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PERITONSILLAR ABSCESS - AETIOLOGY, DIAGNOSTICS AND TREATMENT

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ACADEMIC DISSERTATION

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Kun unohtaa sen,
mitä ei voi muuttaa,
on onnellinen.

– Arvo Ylppö

**To My Family
And Friends**

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ABSTRACT

Peritonsillar abscess (PTA) is the most common otorhinolaryngological infection that requires special health care management. Its treatment varies greatly due to a lack of common clinical guidelines. PTA can be treated invasively (drained at a polyclinic with local anaesthesia or under general anaesthesia in an operating room) or conservatively with medications and observation, usually as an inpatient. Tonsillectomy (TE) is performed on a portion of PTA patients, yet it remains controversial as to which PTA patients would benefit from this procedure. Traditional bacterial culture is ineffective at defining the causative bacteria for PTA. Due to the delay in receiving results, the method is not widely used in clinical decision-making for the treatment of PTA. Rapid microarray methods have been tested, for example on serum and joint fluid samples, but not yet on pus. Most of the bacteria found in PTA are susceptible to penicillin, but, to avoid complications, broad-spectrum antibiotics are frequently used instead. Use of broad-spectrum antibiotics is not only more expensive but is also associated with the development of antibiotic resistance, interactions with other medications and a variety of adverse effects.

The aim of the first study in this thesis was to explore the microbiology of adults with PTA using a modern identification method and to find cofactors among patients with different pathogens. To this end, we examined, using a modern DNA-based microarray method the microbial findings in the pus aspirated from 180 PTA patients. *Fusobacterium necrophorum* proved to be the most prevalent bacteria, occurring more frequently in younger patients; group A *Streptococcus* was the second most common. The microarray method seemed to work well for identifying bacteria directly from pus.

In the second study, the aim was to compare the treatment modalities for PTA in countries closely related to Finland. For this purpose, we sent an electronic questionnaire regarding PTA treatment to all central and university hospitals in Finland, Sweden, Norway and Denmark. The study revealed diversity among treatment modalities between the four countries.

To identify factors predicting a doctor's decision for TE among PTA patients, in the third study, we retrieved data on 819 PTA patients from a national database, which included information on whether a TE was performed within five years after a PTA diagnosis and why. This register-based study showed that young age and previous tonsillar infections increased the probability of having a TE performed.

In the fourth study, the aim was to investigate whether combining metronidazole with penicillin enhances the recovery from PTA and whether metronidazole helps prevent PTA recurrences. A total of 200 prospectively collected patients were randomised to receive either penicillin and placebo or penicillin and metronidazole. The patients filled in an electronic diary daily for the first two weeks and then weekly for the following six weeks. Most patients (90%) healed well without recurrence of PTA; in both groups, 10% of the patients returned with symptom recurrence and the patient ended up having a TE or treatment as an inpatient. Thus, metronidazole neither enhanced the recovery nor prevented recurrences; furthermore, it caused unwanted adverse effects (diarrhoea and nausea).

These four explorations into PTA provided valuable insight. Study findings revealed how PTA patients are currently treated in four Nordic countries and which patients would benefit from a TE and which from a wait-and-see strategy. This information helps to avoid unnecessary operations. Results from the randomisation study can be applied to standardising the widely varying treatment modalities, at least in Finland. In the future, the rapid bacterial identification method could help in choosing the optimal antibiotic. These results make a difference not just for one patient, but for the whole health care system; the treatment is evidence-based and can be offered to those whom it serves best.

TIIVISTELMÄ

Kurkkupaise on tavallisin korva-, nenä- ja kurkkutautien sairaalahoitoa vaativa infektio. Sen hoitokäytännöt vaihtelevat huomattavasti; paise voidaan hoitaa joko kajoavasti, eli tyhjentämällä poliklinikalla paikallispuudutuksessa tai leikkaussalissa yleisanestesiassa, tai konservatiivisesti, eli lääkkeillä, yleensä vuodeosasto-seurannassa. Osalta kurkkupaisepotilaista nielurisat poistetaan joko tulehtuneessa vaiheessa tai myöhemmin infektion rauhoituttua. Ei tiedetä, ketkä kurkkupaisepotilaista hyötyvät nielurisaleikkauksesta. Etenkin anaerobisten bakteerien osalta perinteinen bakteeriviljely on liian hidaskäyttö, eikä sitä käytetä kurkkupaiseen hoitopäätöksen tekoon. Nopeaa mikrosiru-menetelmää on aiemmin kokeiltu esimerkiksi seerumi- ja nivelnestenäytteillä, muttei määrällä. Suurin osa kurkkupaiseen aiheuttajabakteereista on penisilliinille herkkiä, mutta vakavien komplikaatioiden estämiseksi valitaan kuitenkin usein laajakirjoinen antibioottiyhdistelmä. Tässä väitöskirjassa tutkittiin kurkkupaiseen tämänhetkistä aiheuttajakirjoa, sen nykyisiä hoitokäytäntöjä, ja selvitettiin miten eri hoitokäytännöt vaikuttavat potilaan paranemiseen ja ennusteeseen.

Osatyössä yksi, kurkkupaiseen mikrobiologiaa aikuisilla selvitettiin nykyaikaisella bakteerintunnistusmenetelmällä, ja etsittiin yhdistäviä tekijöitä eri aiheuttajien väliltä. Tutkimuksessa selvitettiin modernin DNA-pohjaisen mikrosirumenetelmän avulla 180:n HYS Korvaklinikan päivystykseen tulleen kurkkupaisepotilaan paiseista aspiroidun määrän mikrobiologiaa ja verrattiin etiologisia tekijöitä eri aiheuttajien välillä. *Fusobacterium necrophorum* osoittautui yleisimmäksi aiheuttajaksi; se löytyi 22 %:sta näytteistä ja *Streptococcus pyogenes* toiseksi yleisimpänä 20 %:sta. *Fusobacterium necrophorum* oli yleisempi nuorilla potilailla. Menetelmä vaikuttaisi soveltuvan bakteerintunnistukseen suoraan määräästä.

Toisessa osatyössä selvitettiin Suomen, Ruotsin, Norjan ja Tanskan hoitokäytäntöjä, ja etsittiin ennustetekijöitä kurkkupaisepotilaan nielurisaleikkauksen indikaatioille. Kaikkien Suomen, Ruotsin, Norjan ja Tanskan yliopisto- ja keskussairaaloitasoisten korvayksiköiden ylilääkäreille lähetetyn sähköisen kyselyn avulla kerättiin tietoa

kurkkupaiseiden hoidosta. Kyselytutkimuksessa 72:n (89 %) korvayksikön ylilääkäri vastasi kyselyyn. Tutkimuksesta selvisi, että kurkkupaiseen hoitokäytännöt vaihtelevat huomattavasti eri Pohjoismaissa.

Kolmannessa osatyössä selvitettiin, kuinka monelle HYS Korvaklinikan päivystykseen vuonna 2000 kurkkupaiseen vuoksi tulleelle potilaalle (n=819) tehtiin viiden seuraavan vuoden kuluessa nielurisaleikkaus ja miksi. Tutkimuksesta selvisi, että nuori ikä (<30) ja aiemmat nielurisatulehdukset lisäävät todennäköisyyttä päätyä myöhemmin nielurisaleikkaukseen. Nämä tekijät puoltavat leikkausta, mutta muiden potilaiden kohdalla tilannetta kannattaa seurata.

Neljännessä osatyössä tutkittiin nopeuttaako metronidatsoli penisilliiniin yhdistettynä kurkkupaiseen paranemista aikuisella ja estääkö se kurkkupaiseen uusimista. Yhteensä 200 HYS Korvaklinikan päivystykseen tullutta kurkkupaisepotilasta satunnaistettiin saamaan joko penisilliiniä ja metronidatsolia, tai penisilliiniä ja lumetta. Potilaiden paranemista seurattiin sähköisen oirepäiväkirjan avulla päivittäin kahden viikon ajan, jonka jälkeen viikoittain kahden kuukauden ajan. Sekä metronidatsoli- että plasebo-ryhmässä 10 % potilaista palasi uusineiden oireiden vuoksi. Metronidatsoli ei nopeuttanut paiseen paranemista, eikä estänyt sen uusimista seuraavien kahden kuukauden aikana, mutta lisäsi haittavaikutuksia, eli ripulia ja pahoinvointia.

Tutkimustulosten ansiosta tiedämme, ketkä kurkkupaisepotilaista tulevat todennäköisesti tarvitsemaan nielurisaleikkauksen ja keiden kohdalla saattaa olla parempi odottaa ja seurata. Lääketutkimuksesta saadun tiedon avulla voimme luopua usein tarpeettoman – ja jopa haitallisen - metronidatsolin käytöstä aikuisilla kurkkupaisepotilailla ja yhtenäistää ainakin Suomen lääkehoitokäytännöt. Tulevaisuudessa uusi nopea bakteeritunnistus-menetelmä voisi auttaa mikrobilääkkeen valinnassa. Tutkimustuloksilla on merkitystä paitsi yksittäiselle potilaalle myös koko terveydenhuoltojärjestelmälle. Kurkkupaisepotilas saa tutkittuun tietoon perustuvan hoidon ja hoito voidaan suunnata niille, jotka siitä hyötyvät.

LIST OF ORIGINAL PUBLICATIONS

- I Wikstén J, Laakso S, Mäki M, Mäkitie A, Pitkäranta A, Blomgren K.
Microarray Identification of Bacterial Species in Peritonsillar Abscesses.
Eur J Clin Microbiol Infect Dis 2015 May, 34:905-11.
- II Wikstén J, Blomgren K, Eriksson T, GuldFred L, Bratt M, Pitkäranta A.
Variations in Treatment of Peritonsillar Abscess in Four Nordic
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2012 Apr, 269:1281-4.
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Penicillin neither Prevents Recurrence nor Enhances Recovery of
Peritonsillar Abscess when Compared to Penicillin alone: A Prospective,
Double-blind, Randomised, Placebo-controlled Trial. J Antimicrob
Chemother. In press.

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ABBREVIATIONS

AT	acute tonsillitis
CRP	C-reactive protein
DNA	deoxyribonucleic acid
DNM	descending necrotizing mediastinitis
EBV	Epstein-Barr virus
FN	<i>Fusobacterium necrophorum</i>
HUH	Helsinki University Hospital
GAS	Group A <i>Streptococcus</i>
i.m.	intramuscular
i.v.	intravenous
ID	incision and drainage
NA	needle aspiration
ORL	otorhinolaryngological
p.o.	per oral
PCR	polymerase chain reaction
PTA	peritonsillar abscess
PTC	peritonsillar cellulitis
SD	standard deviation
SMG	<i>Streptococcus milleri</i> group
SVG	<i>Streptococcus viridans</i> group
TE	tonsillectomy
UK	United Kingdom

1 INTRODUCTION

The surgical opening of a peritonsillar abscess (PTA) using incision and drainage (ID) was first described in 1362 by a French surgeon, Guy de Chaliac. In 1859, another French surgeon, Chassaignac, introduced immediate tonsillectomy (TE) as a treatment modality; this method became popular in the beginning of the 20th century ([Chassaignac 1859], Herzon 1995). Since then, numerous studies on the subject have been published. This thesis addresses what is currently known about PTA and its treatments, how that understanding has developed and it presents some new aspects and ideas for future research.

PTA, a potentially fatal infection, is the most frequent otorhinolaryngological (ORL) infection requiring special health care management (Rusan et al. 2009). Although most often associated with acute tonsillitis (AT), PTA may also originate from an infection in the dental area or minor salivary glands (Georgalas et al. 2002, Passy 1994). Due to these aetiological factors, as well as geographical, methodological, and even seasonal factors, microbiological findings in PTA vary. No consensus has been reached on which of the microbes found in bacteriological studies are pathogenic, although the most prevalent of them have been identified (Klug et al. 2011, Powel et al. 2013). Certain bacterial groups have special behavioural patterns, leading some researchers to suggest that different subtypes of PTA exist. Although patient characteristics, such as smoking, young age, male gender and poor oral hygiene, are associated with a higher incidence of PTA, only a few studies have demonstrated an association between different pathogens and the clinical features of PTA (Powel et al. 2013).

There is no evidence to support identifying bacteria in the diagnostics of PTA. Traditional culture is slow and shown to be inefficient, as the results do not affect the choice of treatment (Repanos et al. 2009, Cherikuri et al. 2002); novel, rapid methods could change this. Deoxyribonucleic acid (DNA)-based microarray methods are expensive and not commonly used in clinical practice, but they would allow for

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rapid bacterial identification (Yang et al. 2004). Although previously only tested on blood culture and osteoarticular specimens (Tissari et al. 2010), this novel assay, based on a polymerase chain reaction (PCR) and a microarray set-up, has not been tested directly on pus before.

Patients, society, treating physicians, as well as medical teaching and research, would benefit from a consensus on the treatment of PTA. Four Nordic countries, Finland, Sweden, Norway and Denmark, closely resemble each other in geographical features, population density, education level, health care systems, and having high standards of medicine. Nevertheless, practices for treating PTA differ between these countries, and even within each country (www.euro.who.int/observatory). There are several invasive management choices for PTA. The conservative choice is to treat the patient with intravenous (i.v.) antibiotics and observe as an inpatient. TE is an option, either immediately (immediate TE) or soon afterwards (interval TE), if the patient has had previous tonsillar infections. TE is sometimes required even years afterwards (delayed TE), if the patient suffers from recurrent PTAs (Herzon 1995). If these patients who have a delayed TE could be identified at an earlier stage, they could be operated on sooner, saving them time, expenses and discomfort, as they would avoid multiple sick leaves and visits to health care (Johnson et al. 2003, Herzon et al 2006). Most bacteria found in PTA pus samples are susceptible to penicillin, which, therefore, has been suggested as the primary treatment (Herzon 1995). However, bacteria resistant to penicillin have often been associated with a risk of severe complications (Ridder et al. 2010, Brook 2004). Due to the lack of rapid routine methods to determine the causative pathogen(s), PTA patients are then often treated with empirical antibiotics, often unnecessarily broad in spectrum. This approach increases costs, the risks of adverse effects, as well as bacterial resistance to antibiotics (Davey et al. 2008). Which empiric antibiotic to select for treating PTA patients remains controversial.

The aim of this thesis was to examine the bacterial aetiology and differences in treatment modalities of patients with PTA to obtain evidence-based tools for care of these patients.

2 REVIEW OF THE LITERATURE

2.1 Palatine tonsil and peritonsillar space

2.1.1 Embryology

During the third month of foetal life, the palatine tonsils originate from the endoderm lining the second pharyngeal pouch and the mesoderm of the second pharyngeal membrane, growing as glandular buds containing lymphoid tissue. The plica triangularis (a fold of mucous membrane) arises from the inferior part reaching the anterior pillar, dividing the tonsil into its anterior and posterior portions. A smaller fold, called the plica semilunaris (i.e. supratonsillaris), a remnant of the second cleft, runs between the anterior and posterior pillars. A supratonsillar fossa exists as a small depression at the superior part. Part of the tonsils become embedded in the surrounding mucous membrane as they grow, and only part of them remain visible. The palatine tonsils become fully grown at about six years of age, as the lymphoid tissue generally does. After puberty, tonsil size reduces remarkably due to atrophy of the lymphoid tissue. Tonsil size varies considerably among individuals (Sadler, 2015).

2.1.2 Histology and anatomy

The palatine tonsils are part of the Waldeyer's ring, an accumulation of lymphoid tissue that forms a ring around the pharynx, which includes the lingual, adenoid and tubal tonsils. Palatine tonsils are covered with stratified squamous epithelium on the pharyngeal side and a fibrous capsule on the lateral side. Trabeculae of nerves, as well as lymphatic and blood veins run through the capsule. Palatine tonsils are located between the palatoglossal (anterior pillar) and palatopharyngeal (posterior pillar) arches and are surrounded by the palatoglossus, palatopharyngeus and superior constrictor muscles on the lateral side of the tonsillar bed. Some fibers of the palatoglossus and palatopharyngeus are attached to the surface of the capsule. Traveling through the pterygopalatine ganglion, lesser palatine nerves from the

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maxillary division of the trigeminal nerve and tonsillar branches from the glossopharyngeal nerve supply the innervation. Together the tonsillar branch of the facial artery inferiorly, the ascending palatine artery posteriorly and the tonsillar branch of the dorsal lingual artery anteriorly form the blood supply for the inferior pole. The upper pole receives its blood supply from the ascending pharyngeal artery posteriorly and the descending palatine artery on the anterior surface. It is notable that the internal carotid artery runs at a distance of 2-2.5 cms behind and lateral to the palatine tonsil. Venous blood drains through a peritonsillar plexus. The plexus drains into the lingual and pharyngeal veins, which drain into the internal jugular vein. The lymphatic drainage ends up in the upper deep cervical lymph nodes, particularly the jugulodigastric nodes.

On the surface, each tonsil has numerous crypts. The largest crypt (crypta magna) separates the upper pole from the tonsillar body. The crypts in the superior part of the tonsil open into the fossa supratonsillaris, the ones in the medial and lower parts open onto the oral surface of the tonsil. The surface area of the tonsil is increased by these 12 to 15 crypts. Contents of the tonsillar crypts are expelled by contraction of the tonsillopharyngeus muscle (Standring et al. 2009).

Lateral to two-thirds of the tonsils, between the anterior and posterior pillars, there is a space of loose connective tissue, the peritonsillar space. At inferior and posterior surface of the capsule more intimately connected muscular fibers are present and in the case of enucleation of the tonsil, muscular fibers adherent to the capsule are often dissected within. A group of 20 to 25 mucous salivary glands (Weber's glands) are located in the peritonsillar space and are connected to the surface by ducts in order to clear the crypts. Three other clinically important spaces that are closely related to the peritonsillar space are the submandibular, parapharyngeal and retropharyngeal spaces (Hett et al. 1910, Standring et al. 2009).

2.1.3 Physiology and immunology

As part of the mucosa-associated lymphoid tissue, the palatine tonsils provide early recognition of both airborne and alimentary antigens and act as a first line of defense against pathogens. The dendritic cells in the reticular crypt epithelium transport

exogenous antigens to the B-cell follicles and extrafollicular T-cell areas. Containing mostly CD4+ (helper) T-cells, the tonsils provide both primary and secondary T-cell responses. After stimulation by the T-cells in the extrafollicular space, the immature B-cells colonise the follicles and differentiate into memory and plasma cells, producing various immunoglobulin subtypes (Brandtzaeg 2003). The epithelial cells of tonsils also participate in producing antimicrobial peptides, human β -defensins, the natural antibiotics produced by the body (Ball et al. 2007, Schwaab et al. 2010). Despite this important immunodefence task, tonsil removal has not been shown to affect general health (van den Akker et al. 2006, Böck et al. 1994).

2.2 Peritonsillar abscess

PTA is a collection of pus found between the capsule and the surrounding soft tissue and muscles. Most abscesses develop in the superior part, but abscesses of the inferior and middle parts are also possible, infratonsillar abscesses remain rare (Suzuki et al. 1999, Blair et al. 2015, Licamelli et al. 1998, Monobe et al. 2007) (Figure 1).

Figure 1. Peritonsillar abscess

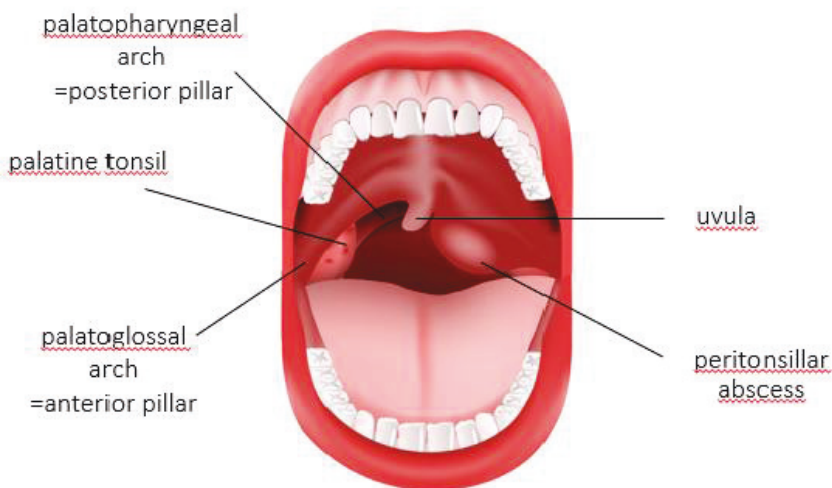


Figure by: Tuomas Rentola

REVIEW OF THE LITERATURE

2.2.1 Epidemiology

2.2.1.1 Incidence

The annual incidence of PTA has been reported as somewhere between 9/100 000 and 41/100 000 (Marom et al. 2010, Klug et al. 2009), depending on the definition of diagnosis (i.e. are peritonsillar cellulitis (PTC) cases included) and the age groups (i.e. are small infants included). Among teenagers, the incidence rate may be as high as 167/100 000 (Klug 2014). Researchers have attempted to establish seasonal peaks, but this phenomenon has not been proven (Marom et al. 2010, Mazur et al. 2015a, Bovo et al. 2016). However, Klug found a seasonal difference concerning pathogens; Group A *Streptococcus* (GAS) was more frequently found in PTA during the winter and spring season than during the summer (Klug 2014).

2.2.1.2 Age

PTA may affect people from the age of one month up to a person's late 80s (Lee et al. 2006). Studies from Sweden and Denmark showed the highest incidence rates to be among 14-21 year olds (124/100 000) and 15-19 year olds (167/100 000) (Risberg et al. 2008, Klug 2014). This usually means the mean age of incidence (26-31 years of age) is higher than the median (22-25 years of age) (Sunnegren et al. 2008, Hanna et al. 2006). In this dissertation, we concentrate on studies concerning adults and adolescents, since pediatric patients' co-operation differs from adults' (Schraff et al. 2001) and their abscesses tend to resolve with more conservative treatment (Kim et al. 2015).

2.2.1.3 Gender

Some studies find an equal male:female ratio of PTA patients (Marom et al. 2010, Gavriel et al. 2009, Hanna et al. 2006), while some studies have shown clear male predominance, even up to ratios as high as 3:1 (Matsuda et al. 2002, Ong et al. 2004, Jokipii et al. 1988, Sunnegren et al. 2008). Many studies show a female peak at earlier ages of PTA diagnosis while men start to predominate in their early 30s (Love et al. 2011, Risberg et al. 2008, Klug 2014, Windfur et al. 2015, Bovo et al. 2016).

2.2.1.4 Side

Some studies describe a slightly higher likelihood of the left side being affected (Mazur et al. 2015a, Costales-Marcos et al. 2012); however, PTA may also occur bilaterally, with the incidence of 0.8-4.9% (Marom et al. 2010, Pham et al. 2012, Watanabe et al. 2010).

2.2.1.5 Recurrence

The recurrence of an adult's PTA varies depending on the reported variables, the follow-up period, and the definition. In some studies, the recurrence is considered to be residual if it occurs within one month of the first occurrence, as was reported by a large Taiwanese study (n=28 837) with a residual rate of 21% and a recurrence rate after the first month of only 5% (Wang et al. 2014). This definition was also used on 86 PTA patients treated with needle aspiration (NA) (Wolf et al. 1994). As a recent large retrospective study (n=4199) showed, most recurrences/residuals occur approximately three months after the first occurrence, proving this division to be artificial (Bovo et al. 2016). In earlier studies of small samples and in those which did not separate residuals from recurrences, the rates of recurrence vary from 8-22% (Herzon 1995, Savolainen et al. 1993, Schechter et al. 1982, Stringer et al. 1988, Ophir et al. 1988, Herbild et al. 1981, Nielsen et al. 1981a), similar to the rate (12%) reported from the recent large retrospective study (Bovo et al. 2016).

2.2.2 Pathogenesis

A lack of clear evidence on the pathogenesis of PTA has driven research to explore new aspects of the disease. PTA has traditionally been known as a complication of AT, but in the last three decades, it has been suggested that infections in the Weber's glands may also be involved (Passy 1994). Likewise, studies of PTA in patients with a previous TE have suggested that factors other than infection of the tonsils may contribute to the pathogenesis (Farmer et al. 2011). Individual host factors such as tobacco smoking and oral hygiene have an effect on the oral flora and may play a role as well (Powell et al. 2013).

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2.2.2.1 Tonsillitis

Microbial findings from AT and PTA have been shown to be similar (Jensen et al. 2015, Brook 2005, Suzuki et al. 2015). Up to 76% of PTA patients have reported suffering from a sore throat prior to diagnosis (Marom et al. 2008). Accordingly, PTA has been considered to be a complication of AT. However, the peak incidence of AT is among 5-15 year olds, while that of PTA is 15-30 years old (Passy 1994). Furthermore, in some studies, up to 68% of patients with PTA have not had preceding tonsillitis symptoms (Dunn et al. 2007, Sunnegren et al. 2008). In a large cohort study (n=685), no correlation between increased rates of AT and peritonsillar infections were found (Kordeluk et al. 2011). These controversies have caused debate to arise questioning the belief that suppurative infections in the tonsils are solely responsible for PTA.

2.2.2.2 Salivary glands

Groups of mucous salivary glands are located in the peritonsillar space and are connected to the surface by ducts in order to clear the crypts. PTA occurrence after a TE supports the theory of local origin of the infection. Also, the typical unilaterality of PTA supports a more local onset (Farmer et al. 2011). Compared to deep neck abscesses, the amylase levels of PTA pus have been shown to be elevated (El Saied et al. 2012). Suspicious of a possible bias caused by contamination, the same group compared the amylase levels of PTAs with those of dental abscesses; a significant difference was also seen between these abscesses, which serves to emphasise the salivary connection, specifically PTA (El Saied et al. 2014). A Chinese group studied the surface of PTA patients' tonsils and found intact tonsils concomitantly with inflamed salivary glands superior to the tonsils; patients without an abscess had normal glands [Chen et al. 1997]. A Thai research group sought to investigate a possible association of PTA with these glands by examining 55 tonsillectomised patients, however, with there being only three PTAs among the group of patients, they were unable to prove any association (Kraitrakul et al. 2011).

2.2.2.3 Periodontal disease

PTA patients seem to have an increased incidence of dental caries (Nasab et al. 2006) and a higher prevalence of periodontal disease than patients with chronic tonsillitis (Georgalas et al. 2002). In a Polish study, only 22% of 111 PTA patients had healthy teeth and the dental status of patients over age 40 was significantly worse than younger patients (Mazur et al. 2015a). As many as 27% of PTA patients have been reported to have had previous dental problems (Fried et al. 1981). Furthermore, lower third molar problems have been shown to increase the number of anaerobic bacteria on tonsils (Rajasuo et al. 1996).

2.2.2.4 Smoking

Numerous studies have reported the increased likelihood of smoking among PTA patients (Dilkes et al. 1992, Kilty et al. 2008, Lehnert et al. 2005, Marom et al. 2010, Hidaka et al. 2011, Klug et al. 2013). The prevalence of smoking is higher among PTA patients than AT patients (Hidaka et al. 2011). Tobacco consumption has been associated with decreased salivary flow and periodontal disease, which may affect the bacteria of the mouth (Eliasson et al. 1991, Sutej et al. 2012, Salvi et al. 1997, Palmer et al. 2005). Brook has studied the effects of smoking on bacterial flora of the mouth and found that e.g. *Prevotella intermedia* and *Fusobacterium nucleatum* are more common in smokers (Brook 2005, 2007, 2011a, 2011b). He also found elevated antibody levels against the same bacteria among PTA patients (Brook et al. 1996). A small study showed a correlation between smoking and morphostructural alterations of tonsils (Torre et al. 2005).

2.2.3 Diagnostics

The diagnostics of PTA vary. Typically, residents are the ones who treat PTA patients at ORL emergency departments, but sometimes a diagnosis is given by general physicians. Experience is desirable, since sometimes PTC can mimic PTA (Herzon et al. 2006, Secko et al. 2015).

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2.2.3.1 Clinical

Symptoms of PTA include severe throat pain, fever, a muffled voice, difficulties and pain with swallowing (dysphagia and odynophagia), and difficulties opening the mouth (trismus) due to inflammation of the mastication muscles. In some cases, ipsilateral otalgia and loss of taste on the posterior third of the tongue occur due to oedema affecting the glossopharyngeal nerve. Symptoms are classically described as occurring over a mean of 4-5 days (range, 1-60) with a fever averaging 37.5-38C (range 36.4-39.5C) (Klug et al. 2009, Stringer et al. 1988). A muffled voice may immediately indicate the diagnosis as soon as the patient speaks. During clinical examination, cervical nodes are often sensitive and swollen. With a headlamp, spatula and light, one can find erythema and oedema superior and lateral to the tonsil as well as on the soft palate, in addition to medialisation of the tonsil and sometimes lateralisation of the uvula. Difficulties in swallowing may occasionally lead to drooling (Gleeson et al. 2008).

2.2.3.2 Microbiological

In the 1990s, a Finnish study group recommended choosing the treatment modality according to bacterial findings (Savolainen et al. 1993), a recommendation later echoed by a study group from Israel (Gavriel et al. 2008). However, several studies have shown that in routine practice culture results, which usually take two to three days, are not implemented in the choice of antibiotic treatment (Kieff et al. 1999, Hanna et al. 2006, Repanos et al. 2009, Cherikuri et al. 2002). Novel, faster approaches have been sought to identify the pathogens. In the late 1990s, a Finnish group tried direct microscopy of the pus aspirates (Lilja et al. 1998) and recently a Danish research group has tried to measure anti-*Fusobacterium necrophorum* (FN) antibody levels in PTA patients with promising results (Klug et al. 2014b). The same group has measured procalcitonin levels in order to detect GAS in tonsillitis patients (Christensen et al. 2014). Novel microarray-based methods are rapidly becoming incorporated into clinical practice, for example in the diagnostics of pneumonia, sepsis, sexually transmitted diseases, as well as in detection of bacterial resistance (Cao et al. 2015, Liesenfeld et al. 2014, Aitken et al. 2015, Shen et al. 2013). Although

shown to be faster and more accurate regarding some components of diagnosis compared to traditional culture (Metso et al. 2014, Järvinen et al. 2009, Laakso et al. 2013), microarray methods still pose multiple difficulties with regard to specificity and costs (Yang et al. 2004). Additionally, microarray studies directly on pus or PTA have not been previously accomplished.

2.2.3.3 Radiological imaging and laboratory testing

In most cases, the diagnosis is clear by clinical evaluation and no imaging is needed. Sometimes, however, PTA is difficult to differentiate from PTC; some researchers recommend intraoral ultrasound as a safe and patient-tolerant procedure, having a specificity of 70% and the sensitivity of 100% (Nogan et al. 2015, Looock 2013, Secko et al. 2015). Computer tomography, or sometimes magnetic resonance imaging, may assist in distinguishing between PTA characteristics and its complications, such as deep neck space infections (Maroldi et al. 2012). Although costly and resource intensive, some researchers have even recommended computer tomography for every suspected PTA patient, in order to avoid unnecessary NA among those cases which are ultimately diagnosed as PTCs (Patel et al. 1992, Scott et al. 1999).

A recent systematic review recommended routine diagnostic blood tests, including full blood count, C-reactive protein (CRP) levels and, in cases of suspected dehydration, electrolytes and urea despite the lack of the evidence (Powel et al. 2012). Undoubtedly, for complicated cases and observation during the recovery period, these tests are helpful tools. Recently, a neutrophil-to-lymphocyte ratio was introduced to help in the prediction of deep neck space infections (Baglam et al. 2015). Routine testing of all PTA for mononucleosis has also been recommended, although co-incidence of mononucleosis is as low as 4-6% (Ryan et al. 2004). Thus, while routine testing may be too resource-intensive to be beneficial, mononucleosis testing can be recommended for inpatient PTA cases, as it may lead to the possible detection of splenomegaly, for which the patient should be advised to avoid contact sports for the following month (Arkkila et al. 1998).

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2.2.3.4 *Differential diagnostics*

Due to the high incidence of PTA among ORL patients, most physicians are familiar with this entity. Although, the diagnosis is typically unambiguous, in some cases it may be difficult to tell the difference between PTA and normal tonsil asymmetry or PTA and swollen tonsils. For those cases where diagnosis remains unclear, differential diagnostics can be of use. Pleomorphic adenoma, lymphoma, acute or chronic myeloid or lymphatic leukaemia, metastasis, squamous cell carcinoma, or even Kaposiform hemangioendothelioma can sometimes cause unilateral or bilateral enlargement of the tonsils (Rokkjaer et al. 2015, Windfur et al. 2015). Internal carotid and thoracic aortic aneurysms mimicking PTA have also been described (Brzost et al. 2015, Perheentupa et al. 2010). Also, parapharyngeal tumors (lipomas, schwannomas, paragangliomas) may mimic PTA (Rajan et al. 2005), as well as parapharyngeal abscesses due to dentogenic aetiology or a foreign body (Gidley et al. 1997).

2.2.4 *Microbiological aetiology*

Inconsistency occurs concerning the microbiology of PTA; variations in sample-taking, culture and incubation methods, result-reporting, as well as diversity in the division of bacteria into subgroups make the reporting challenging (Powell et al. 2013). Controversies also exist as to which bacteria are considered pathogenic (Klug et al. 2011). Recent research has been focusing on how pathogens vary between different patient groups. It has been suggested that PTA microbiology has evolved over the years, but it remains controversial whether the change is due to changes in patient lifestyles, diets, the rate of prescribing antibiotics, or improved bacteriological identification methods (Rusan et al. 2009, Megalamani et al. 2008, Marom et al. 2010).

2.2.4.1 *Diversity in bacteriological findings*

The method of sample taking can vary from aspiration (Jokipii et al. 1988, Jousimies-Somer et al. 1993, Rusan et al. 2009) to swabs from incisional drainage pus (Hidaka et al. 2011) or even tonsillar core tissue (Klug et al. 2011). With swab samples, possible

contamination may interfere with results (Hallander et al. 1975). Both aerobic and anaerobic bacteria, as well as Gram-negative and Gram-positive bacteria, have been found in bacterial samples of PTA. The results may appear to be either monobacterial or polybacterial. The proportion of bacterial samples that are positive with bacterial growth varies from study to study. A large retrospective study (n=847) reported light to moderate bacterial growth as “mixed oral flora” resulting in only 53% positive samples (Klug et al. 2009). In some studies figures as low as 44% positive samples have been reported (Gavriel et al. 2009), while in others, the proportion of positive samples has been as high as 96%-98% (Jousimies-Somer et al. 1993, Cherukuri et al. 2002). Likewise, the prevalence of polybacterial findings varies widely from 7 % (Gavriel et al. 2009) to 87 % (Jokinen et al. 1985), with up to 12 different isolates per sample (Jousimies-Somer et al. 1993). Whether previous antibiotic use influences the results of bacterial culturing remains controversial (Jokipii et al. 1988, Hanna et al. 2006, Klug et al. 2011, Jousimies-Somer et al. 1993, Marom et al. 2010, Mazur et al. 2015a).

2.2.4.2 Pathogenic bacteria

The clinically relevant question is not what is found in PTA samples or how, but rather, which of the organisms are actually pathogenic. This information is crucial for more precise targeting of the treatment. Dividing the bacteria into anaerobic and aerobic ones is hampered by the facultative anaerobes which blur this division and make comparison between the studies difficult. *Prevotella* spp., *Peptostreptococcus*, *Bacteroides fragilis*, *Haemophilus influenzae*, and *Staphylococcus aureus* are common bacteria found in PTA samples most often appearing as polybacterial growth. Although their association with PTA pathogenesis is unclear, it is clear that they typically occur among the most complicated cases (Righini et al. 2006, Ridder et al. 2010, Brook 2004, Nielsen et al. 1996).

If culturing yields monobacterial growth, it reinforces the pathogenic role of the finding, as with SMG (*Streptococcus milleri* group), GAS, and FN (Plum et al. 2015, Mitchelmore et al. 1995, Rusan et al. 2009, Klug et al. 2009 and 2011), although GAS distribution has recently been questioned (Risberg et al. 2010). In Denmark, a study

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group showed that FN was isolated more frequently from the tonsil core samples of PTA patients than the control patients who had undergone elective TE, supporting the belief that FN is a significant pathogen (Klug et al. 2011). *Staphylococcus aureus* was found more frequently in the control samples, than in PTA samples, which indicates its less significant role in PTA pathogenesis. In a later study, the same group concluded that since PTA incidence remains stable during the year, but GAS-related PTA incidence peaks during the winter, FN can be considered a prevalent and significant bacteria in PTA pathogenesis, especially during summer months (Klug 2014). They supported this conclusion by showing higher serum anti-FN antibody levels in PTA patients with positive FN cultures (Klug et al. 2014b). The fact that FN causes various other head and neck infections has been considered to support its role as a pathogen in PTA (Brook 2015). Likewise, a study reporting higher *Fusobacterium nucleatum* and *Prevotella intermedia* antibody levels in PTA patients than in controls, is considered to support the role of these bacteria as pathogens (Brook et al. 1996).

2.2.4.3 Variation of findings among different patient groups

As elementary as it is to identify the pathogenic bacteria of PTA, recognizing the high-risk patient groups would be also important. Although most patients (young, healthy adults) recover well as outpatients prescribed oral medication, some patients require inpatient monitoring and care. Since different bacterial groups produce distinct clinical outcomes, some researchers have proposed the existence of different clinical subtypes of PTA (Powell et al. 2013). Recently, a few studies have focused on the association between different pathogens and the clinical features of PTA. A study from 1993 found a higher prevalence of FN patients with previous tonsillar infections as well as recurrences (Jousimies-Somer et al. 1993). Recently, research has described a dominance of *Streptococcus viridans* group (SVG), in particular SMG, among smokers (Hidaka et al. 2011, Marom et al. 2010). Another study found no correlation between smoking and pathogens, however, no SVG findings were reported in that study (Klug et al. 2013). The coexistence of SMG with anaerobes has been demonstrated by a Finnish study group (Jousimies-Somer et al. 1993) and this

coexistence has been shown to be more prevalent among smokers (Hidaka et al. 2011). FN patients have been shown to be younger and have higher CRP and neutrophil levels (Klug et al. 2009, Klug 2014, Yusuf et al. 2015). However, older patients have also been associated with higher CRP levels (Tachibana et al. 2014, Mazur et al. 2015a), as well as a lower percentage of aerobic bacteria (Gavriel et al. 2015), and longer hospital stays (Marom et al. 2010). Additionally, older patients have been associated with more subtle symptoms and clinical findings and a higher incidence of inferior pole PTAs (Franzese et al. 2003, Monobe et al. 2007) (Table 1).

Table 1. Features of patients in relation to PTA and different bacteria in literature

Reference	Number of patients (n=)	Features	Pathogen	Relation to PTA	Significance
Jokipii et al. 1988	42	Fever	Anaerobic cocci	Higher temperature associated with heavier growth of bacteria	P < 0.025
		Duration of symptoms	Anaerobic cocci	Shorter duration associated with heavier growth of bacteria	P < 0.01
Jousimies-Somer et al. 1993	124	Previous tonsillar/ peritonsillar infection	FN GAS SMG	Higher incidence 52% Lower incidence 25% (Medium incidence 36%)	P < 0.01 P > 0.05
		Recurrences	FN GAS SMG	Higher incidence 57% Lower incidence 19% Lower incidence 43%	P < 0.0001 P < 0.05
		Median age 27 (range 14-80) Median age 44 (range 18-86)		Lower pole PTA Superior pole PTA	p = 0.012
Klug et al. 2009	847	Age	FN	Lower than with other bacteria	P < 0.001
		Neutrophils		Higher than with other bacteria	P < 0.001
		CRP		Higher than with other bacteria	P = 0.01
Marom et al. 2010	427	Age over 40		Longer hospital stay	P = 0.047
				Higher incidence of smoking	P = 0.02
				Higher complication rate	P < 0.001
				Higher rate compared with younger patients	P < 0.001
		Smoking	Gram-positive cocci Gram-negative rods SVG	Higher rate compared with younger patients Higher incidence among patients receiving preceding antibiotics, compared with patients without	P = 0.02 P = 0.04

Hidaka et al. 2011	383	Smoking	Co-existence of SMG and anaerobes	Higher incidence compared with nonsmokers	P < 0.05
Klug et al. 2013	847	Age		Smokers significantly older (median 24) vs nonsmokers (median 19)	P < 0.001
		Neutrophils		No higher levels compared with nonsmokers	P = 0.18
		CRP		Higher levels compared with nonsmokers	P = 0.032
		Smoking	FN GAS	No differences in distribution compared with nonsmokers	
Klug 2014	1617	Age	FN GAS	Among patients 15-24 years of age, FN more frequent Among patients 0-9 years of age, GAS more frequent	P < 0.001 P < 0.001
				Among patients 30-39 years of age, GAS more frequent	P = 0.017
Tachibana et al. 2015	240	Age ≥ 40		Longer duration between symptom onset and complete recovery	P = 0.0004
		CRP > 8.53mg/dL		Longer duration between symptom onset and complete recovery	P = 0.0017
		Previous tonsillar infections		Longer duration between symptom onset and complete recovery	P = 0.022
		No early surgical drainage		Longer duration between symptom onset and complete recovery	P = 0.0014
Mazur et al. 2015a	111	Age ≥ 40		Worse dental status	P = 0.0022
				More comorbidities	P = 0.044
		Previous tonsillar infections		Higher incidence of previous PTA episodes	P = 0.001
Gavriel et al. 2015	282			Higher rate of patients receiving preceding antibiotics	P = 0.0005
		Age > 40	Aerobic growth	Longer hospital stay More prevalent among patients < 40	P = 0.03 P < 0.05

*FN=*Fusobacterium necrophorum*, GAS=Group A *Streptococcus*, SMG=*Streptococcus milleri* group, SVG=*Streptococcus viridans* group

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2.2.4.4 Viruses

The incidence of mononucleosis among PTA patients has been reported at 4-6 % (Ahmad et al. 2010, Ryan et al. 2004, Windfur et al. 2015). Especially when associated with beta-haemolytic streptococci, Epstein-Barr virus (EBV) has been introduced to induce bacterial penetration into tonsillar tissue (Stenfors et al. 2000). A Dutch study group described the case of a patient who was primarily suffering from EBV tonsillitis which was complicated by PTA and descending necrotizing fasciitis caused by FN. They speculated that the superinfection may have been a consequence of decreased immunity caused by the EBV (Geerts et al. 2015). Considering the low incidence of mononucleosis in PTA patients, a relatively low number of PTA patients (n=25) were tested for viruses using PCR. These patients were compared with elective TE patients. No differences were found in the tonsils, with respect to herpes simplex virus-1, adenovirus or EBV (Rusan et al. 2012). There have been some reports of herpes simplex virus-1 tonsillitis mimicking PTA in immunosuppressed patients (Gonen et al. 2006, Hirzel et al. 2015).

2.2.5 Comorbidities and complications

When comorbidities (such as cardiovascular disease, asthma and diabetes) are associated with PTA, they do not influence the clinical course of PTA (Marom et al. 2010). Comorbidities seem to occur more frequently in patients over the age of 40 (Mazur et al. 2015a). Complications that are reported to be associated with PTA range from inflammatory conditions such as necrotizing fasciitis, pyothorax, epiglottitis, descending necrotizing mediastinitis (DNM), and Lemierre's syndrome (Ito et al. 2011, Anderson et al. 2010, Holm et al. 2015, Hagelskjaer et al. 2008, Wolf et al. 2010) to streptococcal toxic shock syndrome (Aalling et al. 2015) and reactive arthritis (Mazur et al. 2015b). The severe complications, such as Lemierre's syndrome and DNM, are most often associated with FN and GAS as well as Gram-negative and/or anaerobic bacteria (*Bacteroides* spp., *Peptostreptococcus* spp., *Prevotella* spp.), and appear as polybacterial infections (Righini et al. 2006, Ridder et al. 2010, Brook 2004, Nielsen et al. 1996).

Complications can be life-threatening and can require rapid diagnostics with radiological imaging and the availability of tracheostomy and intensive care (Motahari et al. 2015, Horváth et al. 2015, Gidley et al. 1997). An Italian group described a total of 14 cases of DNM caused by PTA; the most prevalent bacteria were *Staphylococcus aureus*, *Staphylococcus epidermidis* and SVG. The patients were treated with a combination of penicillin, gentamycin and metronidazole. The mortality was reported to be as high as 30% (Roccia et al. 2007), a remarkably high figure when compared to 12% in another study (Palma et al. 2015). Parapharyngeal abscess is the second most common head and neck abscess (Page et al. 2008, Brook 2009). In a recent report on 63 patients with parapharyngeal abscesses, 33 (52%) had concomitant PTA. Their median age was 45 years, 65% were male and 45% were smokers. Their cultures revealed GAS, SVG and FN as the most prevalent findings (Klug et al. 2014a). More rarely PTA spreads retropharyngeally (Quershi et al. 2015).

2.2.6 Prevention

Prevention of PTA has been examined in only a few studies. In a Cochrane review, the authors concluded that PTA can be prevented by treating sore throats with antibiotics, but in developed countries number needed to treat is high (Del Mar et al. 2006, Spinks et al. 2013). Smoking cessation as well as proper dental hygiene may have beneficial effects on oral flora (Brook 2007). As many as 90% of the deep neck abscess patients are of low socioeconomic status. Educating groups at high risk for PTA about the dangerous complications of the infection and the general importance of proper oral hygiene might reduce the incidence of PTA (Agarwal et al. 2007).

2.3 Treatment of peritonsillar abscess

The lack of consensus on the best treatment for PTA results in great variation. Invasive management procedures, performed at a polyclinic, include three-point NA or ID. After which, the patient can be discharged or taken to the ward, depending on the patient's overall physical condition. TE (i.e. removal of tonsils) can be carried out immediately or after a short recovery period. Conservative treatment (no surgical evacuation of the pus) is also possible, especially for abscesses of lower volume and

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those occurring in children (Johnson et al. 2003). Administration of medical treatments (antibiotics, pain medication, hydration and possible corticosteroids) may be i.v., intramuscular (i.m.) or per oral (p.o.).

2.3.1 Antibiotics and PTA

Since there are currently no rapid methods available in clinical practice to identify the bacteria causing PTA, antibiotic treatment most often remains empirical. Although most PTA pathogens are susceptible to penicillin, in practice, the choice of treatment varies a lot. During this age of increasing bacterial resistance, the choice of drug regimen is more important than ever (Boyanova et al. 2010, McGowan 2001, Mölsted et al. 2008). The most common antibiotics used in the treatment of PTA are addressed here.

2.3.1.1 Penicillin and other betalactames

Penicillins are a group of antibiotics that include phenoxymethyl (p.o.), benzyl (i.v.), procaine (i.m.) and benzathine (i.m.) penicillin; these are susceptible to betalactamase enzymes produced by various bacteria. Of the broader spectrum penicillins, amoxicillin (p.o.) is also widely used in the treatment of PTA; it may also be used in combination with clavulanic acid, a betalactamase inhibitor (Al Yaghchi et al. 2008, Page et al. 2010). Ampicillin (i.v.) is used less frequently. Penicillins are usually well-tolerated by the patient, although cutaneous eruption, diarrhoea and nausea may occur (incidence, 10%). The prevalence of life-threatening anaphylactic reactions is 0.02-0.04% (Gonzalez-Estrada et al. 2015). In individuals allergic to penicillins (and likewise amoxicillin and ampicillin), clindamycin may be used instead. Amoxicillin may cause rash also in patients with simultaneous mononucleosis (incidence 4-6%) (Windfur et al. 2015). In addition cephalosporines, a group of antibiotics related to penicillins, are sometimes used in the treatment of PTA (Rang et al. 2015).

Since the bacteria most often found in PTA (GAS, FN, SMG) are susceptible to penicillin (Klug et al. 2011, Hecht 2006, Tracy et al. 2011), penicillin alone has been suggested to be adequate. In 1995, an American researcher proposed a treatment

guideline for PTA with penicillin as the first choice of treatment for PTA (Herzon 1995, Kieff et al. 1991). In Turkey, a study group randomised 42 patients to receive either i.m. sulbactam-ampicillin or procaine penicillin on an outpatient basis and found no differences in the clinical recovery rates (Yilmaz et al. 1998). In India, a study group treated 34 prospectively collected patients with i.v. benzyl penicillin, and despite microbial growth in culture (21% of which were penicillin resistant), there were no differences in clinical responses (Varghese et al. 2007). An American study group randomised 52 patients into NA and ID groups. The patients received either i.m. procaine penicillin or p.o. phenoxymethyl penicillin, according to expected patient compliance, and only one patient required hospitalisation (Stringer et al. 1988). Another study group from India, randomised 60 patients to ID and NA groups and gave a starting dosage of i.m. procaine penicillin followed by p.o. penicillin for 10 days; all but two patients recovered well on an outpatient basis (Maharaj et al 1991). In a study on 151 patients from Singapore, there was no difference in the length of hospital stay between patients treated with penicillin alone or penicillin and metronidazole combined (Ong et al. 2004). Preadmission antibiotic use was shown to affect the growth of GAS (Jokipii et al. 1988, Mitchelmore et al. 1995) and ORL patient's cultures in general (Rusan et al. 2009), however, controversial results have been reported (Hanna et al. 2006, Jousimies-Somer et al. 1993).

2.3.1.2 *Metronidazole and clindamycin*

Metronidazole belongs to the group of nitroimidazoles, along with tinidazole and ornidazole. It is used in the treatment of many parasites (e.g. trichomonas, amoeba, giardia) and anaerobic bacteria. When administered p.o., metronidazole is found to be well distributed throughout body tissue. The drug is mostly metabolised by the liver and, accordingly, this metabolism is reduced in patients with liver dysfunction. Renal failure only affects excretion of its metabolites. Metronidazole can interact with other drugs (e.g. warfarin, phenytoin, lithium) and it produces a disulfiram-like reaction when used in conjunction with alcohol. When administered in dosages of <2g per day, it is generally well tolerated; adverse effects, such as gastrointestinal

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effects, neutropenia and neuropathies, appear to be related to the dosage and treatment duration (Lau et al. 1992).

A British study group recommends metronidazole in conjunction with penicillin for the treatment of PTA, but their evidence is based on bacteriological findings of PTA, not randomised antibiotic studies (Powell et al. 2012). A national survey conducted in the United Kingdom (U.K.) found the most commonly used treatment modality for PTA was a combination of benzyl penicillin and metronidazole. The authors claimed that several of the antibiotic choices of the prescribing physicians were inappropriate for the treatment of PTA and their concluding recommendation was for monotherapy with penicillin (Visvanathan et al. 2010).

Anaerobes (*Peptostreptococcus* spp., *Prevotella* spp., *Bacteroides* spp.) are becoming increasingly resistant to penicillin (Boyanova et al. 2010) and therefore the usage of metronidazole is often recommended. This practise is supported by reports suggesting that these bacteria are frequently associated with severe complications (Brook 2004, Ridder et al. 2010).

Also, clindamycin, which has a broader spectrum, is sometimes used as the first choice in the treatment of PTA (Ozbek et al. 2005). In Canada, *Streptococcus* spp. have been reported to have reached resistance levels as high as 32% against clindamycin. On the other hand, in that study, even though the bacteria found in culture (e.g. GAS) showed clindamycin resistance, the patients still recovered well using clindamycin without a need for treatment adjustment (Sowerby et al. 2013).

2.3.2 Polyclinical draining

Two polyclinical methods of surgical opening (NA and ID) for the treatment of PTA have been used over the past several decades. Physicians preference for one method over the other has changed over the years due to a number of reasons, some of the main arguments are addressed here (Khayr et al. 2005).

2.3.2.1 Needle aspiration

Since the 1960s, when King introduced this method for the first time [King 1961], several authors have claimed NA to be simple, efficient and cost-effective (Spires et

al. 1987, Johnson et al. 2003, Herzon et al. 1981, Herzon 1984). Findings regarding NA usage and effectiveness are varied. A national audit carried out in the U.K. (n=101) revealed that 61% of respondents chose NA as their initial treatment for PTA (Mehanna et al. 2002); an Irish study group reported 71% (Ryan et al. 2014). However, an audit in the United States revealed only 32% of physicians chose NA as their initial treatment for PTA (Herzon 1995). One study of 104 PTA patients reported complete recovery following NA in 85% of the patients, but there was no comparison with any other treatment (Ophir et al. 1988). Another study showed that 10% of 52 patients needed re-aspiration (Schechter et al. 1982). Need for re-aspiration has been shown to be dependent of the pus volume (Viljoen et al. 2007). A study of 60 randomised patients reported no difference in recovery when NA was compared with ID (Maharaj et al. 1991). The same result was found with 52 patients in Texas (Stringer et al. 1988).

2.3.2.2 *Incision and drainage*

Since its introduction in the 14th century, ID has encountered opposition, but it remains the gold standard at many ORL units, including ours. Although painful to the patient, ID is usually a simple procedure that offers immediate pain relief and allows rapid discharge of the patient (Nwe et al. 2000). Compared to NA, ID has shown somewhat lower recurrence rates of PTA (Wang et al. 2014, Wolf et al. 1994). The definition of recurrence however, has remained controversial (Herzon 1995). When, in 2010, a German hospital changed its treatment modality for PTA from immediate TE to ID, hospital stays shortened from seven to four days (Windfur et al. 2015). ID has been recommended as the first-line treatment for patients older than 30 years of age (Nielsen et al. 1981a).

2.3.3 *Tonsillectomy*

Although the most frequent procedure performed in many ORL units and most often safe to proceed, the operation is associated with quite constant post-operation bleeding rate burdening especially the expensive emergency duty. Recovery after the operation is uncomfortable despite adequate pain medication, thus, a two week sick

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leave is recommended. In addition to the more common complications (bleeding, nerve palsy, change in swallowing or voice), a TE can also be fatal. Therefore, a TE must be well justified every time (Seshamani et al. 2014, Hoddeson et al. 2009). TEs are divided into two types (immediate TE and interval TE) depending on the time from PTA episode to the procedure.

2.3.3.1 *Immediate TE*

The procedure most commonly known as 'immediate TE' has also been called by other names including TE à chaud, hot TE, quinsy TE and abscess TE. In one study, a total of 51 patients were randomised into immediate and interval TE groups. In the group undergoing immediate TE, sick leave was reduced from 18 to 10 days, the operation was considered easier to perform, and bleeding was less severe (Fagan et al. 1994, Nielsen et al. 1981b). A reduction of sick leave (from 7.2-9 to 4.4-5.5 days) was also shown in another study comparing immediate and interval TEs (Lockhart et al. 1991). With the high number of cases where pus is found intraoperatively (despite initial drainage), the choice of an immediate is well supported, especially if inferior pole/ parapharyngeal spread is suspected (Berry et al. 2008, Page et al. 2010). In a large retrospective study (n=6329) of TE patients, no difference in the bleeding rates (2.9% vs. 2.8%) was found between immediate and interval TEs (Windfur et al. 2001). A Danish study found comparable rates of bacteremia between immediate and interval TEs (Klug et al. 2012). At least in cases, where recovery from PTA is not achieved by other methods, immediate TE is recommended (Herzon 1995).

2.3.3.2 *Interval TE*

In a survey carried out in the U.K., interval TE was recommended by 15% of 571 ORL surgeons, even after the first episode of PTA (Raut et al. 2000). Some authors claim that, compared with interval TE, immediate TE has several disadvantages, such as the increased risk associated with carrying out an operation in conjunction with a generalised infection, high fever, potential co-existent mononucleosis and/or airway restriction due to trismus. In addition to these, expensive personnel and difficulties identifying the tissue have also been mentioned; some even consider immediate TE contraindicated (Suzuki et al. 1999). Post-operative hemorrhage rates, as high as 22%

-after immediate TE, have been cited as reason to favor interval TE (Dünne et al. 2003). Johnson et al. (2003) published an encompassing evidence-based review and found no indication that any one surgical procedure was better than another. Speculations about immediate TE being easier to proceed due to the tonsil already being in a partly dissected state and the difficulty (due to bleeding and post-operative pain) of removing potentially scarred tissue in an interval TE, remain anecdotal.

2.3.4 Other aspects

Whether PTA patients should be treated as out- or inpatients has been debated for decades. Although many studies have demonstrated the safety of patients being treated as outpatients (Maharaj et al. 1991), according to a survey conducted in the U.K., 94% of the participants treated most of their PTA patients as inpatient (Mehanna et al. 2002). This approach is also common in Germany with a mean inpatient duration of four days (range, 1-13) (Windfur et al. 2015). Need for hospitalisation was associated with a re-accumulation of pus (Sowerby et al. 2013). Hospitalisation may sometimes be required, for example, due to a patient's long travel distance or other patient-dependent factors (Varghese et al. 2007).

A German study showed no clinical difference in laboratory parameters, pain levels or swallowing difficulties among 105 PTA patients randomised to receive either penicillin or no antibiotics at all after immediate TE (Knipping et al. 2002). Whether or not surgical opening plays a significant role in patient recovery from PTA remains to be seen. Although typically the evacuation of pus by opening the abscess cavity is recommended, noninvasive management modalities for PTA patients have also been tested. Ten years ago, an American researcher introduced solely medical management for PTA patients employing cephalosporines, which resulted in only 4% of patients needing further assessment (Lamkin et al. 2006), however, in another study an association between a longer length of hospitalisation and noninvasive treatment modality was shown (Tachibana et al. 2014). A total of 5% of surgeons, in the previously described survey study from the U.K., chose antibiotics alone as the initial treatment for PTA (Mehanna et al. 2002). In addition to antibiotics, pain medication, hydration and possible corticosteroids must not be forgotten when

REVIEW OF THE LITERATURE

treating PTA patients (Ozbek et al. 2004, Johnson et al. 2005). In a placebo-controlled study, a high dose corticosteroid was found to be favorable compared to antibiotics alone (Hardman et al. 2014). The use of corticosteroids should always be meticulously considered, since their impact on the postoperative bleeding rate after immediate TE remains controversial (Tolska et al. 2013).

3 AIMS OF THE STUDY

The objective of this thesis was to improve our understanding of bacterial aetiology and the different treatment modalities of PTA.

The specific aims were:

1. To analyse a series of pus samples aspirated from adult patients with PTA by identifying the bacterial species with a modern microarray method, and to modify it for this purpose. (Study I)
2. To characterise and find possible correlating factors among patients with different pathogens. (Study I)
3. To understand the variation in the treatment modalities for PTA patients in secondary and tertiary public health care in four Nordic countries. (Study II)
4. To find possible predictive factors for delayed TE in order to better understand when a patient with PTA should have a TE and when to recommend a “wait and see” policy. (Study III)
5. To evaluate the efficacy of metronidazole administration in conjunction with penicillin in preventing the recurrence of PTA in adult outpatients treated with ID, and to learn if metronidazole enhances the recovery of PTA when compared to penicillin alone. (Study IV)

4 SUBJECTS AND METHODS

Three studies in this dissertation involved patient recruitments. All of the patients visited the Emergency Department of Otorhinolaryngology— Head and Neck Surgery, Helsinki University Hospital (HUH) in Helsinki, Finland, which is a tertiary care unit with a catchment area of ca 1.4 million inhabitants.

4.1 Participants

Study I, IV

We prospectively recruited all (n=552) patients over the age of 18 who were referred to the emergency department of ORL with a suspicion of PTA between February 2010 and April 2011. A physician on duty recruited the patients. Patient inclusion criteria were: their referring doctor suspected PTA, they consented to participate, had daily access to e-mail, spoke and understood Finnish or Swedish, had an adequate birth control method if female, and a final diagnosis of PTA. Patient exclusion criteria were: an allergy to penicillin or metronidazole, use of metronidazole in the preceding month, pregnancy, breast-feeding, renal or liver insufficiency, alcohol abuse, participation in another clinical trial at the same time, current condition required inpatient care, a TE was scheduled within the next 30 days, or currently a military conscript. The study was registered at www.clinicaltrials.gov with the identifier: NCT01255670. For study IV, a sample size of 200 was estimated to be adequate; recruitment of patients continued until this was achieved.

Study II

We included all university and central hospitals in Finland (n=20), Sweden (n=27), Norway (n=19), and Denmark (n=15). We asked all ORL department chief physicians to participate; if the physician did not treat PTA patients, he or she was asked to forward the questionnaire on to a colleague who did.

Study III

In this retrospective study, we included all patients (n=809) over age six who were admitted to the emergency department of ORL in HUH during the year 2000 due to a peritonsillar infection. The patients were collected from the hospital database by the International Statistical Classification of Diseases 10th edition (ICD-10) code J36 (PTA and PTC). The diagnosis was confirmed as an abscess if pus was evident following NA or ID or if the abscess had ruptured spontaneously, according to the treating physician's documentation. Otherwise, the diagnosis was confirmed as PTC. In some cases, the abscess was found only when performing an immediate TE.

4.2 Methods

4.2.1 Questionnaires (I, II, IV)

In studies I and IV, before agreeing to participate, each participant completed a questionnaire that detailed their current level of pain, the presence or absence of fever, and any difficulties they had experienced in opening their mouth or swallowing (appendix 1). In study IV, each participant was e-mailed the same questionnaire, daily for the first two weeks and then weekly for the following six weeks. Of the questionnaire, the questions I-V were scaled as follows: 0 - no symptoms, 1 - minor symptoms and 2 - intense symptoms; questions I- III were combined as throat-related symptoms and questions IV and V were assessed separately. In question VI, addressing the adverse effects (gastrointestinal symptoms, neurological symptoms and rash), each parameter was assessed as the number of days the symptom appeared during the first two weeks.

In study II the questionnaire (appendix 2) included 23 multiple-choice questions inquiring about typical PTA treatment in each ORL clinic, such as how the abscess opening is achieved, whether the abscess is treated noninvasively, whether the management differs between distinct age groups, whether the patient eventually undergoes a TE, the choice of antibiotic(s) prescribed, and whether treatment is on an inpatient or outpatient basis. The multiple-choice questions had 2-12 answer

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choices, and for some questions, more than one answer was possible. The questionnaire was created by the study group and was tested on residents. It was distributed via the web-based Webropol survey and analysis software, arrived by e-mail and took approximately five minutes to complete. The responses were automatically transferred to Webropol and MS Excel.

4.2.2 Medical records (I, III, IV)

In studies I and IV, patients medical records were reviewed afterwards and all episodes of symptom recurrences and hospital visits, as well as age, gender, smoking, duration of symptoms before admission, and previous antibiotic treatment were recorded.

In Study III, we reviewed medical records of participants and collected data on preadmission antibiotics, previous abscesses or tonsil infections, as well as noting whether care was on an outpatient or inpatient basis and whether the antibiotics were effective against anaerobic bacteria. Utilizing the database from the National Institute for Health and Welfare to match follow-up data on all of these PTA and PTC cases, we recorded those who had undergone a TE or adenotonsillectomy between 2000 and 2005. We noted whether an immediate or interval TE was performed, as well as how many of the patients required a delayed TE within the five years of follow-up.

4.2.3 Sample collection, PCR and microarray (I, IV)

ORL residents trained to treat PTAs first applied a 1% lidocaine-adrenalin anaesthetic and localised the abscess cavity by aspiration with a 5 ml syringe and a long 25 Gauge needle. Afterwards, they incised the mucous membrane with a No. 11 scalpel blade and drained the abscess using suction and a pair of an angulated forceps. Pus aspirate samples were delivered to the laboratory for further analysis. Drainage was categorised as either *exiguous* or *extensive*, according to the treating physician's documentation (+ for exiguous, ++ for extensive). No routine laboratory tests or radiological imaging was performed.

After DNA extraction (see detailed study I methods), the samples were analysed with

the modified Prove-it™ Bone and Joint assay, which is based on a broad-range PCR and microarray analysis capable of identifying over 60 bacterial species. The assay amplifies specific regions of the bacterial topoisomerase genes *gyrB* and *parE*, and the methicillin resistance gene *mecA*. The microarray analysis identified the biotinylated PCR products through hybridization with target-specific oligonucleotides. The results were achieved by running the data through the StripArray Reader and the Prove-it™ Advisor analysis software (version 1.1.0.0), which included the name(s) of the bacterial target(s). Negative extraction and PCR controls were utilised in each test series, as were hybridization controls in each Prove-it™ analysis.

Samples that tested negative for the modified microarray assay underwent further gel electrophoresis analysis with DNA sequencing of the bacterial *gyrB/parE* regions (see detailed study I methods). After analysis of the DNA sequences, The BLAST algorithm served to locate homologous sequences in the European Bioinformatics Institute database and the National Center for Biotechnology Information database, as well as to find homologous sequences archived in the Mobidiag Biobank (Altschul et al. 1990). If the homologous searches identified homologous or highly similar DNA sequences, the name of the identified bacterial species or taxon was recorded. Finally, the bacterial findings were summarised using both the microarray and DNA sequencing analysis results. The samples verified to be positive from the bacterial *gyrB/parE* amplification by gel electrophoresis but failed to achieve bacterial identification in the subsequent DNA sequencing were categorised as undefined. The samples were reported as negative, if neither the Prove-it™ assay nor DNA sequencing detected bacteria.

4.2.4 Interventions, randomisation and outcomes (IV)

After ID of the PTA and collection of the pus, the patients were randomised to receive either p.o. phenoxymethyl penicillin 1 million IU x3x10 and metronidazole 400mg x3x7 (the combination group, n=100) or phenoxymethyl penicillin 1 million IU x3x10 and placebo (the penicillin group, n=100). The placebo, prepared by a hospital pharmacist, was cellulose packed in a gelatine capsule, similar in appearance to the

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metronidazole capsule. The allocation sequence was generated in the hospital pharmacy by staff who were not participating in the study. The placebo vs. metronidazole containers were delivered to emergency department and nurses handed out the medication by the study number. The entire study group was blinded during the study period. The allocation key was opened after all analyses were completed. Predetermined clinical significance was established for analyzing the difference in outcome measures between the groups.

The primary outcome was defined as the efficacy of metronidazole, in conjunction with penicillin, to prevent the recurrence of PTA within 56 days. Any patients who returned to the hospital or contacted the study group by e-mail due to worsening symptoms or their overall condition were assessed separately. All patients requiring a re-opening of the abscess, inpatient treatment or a re-consideration of antibiotic treatment were considered as having a recurrence, the primary outcome. If they contacted the study group or the hospital for minor symptoms (subtle throat pain, a common cold, a slight temperature) with no signs of a PTA, they were considered not to have had a recurrence. However, these minor symptom reports were recorded and used for a separate subgroup analysis.

The secondary outcome was defined as the ability of metronidazole, in conjunction with penicillin, to enhance the recovery of PTA within 28 days. The secondary outcome, recovery, was based on three variables: throat-related symptoms (soreness, difficulties in opening mouth or in swallowing), fever and overall physical condition. Recovery was considered achieved the day that the patient felt, for the first time, that he/she had no symptoms; additionally, the following day was required to be symptom-free.

A 20% difference in the number of patients between the groups was considered significant for the primary outcome. For the secondary outcome, a significant clinical difference between the groups was considered to be a reduction of symptoms by one day. To achieve 90% power for the study, using alpha 0.05, a sample size of 88 was calculated to be sufficient for each group. To replace any possible protocol violators or dropouts, a sample size of 100 per group was estimated to be adequate.

4.3 Statistical analyses

For all the studies, the study group and a professional statistician performed the statistical analyses using the 2009 NCSS (Kaysville, UT, USA) statistical analysis software to calculate Fisher's exact tests, Kruskal-Wallis tests, and Mann-Whitney U-tests. P-values < 0.05 were considered to be significant.

4.4 Ethical considerations

The Research Ethics Committee of HUH approved all three studies (I, III, and IV) involving patient recruitment for this dissertation. Each patient in studies I and IV provided his or her own written informed consent, which was not required in the retrospective chart review study (III). For study II only physicians were interviewed thus ethics approval was not required.

RESULTS

5 RESULTS

5.1 Demographics of PTA patients (III, IV)

In the prospective study (IV), there were 552 consecutive patients referred for recruitment due to the suspicion of PTA, however, 85 chose not to participate and further 267 did not meet the inclusion criteria. The required 200 patients were recruited over a 14 month period. Most (80 %) of them had a normal overall physical condition, 55% were male and 40% were smokers. The median age of them was 31 years (range, 18–65), and the median duration of symptoms was 5 days (range, 1–30) (Table 2).

Table 2. Baseline characteristics of 200 prospectively collected patients with peritonsillar abscess in the combination group (penicillin & metronidazole) and in the penicillin group (penicillin & placebo) (Study IV).

Characteristics		Combination group (n=100)	Penicillin group (n=100)
Age, years	median	31	31
	range	18-65	18-64
Male		53	56
Smoker		35	45
Healthy		82	77
Cardiovascular risk factor* and medication		8	5
Asthma		4	6
Preadmission antibiotics		31	25
Symptoms at admission			
Total, scale 0-10	mean (SD)	6.1 (2.2)	5.9 (2.2)
Throat, scale 0-6		4.18 (1.27)	3.89 (1.28)
Fever, scale 0-2		0.81 (0.87)	0.90 (0.89)
Overall physical condition, scale 0-2		1.15 (0.76)	1.15 (0.73)
Duration of symptoms before admission, days	mean (SD)	5.9 (3.5)	6.0 (4.9)
	range	1-18	1-30

*Diabetes mellitus, hypertension, or hypercholesterolemia

In the retrospective study (III), there were 798 patients, of which 53% were male and 41% had received preadmission antibiotics, with 6% of those being broad in spectrum. Taking into consideration the catchment area of 1.4 million inhabitants, incidence of peritonsillar infection turned out to be 58/100 000 and of PTA 46/100 000.

5.2 Bacterial findings (I)

Of the available 200 pus samples from study patients, a total of 180 samples were used in the final analysis, after using 10 test samples to modify and test the microarray method and failing to collect another 10. A total of 89% (n=160) of samples tested positive after combining the microarray and DNA sequencing results; microarray alone produced 53% of the positive results, which detected up to 70% of the bacteria available on the panel (for instance *Prevotella* spp., *Peptostreptococcus* and SVG lacking). We failed to identify any bacterial species in 11 bacterial positive samples, leaving 149 (83%) samples with an identified bacteria. The controls for each test series performed properly. Only one bacterial species was identified in the majority (87%) of samples. Of the 169 different bacterial species found, 94 (56%) were Gram-negative and 75 (44%) were Gram-positive. A total of 54% (n=92) were categorised as aerobic or facultative anaerobic bacteria and 46% (n=77) as anaerobic. The most common anaerobic bacterial species was FN (26%) and the most common aerobic species was GAS (24%) (Table 3). No positive *mecA* findings were reported.

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Table 3. Bacterial species identified by the microarray assay and DNA sequencing (Study I).

Aerobic bacteria including facultative anaerobic bacteria	Number of cases identified	Gram-negative	Anaerobic bacteria	Number of cases identified	Gram-negative
<i>Streptococcus pyogenes</i>	40	x	<i>Fusobacterium necrophorum</i>	44	44
<i>Haemophilus influenzae</i>	14	14	<i>Prevotella oris</i>	26	26
<i>Streptococcus milleri</i> group	12	x	<i>Prevotella</i> spp.	4	4
<i>Streptococcus viridans</i> group	6	x	<i>Peptostreptococcus micros</i>	2	x
<i>Streptococcus pneumoniae</i>	4	x	<i>Bacteroides fragilis</i> group	1	1
<i>Staphylococcus aureus</i>	4	x			
Coagulase negative <i>staphylococcus</i>	4	x			
<i>Aggregatibacter aphrophilus</i>	2	2			
<i>Neisseria</i> spp.	2	2			
<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	2	x			
<i>Enterobacter cloacae</i>	1	1			
<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>	1	x			
Total	92	19		77	75

5.3 Comparison of patient factors across those affected with different bacteria (I)

FN, GAS and SMG were assessed as individual agents, and the rest of the bacteria together as “others”. FN patients were significantly younger (median age: 23 years) compared to patients with GAS, SMG, or other bacteria (median age: 33 years) ($p < 0.001$). They also exhibited more severe symptoms at admission ($p = 0.04$), according to the five-question survey. No significant difference between the four groups was found regarding gender, smoking, duration of symptoms or preadmission antibiotic treatment. In the SMG group ($n = 12$), 11 patients (92%) were men, 3 (25%)

were smokers and the median duration of symptoms was 4.5 days; in comparison to the other groups, no significant differences were shown in these variables ($p=0.05$, $p=0.51$ and $p=0.12$, respectively). The majority (83%) of these samples included more than one bacteria; only two were unibacterial.

5.4 Differences in PTA treatment in four Nordic countries (II)

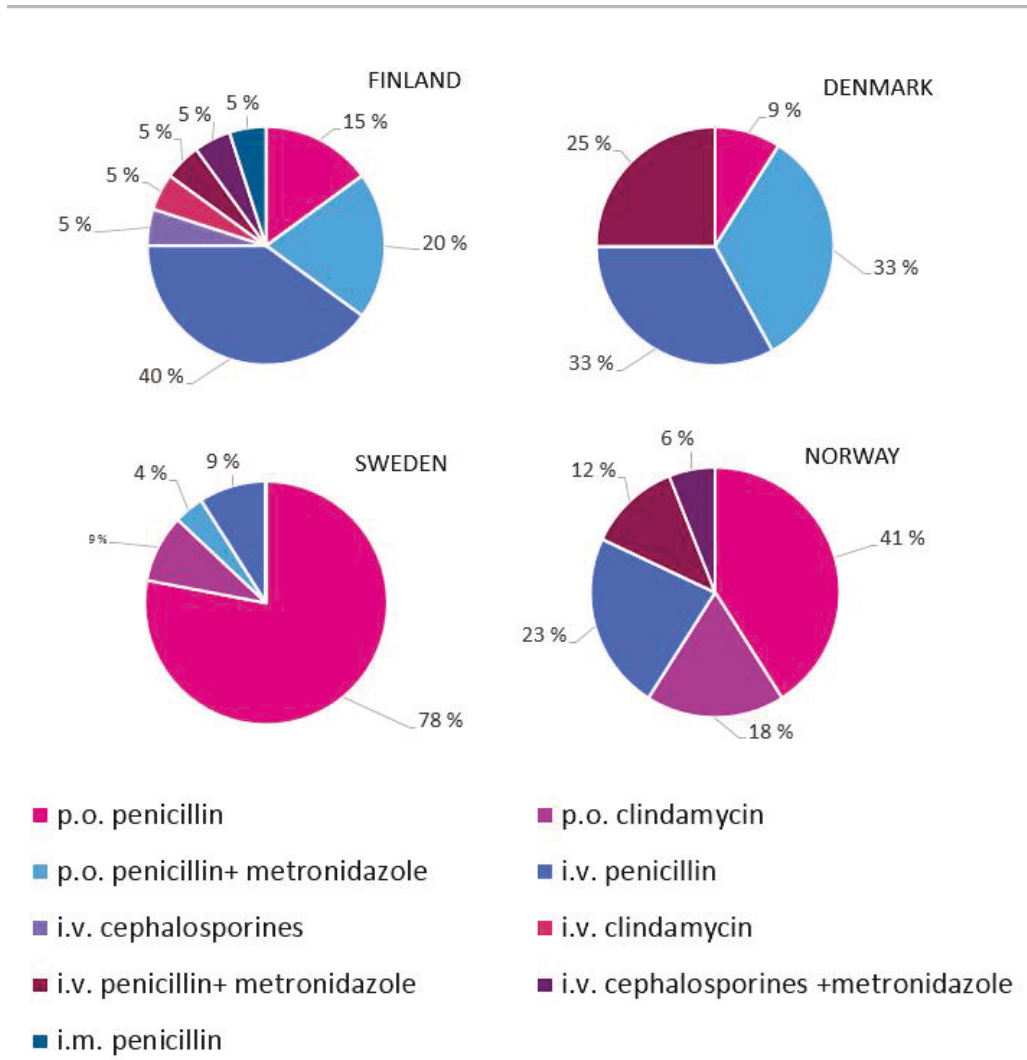
A response rate of 90% ($n=73$) was achieved when the questionnaire regarding treatment modalities of PTA was e-mailed to the physicians in the four countries. Of the 81 invited centers, eight did not respond; one Norwegian, four Swedish, and three Danish. Most respondents (88%) considered the treatment policy of PTA in their hospital to be uniform and 68% felt that the treatment policy had not changed in the past 3 years. No one disagreed with the statement 'ORL specialists should take care of PTA patients, not physicians in primary health care'. Specific PTA-related training in the previous three years was rare (only 15%). A total of 5% ($n=4$) of the respondents reported always performing a TE on a PTA patient. Over one-third (37%) reported doing so in cases of bilateral PTA. Most (80%) reported that they regularly performed abscess cavity re-openings (daily or every other day). Children under seven years old were most often reported to undergo a TE. Four respondents reported choosing NA or ID if the child's co-operation permitted it. Only two chose inpatient treatment with i.v. antibiotics as a first-line therapy. As many as five respondents (7%) reported treating their pediatric patients with PTA under general anaesthesia without performing a TE. The degree of co-operation seemed to determine the treatment among patients 8-15 years old.

The greatest variation between countries was seen in the treatment of patients over age 16. Clear differences emerged in the treatment of patients as inpatients vs. outpatients: 33% as inpatients in Denmark, 50% in Finland, 19% in Norway and 9% in Sweden. Even though, overall, 54% chose p.o. antibiotics as the first-line treatment, compared with i.v. antibiotics, the country-specific analysis showed great

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variation. Likewise, the administration rate of one vs. multiple antibiotics varied: multiple antibiotics were used by 58% in Denmark, 30% in Finland, 18% in Norway and 4% in Sweden. For most respondents (65%), penicillin (p.o. or i.v.) was the first choice. Combining metronidazole with penicillin or cephalosporins was most common in Denmark. No one chose macrolides as their first-line antibiotic (Figure 2). In Denmark, nearly all respondents (92%) reported immediate TE as the type of TE performed on patients over 16 years old. In the other three countries, especially in Sweden, TEs were performed more often after a 1-6 month recovery period in this age group.

Figure 2. Antibiotic used as a first choice for treatment of PTA in four Nordic countries (Study II).



The participating units were divided to large (over 10 ORL specialists, n=22) and small (10 or fewer ORL specialists, n=49) clinics. Comparison of treatment modalities between these showed no significant differences. In both, 82% of the respondents re-opened the abscess cavity. Patients were treated primarily as

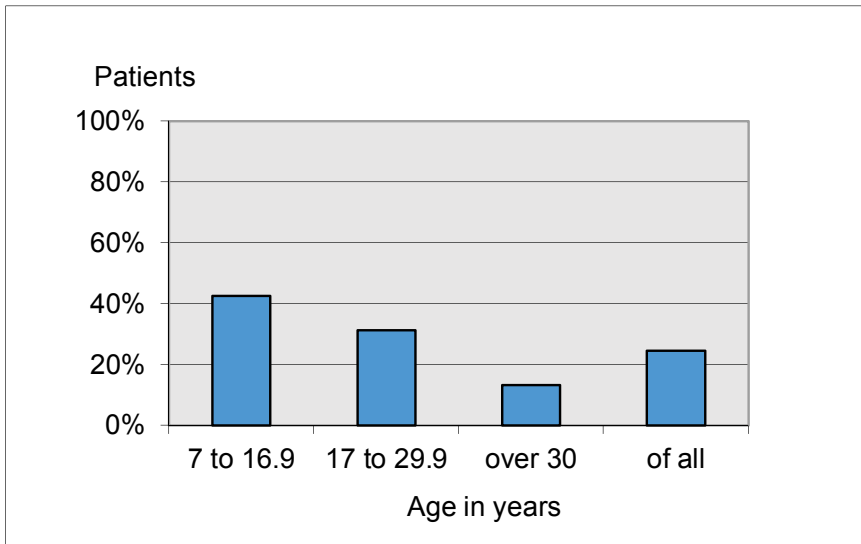
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inpatients in 31% of the small clinics, and 18% of the large clinics ($p = 0.386$). Immediate TE, was performed in 55% of the cases in large clinics, and 38% of cases in small clinics ($p = 0.282$).

5.5 TE after PTA (III)

The final sample included data from 798 patients (11 were excluded due to missing records). Of these, 40% ($n=322$) underwent a TE by the end of 2005. The most common reasons for an immediate TE ($n=106$) were: limited co-operation of the patient, unsuccessful drainage at the polyclinic and delayed recovery. Previous abscesses or several previous tonsil infections were the most common reasons for an interval TE ($n=53$). Of the 639 patients treated without a TE after the PTA episode, 163 (26%) required, however, a delayed TE during the 5-year follow-up period. The most common reasons for delayed TE being a recurrent abscess (65%) and chronic tonsillitis (29%). The recurrence rate of PTA was 16.5%, among patients who ended up being tonsillectomised. When comparing the delayed TE group with the non-operated group, no effect on the probability of later surgery was found regarding differences in previous abscesses, follow-up visits, re-openings, use of broad-spectrum antibiotics or treatment as an outpatient vs. inpatient. Of the patients in the delayed TE group, 37% had had tonsillar infections before their peritonsillar infection, whereas, of those not operated on, only 22.1% had had previous tonsillar infections ($p=0.067$). To further analyse the data, the patients treated without a TE after the PTA episode were divided into three age groups: 7–16 years old ($n=109$), 17–30 years old ($n=288$) and 30+ years old ($n=242$). Age seemed to affect the probability of ending up being tonsillectomised; with a delayed TE recorded for 43% of the youngest age group, 31% of the middle age group and only 13% of the oldest age group ($p<0.001$) (Figure 3).

Figure 3. Age distribution among patients ending up having delayed TE (Study III).



5.6 Penicillin vs. combination (IV)

A total of 200 prospectively recruited patients were randomised into two groups: penicillin and combination; six patients had to interrupt the intervention (two in the first group and four in the latter group), mainly due to nausea or urticarial caused by the study drugs. All patient charts were reviewed and PTA recurrences (primary outcome) within 56 days was recorded. In both groups, 10 patients returned to the hospital due to renewed abscess-related symptoms. Out of these 20 patients, 8 had received preadmission antibiotics, 14 (70%) were male and 7 (35%) were smokers. All 6 females were under 31 years of age and all *Prevotella oris* + SMG findings occurred in males (Table 4). Most recurrences (65%) occurred after 3 days from the first episode, with a median of 9.5 days (range, 1-22) in the combination group and 12.5 days (range, 1-42) in the penicillin group. No significant difference was found between the two groups regarding age, gender, preadmission antibiotics, smoking, success of the initial opening or day of the recurrence.

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Table 4. Details of the 20 PTA patients with recurrence (Study IV).

COMBINATION GROUP					
AGE	GENDER	OPENING SUCCESS	DAY OF RERURRENCE	FINDINGS*	OUTCOME
18	F	(+)	1	FN	antibiotics were changed
21	F	(++)	19	FN + GAS	tonsillectomised
22	M	(++)	17	FN	new antibiotics described
22	M	(++)	14	FN	new antibiotics described
25	F	(+)	2	FN	antibiotics were changed
40	M	(++)	14	<i>Prevotella oris.</i> + SMG	new antibiotics described
47	M	(++)	1	<i>Prevotella oris.</i> + SMG	antibiotics were changed
60	M	(++)	1	Coag.neg. <i>staphylococc.</i>	inpatient treatment
64	M	(++)	22	No sample available	new antibiotics described
64	M	(+)	4	FN	antibiotics were changed
PENICILLIN GROUP					
AGE	GENDER	OPENING SUCCESS	DAY OF RECURRENCE	FINDINGS*	OUTCOME
19	F	(++)	24	No sample available	new antibiotics described
19	F	(+)	14	FN	new antibiotics described
20	M	(++)	15	FN	new antibiotics described
21	M	(++)	15	FN	tonsillectomised
24	M	(++)	42	<i>Prevotella oris.</i> + SMG	new antibiotics described
31	F	(++)	5	Unidentified	antibiotics were changed
40	M	(++)	2	<i>Prevotella oris.</i> + SMG	inpatient treatment
46	M	(++)	1	FN	tonsillectomised
57	M	(+)	1	<i>Prevotella oris.</i> + SMG	tonsillectomised
53	M	(+)	6	<i>Haemophilus influenzae</i>	antibiotics were changed

*FN=*Fusobacterium necrophorum*, GAS=group A *Streptococcus*, SMG=*Streptococcus milleri* group

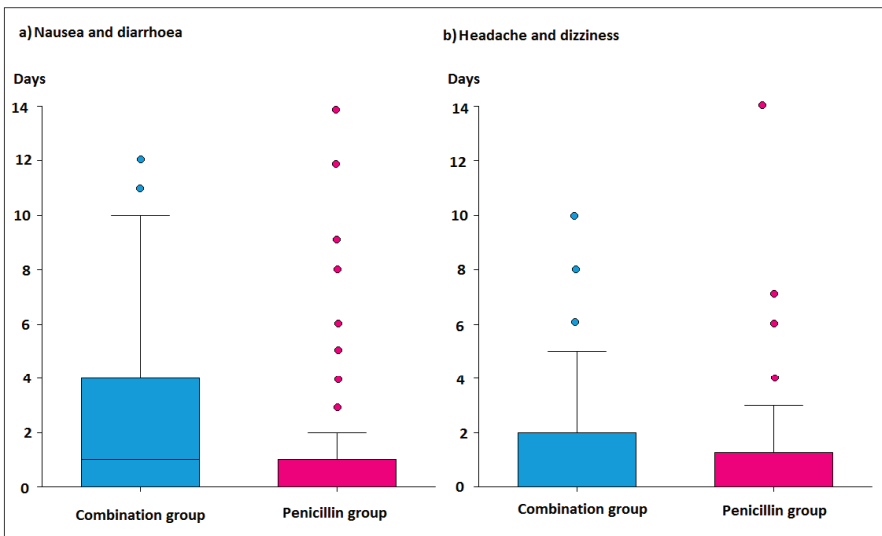
A total of 156 patients (78%) completed all daily/weekly questionnaires over their study participation time. From the combination and penicillin groups, respectively, 13 and 11 patients answered only until their symptoms were relieved. Eight patients in the combination group and 12 in the penicillin group did not answer questionnaires at all, or answered only for a few days. Their answers were not included in the secondary outcome analyses. Additionally, answers from the patients with a recurrence or interruption were excluded. Accordingly, recovery from PTA, the secondary outcome, was assessed as treatment per protocol for the patients who answered until they were recovered, $n=154$. The mean (SD) duration of throat-related symptoms for the combination and penicillin groups, respectively, was 5.6 (5.0) days and 5.3 (2.7) days, fever 1.5 (0.9) days and 1.6 (1.0) days and abnormal overall physical condition 4.0 (3.9) days and 4.5 (4.9) days, with no significant differences between the groups regarding any of the symptoms. When performing an intention-to-treat analysis, $n=100$ vs. $n=100$, no significant differences were found in throat-related symptoms ($p=0.13$), fever ($p=0.16$) or overall physical condition ($p=0.30$).

From patient e-mail responses and medical records, a subgroup analysis for minor symptoms (subtle throat pain, common cold, slight temperature) was completed. Minor symptoms during the 56-day study period were experienced by 16 patients in the combination group and 18 patients in the penicillin group, with a mean (SD) occurrence of 19 (12.0) and 24 (12.5) days after the beginning of the intervention, respectively. No difference was found between the groups when comparing these patients to patients with no symptoms during the study period ($p=0.518$).

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The adverse effects (gastrointestinal symptoms, neurological symptoms and rash) were analysed as additional outcomes. The mean (SD) duration of nausea and diarrhoea for the combination and penicillin groups, respectively, was 2.4 (3.2) days and 1.3 (2.7) days ($p=0.01$), headache and dizziness 1.3 (2.1) days and 1.2 (2.3) days ($p=0.77$) and rash 0.3 (1.1) and 0.2 (1.2) ($p=0.37$) (Figure 4).

Figure 4. Number of days (y-axis) the patient reported gastrointestinal or neurological symptoms during the first 14 days in the combination group (penicillin + metronidazole) and in the penicillin group (penicillin + placebo) (Study IV).



6 DISCUSSION

6.1 Demographics of PTA patients

We examined PTA patients both prospectively and retrospectively. Incidences of peritonsillar infection (58/100 000) and of PTA (46/100 000) in our investigation were in line with the literature (Marom et al. 2010, Klug et al. 2009, Klug 2014). Median duration of symptoms before admission was five days, which is in accordance with earlier findings (Klug et al. 2009, Stringer et al. 1988). The retrospective study (III) included PTA patients aged six years or older. For the prospective randomisation study (IV), we excluded patients under 18 years of age and who otherwise did not meet the inclusion criteria. The median age of participants in that study was 31, slightly higher than in the literature (Sunnegren et al. 2008, Hanna et al. 2006), but is explained by the fact that only adults were included.

Of the 200 patients in study IV, 55% were male and 40% were smokers. In the retrospective study (III) 53% were male. These proportions are consistent with other studies (Marom 2010 et al., Gavriel et al. 2009, Hanna et al. 2006), even though our study populations of PTA patients were narrowed. On the other hand, in some recent studies a clear male predominance (3:1) has been seen (Matsuda et al. 2002, Ong et al. 2004), which was not evident in our study populations. This predominance may partly be due to higher smoking rates among men in Eastern Asia; for example, the smoking prevalence in Japan is 40% among males and 10% among females. A similar difference between genders in the Finnish population is not seen; among Finns between the ages of 15 and 64, smoking rates for males (19%) and females (13%) are more similar (National Institute of Health and Welfare). Smoking among PTA patients in study IV was clearly higher (40%) than the general population. In the Danish population, a similar difference between the general population (mean overall rate, 27%) and PTA patients was seen; among the Danish PTA patients, 32% of females and 40% of males were smokers (Klug et al. 2013), showing less of a gender difference than in Japan.

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Many studies show the predominance of female PTA patients at earlier ages with men beginning to predominate after age 30 (Love et al. 2011, Risberg et al. 2008, Klug 2014, Windfur et al. 2015, Bovo et al. 2016). In our investigation, such calculations were not performed. It has previously been demonstrated that among teenagers, TEs are performed more often on girls (Mattila et al. 2001), which may partly explain the increase of male incidence later. Whether this is associated with differences in hormones or smoking rates warrants further research.

According to the retrospective study (III), computing only those patients who ended up having a TE after recurrence of PTA, the recurrence rate was 16.5%. When addressing this issue, one major problem encountered is the definition of recurrence in the literature. Some authors define it as a residual of the same PTA episode (not a recurrence) when the patient is re-admitted within one month (Wang et al. 2014). This definition causes discrepancies when comparing studies. Often, studies compare two different treatment modalities. An encompassing review by Johnson et al. (2003) showed no difference in recurrence rates between the different surgical modalities for PTA. Since we did not include the group of patients treated at outpatient clinics after a recurrent PTA, our study's PTA recurrence rate might be biased slightly lower than normal, however, our result (16.5%) is in the middle of the range of the 8-22% reported by other studies (Herzon 1995, Savolainen et al. 1993, Schechter et al. 1982, Stringer et al. 1988, Ophir et al. 1988, Herbild et al. 1981, Nielsen et al. 1981a). Because our ORL unit most often performs a TE on a patient after their second episode of PTA, a minor bias exists.

6.2 Microarray as bacterial identification tool

The microarray method did not achieve bacterial identification rates as high as traditional bacterial culture, which has identified bacteria in up to 96-98% of samples (Jousimies-Somer et al. 1993, Cherukuri et al. 2002) as well as being able to identify multiple bacteria in up to 87% of cases (Jokinen et al. 1985). However, there is wide variation in these findings and our results match up quite well with most of the earlier studies (Gavriel et al. 2009, Jousimies-Somer et al. 1993). In our study, 11% tested

negative, which may partly be due to sample diversity and incomplete adjustment of the microarray method. With serum and joint fluid samples, a sensitivity as high as 95% has been reached (Tissari et al. 2010). Only 13% of our samples were polybacterial, which may partly be explained by competition from multiplication, although, as many as five bacterial species have been identified simultaneously (Tissari et al. 2010) and up to 60 bacterial species are included in the panel (Järvinen et al. 2009). Due to the microarray being unable to identify 64 of the samples, DNA sequencing was employed, however, DNA sequencing allows for only one identification at a time, so this may have affected the results. One problem interfering with the traditional culture method is the possible influence of preadmission antibiotics on the results. Such a problem does not exist with the microarray method, since it detects the DNA of dead bacteria as well. When assessing pathogens in joint fluid, microarray has been proven to be even more accurate than traditional culture (Metso et al. 2014). Even though our data included no positive *mecA* samples, the susceptibility of bacteria to antibiotics remains an important additional advantage to this method (Zhu et al. 2007, Tissari et al. 2010). Despite a desire for further method adjustment, these findings are similar to those in the literature. Since the method is much more rapid than traditional culture, this method can be considered a promising tool for future pathogen detection directly from pus (Metso et al. 2014).

6.3 Bacterial findings of PTA

Our results support previous findings of GAS and FN being the most prevalent bacteria in PTAs (Plum et al. 2015, Mitchelmore et al. 1995, Rusan et al. 2009, Klug et al. 2009, 2011). *Prevotella* spp. was the third most prevalent, similar to earlier studies (Jousimies-Somer et al. 1993, Suzuki et al. 2015, Klug et al. 2011), but its role in the pathogenesis of PTA is uncertain. Focus on the prominence of SMG in PTA patients began decades ago (Jousimies-Somer et al. 1993, Mitchelmore et al. 1995) and has remained of interest (Hidaka et al. 2011). SVG was shown to be frequently present also in non-abscessed TE patients, but SMG was not assessed separately in this highly comprehensive study (Klug et al. 2011). Pathogenic synergy of SMG with anaerobes, especially *Prevotella* spp., has been seen in pneumonia (Shinzato et al.

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1994). *Peptostreptococcus*, *Haemophilus influenzae* and *Staphylococcus aureus* were also found with high frequency, as in earlier studies, but were often found as polymicrobial growth and their role in PTA development remains unclear (Klug et al. 2009, Hidaka et al. 2011, Jousimies-Somer et al. 1993, Mitchelmore et al. 1995, Powell et al. 2013).

In summary, recent studies (Powell et al. 2013, Hidaka et al. 2011, Klug et al. 2009, 2011) have paid the most attention to GAS, FN and SMG, thus, these three bacterial groups and their association with special features of PTA patients are addressed in more detail in the next section.

6.4 Diversity of findings among different patient groups

It would be beneficial to be able to identify different subtypes of PTA, as this may influence the type of treatment chosen. Smoking has been associated with a higher incidence of PTA in many studies (Dilkes et al. 1992, Kilty et al. 2008, Lehnert et al. 2005, Marom et al. 2010, Hidaka et al. 2011, Klug et al. 2013). As we have learned from previous studies, smoking alters the oral and nasopharyngeal bacterial flora, which could predispose smokers to PTA (Brook 2005, 2007, 2011a, 2011b). The association of smoking with certain bacteria has been studied only recently. The prevalence of SVG, in particular SMG, among PTA patients who smoke seems higher than other bacteria (Marom et al. 2010, Hidaka et al. 2011, Klug et al. 2013). In our study (I), only three of 12 SMG patients were smokers, and no difference was found when compared with GAS or FN patients. Smoking could be strongly bound to aetiological and epidemiological differences in age, gender and geographical location. Also, patients' self-reported habits can vary and the definition of a smoker may vary by individual. As noted in two previous studies, a more precise definition (cigarettes per day, period of smoking) is needed (Klug et al. 2013, Hidaka et al. 2011). Since there are difficulties in the ability to assess the effects of passive smoking and of previous smoking, Hidaka proposes measuring blood nicotine levels (Hidaka et al. 2011).

Interestingly, SMG has recently been associated with male gender (Hidaka et al. 2011, Han et al. 2001, Hirai et al. 2005). Whether this is due to hormonal factors or

smoking habits remains unanswered. In our study (I), all but one of the twelve patients with SMG were male, but comparison with FN and GAS patients showed no significant difference ($p=0.05$). Among the 20 patients in the randomisation study (IV) who experienced recurrence, all five patients who had SMG co-existing with *Prevotella oralis* were male. SMG's co-existence with *Prevotella* spp. has also been noted earlier (Shinzato et al. 1994), which makes this male patient group, with the bacterial combination described above interesting, and further investigation is required.

In several previous studies, FN has been associated with younger patients, and GAS more often with patients over 30 (Klug et al. 2009, Klug 2014, Yusuf et al. 2015); this was our result as well. An older Finnish study (Jousimies-Somer et al. 1993) demonstrated a higher frequency of FN in patients with previous tonsillar infections, but this was not confirmed in our study. Also, stronger immunological responses associated with FN have been found (Klug et al. 2009, Yusuf et al. 2015), which is in agreement with the finding that our patients with FN suffered from more severe symptoms. In a study from Israel, more severe symptoms were seen in elderly patients, but FN was not reported at all (Marom et al. 2010). Patient group over 40 years of age has shown to have worse dental status and more comorbidities compared to younger PTA patients (Mazur et al. 2015a). PTA in older patients may also occur with more subtle symptoms and findings, and a higher incidence of inferior pole PTAs may be seen (Franzese et al. 2003, Monobe et al. 2007). This means further study and more focused medical attention is required for certain populations of PTA patients, namely, young patients with severe symptoms and possible FN, as well as, elderly male smokers with dental problems and possible SMG. Whether smoking, age, comorbidities (diabetes, asthma, cardiovascular disease) or possible medications are associated with changes in salivary flow resulting in changes in oral flora, is an area of study that has not been explored.

6.5 Treatment differences in four Nordic countries

A respective response rate of 90% was achieved in the survey study (III), which may partly be due to the straightforward web-based survey protocol. Interestingly, but not

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unexpected, great variation in treatment modalities of PTA was found even between the closely related Nordic countries. The greatest differences were seen between Denmark and Sweden in p.o. vs. i.v. administration and use of one vs. multiple antibiotics. In Sweden, most PTA patients over age 16 are treated as outpatients (91%), most of those being prescribed p.o. penicillin (78%). In Denmark, p.o. penicillin is the first choice in less than 10% of cases, however, metronidazole combined with penicillin is prescribed in over half (58%) of the cases. Local bacterial findings and susceptibility patterns may affect the choice of treatment, although according to ours and other studies, at least Denmark and Finland have a similar PTA pathogen spectrum (Jousimies-Somer et al. 1993, Klug et al. 2009).

Also, great variation was seen between immediate vs. interval TE and outpatient vs. inpatient care. In most countries, if TE is accomplished, it is most often performed after a recovery period, however, in Denmark, most TEs are performed immediately. While shown to have some advantages over interval TE (Fagan et al. 1994, Nielsen et al. 1981b, Lockhart et al. 1991) due to a lack of resources it may be impossible to provide immediate TEs (especially in smaller hospitals), therefore, interval TE is sometimes advisable. As shown in several studies, older people do not necessarily benefit from a TE (Nielsen et al. 1981a, Herbild et al. 1981). Among these patients, if TE is necessary, a one-sided TE (reducing the post-operative bleedings by half) could be considered. Afterwards, smoking cessation and a dental visit to check the third molars are advisable. A Danish group showed pathogens as occurring on both the affected and non-affected sides, which indicates that once the pathogens are present, other factors (e.g. salivary duct blockage) may lead to the actual abscess formation (Klug et al. 2011).

Re-openings of the abscess cavity were performed by most of the respondents (80%), which can be considered high since recurrences have been described in only 10% of PTA patients (Herzon 1995). In all four countries, most PTA patients under the age of seven end up having a TE. According to recent studies, a more conservative approach could be considered for this age group (Kim et al. 2015), which comes back to our assertion that different patient subgroups should have different treatment modalities. Whether pediatric patients gain long-term benefits from more

conservative treatment warrants cost-effectiveness studies, comparing different treatment modalities in this age group.

6.6 TE after PTA

Consistent with many other studies (Nielsen et al. 1981a, Herbild et al. 1981, Powell et al. 2012), our results reinforce the understanding that not all PTA patients require a TE. Therefore, immediate TE should not be the first-line treatment for all PTA patients, nor should every PTA patient to be scheduled for an interval TE. It is sometimes evident that immediate TE is required (limited co-operation or incomplete recovery), but in most cases, polyclinical drainage or conservative treatment and a wait-and-see strategy is more advisable. Several studies have shown that young age and previous tonsillar infections increase the risk of a later TE (Herbild et al. 1981, Wang et al. 2014, Nielsen et al. 1981a), although some discrepancy on this remains (Shaul et al. 2015, Wolf et al. 1994). To gain immediate pain relief and avoid multiple sick leaves, immediate TE could be offered to the appropriate patients, provided the required personnel is available to perform the surgery.

On the other hand, as shown in our study and others (Nielsen et al. 1981a, Herbild et al. 1981), patients over age 30 (or 40) require TEs less often than younger ones. This may be due to PTAs that are more salivary gland-based, since smoking and periodontal disease are predominant in the older patient population (Mazur et al. 2015a), however, this theory is currently mostly speculation. A history of tonsillar infections per se does not warrant a TE either, since PTA may not be a complication of AT at all, but instead a complication of salivary gland infection (Passy 1994). It should also be noted that PTA may occur even after a TE, therefore, previous PTA alone should not be an indication for a TE either (Farmer et al. 2011). PTA occurring after a TE has been thought to be mostly due to tonsillar remnants after an incomplete TE, but as shown by a German study group, this is not always the case; out of 31 PTA patients with a previous TE, 11 patients were not found to have any remnants of tonsillar tissue (Windfur et al. 2015).

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A study group from Israel showed that elevated pus amylase levels occurred more frequently in PTA than in dental abscesses (El-Saied et al. 2014) and that this elevation was seen only among the first occurrence of PTA (El-Saied et al. 2010). One could speculate that reoccurring PTA is more often a complication of AT, which supports the decision of a TE. One theory suggests that, once affected, the salivary glands lose their functionality due to scarring and their ability to flush the tonsils clean is diminished. As a result, the affected tonsil(s) more easily develop recurrent PTA as a complication of AT. Another theory suggests that because of scarring, the amylase levels cannot be measured in recurrent PTA. A study group from Thailand examined tonsillectomised PTA patients and reported that, in contrast to the non-affected side, there were no salivary glands on the affected side of two of three tonsils. This supports the theory of damaged glands predisposing the patient to infection on the side previously suffering a PTA (Kraitrakul et al. 2011). A Finnish study group showed, with immunofluorescence, a reduction in the levels of IgA in PTA pus, which could reflect a blockage or damage to IgA-secreting cells (Lilja et al. 1998). Future studies should address the question of whether the first occurrence of PTA is more often associated with salivary gland infection than with a preceding tonsillitis. This emphasizes the fact that a TE should not be routinely performed after the first PTA.

6.7 Antibiotic treatment of PTA

Penicillin is an inexpensive and usually well-tolerated drug, effective against most PTA-causing bacteria. Our study (IV) is in agreement with earlier findings of penicillin being sufficient, when treating generally healthy adult patients as outpatients (Herzon 1995, Maharaj et al. 1991, Tuner et al. 1986, Sexton et al. 1987). In our study, 10% of PTA patients required further attention, which also agrees with earlier studies (Herzon 1995, Wolf et al. 1994). In our unit, according to hospital guidelines, most patients are discharged with p.o. penicillin and metronidazole without scheduled re-openings, which saves hospital resources. From now on, if penicillin alone is prescribed for treatment of PTA, then the patient must be informed of possible complications and alerted that if their symptoms get worst they should contact their clinic immediately. In older patients with smoking and poor oral

hygiene, more broad-spectrum antibiotics are still probably needed. A study group from Israel showed an advantage of broader spectrum antibiotics over penicillin on PTA patients treated with NA (Shaul et al. 2015). Whether outpatient treatment with p.o. penicillin is sufficient for full recovery among patients treated with NA or patients having PTC (where no clear accumulation of pus is found) remains unknown.

6.8 Limitations of the study

The lack of use of traditional bacterial culture in the study I could be considered a clear limitation. Results would have made more impact and been more comparable with other studies, if the samples were also tested using traditional culture for comparison and confirmation. However, since sample-taking procedures are not in clinical use in our unit, the collection and analysis would have increased the study costs and duties for personnel. Another limitation is the retrospective nature of study III, but, to create a prospective study to investigate the same study questions would be time-consuming and expensive, which may override the benefit. Also, the selection of only PTA patients this study III would have made our results more clear. In study IV, one limitation is the lack of proper compliance monitoring, but to organise the same size study with 100% compliance would require a great amount of additional resources.

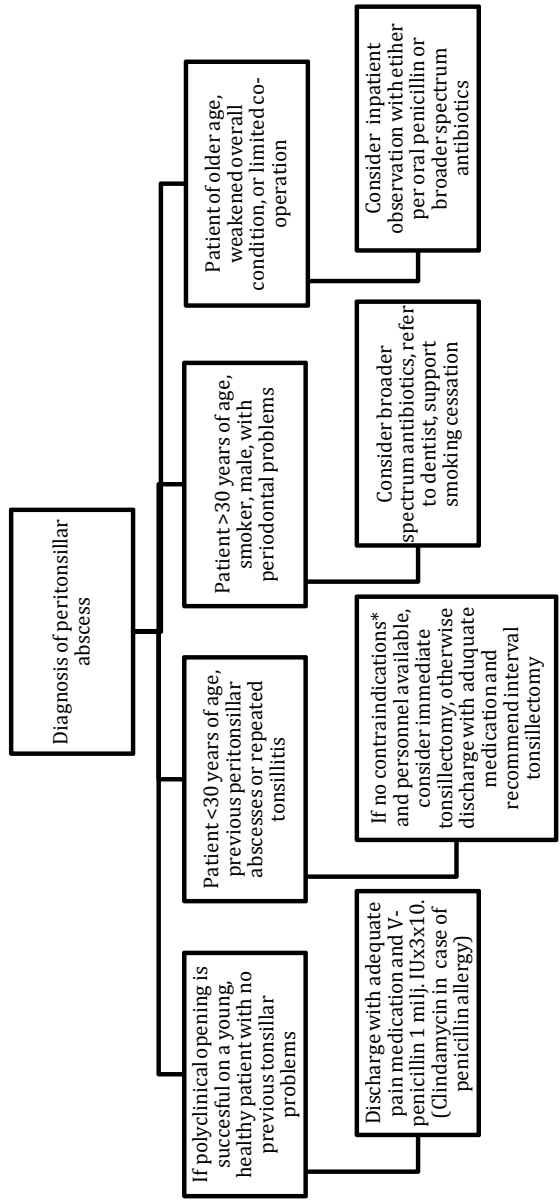
6.9 Future aspects

Many topics addressed here warrant further research. First, the microarray method, which initially appears to be a promising tool, should be tested with control cultures to verify the results, and the method should be adjusted to better accommodate the diversity of samples. This rapid identification method could change the empiric treatment of PTA and other abscesses to be more evidence based. Other focuses for future research include investigating patient characteristics such as age, dental health, smoking and salivary flow to potentially define clinically different PTA subgroups. Certain patient groups should be educated regarding smoking cessation

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and better oral hygiene (Figure 5). Penicillin as a monotherapy should be introduced into other Nordic countries, as it is already widely used in Sweden. Unification of treatment modalities for PTA should be attempted. Finally, cost-effectiveness of individual treatment modalities should be addressed.

Figure 5. An algorithm for the treatment of PTA based on our studies and those previous



*bleeding disorder, anaesthetic contraindication

The present series of studies investigated the bacterial aetiology and different treatment modalities of peritonsillar abscess (PTA).

The main findings are as follows:

1. *Fusobacterium necrophorum* and Group A *Streptococcus* are the most prevalent bacteria found in PTA. Bacterial microarray is a valid and suitable method for identifying bacteria directly from pus aspirates, although detailed adjustment is required.
2. Further analysis of the bacterial findings of PTA reveals that *Fusobacterium necrophorum* is associated with younger PTA patients and more severe symptoms.
3. Large variation, both nationally and internationally, in the treatment of PTAs is observed upon analysing questionnaire data from four closely related Nordic countries.
4. Analysis of patients who undergo a tonsillectomy within five years of a PTA diagnosis, shows that young age and prior tonsillar infections are factors recommending performance of a tonsillectomy on a PTA patient.
5. Compared with penicillin alone, metronidazole neither enhances recovery nor prevents recurrence of PTA when combined with penicillin. Instead, it increases undesired adverse effects.

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APPENDIX

Appendix 1. Symptom diary

I. Soreness of throat ()

- 0) My throat is not at all sore.
- 1) My throat is somewhat sore.
- 2) My throat is very sore.

II. Difficulty or pain on swallowing ()

- 0) No difficulty swallowing and slight pain at most.
- 1) No difficulty swallowing, but it is clearly painful.
- 2) Pain makes swallowing impossible or almost impossible.

III. Difficulty or pain on opening the mouth ()

- 0) Opening the mouth is easy and painless.
- 1) Opening the mouth is somewhat painful and I cannot open it fully.
- 2) Opening the mouth is very difficult and painful.

IV. Fever ()

- 0) My temperature is normal.
- 1) I believe I have a temperature, but I have not measured it.
- 2) I have fever. How high? ____

V. General condition ()

- 0) I feel healthy and able to perform my daily tasks.
- 1) I feel moderately fine, but I cannot perform my daily tasks as well as usual.
- 2) I am clearly ill and unable to do much anything.

VI. During the past 24 hours I have had () (several options may apply)

- A) Diarrhoea, nausea or other symptoms concerning the digestive tract
- B) Dizziness or headache
- C) Rash
- D) Pain that I have treated with painkillers

Other issues related to your health or general condition that you wish to bring to the research physicians' attention:

Appendix 2. Multiple-choice questionnaire

1. How do you treat a peritonsillar abscess at the emergency department when the patient is under 7 years of age?

- a) Lance it with scalpel and forceps (incision)
- b) Drain it by aspirating it in one or more places
- c) Nothing, the abscess will be lanced under general anaesthesia in connection with a tonsillectomy
- d) Nothing; the abscess will be lanced under general anaesthesia, but a tonsillectomy will not be performed
- e) Other (please specify)

2. How do you treat a peritonsillar abscess at the emergency department when the patient is between 8 and 15 years of age?

- a) Lance it with scalpel and forceps (incision)
- b) Drain it by aspirating it in one or more places
- c) Nothing, the abscess will be lanced under general anaesthesia in connection with a tonsillectomy
- d) Nothing; the abscess will be lanced under general anaesthesia, but a tonsillectomy will not be performed
- e) Other (please specify)

3. How do you treat a peritonsillar abscess at the emergency department when the patient is over 16 years of age?

- a) Lance it with scalpel and forceps (incision)
- b) Drain it by aspirating it in one or more places
- c) Nothing, the abscess will be lanced under general anaesthesia in connection with a tonsillectomy
- d) Nothing; the abscess will be lanced under general anaesthesia, but a tonsillectomy will not be performed
- e) Other (please specify)

4. Do you usually treat peritonsillar abscess patients of under 16 years of age

- a) = As outpatients
- b) = As inpatients

5. Do you usually treat peritonsillar abscess patients of over 16 years of age

- a) = As outpatients
- b) = As inpatients

6. How often do you drain the opened abscess cavity later on (drainage)?

- a) Daily until there is no more pus
- b) Every other day until there is no more pus
- c) Only as necessary
- d) I do not drain them
- e) I use other methods

7. When do you perform a tonsillectomy due to a peritonsillar abscess? You may choose more than one option.

- a) Always
- b) If the patient is under 7 years of age
- c) If the patient is between 8 and 15 years of age
- d) If the abscess cannot be opened under local anaesthesia
- e) If the peritonsillar abscess recurs
- f) If the healing process is delayed
- g) If the patient has bilateral abscesses
- h) If the peritonsillar abscess coincides with mononucleosis
- i) If the patient has had several cases of tonsillitis before developing the peritonsillar abscess
- j) Other reasons or comments

8. If you decide on tonsillectomy, how soon after diagnosing the peritonsillar abscess do you attempt to perform tonsillectomy on a patient under 7 years of age?

- a) Within 24 hours
- b) Within 1-3 days
- c) Within 4-7 days
- d) Within a month
- e) Within three months
- f) Within six months
- g) Depends on the indication for surgery (please specify)

9. If you decide on tonsillectomy, how soon after diagnosing the peritonsillar abscess do you attempt to perform tonsillectomy on a patient between 8 and 15 years of age?

- a) Within 24 hours
- b) Within 1-3 days
- c) Within 4-7 days
- d) Within a month
- e) Within three months
- f) Within six months
- g) Depends on the indication for surgery (please specify)

10. If you decide on tonsillectomy, how soon after diagnosing the peritonsillar abscess do you attempt to perform tonsillectomy on a patient over 16 years of age?

- a) Within 24 hours
- b) Within 1-3 days
- c) Within 4-7 days
- d) Within a month
- e) Within three months
- f) Within six months
- g) Depends on the indication for surgery (please specify)

11. If the abscess cannot be drained under local anaesthesia and you decide on tonsillectomy, how soon after diagnosing the peritonsillar abscess do you attempt to perform it?

- a) Within 24 hours
- b) Within 1-3 days
- c) Within 4-7 days
- d) Within a month
- e) Within three months
- f) Within six months
- g) In our hospital, tonsillectomy is not usually performed in such cases

12. If the patient has had recurring peritonsillar abscesses and you decide on tonsillectomy, how soon after diagnosing the peritonsillar abscess do you attempt to perform it?

- a) Within 24 hours
- b) Within 1-3 days
- c) Within 4-7 days
- d) Within a month
- e) Within three months
- f) Within six months
- g) In our hospital, tonsillectomy is not usually performed in such cases
- h) Depends on the age of the patient or other factors (please specify)

13. If the patient has a bilateral abscess and you decide on tonsillectomy, how soon after diagnosing the peritonsillar abscess do you attempt to perform it?

- a) Within 24 hours
- b) Within 1-3 days
- c) Within 4-7 days
- d) Within a month
- e) Within three months
- f) Within six months
- g) In our hospital, tonsillectomy is not usually performed in such cases
- h) Depends on the age of the patient or other factors (please specify)

14. Do you primarily treat peritonsillar abscess patients with

- a) = oral antibiotics?
- b) = IV antibiotics?

15. Do you primarily treat peritonsillar abscess patients with

- a) = a single antibiotic?
- b) = multiple simultaneous antibiotics?

16. I usually prescribe the following antibiotic regimen to a peritonsillar abscess patient (select one)

- a) oral penicillin
- b) oral cephalosporines
- c) oral clindamycin
- d) oral macrolides
- e) oral penicillin + metronidazole
- f) oral cephalosporine + metronidazole
- g) IV penicillin
- h) IV cephalosporines
- i) IV clindamycin
- j) IV penicillin + metronidazole
- k) IV cephalosporine + metronidazole
- l) other, which?

17. Have treatment practices of peritonsillar patients in your hospital changed during the past three years? You may choose more than one option.

- a) Yes, tonsillectomies are performed less frequently.
- b) Yes, tonsillectomies are performed more frequently.
- c) Yes, medication is now supplemented by an antibiotic substance against anaerobic bacteria.
- d) Yes, patients are hospitalised less frequently.
- e) Yes, patients are hospitalised more frequently.
- f) Yes, hospitalisation periods have been shortened.
- g) Yes, hospitalisation periods have been extended.
- h) Yes, routine drainage is performed less frequently.
- i) Yes, routine drainage is performed more frequently.
- j) Yes, abscesses are now drained by aspirating.
- k) Yes; (please specify)

18. Which hospital district do you work in?

19. How many otorhinolaryngologists are there in your otorhinolaryngology unit?

20. How many doctors in your unit are specialising in otorhinolaryngology?

21. Have you participated in training on peritonsillar abscesses during the past three years?

22. In your opinion, where are the majority of peritonsillar abscess cases in your hospital district treated?

23. Does your hospital have consistent treatment practices for peritonsillar abscesses?

24. Do you wish to raise other issues regarding the treatment of peritonsillar abscesses at your hospital or to give feedback on the questions above?

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