Clinical Study Protocol

Incision and Drainage or Tonsillectomy for Treatment of Peritonsillar Abscess (SiLAPe): A Randomized Clinical Trial

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Sponsor

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Table of Contents

1. Protocol Synopsis 3

2. Responsibilities 4

3. Scientific Background and Project Description 5

4. Study objectives 7

5. Study design and conduct 8

6. Patient recruitment 13

7. Biometry 15

8. Modifications regarding the study plan 16

9. Ethical and legal issues 17

10. Publication 19

11. Literature 20

12. Signatures of the department directors and investigators 21

13. Attachments 22

1. Protocol Synopsis

TITLE	
PROTOCOL:	SiLAPe (SiLAPe, German: *Spaltung in Lokalanästhesie oder Abszesstonsillektomie bei Peritonsillarabszess*)
ISRCTN registry, No.	Isrctn.com/ISRCTN81718286
DESIGN	Prospective randomized controlled interventional clinical trial
AIM OF THE STUDY:	The aim of this study is to evaluate whether tonsillectomy is more effective than incision and drainage in treating peritonsillar abscess considering patient-reported outcomes
PRIMARY OBJECTIVE:	Investigation whether tonsillectomy is more effective than incision and drainage in local anesthesia in treating peritonsillar abscess considering patient-reported pain experience and relief
PRIMARY OUTCOME MEASURE:	Pain experience (numeric rating scale) and pain relief (visual analogue scale)
SECONDARY OBJECTIVES:	Provision of insights about disease- and treatment-associated patient satisfaction, recovery time and Health-Related Quality of Life
SECONDARY OUTCOME MEASURES:	Patient satisfaction, quantity of basic analgesia and on-demand medication, trismus (cm), body temperature, inflammatory markers, rate of actual pus drainage; regarding incision and drainage intervention, the number of required punctures as well as stab incisions, whether additional reopening of the abscess cavity was required the following days as well as the rate of residual pus drainage; complications, Health-related quality of life disease-specific (Tonsillectomy Outcome Inventory-14) and in general (15D-questionaire), therapeutic benefit (Glasgow Benefit Inventory), duration of hospital stay, time until return to occupational activities as well as full recovery, rate of recurrent tonsillitis, recurrent peritonsillar abscess, or secondary tonsillectomy, Spectrum of microorganisms
STUDY POPULATION:	Male and female patients with peritonsillar abscess aged >18 years
NUMBER OF PATIENTS:	30 patients
INCLUSION CRITERIA:	Peritonsillar abscess, age >18 years, Ability to give informed consent to the study, patients must read and understand the information sheet as well as the informed consent form and must sign the informed consent form
EXCLUSION CRITERIA:	Missing written informed consent, secondary diagnoses that require constant analgesic treatment, psychiatric disorders, especially somatization disorders and affective disorders (mania, depression, etc.), pregnancy and lactation, chronic renal or hepatic dysfunctions, gastric or intestinal ulcerations, bone marrow diseases, diseases of the hematopoietic system, medication interfering with blood coagulation taken within the last 10 days (e.g. ASS,

	Coumarin-derivates or other anticoagulant substances), severe comorbidities associated with increased risk of general anesthesia, at the discretion of the investigator, limited cooperation, or such a pronounced lockjaw that makes incision and drainage in local anesthesia impossible
COORDINATING INVESTIGATOR:	XXXX
PARTICIPATING CENTERS:	XXXX
STUDY INTERVENTIONS:	Tonsillectomy or incision and drainage in local anesthesia, inpatient treatment including analgesia and i.v.-antibiotics
DURATION OF TREATMENT:	Inpatient stay of up to 5 days
FOLLOW UP:	After 1 and 6 months, prepared patient reply letter

2. Responsibilities

2.1 Principal Investigator

XXXX

2.2 Test center

XXXX

2.3 Investigators

XXXX

2.4 Sponsor

XXXX

3. Scientific Background and Project Description

3.1 Title

Incision and Drainage or Tonsillectomy for Treatment of Peritonsillar Abscess (SiLAPe) - A Randomized Clinical Trial

3.2 Background

Peritonsillar abscess (PTA) is a common and potentially life-threatening disease, with an estimated annual incidence of 30 per 100,000 persons of age between 5 to 59 years (Herzon 1995).

In addition to the typically unilateral peritonsillar abscess formation, there is rapid spread of inflammation to the soft tissues of the neck. Clinically, PTA presents with sore throat, “hot potato” voice, odynophagia, up to inability to swallow and lockjaw (trismus).

On clinical examination, there is severe swelling of the tonsil with unilateral prominence of the palatine arch and displacement of the uvula. Peritonsillar abscess with pus accumulation between the tonsillar capsule and the pharyngeal constrictor muscle must be distinguished from peritonsillitis, a phlegmonous inflammation without pus accumulation located at the same site. Differentiation or correct diagnosis is often only possible by puncture and abscess drainage (Brodsky, Sobie et al. 1988). In order to prevent a spread into the parapharyngeal space as well as further extension via the cervical fascias with dangers such as a necrotizing spread to the carotid space or airway obstruction due to massive swelling, the therapy is an urgent surgical drainage of the abscess (Powell and Wilson 2012). This can be achieved by incision under local anesthesia or tonsillectomy under general anesthesia. Both procedures are regularly performed treatment strategies in Germany. Aim is the complete abscess drainage without residuals or further accumulation of pus, which would require further interventions during the course of treatment.

The superiority of one method above the other in terms of pain reduction, peri- and postinterventional symptom perception and quality of life, time until complete recovery/return to occupational activities, and recurrences of acute tonsillitis and peritonsillar abscesses has not been conclusively established (Powell and Wilson 2012).

3.3 Project

A prospective randomized trial (SiLAPe, German: *Spaltung in Lokalanästhesie oder Abszesstonsillektomie bei Peritonsillarabszess*) was designed to evaluate incision and drainage in local

anesthesia or tonsillectomy in general anesthesia for the treatment of PTA. Since the disease as well as its therapy are very painful, especially pain experience, subjective pain relief by the treatment, patient satisfaction and health-related quality of life will be examined. Moreover, parameters of successful treatment will be examined, such as sufficient drainage. Particularly in the case of incision under local anesthesia without tonsillectomy, clinical experience shows that the abscess is not always drained completely at the first attempt or that the drainage path closes again, and subsequent blunt drainage procedures for reopening of the abscess cavity are necessary.

Screening for study eligibility occurs at first consultation with one of the investigators and, if the patient gives informed consent, randomization to one of the treatment arms follows. Treatment is then carried out according to the current clinical standard of one or the other treatment arm. A continuous reevaluation of the treatment success and, if necessary, a change of the treatment strategy is guaranteed, so that the health of the seriously ill patient is the highest priority.

3.4 Question

Which treatment procedure for peritonsillar abscess (incision and drainage in local anesthesia versus abscess tonsillectomy) is superior in terms of pain relief and patient satisfaction?

4. Study objectives

The study will examine which surgical procedure is superior for the treatment of peritonsillar abscess in terms of subjective pain experience and relief and patient satisfaction. In addition, the success of the treatment will be investigated with regard to the following parameters:

- Reduction of swallowing difficulties
- Duration until complete recovery
- Rate of pus drainage by the corresponding procedure
- Potential repeating procedures for complete pus drainage
- Change of treatment strategy due to clinical course
- Reduction of trismus
- Analgesics consumption
- Course of laboratory inflammatory parameters
- Rates of recurrent tonsillitis, peritonsillar abscesses, or delayed tonsillectomy
- Complications

5. Study design and conduct

5.1 Study design

It is a prospective randomized trial.

5.2 Study conduct

All patients will be treated without deviation from regular and established treatment strategies also after consenting to the study. Both procedures being investigated are established for the treatment of peritonsillar abscess and have been performed many times by the investigators. After diagnosis, the patient will be informed about the study and treatment options. If consent is given, randomization is performed by using consecutively numbered trial envelopes, so that therapy can be started immediately. In case of rejection, the patient is treated according to his or her wishes.

The treatment is performed inpatient. After the patient has given consent and been randomized, a venous catheter will be inserted, and blood will be taken to determine the parameters of inflammation. Body temperature is also taken. Before the abscess will be drained, the subjective pain perception will be assessed by means of the Numerical Rating Scale (Gagliese, Weizblit et al. 2005) and the health-related quality of life (HRQoL) by means of a questionnaire (disease-specific HRQoL by using the Tonsillectomy Outcome Inventory-14 (Skevas, Klingmann et al. 2012) and general HRQoL by using the 15D-questionaire (Sintonen 1981)). The severity of the lockjaw is measured using a ruler.

In accordance with the current recommendations of the Paul Ehrlich Society for Chemotherapy e. V., each patient receives initial intravenous antimicrobial therapy with group 2 cephalosporin (cefuroxime) in combination with clindamycin. On the third day, this treatment can be continued orally (Bodmann and Grabein 2010). The total duration should be 9 days to prevent further complications of postinfectious glomerulonephritis and rheumatic fever (Del Mar, Glasziou et al. 2006).

The procedures for abscess drainage are described below:

Incision and drainage in local anesthesia:

10 min before the beginning of the intervention, the patient receives paracetamol 1000 mg i.v. (Perfalgan®) as systemic analgesia. The patient lies with the upper body elevated by about 45°. The mucous tissue is anesthetized with a superficial anesthetic by applying 5 doses of Xylocain® spray (1 dose contains 10 mg lidocaine, total dose 50 mg). After 3-5 minutes of exposure time, lidocaine 2 % is injected at the maximum point of the mucosal protrusion for local anesthesia. Subsequently, a

puncture is made with a 20 G x 2 ¾'' needle to identify the abscess. If pus is aspirated, a stab incision is made using a scalpel (size 11) and the abscess cavity is then cleaved using Hartmann's ear tamponade forceps. A swab is obtained from the aspirated pus or the opened abscess cavity for microbiological examination. The cavity is completely emptied with the "Eicken" suction tube, after which the patient is given water to rinse the mouth.

Abscess tonsillectomy:

Prenote: Usually, a unilateral tonsillectomy is performed for abscess drainage. The risk of postoperative bleeding seems to be higher on the contralateral side than on the abscess side (Windfuhr and Remmert 2005), so that a bilateral tonsillectomy is only justified in case of pre-existing chronic recurrent tonsillitis and fulfillment of the latest criteria for tonsillectomy according to the AWMF guideline of 08/2015 (Berner, Steffen et al. 2015). The appropriate medical history is taken in advance and the decision to perform unilateral or bilateral tonsillectomy is subsequently discussed with the patient. The direct comparison of the treatment procedures being investigated is only valid for unilateral tonsillectomy. Patients receiving bilateral tonsillectomy are followed up in the same way, as they deserve the same high standard of care, but the evaluation is not performed to answer the primary question.

The procedure is performed under general anesthesia using the technique of extracapsular tonsillectomy. Balanced anesthesia is initiated by the colleagues of anesthesiology. The patient is placed in supine position with the head reclined. After insertion of the Mc-Ivor-retractor, the tonsil of the affected side is luxated from its bed and, after mucosal incision, the tonsillar capsule is sought out using the spreading technique with scissors. The tonsil is then dissected out of its bed using the dissection technique, which opens the abscess cavity. By puncture and aspiration, the surgeon can exclude or identify other abscess foci if suspected and split them. Anesthesia ends with application of a diclofenac suppository (100 mg) for analgesia. A swab is collected from the extracted pus. The tissue will be handed in for histopathologic examination.

Analgesia post intervention

For analgesia, the patient receives a basic medication consisting of Voltaren Dispers® (50 mg diclofenac, maximum daily dose 150 mg) p.o., 3 x daily. For medication on demand, 30 drops of Novalgin® p. o. (750 mg metamizole, daily maximum dose 3000 mg) can be taken up to 4 x daily. In case of persistent inability to swallow, the basic medication can be replaced by Perfalgan® (1000 mg paracetamol, daily maximum dose 4000 mg) i.v..

In the case of insufficient pain reduction due to this treatment, and if the patient wishes to extend the therapy, Valoron N Retard® 50/4 mg or 100/8 mg (tilidine/naloxone) 1-0-1 can be added. For gastric protection, Pantoprazole 20 mg p. o., 1 x daily is additionally applied. In case of allergies or intolerances, deviation of this standard regimen is possible. Appropriate documentation is obligatory.

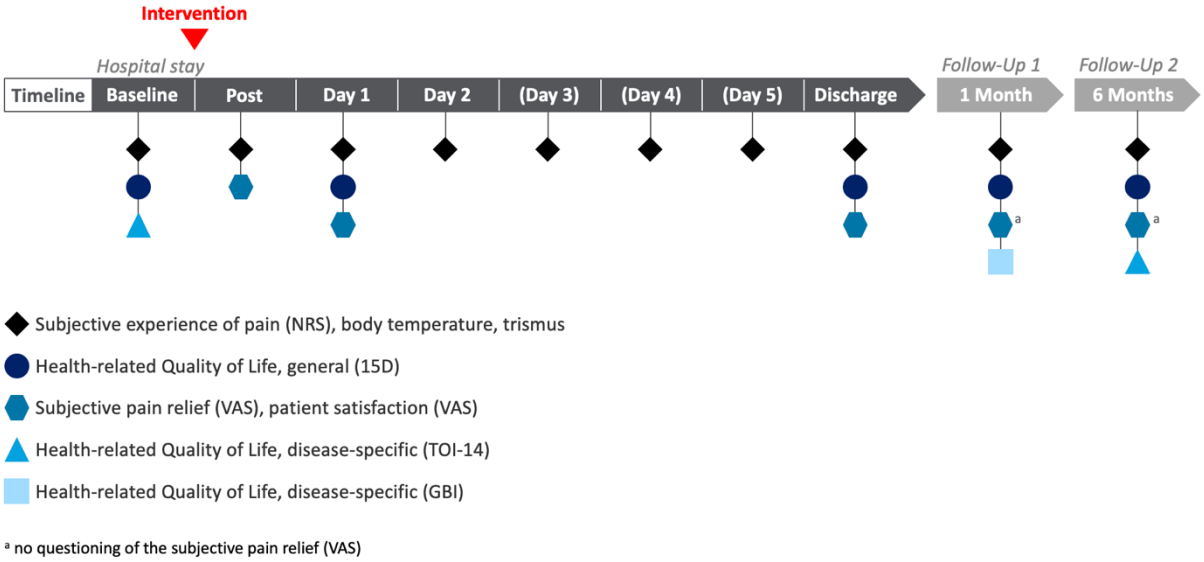
Further data collection:

Subjective pain experience is measured using a standardized and validated Numerical Rating Scale (Gagliese, Weizblit et al. 2005). The patient is instructed in its use. The first survey was completed before intervention. The general pain perceptions at rest and the pain perceptions during swallowing are asked. This is also done 30 minutes after abscess drainage or when the patient is back at ward after tonsillectomy. At this time, a visual analog scale (VAS) is also used to answer the question of whether and how pronounced pain relief is experienced as a result of the procedure. The VAS will also be used to determine patient satisfaction ("How satisfied were you with the intervention to open the pus cavity?"). On the day after intervention, general pain perception at rest and pain perception during swallowing will be asked every 2 hours, but especially before and 30 to 60 minutes after i.v. or oral pain medication. On the following days until hospital discharge, pain perception is assessed every three hours, but especially again before and 30 to 60 minutes after i.v. or oral analgesic intake.

During the inpatient stay, body temperature and the extent of trismus are measured daily. Laboratory tests to track the inflammatory markers are performed at least on day 2 after the intervention. In addition, analgesic intake (basic analgesia and medication on demand provided to the patient), post-interventional complications, the duration of the inpatient stay, the duration until returning to work or comparable occupational activities, and the time until complete remission of symptoms are documented (letter with stamped envelope for answering is given to the patient, see appendix).

The general quality of life questionnaire (15D-questionaire (Sintonen 1981)) will be given again to be answered on days 1 after intervention and at discharge. The Glasgow Benefit Inventory (Robinson, Gatehouse et al. 1996) to assess the post-therapeutic benefit as well as the disease-specific questionnaire on health-related quality of life (Tonsillectomy Outcome Inventory-14 (Skevas, Klingmann et al. 2012)) will be given to the patient at follow-up examinations one and 6 months after intervention.

Study protocol:



5.3 Outcome measures

Primary outcome measures

- Subjective pain experience at rest and during swallowing (numeric rating scale); subjective pain relief as a result of the intervention (visual analogue scale)

Secondary outcome measures

- Patient satisfaction (How satisfied were you with the procedure of opening the abscess cavity?; Visual Analogue Scale).
- Quantity of basic analgesia and on-demand medication
- Trismus (cm)
- Body temperature
- Inflammatory markers
- Rate of actual pus drainage; regarding ID intervention, the number of required punctures as well as stab incisions, whether additional reopening of the abscess cavity was required the following days as well as the rate of residual pus drainage
- Complications

- Health-related quality of life disease-specific (TOI-14 (Skevas, Klingmann et al. 2012)) and in general (15-D (Sintonen 1981))
- Therapeutic benefit (Glasgow Benefit Inventory (Robinson, Gatehouse et al. 1996))
- Duration of hospital stay
- Time until return to occupational activities as well as full recovery
- Rate of recurrent tonsillitis, PTAs, or secondary tonsillectomy
- Spectrum of microorganisms

5.4 Risk-benefit assessment and precautionary considerations

There will be no deviations from regular treatment strategies within this trial. There is no increased risk for patients by participating. Established treatment strategies will be compared. A switch to the other strategy is possible at any time at the discretion of the physician. If this happens at the beginning, the patient will drop out of the study. If the decision is made to perform a tonsillectomy after incision and drainage in local anesthesia due to insufficient improvement, the patient remains in the study and the change of regimen is evaluated accordingly. Deviations from drug treatment strategies (antibiotics, analgesics, steroids) are allowed at the discretion of the physician and will be carefully documented. With the objective of the study to review surgical procedures for the treatment of peritonsillar abscess in terms of subjective pain experience and relief, patient satisfaction and treatment success, there is benefit to the community. By participating in the study, the patient is guaranteed treatment according to the latest scientific findings and the highest level of evidence for the treatment of peritonsillar abscess. In this respect, there is also a benefit for the individual (individual benefit).

5.5 Study termination

Study termination for one individual participant (drop-out)

One or more of the following circumstances may lead to a study termination of a single participant (this participant will be counted as a drop-out):

- Withdrawal of informed consent by the patient
- Severe violation of the study protocol
- Occurrence of any exclusion criteria

Termination of the entire study

The investigator may, for the benefit and in the interest of the patients, terminate the entire study at any time if unforeseen circumstances arise. In this case, the Ethics Committee will be informed.

6. Patient recruitment

6.1 Number of patients and duration of study

Intended number of patients: 30 cases

Duration of the study: Inclusion of patients within two years from the start of the study.

6.2 Selection of patients

The overall collective consists of patients presenting to the university hospitals ENT clinic as emergencies for treatment of peritonsillar abscess. The treatment is obligatory surgical and requires an inpatient observation phase and further treatment. Before starting treatment, patients will be informed about the study by the investigators. If patients wish to participate and have signed informed consent, they are included in the study. Randomization and treatment will follow according to the above protocol. With approximately 4 cases/month of patients with peritonsillar abscess presenting at the hospital, inclusion of 30 cases within a 24-month period is achievable.

6.3 Inclusion criteria

- Peritonsillar abscess
- Male and female patients, age >18 years
- Ability to give informed consent to the study
- Patients must read and understand the information sheet as well as the informed consent form and must sign the informed consent form

6.4 Exclusion criteria

- Missing written informed consent
- Secondary diagnoses that require constant analgesic treatment
- Psychiatric disorders, especially somatization disorders and affective disorders (mania, depression, etc.)
- Pregnancy and lactation
- Chronic renal or hepatic dysfunctions
- Gastric or intestinal ulcerations
- Bone marrow diseases, diseases of the hematopoietic system

- Medication interfering with blood coagulation taken within the last 10 days (e.g. ASS, Coumarin-derivates or other anticoagulant substances)
- Severe comorbidities associated with increased risk of general anesthesia
- At the discretion of the investigator, limited cooperation, or such a pronounced lockjaw that makes incision and drainage in local anesthesia impossible

7. Biometry

7.1 Study design

It is a prospective randomized trial.

7.2 Sample size planning

30 patients are intended to be included within a defined period of 2 years. Thirty patients is the expected number of patients that may realistically be included in this study period.

Regarding the primary outcome measure of the presented study project, Collison et al., for example, were able to show a significant difference in pain experience after two different procedures of tonsillectomy with a comparably large collective of 28 patients (Collison and Weiner 2004).

7.3 Data collection and analysis

The treatment strategies (incision and drainage in local anesthesia and abscess tonsillectomy) are established procedures that are performed on a regular basis at the study sites. Participation in the study does not change the treatment strategies, nor does the application of medication, clinical control examinations, laboratory tests and swab examinations differ from usual treatment of peritonsillar abscess. Solely the standardized data documentation is additionally carried out with the help of a study protocol, which is maintained parallel to the regular documentation in the patient's records during inpatient stay and at control examinations. In addition, as an important part of the study, patients receive a folder with questions to periodically evaluate their current subjective pain experience and by above-mentioned questionnaires to determine health-related quality of life and post-therapeutic benefit. The date on which the patient has fully recovered will be communicated after discharge from the hospital, using a prepared response letter sent by post.

All data are collected exclusively by physicians of the study sites. If necessary, data collection will be supported by an instructed medical doctoral student. If necessary, analysis will be performed in cooperation with a professional statistician.

8. Modifications regarding the study plan

All study protocol modifications will be reported to the Ethics Committee. For protocol changes that are not exclusively formal and include changes relevant to the participant, a new vote of the Ethics Committee will be obtained. Any complications and serious undesired events occurring during the progress of the research project will be reported promptly to the Ethics Committee.

9. Ethical and legal issues

9.1 Legal basis

The legal basis is known by all physicians involved in the study.

9.2 Vote of the Ethics Committee

A positive vote by the Ethics Committee is a precondition for the initiation of the study. The Ethics Committee will be informed immediately in the event of the occurrence of serious events, study termination or changes in the study protocol.

9.3 Insurance

No additional insurance is required for this study.

9.4 Principal investigator of the clinical study

The clinical principal investigators confirm by signing the protocol that they are registered physicians with at least two years of experience in conducting clinical trials. The principal investigators of the clinical trial control the proper progress of the project. They can be contacted during the entire duration of the study.

9.5 Investigators

By signing the study protocol, the investigators confirm that they have read and understood the study protocol and that they will work in accordance with the study protocol. The investigators guarantee the confidentiality of all information.

9.6 Multicenter studies

The present study is a two-center study classified monocentric since enrollment of patients did not occur parallel at both study sites and is performed by the same study team.

9.7 Archiving and data protection

The data obtained in the project will be stored on the server of the patient network of the university hospitals in accordance with the guidelines for handling and securing patient- and research-related data. All data collected in connection with the study will be treated confidentially. All staff members

with whom contact is made are fully bound by medical confidentiality and corresponding data protection regulations. Data in which the patient is mentioned by name or from which it is possible to make inferences about the person are not released from the care of the hospital and its employees who are bound by confidentiality.

Any use and further processing of the collected data will only be undertaken in pseudonymized form. Pseudonymization means encoding of data/samples without naming only coded with numbers. The assignment of data or samples to a person is only possible if the key with which the data was pseudonymized is used for this purpose. The personal data/samples are stored separately from the pseudonymized data under special protective arrangements. Decoding is only possible by responsible study investigators, who are subject to medical confidentiality. Third parties do not receive access to the original documents.

For the storage of the data collected in the study, the professional code of conduct for physicians of the Medical Association of Lower Saxony, in its current version, is authoritative as a legal regulation, which provides a storage obligation until 10 years after completion of the treatment (§ 10 (3)). Further storage will not be performed.

Data will only be presented or passed on to external persons or companies, at congresses or in the scientific press if it is not possible to make any inferences about the participants. The data will only be presented or passed on for scientific purposes.

The consent to participate in the study can be withdraw by the patient at any time, also subsequently, informally, verbally, by telephone or in written form to the principal investigator of the clinical study (CONTACT DETAILS). This will result in the immediate deletion of the personal data stored in the context of the study. These data will also no longer be evaluated or used in the context of the study. No disadvantage arises for the patient regarding the treatment at the university hospital.

10. Publication

The results of the presented clinical study will be published after termination according to scientific criteria in a scientific journal. No industrial sponsor has the right to object to this.

11. Literature

Berner, R., G. Steffen, N. Toepfner, F. Waldfahrer and J. P. Windfuhr (2015). S2k-Leitlinie 017/024: Therapie entzündlicher Erkrankungen der Gaumenmandeln – Tonsillitis. AWMF Online. **08/2015**.

Bodmann, K. F. and B. Grabein (2010). "Empfehlungen zur kalkulierten parenteralen Initialtherapie bakterieller Erkrankungen bei Erwachsenen - Update 2010." Chemother J **19**(6): 179-255.

Brodsky, L., S. R. Sobie, D. Korwin and J. F. Stanievich (1988). "A clinical prospective study of peritonsillar abscess in children." Laryngoscope **98**(7): 780-783.

Collison, P. J. and R. Weiner (2004). "Harmonic scalpel versus conventional tonsillectomy: a double-blind clinical trial." Ear Nose Throat J **83**(10): 707-710.

Del Mar, C. B., P. P. Glasziou and A. B. Spinks (2006). "Antibiotics for sore throat." Cochrane Database Syst Rev(4): CD000023.

Gagliese, L., N. Weizblit, W. Ellis and V. W. Chan (2005). "The measurement of postoperative pain: a comparison of intensity scales in younger and older surgical patients." Pain **117**(3): 412-420.

Herzon, F. S. (1995). "Harris P. Mosher Award thesis. Peritonsillar abscess: incidence, current management practices, and a proposal for treatment guidelines." Laryngoscope **105**(8 Pt 3 Suppl 74): 1-17.

Powell, J. and J. A. Wilson (2012). "An evidence-based review of peritonsillar abscess." Clin Otolaryngol **37**(2): 136-145.

Robinson, K., S. Gatehouse and G. G. Browning (1996). "Measuring patient benefit from otorhinolaryngological surgery and therapy." Ann Otol Rhinol Laryngol **105**(6): 415-422.

Sintonen, H. (1981). "An approach to measuring and valuing health states." Soc Sci Med Med Econ **15**(2): 55-65.

Skevas, T., C. Klingmann, P. K. Plinkert and I. Baumann (2012). "[Development and validation of the Tonsillectomy Outcome Inventory 14]." Hno **60**(9): 801-806.

Windfuhr, J. P. and S. Remmert (2005). "[Trends and complications in the management of peritonsillar abscess with emphasis on children]." Hno **53**(1): 46-57.

12. Signatures of the department directors and investigators

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13. Attachments

Participants Information sheet

Informed consent form

Case Report Form

Study-related questionnaires for participants

Prepared response letter regarding recovery