of the reduced mobility indicating RAT. The volume of the tonsils is not relevant to establish the diagnosis of tonsillitis but in relation to symptoms such as upper airway obstruction or impaired swallowing.

Number of inpatient treatments to cure "chronic tonsillitis" in Germany, 2013. Source: German Federal Statistical Office, numbers of patients per age group for the diagnosis identified by ICD-10 code [6]



Number of inpatient treatments to cure "acute tonsillitis", "peritonsillar abscess", "infectious mononucleosis" in Germany, 2013 Source: German Federal Statistical Office, numbers of patients per age group for diagnosis identified by ICD-10 code [6]



Guideline scope and purpose

This guideline focuses intensively on surgical indications of tonsillectomy, including tonsillotomy. The formerly published guideline of the German Society of General and Family Medicine (DEGAM) on the topic of "Sore Throat" [7] and of the German Society of Otorhinolaryngology Head and Neck Surgery on the topic of "Antibiotic Therapy of Infections of the Head and Neck" [8] are currently under review and will be published in due course. The panel therefore refrained from an additional literature review concerning diagnostics and conservative therapy of tonsillitis. Instead, the validity of several recommendations was checked whenever needed and the relevant literature cited and briefly summarized. The primary purpose of this guideline is to provide clinicians with a consented interdisciplinary guidance to the different conservative and surgical treatment options. Therapy is aiming at: symptom regression, avoidance of complications, reduction in the number of disease-related absences in school or at work, increased cost-effectiveness and improved quality of life.

Materials and methods

The guideline panel was chosen to represent fields of pediatrics, pediatric infectiology, otolaryngology-head and neck surgery, and consumers. Elected panelists of different societies were invited on behalf of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO KHC, Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie e.V.) such as the German Society of Pediatric and Adolescent Medicine (DGKJ, Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.), the German Society of Pediatric

Infectiology (DGPI, Deutsche Gesellschaft für Pädiatrische Infektiologie e.V.), and the German Association of Oto-Rhino-Laryngologists (BVHNO, Deutscher Berufsverband der Hals-Nasen-Ohrenärzte e.V.). The guideline was developed according to the protocol of the National Working Group of Medical Societies (AWMF, Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften) and the National Medical Quality Center (AZQ, Ärztliches Zentrum für Qualität) [9]. The panel used an explicit and transparent a priori protocol for creating actionable statements supported by the relevant literature. Every change of the initial document was distributed among the panelists and archived step-by-step by the first author (JPW). Potential conflicts of interest were compiled for all panel members, discussed and finally disclosed. All recommendations and statements were consented by means of Delphi procedure or in the context of a consensus conference using a formal consensus procedure (nominal group process). First, the evidence situation was described from an expert point of view with subsequent discussion. According to the distributed handouts, the recommendation drafts were submitted to be reviewed by each panelist and dissenting proposals were noted. In all of the following statements and recommendations, a 100 % consensus was achieved (4/4). For standardization of the recommendations of the guideline, a consistent formulation was used. Based on the recommendations of the AWMF, the literature used for this guideline was not consequently classified according to the levels of evidence and no recommendations according to GRADE were stated. The present guideline applied the criteria mentioned in "The Oxford 2011 Levels of Evidence" that were published by the Oxford Centre for Evidence-Based Medicine (OCEBM) in 1998 [10]. During the 10 months devoted to guideline development ending in September 2015, the group met three times with monthly electronic review and feedback on each guideline draft to ensure accuracy and full transparency. The final version of the guideline was distributed to each of the involved societies and responses incorporated into the guideline. The final version was submitted to the AWMF for publication. A review process is scheduled for 2019 or sooner if significant evidence warrants earlier re-consideration.

Target audience

This guideline is intended for all clinicians in any setting who interact with patients suffering from tonsillitis at any age to reduce inappropriate variation in clinical care, improve clinical outcome and reduce harm. Furthermore, this guideline may also provide sufficient information for a variety of persons and institutions involved in health policy. The recommendations of the guideline refer to patients without underlying immunological diseases or immune suppression who suffer from tonsillitis. According to the typical age of disease onset, children and adolescents are the main target group for the recommendations of this guideline. The guideline provides therapeutic orientation, in some cases, a deviation from those recommendations might be justified. The guideline was not intended for specific entities such as patients with periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA), IgA nephropathy, Psoriasis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), or patients suffering from rheumatic fever or other relevant basic diseases. Very specific pathogen induced entities such as diphtheria or tuberculosis are also not within the scope of this guideline.

Definitions and recommendations

1. Patients with acute sore throat with/without dysphagia should be classified with regard to the diagnosis of "acute tonsillitis", "acute pharyngitis", or "acute tonsillo-pharyngitis".
2. The term of recurrent acute tonsillitis (RAT) is used with the understanding of repeated episodes of acute tonsillitis interrupted by intervals without or insignificant complaints. The imprecise term "chronic tonsillitis" should no longer be used.
3. Scarlet fever is a systemic disease caused by β-hemolytic streptococci. For diagnosis, specific criteria must additionally be fulfilled indicating the exotoxin-mediated systemic disease.

Degree of recommendations

The degree of recommendation was described following current proposals [11, 12] and completed by an own evaluation criterion "is not required".

Degree of recommendation	Description	Significance
A "Is (not) recommended"	At least one randomized controlled trial (RCT) of good overall quality and consistency that refers directly to the specific recommendation and was not extrapolated ("Is" or "is not" recommended)	It is not very probable that further research will change the confidence placed in the treatment effect

Degree of recommendation	Description	Significance
B "Can (not) be recommended"	Well performed clinical study, however, no RCT, with direct relation to the recommendation or extrapolation of evidence level 1, if the reference to the specific question is missing ("Can" or "cannot" be recommended)	Further research has probably a major impact on the confidence placed in the treatment effect and should change this assessment
0 "Can be considered"	Reports of expert circles or expert opinion and/or clinical experience of reputed authorities, or extrapolation of evidence levels 2 or 3, directly applicable clinical trials of good quality do not exist/ are not available ("Can be considered")	Further research has probably a major impact on the confidence placed in the treatment effect and will probably change this assessment. The assessment of the treatment effect is very uncertain
"Is not required"	Sound proof by scientific argumentation without the necessity of systematic reviews, trials of evidence level 3 or higher of scientific evidence	Recommendation against intervention/ measures

Results

Recommendations

1. For differentiation of viral tonsillitis and tonsillitis caused by *β*-hemolytic streptococci, the assessment should be performed based on a diagnostic scoring system (modified Centor Score / McIsaac Score).
2. If therapy is considered, a positive score of ≥ 3 should lead to pharyngeal swab for rapid antigen detection or culture in order to identify *β*-hemolytic streptococci.
3. Routinely performed blood tests with regard to acute tonsillitis are not indicated.
4. After acute streptococcal tonsillitis, there is no need for routine follow-up examinations of pharyngeal swab.
5. After acute streptococcal tonsillitis, routine blood tests or urine examinations or cardiologic diagnostics such as ECG are not indicated.

This guideline complies with the guideline of the German Society for General and Family Medicine (DEGAM) entitled "Sore Throat" [13], dated October 2009. The panelists therefore included statements of this guideline and added information obtainable from the literature published after November 1, 2009 whenever needed. Information concerning rheumatic fever and post-streptococcal arthritis, was cited from a guideline published in June 13, 2012 by the German Society of Pediatric Cardiology [14].

The systematic literature search was based on the following keywords: *Pyogenes; group A; ß hemolytic; streptococcus; streptococcal; tonsillitis; pharyngitis; tonsillopharyngitis; sore throat; Diagnosis; diagnostic; throat commensal; throat pathogen; McIsaac; Centor; microbiological culture; RADT; Rapid antigen detection; Titer; serology; streptolysin; antistreptolysin; dnase; CRP; C reactive protein; cytokine; WBC; ANC; leucocytosis; neutrophilia; peritonsillar; retropharyngeal; tonsillar; abscess; Epstein Barr; Plaut Vincent; Lemierre; scarlatina.* Time filter: January 1, 2009, to October 1, 2014.

Spectrum of pathogens

Several hundreds of different bacteria and viruses are detectable in the nasopharynx [15]. It is difficult to distinguish between commensal and (potentially) pathogenic germs because of the complex interrelationship of the present microflora [16]. Additionally, the anatomical division of the nasopharyngeal space only partly correlates with the germ-specific infection sites. Even the histological differentiation between epithelial, respiratory, and lymphatic tonsillar tissue is not completely congruent to the clinically observed infection process, which may extend to several tissues [15, 16]. Only in half to two-third of all patients suffering from tonsillitis, a known bacterial or viral agent or several potential pathogens are detectable [17]. Apart from GABHS, no systematic evidence-based trials regarding eradication or therapy exist on other bacterial species. Hence, this clinical guideline intended to focus on the most common, clinically relevant pathogens.

Acute tonsillitis is caused by viral infection in 70–95 % of all cases [7, 18]. Depending on the age, different spectrums of pathogens are found [18]. In children, Adenovirus 1–7, 7a, 9, 14, and 15; Influenza-Virus A and B; Parainfluenza-Virus 1–4; Epstein–Barr-Virus (EBV), Human-Herpes-Virus 4 (HHV4), and Enteroviruses including Coxsackie-Viruses are most commonly involved, less frequently rhinoviruses or the respiratory syncytial virus (RSV) [18]. In adults, up to 50 % of especially mild forms of tonsillitis are caused by Rhinoviruses or Coronaviruses [18]. In particular Adenoviruses may cause relevant tonsillitis with even purulent exudation [16]. In some cases of tonsillitis, adenoviruses are detected together with GABHS [18], suggesting GABHS colonization. Rare pathogens causing tonsillitis are the Cytomegalovirus (CMV) and the Human-Immunodeficiency-Virus (HIV). EBV tonsillitis is somewhat exceptional due to a potential involvement of the liver and spleen (Pfeiffer's disease; infectious mononucleosis, IM) [19]. More rarely, a primary CMV infection

manifests with IM (see also ICD10 B27.1). GABHS, i.e. *Streptococcus pyogenes,* are the most common bacterial origin of tonsillo-pharyngitis in immunocompetent children (20–30 %) and adults (5–15 %). The infection occurs with a peak at the age of 3–14 years [18] which is mirrored by clinical scores [20, 21]. The value of a proven β-hemolytic group C or G streptococci infection compares clinically to a proven GABHS infection [22, 23]. Streptococci of group C and G have some virulence factors in common with GABHS, such as for example the M protein [24, 25]. The M protein is one of the main virulence factors of GABHS; different M protein subtypes are known to be associated with rheumatic fever [26, 27]. Studies from other countries with a high prevalence of rheumatic fever further indicate a certain association between other β-hemolytic streptococci of group C and G and an occurrence of streptococcal secondary disease [28, 29].

Beside numerous anaerobes, many subspecies of the category *Moraxella, Neisseria,* and *Haemophilus* are further commensals. In addition to the majority of non-pathogenic Neisseria, rarely also *Neisseria gonorrhoeae* (gonococci) may trigger tonsillitis (especially in adults) [7]. In Germany, *Neisseria meningitidis* (meningococci) are detected as pharyngeal commensals in 10 % of the population [30]. The majority of the meningococcus strains has to be classified as non-pathogenic in healthy people [31]. *Neisseria meningitidis* does not belong to the pathogens causing tonsillitis. For predisposition of meningococcal infection triggered by previous virus infection of the respiratory tract (including viral tonsillitis), different references are found in the literature. The transmission of meningococci occurs through direct contact with oropharyngeal secretions of index patients with acute meningococcal infection [30–32]. *The role of Haemophilus influenzae* type b (Hib), non-typable *Haemophilus* strains, and bacteria of the genus *Moraxella* in relation to tonsillitis is insignificant.

Among anaerobes, *Fusobacterium necrophorum* plays an exceptional role and is isolated especially in patients suffering from an oropharyngeal infection with abscess formation and thrombosis of the internal jugular vein (Lemièrrés syndrome) [33]. A unilateral ulcer formation is reported in cases with a mixed infection with spirochaetes (*Treponema vincentii* and others) and fusobacteria (*fusobacterium nucleatum* and others). The findings in these cases of the so called Vincentís angina include a pain-free unilateral gray-greenish tonsillar exudation associated with a significant cloaca-like halitosis and potentially cervico-buccal abscess development [34]. An extremely rare infection is caused by *Corynebacterium diphtheriae*. Patients present with a white-grayish pseudo-membranes which are not limited to the tonsils but involve the surrounding mucosa of the soft palate and pharynx. The mucosa is extremely vulnerable, bleeds easily and patients are threatened by acute upper airway obstruction [35, 36]. Among others, very rare pathogens causing tonsillitis are: *Corynebacterium ulcerans, Corynebacterium/Arcanobacterium haemolyticum, Fancisella tularensis, Yersinia pestis, Yersinia enterocolitica, Treponema pallidum, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Chlamydia psittaci*.

Swabs taken from patients with peritonsillar abscess often reveal β-hemolytic streptococci, *Staphylococcus aureus,* and *Haemophilus influenzae,* as well as anaerobes such as fusobacteria, peptostreptococci, and *Prevotella*.

Differential diagnosis of tonsillitis

Acute tonsillitis is to be a clinical diagnosis [7]. Furthermore, parameters like the patienťs history, clinical symptoms, and laboratory values are required to distinguish between viral and bacterial origin of tonsillitis [7, 37]. It should be emphasized, that even positive results in laboratory tests such as C-reactive protein (CRP), serological parameters like positive anti-streptolysin-O titers (ASLO) or tonsil swabs (rapid antigen detection or microbiological culturing) do not prove a tonsillitis in asymptomatic patients [7, 37]. An asymptomatic person with microbiological proof of β-hemolytic streptococci in the pharyngeal swab is a so-called carrier of β-hemolytic streptococci [7, 37]. In contrast, the clinical diagnosis in symptomatic patients can be confirmed either by means of bacterial culture or rapid antigen detection [7], otherwise it remains only a clinical suspicion. The detection of bacterial commensals does not confirm a bacterial infection in symptomatic patients but suggests viral etiology [7]. Determination of ASLO values is not indicated to establish the diagnosis of tonsillitis (see below) [38–40]. The immune response against streptococci does not lead to a complete immune protection so that streptococcal infection might re-occur [5]. Reinfection means a new infection with the same streptococcus strain, which might even occur endogenously by persistence of the pathogens. An recurring infection with another streptococcus strain is defined as new infection of the same site. In most cases, it is transmitted exogenously by contact persons with acute tonsillo-(pharyngitis). In the light of this clinical guideline, a differentiation is irrelevant.

Scarlet fever

Scarlet fever is an exotoxin-mediated systemic disease caused by streptococci [41] and is different to streptococcal tonsillitis or any other (purulent) tonsillitis associated with exanthema [41, 42]. It may occur even without tonsillitis, after TE, or even without exanthema. Since the differential

diagnosis between scarlet fever and viral tonsillitis with exanthema plays a major role in primary medical consultation, for the diagnosis of scarlet fever at least one further criterion beside fever (and possibly tonsillitis) has to be fulfilled. In cases of scarlet types deviating from the classical course, a positive testing for streptococci is essential to at least confirm the presence of a suspected β-hemolytic streptococcal infection [42, 43]. The abrupt onset of scarlet fever is most commonly characterized by shivering, high fever, tachycardia, headaches, and short-time vomiting. The face is reddened with a pale triangle around the mouth. Almost regularly, sore throat, swallowing complaints, and cervical lymph node swellings are found. The tonsils may be significantly swollen and reddened but may also appear dotted with whitish or yellowish spots of pus, sometimes even confluent coatings are observed. The enanthema is limited to the soft palate. At the beginning, it is speckled and of bright red until it changes to a darker red color. Beside the typical bad breath, the tongue is first whitish coated ("white strawberry tongue") until after some days the lingual papillae become clearly obvious ("red strawberry tongue"). The rash begins in the axillae and groin region followed by the chest, neck, and back and is sometimes itching. Finally the trunk and especially the inner surfaces of the extremities are involved. Palpation of the skin surface is comparable to sandpaper. The initially speckled, pale red rash turns red after 1–2 days and becomes confluent in many areas to a diffuse erythema with positive diascopy. Applying soft pressure to the red rash, white stripes appear for a short time. Petechias may also occur because of an increased capillary fragility. After 3–4 days, the exanthema is regressive in reverse sequence of its occurrence. The fever decreases with a slight delay. Often the scarlet exanthema is confluent, but may also present as a delimited picture. Only few patients present with small whitish to yellowish vesicles. They clearly contrast with the scarlet exanthema, dry out after some days and peel off. Desquamation starts in the face, at the auricles, axillae and groin region, followed by the palms, fingers, toes, and plantar skin. The process is limited most commonly to 4–6 weeks after onset of the disease onset, but may rarely last for some months [43]. Cases of scarlet fever resulting from wound infections as well as invasive infections caused by exotoxin-producing streptococci have been described [42]. In contrast to tonsillitis resulting from a local infection by streptococci, patients with scarlet fever typically present with a systemic immune response to the pyrogenic streptococcal exotoxins [41, 42].

Infectious mononucleosis (Pfeiffer's disease)

Regarding differential diagnosis, the EBV-associated tonsillitis must be distinguished from streptococcal tonsillitis [44–46]. The suspicion of EBV-associated IM generally results from the classical three symptoms of tonsillo-pharyngitis, fever, and cervical lymph node swellings which are found in 98 % of the patients. In contrast to streptococcal tonsillitis, rather extensive than speckled coatings are visible on the tonsillar surface. Furthermore, lymph node swellings are not only palpable in front of but also behind the sternocleidomastoid muscle. Other symptoms of IM occurring rather frequently are splenomegaly and hepatomegaly. The more rare symptoms are manifold and may present in nearly all organ systems. Among the possible acute complications of IM count e.g. airway obstruction due to tonsillar hyperplasia, rupture of the spleen, cytopenia, and neurological symptoms.

Objectives of diagnostics

In accordance with the national [7] and international guidelines [37, 47, 48], the diagnostic objective of this guideline aims at optimal health outcomes, minimized harm and diminished unnecessary and inappropriate therapy. Therefore, the estimation of a streptococcal infection by a valid clinical score will be shown as the essential first step. The approach is not transferrable to diphtheria, since even the slightest clinical suspicion of diphtheria mandates immediate inpatient hospitalization and medical therapy [35, 36].

Centor score and McIsaac score

To date, there exists neither a single parameter to distinguish between a viral or bacterial tonsillitis, nor to specifically diagnose GABHS tonsillitis [7, 47–57]. Suggested by Centor et al. [50] as early as 1981, the Centor score is an appropriate screening method for acute tonsillitis but limited to patients of at least 15 years of age (Table 1). The modified Centor score, as suggested by McIsaac (Table 2), corrects for age, and therefore can be used in adults as well as in children [20, 21]. Both tools were designed to estimate the probability that pharyngitis is of streptococcal origin, and to guide management [51]. Only in patients with a score of 3 and more (Centor or McIsaac), a rapid test or culture should be considered, if relevant. This is not suggested in patients with a score of 2 and less except these patients present with a persisting illness or unilateral finding [15, 95].

In the classification system of the simplified "Walsh Clinical Prediction Rules" the contact with GABHS tonsillitis is considered with one point, and coughing with the subtraction of one point [52]. In the "FeverPAIN" score, different aspects are included, such as fever within the last 24 h prior to consultation in combination with P = purulence, A = attend rapidly (within 3 days after appearance of the symptoms), I = inflamed tonsils, N = no

Table 1 Centor-score

Symptom	Score
Body temperature (in the history) > 38 °C	1
No cough	1
Cervical lymph node swellings	1
Tonsillar swelling or exudation	1

Total score	Probability of GABHS proof in the swab (%)
0	~2.5
1	~6–7
2	~15
3	~30–35
4	~50–60

Table 2 McIsaac score (modified Centor score)

Symptom	Score
Body temperature (in the history) > 38 °C	1
No cough	1
Cervical lymph node swelling	1
Tonsillar swelling or exudation	1
Age (years)	
3–14	1
15–44	0
≥45	−1

Total score	Probability of GABHS proof in the swab (%)
−1 or 0	1
1	10
2	~17
3	~35
4 or 5	~50

cough/coryza [22, 53]. Finally, a different approach was designed to include the patients perception with a "home score" for identification of pharyngitis [54]. It remains to be clarified whether or not the newer scoring systems are superior to the aforementioned scoring according to Centor or McIsaac [20, 21]. According to the aforementioned national and international guidelines, the McIsaac Score for clinical assessment of the probability of GABHS tonsillitis is still suggested as the preferable clinical screening tool.

Microbiological diagnostics

Sampling, storage, and transportation

The technique of sampling is crucial for the diagnostic quality of the pharyngeal swab [56, 57]. The tongue should be pressed down and the swab should be rubbed in a turning way over both tonsils or the lymphatic strands and the posterior pharyngeal wall. Further touching of the intraoral mucosa or the saliva should be avoided [57]. By means of special swabs, e.g. nylon flock swabs with highly adsorptive superficial coating, may improve the sampling capacity and releasing of the primary material to the transportation medium in addition to the sensitivity of the pharyngeal swab [58]. After taking of the sample, immediately a culture should be started or the rapid test should be performed. Otherwise, the pharyngeal swab should be inserted into a culture medium for transportation ("moist swab"). If an immediate transportation to the lab is not possible, the swab should be stored in the refrigerator for max. 12 h at 4–6 °C [57]. If anaerobe infection is suspected (e.g. for the evidence of pathogens in peritonsillar abscesses), special transportation kits or the immediate transportation to the lab and the additional timely culture with the special requirement of anaerobe identification is essential. A routinely performed diagnostic follow-up control of bacterial pharyngeal infections after antibiotic therapy is not necessary.

Rapid tests for detection of streptococci

For quick evidence of GABHS, so-called rapid antigen detection tests (RADT) may be applied. Most of them are optic immunoassays (OIA) or enzyme-linked immunosorbent assay (ELISA), or latex agglutination procedures. RADT are based on the identification of the Lancefield streptococci group antigen A. Most rapid tests are exclusively optimized for the identification of GABHS in pharyngeal swabs. Other β-hemolytic streptococci, e.g. group C and G as well as other species, are not assessed by the RADT tests. The sensitivity and specificity of the RADT for GABHS identification vary between 65.6 and 96.4 % or 68.7 and 99.3 %, respectively, depending on the manufacturer and the performance of the user [59–61]. In particular, a high inoculum quantity and well performed pharyngeal swab may improve the GABHS identification by means of rapid tests [62]. RADTs with clearly defined results such as optic immunoassays, are superior to latex agglutination procedures, especially when applied by persons who are not experienced in the evaluation of the test result [63]. Training of the users may increase the validity of the findings of the RADT findings [64]. However, especially the sensitivity of the RADTs is lower in comparison to microbiological culture [62]. Thus, rapid tests are recommended in particular in countries with only low incidence of streptococcal secondary diseases where a negative result of the rapid test is considered as being sufficient [62]. In cases of negative results of the rapid test and the urgent suspicion of bacterial pharyngeal infection, the identification by microbiological culture should be

attempted [7]. Mostly, microbiological culture is less expensive than rapid test procedures. However, one disadvantage of culturing is the time that is required until the result of the test is available [7].

Microbiological culture

GABHS are Gram-positive, β-hemolytic chains of cocci. The evidence of β-hemolytic streptococci can be provided as overnight culture at 37 °C in room air on 5 % Columbia blood agar or according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) currently on Mueller–Hinton agar with 5 % defibrinated horse blood and 20 mg/L β-NAD (MHF) at 35 +/− 1 °C in room air enriched with 4–6 % CO_2 for 16–20 h [65]. A routine antimicrobial resistance testing of streptococci is not recommended. An unidentified β-hemolysis cannot fully exclude the presence of GABHS [66]. Lancefield groups of β-hemolytic streptococci are characterized by seroagglutination. The evidence of β-hemolytic streptococci leads to the classification into the according Lancefield groups by means of sero-agglutination. Streptococci of the Lancefield group C and G mostly belong to the species of *Streptococcus dysgalactiae, Streptococcus equi, Streptococcus constellatus,* or *Streptococcus anginosus* [24]. A crossreactivity of different β-hemolytic streptococci on the Lancefield group agglutinant is possible [24]. Beside the determination of β-hemolysis on blood agar, Lancefield typing, and the determination of metabolic reactions, different procedures are applied for phylogenetic differentiation of β-hemolytic streptococci that are reserved to special laboratories (emm-typing, t-typing, 16S rRNA sequence similarity, multilocus sequence analysis, average amino acid identity, genome-to-genome distance, genome sequences/signatures, codon usage bias etc.) [24]. In outbreak situations, for the identification of infection chains, or for differentiation between re- or new infection, a molecular genetic typing of the M protein (emm gene sequence) can be performed [67, 68]. The microbiological evidence of bacteria in the pharyngeal swab proves the existence of bacteria in the swab site: It is noteworthy to repeat that a positive result neither confirms the infection nor the disease. The detection alone of β-hemolytic streptococci in the pharyngeal swab does not allow secure differentiation between the streptococcal carrier status and streptococcal tonsillo-pharyngitis [17, 69]. Beside the nutrition media and the incubation conditions, the sensitivity of the culture also depends on the time of recording of findings (after 24 or 48 h) as well as the interpretation by the responsible person. A massive cultural growth of β-hemolytic streptococci makes the presence of an infection more probable [70]. The semi-quantitative interpretation of the findings, however, depends crucially from the quality of the swab and other pre-analytic conditions.

The cultural proof of anaerobes, as also of *Corynebacterium diphtheriae,* is provided upon special request on special culture media. Beside the cultivation of *Corynebacterium diphtheria,* polymerase chain reaction (PCR) allows identifying the diphtheria toxin gene and Elek's immuno diffusion test may prove the secreted toxin [36].

Evidence of pathogens in viral tonsillitis

The molecular genetic proof of viral (tonsillitis) pathogens can be provided by means of multiplex-PCR. For different viruses (e.g. adenoviruses [71]) also rapid test procedures are at disposition. Because of the missing therapeutic consequence, the use of rapid tests or multiplex PCR for virus detection is almost always insignificant in the clinical routine.

Diagnostics in case of suspected Epstein-Barr virus infection

The molecular genetic identification of EBV in the pharyngeal swab by means of EBV specific PCR is not able to differentiate between acute tonsillar EBV infection and EBV re-activation (e.g. in the context of tonsillitis of other origin). An EBV positive immune status is found in more than 90 % of the population at an age of 30 years or older. EBV positive tested persons excrete the virus periodically with the pharyngeal secretion. Therefore, the test result is insignificant in these patients [72]. The clinical suspicion of IM should be confirmed by laboratory examinations in doubtful cases or in cases of high risk patients (pregnancy, HIV infection, immune deficiency). A reliable distinction of EBV associated IM from e.g. CMV associated IM is only possible by pathogen-specific serology and/or evidence of the pathogens. The proof of the pathogens in the routine is not necessary. Much more, the serology is decisive for therapy (see below).

	Anti-VCA-IgG	Anti-VCA-IgM	Anti-EA (D)	Anti-EBNA
	Virus capsid antigen (VCA)		Early antigen [EA (D)]	EBV nuclear antigen (EBNA)
EBV negative/no previous EBV infection	−	−	−	−
Acute EBV infection	+	+	+/−	−
Previous EBV infection	+	−	−	+

	Anti-VCA-IgG	Anti-VCA-IgM	Anti-EA (D)	Anti-EBNA
	Virus capsid antigen (VCA)		Early antigen [EA (D)]	EBV nuclear antigen (EBNA)
Chronically active EBV infection	+++	−/+	+++	−/+
EBV re-activation (systemic lymphoproliferation)	++	−/+	++	−/+

A new EBV primary infection can be expected in cases of evident anti-VCA-IgM and anti-VCA-IgG without proof of anti-EBNA-IgG in the classical serological screening procedures (e.g. CLIA, ELISA, formerly also indirect immunofluorescence). It must be noted that the absence of anti-VCA-IgM in young children does not exclude primary EBV infection. Furthermore, the absence of EBNA-IgG is no proof of a new EBV infection but is also observed in some healthy EBV carriers and patients with immune deficiency. In immunocompetent patients, the suspicion of new EBV primary infection can be confirmed in cases of doubt by differentiation of the EBV specific IgG antibody status in the EBV immunoblot or EBV line assay. In children older than 5 years of age and adults (up to 90 %), even heterophilic antibodies can be identified in the context of EBV immune reaction as rapid test procedures in the modified Paul-Bunnel-test (monospot). These antibodies, however, are not EBV-specific with a sensitivity and specificity of approximately 90 % [73, 74].

Clinical–chemical laboratory diagnostics

For the diagnosis of β-hemolytic streptococcal tonsillo-pharyngitis, blood examinations are of clearly lower sensitivity and specificity compared to clinical scoring systems and the detection of the bacteria. Additional laboratory examinations cannot significantly increase the diagnostic accuracy of Centor or McIsaac Score and RADT [75]. No laboratory parameter allows a reliable differentiation between bacterial and viral etiology of tonsillo-pharyngitis. In a group of adult patients with GABHS tonsillitis, the mean values of the CRP value, total number of leukocytes, and total number of neutrophil granulocytes were found to be increased, but mostly with an only low sensitivity (66–90 %) and specificity (45–75 %)—as shown in a current prospective evaluation of adults [75]. In the last mentioned study, furthermore no difference between the procalcitonin concentrations of both groups could be found [75]. In another study, the evaluation of the erythrocyte sedimentation rate (ESR) in adults with sore throat did not provide any difference between patients with or without GABHS evidence and thus no clinically relevant additional information [76]. An Italian trial revealed higher CRP values and ESR in children with tonsillitis as well as a higher total number of leukocytes compared to healthy children. However, a differentiation between viral and bacterial etiology was not found [77].

Among all blood parameters, the CRP value still seems to be at least of limited diagnostic value. In a German evaluation of adult patients suffering from sore throat, the best accuracy of a dichotomization of the CRP values of <35 mg/L (improbable GABHS detection) and >35 mg/L (probable GABHS detection) was found for the combination of CRP value and clinical score for diagnosis of GABHS pharyngitis [77]. In a Norwegian study of children and adults suffering from pharyngitis, the identification of streptococci was increased with a CRP value of 25 mg/L, however, only with a likelihood ratio of 1.3–1.6 [78]. Up to now, no correlation of inflammation parameters with the risk of purulent or immunogenic streptococcal secondary disease could be revealed. Even in cases of florid peritonsillar abscess, the inflammation parameters may be false negative.

If a new EBV primary infection is suspected, the blood count may be helpful to distinguish from streptococcal tonsillitis. Typically, the blood count of a patient with acute EBV-associated IM reveals leukocytosis with lymphocytosis whereas the streptococcal tonsillitis is rather associated with neutrophilia. Additionally, atypical reactive lymphocytes are found in the blood smear in classical IM caused by EBV or CMV. In the context of EBV primary infection, increased values of lactate dehydrogenase (LDH) and increased transaminase values are frequently observed.

A routinely performed evaluation of laboratory inflammation parameters is not recommended in suspected or present tonsillitis. Blood counts may be helpful in single cases but they should only be considered in selected cases.

Streptococci antibody test (e.g. antistreptolysin-O titer)

Recommendation

The determination of the antistreptolysin-O titer (ASLO titer) and other streptococcal antibody titers does not have any value in acute and recurrent tonsillitis / pharyngitis and thus should not be performed.

The ASLO titer and all other currently known human antibody titers against β-hemolytic streptococci (e.g. anti-hyaluronidase, anti-DNase B etc.) do not provide valid diagnostic criteria for the diagnostics of tonsillitis so that there is no need for determination [7]. In the literature, there is no reference revealing an evidence basis that might justify the indication of tonsillectomy based on streptococcal antibody titers beyond a specific cut-off value. This conclusion complies with the national DEGAM guideline [7] as

well as to the results of the new, current literature research in the context of the present guideline. Regarding the streptolysins, as for example streptolysin S (SLS) and streptolysin O (SLO), these are virulence factors that are produced among others by β-hemolytic streptococci. When growing on blood agar, these cholesterol-binding, oxygen-labile exotoxins lead to the known characteristic bright and transparent zone caused by β-hemolysis [79]. They belong to the first identified streptococcal virulence factors. Antibodies against streptolysins can be measured in the blood and can be valued as expression of an immune response to streptococci. However, because of their high variability, it is difficult to use them as diagnostic parameter in relation to tonsillitis/pharyngitis. Up to now, the streptolysin antigen does not have any clearly determined pathogenetical relevance in the context of β-hemolytic streptococcal infections or β-hemolytic streptococcal sequelae. The so-called antistreptolysin O titer (ASLO titer) or the ASLS or ASLO values describe the human antibody production against those streptococcal antigens. The antibody production may be triggered by an acute β-hemolytic streptococcal infection. However, even severe β-hemolytic streptococcal infections were not necessarily followed by increased ASLO levels. A study of 87 healthy persons did not reveal any significant correlation between the ASLO level and the high sensitive CRP (hsCRP) as biomarker for an inflammatory immune reaction [80]. The authors concluded that there is no relation between the titer level and possible active inflammation in otherwise healthy patients [80]. The intensity of the immune response as a reaction to an acute streptococcal infection in terms of titer levels do vary interindividually. Approximately 40 % of all patients with a proven GABHS tonsillitis show elevated titer levels after the infection. Furthermore, elevated ASLO titers may persist in asymptomatic patients with or without GABHS proof as well as GABHS infections appear in other individuals without a significant titer increase and even a very rapid titer decrease might be observed during recovery [38, 39].

In summary, numerous streptococcal virulence factors are known and the indication of new virulence factors is continuously increasing. Theoretically, a human immune response to many of those virulence factors can be measured. The antiDNase B titer, also known as antistreptodornase B titer or ASD B value, is a human antibody against a streptococcal desoxyribonuclease. In the context of AHT or AHD titer, a human antibody against the streptococcal hyaluronidase is measured. All those virulence factors seem to play a potential role in the infection processes triggered by streptococci. However, a clinical relevance of the produced antibody response with a clear cut-off value relevant enough for therapeutic decisions does not exist. These virulence factors and thus also the antibody production are not specific for GABHS. Other streptococci such as for example streptococci of group B, C, and G may also have those virulence factors. All streptococci antibodies that were clinically evaluated up to now do not allow any prospective risk assessment of which the development of purulent or immunogenic streptococcal secondary disease may be deducted. Only in cases of a clinically suspected streptococcal secondary disease, the assessment of the antibody response and the follow-up of the titer development may be helpful in the absence of other diagnostic options and thus contribute to the confirmation of the clinical-anamnestic suspicion of a previous β-hemolytic streptococcal infection [81, 82]. For determination of the antibody response against streptococci, mostly latex agglutination or enzyme-linked immunosorbent assays are used. The results may alter because of cross-reacting antibodies, antigen neutralizing serum factors, protein deficiency, immune deficiency, etc. The exact application of streptococcal antibodies in the context of rheumatic diseases [e.g. acute rheumatic fever (ARF), acute post-streptococcal glomerulonephritis (APSGN), etc.] will not be dealt with in this guideline because no consequences for specific action in the context of acute or recurrent tonsillitis result. An increased antibody response against streptococci (e.g. an increased ASL titer) neither indicates a protection against acute streptococcal infections nor an increased risk of acute streptococcal disease, nor an increased risk of purulent or immunogenic streptococcal secondary disease [38]. No prediction can be made regarding the streptococci carrier status or an increased contagiousness [82].

Diagnostics in cases of suspected peritonsillar abscess

In a most recent meta-analysis, 45 clinical studies were included, published between 1991 and 2011 [83]. Articles published between 2011 and October 2014 were reviewed by the panelists and did not reveal contradicting results to the meta-analysis. Primarily, peritonsillar abscess is a clinical diagnosis that is characterized by fever, pain, unilateral swelling of the tonsil, sometimes including the cheeks/neck, dysphagia with changed voice ("hot potato voice"), odynophagia, hypersalivation and trismus. In most cases, the general condition of the patients is significantly reduced. In cases of dyspnea, stridor, or other signs of upper airway obstruction, problems during intubation may occur, requiring skilled staff and adequate instrumentation. Peritonsillar cellulitis, intratonsillar abscess, IM, cervical lymphadenitis, (abscessing) dental and gingival infections, sialadenitis, sialolithiasis, malign tumors, mastoiditis, or an aneurysm of the internal carotid artery should be excluded in the differential diagnosis. Inflammation values (e.g. white blood cell count and CRP) may be helpful in cases of

clinical suspicion of peritonsillar abscess. It is noteworthy to emphasize, that their sensitivity and specificity are only moderate. As a result of odynophagia, some patients present with relevant dehydration. Therefore, a shift of serum electrolytes should be checked by blood tests. In contrasts to the meta-analysis, the panelists do not recommend intraoral sonography since this method is uncommon in Germany and conclusions in the literature were drawn from small sample sizes. If abscessing is clinically presumed beyond the peritonsillar space, imaging by means of magnetic resonance imaging (MRI) or computed tomography (CT) of the head and neck are recommended. CT scan is able to confirm the diagnosis of peritonsillar abscess with a sensitivity of up to 100 % and a specificity of 75 % and it can—nearly always available and cost-effective—identify further abscessing. MRI allows a better soft tissue resolution and depiction of the vessels without radiation exposure and thus it is recommended especially for children. To facilitate the identification of infectious organisms, a swab from the throat/aspirated pus and culture are to be considered. The results may help to select the most appropriate antibiotic once the organism is identified, limiting the risk of antibiotic resistance.

Reporting obligations in cases of tonsillitis and pathogen evidence in the pharyngeal swab

Reporting obligations in Germany are continually updated and published by the Robert Koch Institute (RKI) [84]. Scarlet fever, however, is subject to reporting only in some federal states (Saxony, Saxony-Anhalt, and Thuringia). The responsible people of community institutions are obliged to inform the responsible health authorities immediately if infections or diseases occur bearing the risk of further distribution and to reveal data on the disease and the affected people. It is not necessary to report the evidence of *Neisseria meningitidis* in the pharyngeal swab in asymptomatic patients. The health authorities are to be informed immediately in the event of occurrence of diphtheria infections or suspected cases.

Nonsurgical therapy: general remarks

Usually, the clinical course of an acute episode of tonsillitis, with or without a proven GABHS infection, is self-limiting. Antibiotic therapy is indicated only in case of a highly suspected or proven β-hemolytic streptococci infection (of group A, C, or G). Today, pathogens like. *Corynebacterium diphtheria* are extremely rare and therefore beyond the scope of this guideline). Inadequate administration of antibiotic therapy may result in bacterial resistances. Therefore, it is essential to consider the patient's or parent's wish of symptom relief apart from the evidence level for medical advices. For mere symptom relief, especially within the first 3 days after disease onset, for example acetaminophen (Paracetamol), non-steroidal anti-inflammatory drugs like ibuprofen can be applied with satisfactory results. Because of the possible hepatotoxicity, acetaminophen should not be recommended if EBV infection is suspected or confirmed. The effect of local anesthetics and local antiseptics in the sense of pharyngeal sprays, lozenges, and oral rinses is not proven.

If EBV infection is suspected or confirmed, physical rest, sufficient iv-hydration, analgesia, and antipyretic medication should be in the focus of treatment. Because of the high risk of cross-reaction rash (about 90 %), treatment with ampicillin is contraindicated. The large size of the infected tonsils may result in significant upper airway obstruction, and patients may benefit from administration of anti-inflammatory steroids to downsize the tonsils. Hence, tonsillectomy, tracheostomy, and/or intubation may become superfluous. The benefit potential of steroids must be weighed against the risks of steroid therapy. Antiviral drugs, such as *Acyclovir* were not identified as efficacious and others (Valaciclovir, Ganciclovir) are still subject of clinical studies. More recent studies evaluated the benefit of antibiotics against anaerobes (Metronidazol), but the results have not yet accessed clinical routine [44].

Antibiotic therapy

For patients with sore throat in times and regions without epidemic occurrence of β-hemolytic streptococcal infection, a low regional incidence of streptococcal sequelae and a McIsaac-Score of at least 3, oral medication is recommended as follows [5, 7, 95]:

1. Age 3–14 years:

   Penicillin V (100,000 IU/kg/day in three doses for 7 days), or

   Phenoxymethylpenicillin–Benzathin (50,000 IU/kg/day in two doses for 7 days)

   In case of allergy/incompatibility:

   Erythromycin-estolate (40 mg/kg/day in three doses for 5 days), or

   1st generation cephalosporin (e.g. cefadroxil 50 mg/kg/day in two doses for 5 days)

2. Age 15 years and older:

   Penicillin V (3×0.8–1.0 Mio IU/day for 7 days)

   In case of allergy/incompatibility:

   Erythromycin-estolate (3×500 mg/day for 5 days), or

   1st generation cephalosporin (e.g. cefadroxil 2×1000 mg/day for 5 days)

   It could be shown that the treatment with oral cephalosporins over 5 days is not inferior to a penicillin V

therapy of 10 days [95]. A direct comparison of the effectiveness, however, cannot be concluded because in this study no comparison group with 5 days of penicillin therapy was considered. According to a meta-analysis, the treatment with oral cephalosporins is slightly superior to the one with penicillin V from a microbiological point of view [7]. The treatment with oral cephalosporins, however, is more expensive and additionally, there is no evidence that the higher bacteriological recovery rate is of significant clinical relevance [7]. Only very selected indications support administration of oral cephalosporins (for example: cefadroxil, cefalexin) including the failure of penicillin V, frequent recurrences, and whenever a more reliable eradication of β-hemolytic streptococci is desirable. In cases of allergy against penicillin, macrolides (e.g. Erythromycin-estolate 40 mg/kg body weight/day in two single doses) are a valuable alternative [5, 47, 96]. A resistance rate of 10–12 % and their regional differences in Germany must be considered. Another alternative is clindamycin (20 mg/kg body weight/day in three single doses). In Germany, a GABHS-recurrence rate of 5 % after clindamycin therapy was reported. In cases of allergies (acute type) against beta-lactam antibiotics, cephalosporins should not be applied because of frequent cross reactions [5, 7].

Cotrimoxazol (trimethoprim/sulfamethoxazol) and tetracyclines should not be prescribed because of their insufficient effectiveness and possible side effects [7, 97].

With adequate therapy, most of the patients, especially adolescents and adults, are free of symptoms within 48 h. If this is not the case, therapy compliance must be questioned and the diagnosis be revised. There is no need to perform pharyngeal swab after the end of antibiotic therapy, apart from patients with risk factors (e.g. ARF in the patient's history). This aspect also applies to urinary controls or ECG examinations.

It is noteworthy to repeat that bacterial commensals of the oral and pharyngeal flora (e.g. unencapsulated strains of *Haemophilus influenzae*) are not considered as causal for tonsillitis if identified in the pharyngeal swab (exception: immunosuppressed patients). A bacterial tonsillo-pharyngitis triggered by other pathogens—apart from GABHS—is clearly rarer than viral etiology.

Antibiotic therapy: advantages

- The duration of contagiousness is reduced. After 24 h at the latest, patients undergoing antibiotic therapy are no longer contagious [85]. A reduced infection rate due to antibiotic therapy of GABHS tonsillo-pharyngitis is not confirmed by studies [7].
- The symptoms of tonsillo-pharyngitis and fever are relieved more rapidly. This effect, however, is only found to a moderate extent. A Cochrane analysis showed an average difference between antibiotic and placebo treatment of 16 h. Spontaneous healing occurred in adults on day 3 in approximately 40 % and increased to roughly 85 % on day 7 [86].
- Purulent complications can potentially be reduced. However, this effect is not sufficiently evidence-based. The occurrence of peritonsillar abscesses as complication of tonsillo-pharyngitis in Germany is so rare that current RCTs disposing of the usual number of cases do not statistically confirm the preventive effect of antibiotics [7, 87–91].
- Immunogenic secondary diseases such as acute rheumatic fever (ARF) or acute post-streptococcal glomerulonephritis (APSGN) are potentially avoided. It should be noted that this conclusion is drawn from studies of the 1950s with intramuscular application of penicillin at the onset [86, 92–94]. The extremely low risk of immunogenic streptococcal secondary disease currently does not justify the routinely performed antibiotic application in cases of confirmed or suspected GABHS tonsillo-pharyngitis in Germany [7].

Antibiotic therapy: disadvantages

Side effects, like the evolutionary pressure on the whole microbiome of the treated patient and thus the promotion of bacterial resistances as well as health care costs. A reduction of absences in school or at work due to antibiotic therapy could not be confirmed by studies [87, 88, 90, 91].

Acknowledgments The authors would like to thank Susanne Zapf, Marburg University Hospital, Marburg, Germany, for her invaluable help in translating this clinical guideline.

References

1. https://faktencheck-gesundheit.de/fileadmin/daten_fcm/Dokumente/FCM_Report_Web.pdf. Accessed 1 Oct 2014
2. Stelter K (2014) Erkrankungen der Gaumenmandeln im Kindesalter. Laryngo- Rhino-Otologie 93(Suppl 1):S84–102
3. Stelter K (2014) Tonsillitis and sore throat in children. GMS Curr Top Otorhinolaryngol Head Neck Surg 13:07
4. Bathala S, Eccles R (2013) A review on the mechanism of sore throat in tonsillitis. J Laryngol Otol 127:227–232
5. Scholz H, Berner R, Duppenthaler A, Forster J, Töpfner N (2013) Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI), DGPI Handbuch: Infektionen bei Kindern und Jugendlichen, 6. überarbeitete Auflage, Infektionen durch ß-hämolysierende Streptokokken der Gruppe A. Georg Thieme Verlag, Stuttgart, pp 509–516
6. Statistisches Bundesamt Gesundheit. Diagnosedaten der Patienten (2015) und Patientinnen in Krankenhäusern (einschl. Sterbe- und Stundenfälle). Fachserie 12 Reihe 621
7. www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/LL-14_Langfassung_ZD.pdf. Accessed 1 Oct 2014

8. http://www.awmf.org/uploads/tx_szleitlinien/017-066_S2_Antibiotikatherapie_der_Infektionen_an_Kopf_und_Hals_abgelaufen.pdf. Accessed 1 Oct 2014
9. http://www.awmf.org/leitlinien/awmf-regelwerk.html. Accessed 1 Oct 2014
10. http://www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf. Accessed 1 Oct 2014
11. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), (AWMF) AdWMF (2010) Programm für Nationale VersorgungsLeitlinien. Methoden-Report; 4. Auflage
12. Kunz R, Burnand B, Schünemann HJ (2008) Das GRADE-System. Ein internationaler Ansatz zur Vereinheitlichung der Graduierung von Evidenz und Empfehlungen in Leitlinien. Der Internist 49:673–680
13. www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Krankenhaeuser/Tabellen/Diagnosen_Kinder.html. Accessed 01 Jun 2015
14. http://www.awmf.org/uploads/tx_szleitlinien/023-027l_S2k_Rheumatisches_Fieber_Kinder_Jugendliche_2014-06.pdf. Accessed 1 Oct 2014
15. http://www.homd.org. Accessed 1 Oct 2014
16. Esposito S, Blasi F, Bosis S et al (2004) Aetiology of acute pharyngitis: the role of atypical bacteria. J Med Microbiol 53:645–651
17. Del Mar C (1992) Managing sore throat: a literature review. I. Making the diagnosis. Med J Aust 156:572–575
18. Putto A (1987) Febrile exudative tonsillitis: viral or streptococcal? Pediatrics 80:6–12
19. Walther LE, Ilgner J, Oehme A et al (2005) Die infektiöse Mononukleose. Hno 53:383–392 **quiz 393**
20. McIsaac WJ, Goel V, To T, Low DE (2000) The validity of a sore throat score in family practice. CMAJ 163:811–815
21. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE (2004) Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA 291:1587–1595
22. Little P, Hobbs FD, Mant D, McNulty CA, Mullee M, Investigators P (2012) Incidence and clinical variables associated with streptococcal throat infections: a prospective diagnostic cohort study. Br J Gen Pract 62:e787–e794
23. Rantala S (2014) Streptococcus dysgalactiae subsp. equisimilis bacteremia: an emerging infection. Eur J Clin Microbiol Infect Dis 33:1303–1310
24. Jensen A, Kilian M (2012) Delineation of Streptococcus dysgalactiae, its subspecies, and its clinical and phylogenetic relationship to Streptococcus pyogenes. J Clin Microbiol 50:113–126
25. Brandt C, Spellerberg B (2009) Human infections due to Streptococcus dysgalactiae subspecies equisimilis. Clin Infect Dis 49:766–772
26. Barouxm N, D'Ortenzio E, Amédéo N et al (2014) The emm-cluster typing system for Group A Streptococcus identifies epidemiologic similarities across the pacific region. Clin Infect Dis 59:e84–e92
27. Steer AC, Law I, Matatolu L, Beall BW, Carapetis JR (2009) Global emm type distribution of group A streptococci: systematic review and implications for vaccine development. Lancet Infect Dis 9:611–616
28. Nitsche-Schmitz D, Chhatwal G (2013) Host-pathogen interactions in streptococcal immune sequelae. Curr Top Microbiol Immunol 368:155–171
29. Reissmann S, Gillen C, Fulde M et al (2012) Region specific and worldwide distribution of collagen-binding M proteins with PARF motifs among human pathogenic streptococcal isolates. PLoS One 7:e30122
30. http://www.rki.de/DE/Content/InfAZ/M/Meningokokken/Meningokokken.html. Accessed 1 Oct 2014
31. Tenenbaum T (2013) Meningokokkeninfektionen. Georg Thieme Verlag, Stuttgart
32. http://www.awmf.org/uploads/tx_szleitlinien/030-089l_S1_Ambulant_erworbene_bakterielle_Meningoenzephalitis_2012_1.pdf. Accessed 1 Oct 2014
33. Righini C, Karkas A, Tourniaire R et al (2014) Lemierre syndrome: study of 11 cases and literature review. Head Neck 36:1044–1051
34. Gebhardt B, Herrmann K, Roessner A, Vorwerk U (2010) Differenzialdiagnostik der nekrotisierenden Tonsillitis. Laryngo-Rhino- Otologie 89:266–269
35. www.rki.de/DE/Content/InfAZ/D/Diphtherie/Diphtherie.html;jsessionid=42223A110C4CC5E49420A68996633F91.2_cid390?nn=2386228. Accessed 1 Oct 2014
36. Berner R, Scholz H, Sing A (2013) Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI), DGPI Handbuch: Infektionen bei Kindern und Jugendlichen, 6. überarbeitete Auflage, Diphtherie. Georg Thieme Verlag, Stuttgart, pp 228–231
37. Chiappini E, Regoli M, Bonsignori F et al (2011) Analysis of different recommendations from international guidelines for the management of acute pharyngitis in adults and children. Clin Ther 33:48–58
38. Johnson DR, Kurlan R, Leckman J, Kaplan EL (2010) The human immune response to streptococcal extracellular antigens: clinical, diagnostic, and potential pathogenetic implications. Clin Infect Dis 50:481–490
39. Hill HR (2010) Group A streptococcal carrier versus acute infection: the continuing dilemma. Clin Infect Dis 50:491–492
40. Sen ES, Ramanan AV (2014) How to use antistreptolysin O titre. Arch Dis Child Educ Pract Ed 99:231–237
41. Silva-Costa C, Carrico JA, Ramirez M, Melo-Cristino J (2014) Scarlet fever is caused by a limited number of Streptococcus pyogenes lineages and is associated with the exotoxin genes ssa, speA and speC. Pediatr Infect Dis J 33:306–310
42. Toepfner NB, Scharlach R (2014) Kinder- und Jugendarzt 45
43. Schleissner F (1912) Beiträge zur Kenntnis der Streptokokken bei Scharlach. Z Kinderheilk 3:28–64
44. Lennon P, Crotty M, Fenton JE (2015) Infectious mononucleosis. BMJ 350:h1825
45. Balfour HH Jr, Dunmire SK, Hogquist KA (2015) Infectious mononucleosis. Clin Transl Immunol 4:e33
46. Vouloumanou EK, Rafailidis PI, Falagas ME (2012) Current diagnosis and management of infectious mononucleosis. Curr Opin Hematol 19:14–20
47. Shulman ST, Bisno AL, Clegg HW et al (2012) Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis 55:1279–1282
48. Group ESTG, Pelucchi C, Grigoryan L (2012) Guideline for the management of acute sore throat. Clin Microbiol Infect 18(Suppl 1):1–28
49. Hafner JW (2005) Evidence-based emergency medicine/rational clinical examination abstract. The clinical diagnosis of streptococcal pharyngitis. Ann Emerg Med 46:87–89
50. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K (1981) The diagnosis of strep throat in adults in the emergency room. Med Decis Making 1:239–246
51. Fine AM, Nizet V, Mandl KD (2012) Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. Arch Intern Med 172:847–852
52. McGinn TG, Deluca J, Ahlawat SK, Mobo BH Jr, Wisnivesky JP (2003) Validation and modification of streptococcal pharyngitis clinical prediction rules. Mayo Clin Proc 78:289–293
53. Little P, Hobbs FD, Moore M et al (2014) Primary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with

nested qualitative study and cost-effectiveness study. Health Technol Assess 18:vii–xxv, 1–101
54. Fine AM, Nizet V, Mandl KD (2013) Participatory medicine: a home score for streptococcal pharyngitis enabled by real-time biosurveillance: a cohort study. Ann Intern Med 159:577–583
55. Toepfner N, Berner R, Duppenthaler A, Forster J, Scholz H (2013) Tonsillopharyngitis. In: Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI), DGPI Handbuch. Infektionen bei Kindern und Jugendlichen. Georg Thieme Verlag, Stuttgart 6. überarbeitete Auflage, Seiten, pp 785–788
56. Kurtz B, Kurtz M, Roe M, Todd J (2000) Importance of inoculum size and sampling effect in rapid antigen detection for diagnosis of Streptococcus pyogenes pharyngitis. J Clin Microbiol 38:279–281
57. http://www.awmf.org/uploads/tx_szleitlinien/029-018l_S1_Gewinnung_Lagerung_Transport_von_Proben.pdf
58. Lasseter GM, McNulty CA, Hobbs FD, Mant D, Little P (2011) Group PRcSMI. Effect of swab type on the analytical sensitivity of five point-of-care tests for group A streptococci. Br J Biomed Sci 68:91–94
59. Madurell J, Balague M, Gomez M, Cots JM, Llor C (2010) Impact of rapid antigen detection testing on antibiotic prescription in acute pharyngitis in adults. FARINGOCAT STUDY: a multicentric randomized controlled trial. BMC Fam Pract 11:25
60. Ruiz-Aragon J, Rodriguez Lopez R, Molina Linde JM (2010) Evaluation of rapid methods for detecting Streptococcus pyogenes. Systematic review and meta-analysis. Anales de Pediatria 72:391–402
61. Lasseter GM, McNulty CA, Richard Hobbs FD, Mant D, Little P, Investigators P (2009) In vitro evaluation of five rapid antigen detection tests for group A beta-haemolytic streptococcal sore throat infections. Fam Pract 26:437–444
62. Cohen JF, Chalumeau M, Levy C et al (2012) Spectrum and inoculum size effect of a rapid antigen detection test for group A streptococcus in children with pharyngitis. PLoS One 7:e39085
63. Gerber MA, Shulman ST (2004) Rapid diagnosis of pharyngitis caused by group A streptococci. Clin Microbiol Rev 17:571–580 **table of contents**
64. Toepfner N, Henneke P, Berner R, Hufnagel M (2013) Impact of technical training on rapid antigen detection tests (RADT) in group A streptococcal tonsillopharyngitis. Eur J Clin Microbiol Infect Dis 32:609–611
65. www.eucast.org. Accessed 1 Oct 2014
66. Dierksen KP, Tagg JR (2000) Haemolysin-deficient variants of Streptococcus pyogenes and S. dysgalactiae subsp. equisimilis may be overlooked as aetiological agents of pharyngitis. J Med Microbiol 49:811–816
67. www.nrz-streptococcus.de. Accessed 1 Oct 2014
68. www.cdc.gov/streplab. Accessed 1 Oct 2014
69. Gerber MA, Tanz RR, Kabat W et al (1999) Potential mechanisms for failure to eradicate group A streptococci from the pharynx. Pediatrics 104:911–917
70. Haverkorn MJ, Valkenburg HA, Goslings WR (1971) Streptococcal pharyngitis in the general population. I. A controlled study of streptococcal pharyngitis and its complications in the Netherlands. J Infect Dis 124:339–347
71. Morozumi M, Shimizu H, Matsushima Y et al (2014) Evaluation of new immunochromatographic assay kit for adenovirus detection in throat swab: comparison with culture and real-time PCR results. J Infect Chemother 20:303–306
72. Schuster V, Korn K, Nadal D, Wagner H-J (2013) Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI), DGPI Handbuch: Infektionen bei Kindern und Jugendlichen, 6. überarbeitete Auflage, Epstein Barr Virus Infektionen. Georg Thieme Verlag, Stuttgart, pp 249–252
73. Gulley ML, Tang W (2008) Laboratory assays for Epstein–Barr virus-related disease. J Mol Diagn JMD 10:279–292
74. Bauer G (2001) Simplicity through complexity: immunoblot with recombinant antigens as the new gold standard in Epstein–Barr virus serology. Clin Lab 47:223–230
75. Christensen AM, Thomsen MK, Ovesen T, Klug TE (2014) Are procalcitonin or other infection markers useful in the detection of group A streptococcal acute tonsillitis? Scand J Infect Dis 46:376–383
76. Hjortdahl P, Melbye H (1994) Does near-to-patient testing contribute to the diagnosis of streptococcal pharyngitis in adults? Scand J Prim Health Care 12:70–76
77. Gulich M, Triebel T, Zeitler HP (2002) Development and validation of a simple, two-step algorithm to identify streptococcal infection in adults with sore throat. Eur J Gen Pract 8:57–61
78. Lindbaek M, Hoiby EA, Lermark G, Steinsholt IM, Hjortdahl P (2005) Clinical symptoms and signs in sore throat patients with large colony variant beta-haemolytic streptococci groups C or G versus group A. Br J Gen Pract 55:615–619
79. Sierig G, Cywes C, Wessels MR, Ashbaugh CD (2003) Cytotoxic effects of streptolysin o and streptolysin s enhance the virulence of poorly encapsulated group a streptococci. Infect Immun 71:446–455
80. Nava A, Robles G, Mendoza AC et al (2007) Correlation between serum levels of antistreptolysin O and C reactive protein. Rev Alerg Mex 54:201–204
81. Sethi S, Kaushik K, Mohandas K, Sengupta C, Singh S, Sharma M (2003) Anti-streptolysin O titers in normal healthy children of 5–15 years. Indian Pediatr 40:1068–1071
82. Servizio sanitario regionale Emilia-Romagna. Faringotonsillite in etá pediatrica; Linea guida regionale. Bologna ISsrJ. http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/doss153/link/doss153.pdf
83. Powell J, Wilson JA (2012) An evidence-based review of peritonsillar abscess. Clin Otolaryngol 37:136–145
84. www.rki.de/DE/Content/Infekt/IfSG/Meldepflichtige_Krankheiten/Meldepflichtige_Krankheiten_node.html. Accessed 1 Oct 2014
85. www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Streptococcus_pyogenes.html;jsessionid=3CBF0B59C7B85D5D94C05816495FFC7E.2_cid298#doc2374548bodyText6. Accessed 01 July 2015
86. Spinks A, Glasziou PP, Del Mar CB (2013) Antibiotics for sore throat. Cochrane Database Syst Rev 11:CD000023
87. Zwart S, Sachs AP, Ruijs GJ, Gubbels JW, Hoes AW, de Melker RA (2000) Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. BMJ 320:150–154
88. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL (1997) Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. BMJ 315:350–352
89. Howe RW, Millar MR, Coast J, Whitfield M, Peters TJ, Brookes S (1997) A randomized controlled trial of antibiotics on symptom resolution in patients presenting to their general practitioner with a sore throat. Br J Gen Pract 47:280–284
90. Zwart S, Rovers MM, de Melker RA, Hoes AW (2003) Penicillin for acute sore throat in children: randomised, double blind trial. BMJ 327:1324
91. Dagnelie CF, van der Graaf Y, De Melker RA (1996) Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. Br J Gen Pract 46:589–593
92. Wannamaker LW, Rammelkamp CH Jr, Denny FW et al (1951) Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin. Am J Med 10:673–695

93. Denny FW, Wannamaker LW, Brink WR, Rammelkamp CH Jr, Custer EA (1950) Prevention of rheumatic fever; treatment of the preceding streptococcic infection. J Am Med Assoc 143:151–153
94. Chamovitz R, Catanzaro FJ, Stetson CA, Rammelkamp CH Jr (1954) Prevention of rheumatic fever by treatment of previous streptococcal infections. I. Evaluation of benzathine penicillin G. New Engl J Med 251:466–471
95. Pichichero ME, Casey JR (2007) Bacterial eradication rates with shortened courses of 2nd- and 3rd-generation cephalosporins versus 10 days of penicillin for treatment of group A streptococcal tonsillopharyngitis in adults. Diagn Microbiol Infect Dis 59:127–130
96. Gerber MA, Baltimore RS, Eaton CB et al (2009) Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on functional genomics and translational biology, and the Interdisciplinary Council on quality of care and outcomes research: endorsed by the American Academy of Pediatrics. Circulation 119:1541–1551
97. Bisno AL, Stevens DL (2005) Streptococcus pyogenes. Elsevier Churchill Livingstone, Philadelphia