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Predisposing Factors, Changing Characteristics, and Advanced Diagnostics

Jarno Velhonoja

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To my family

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ABSTRACT

Deep neck infections are most commonly caused by spreading of odontogenic or tonsillopharyngeal infections. They are often purulent inflammations or abscesses of the floor of the mouth or fascial planes of the neck. Intravenous antimicrobial therapy and even surgery is often warranted to manage these infections. Cross-sectional imaging using computed tomography or magnetic resonance imaging is crucial when planning surgery and assessing the extent of the infection.

This clinical study of 277 patients retrospectively reviewed aggravating factors, complications, and microbiological etiology between 2004 and 2015. It also evaluated the feasibility of using magnetic resonance imaging as a primary imaging modality in cases of acute neck infection. The results showed that deep neck infections are a growing problem and that the proportion of odontogenic infections has increased significantly. The mortality rate was 1.4% and complications were observed in one in five patients. Magnetic resonance imaging was found to be a feasible and accurate diagnostic tool when neck infection was suspected.

Pediatric deep neck infections are more rarely encountered and are more often caused by pharyngeal or lymph node infections than dental infections. The study showed that faster surgical treatment significantly shortened the length of hospital stay among children. In addition, to ensure adequate diagnostics, the importance of obtaining cross-sectional imaging instead of ultrasound was emphasized in cases of suspected deep neck infection. In the prospective part of the study, preventive and predisposing factors and causes of severity were analyzed. The study confirmed that poor oral hygiene and limited access to dental care were background factors of infections requiring hospital treatment. Patients who frequently used acute dental care services were a particular risk group. In this study, dental infections, especially manifestations of advanced caries, were the main origin of adult deep neck infections that require hospital treatment, although these are often preventable. Thus, investments in good oral health, education, and adequate access to basic dental care could help reduce the economic burden, complications, and mortality caused by these infections.

KEYWORDS: Deep neck infections, abscess, acute neck imaging

TURUN YLIOPISTO
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TIIVISTELMÄ

Kaulan syvä infektio on usein hammas- tai nieluperäisen tulehduksen edetessä ilmenevä jopa henkeä uhkaava bakteeri-infektio. Se on märkäinen infektio, joka etenee tyypillisesti suunpohjan tai kaulan sidekudoksen välitiloissa. Hoitona käytetään suoneen annettavia antibiootteja sekä suun, leukojen ja kaulan alueen kirurgiaa ja tarvittaessa tehohoitoa. Kuvantaminen ohjaa erityisesti kirurgista hoitoa ja leikekuvantaminen diagnostiikan alkuvaiheessa tehdään tietokonetomografialla tai magneettikuvantamisella.

Tässä potilastutkimuksessa selvitettiin retrospektiivisesti taudin kulkuun vaikuttavia tekijöitä, komplikaatiota ja mikrobiologiaa 277 potilaalla sekä magneettikuvantamisen käyttöä päivystyksellisessä kaulan kuvantamisessa. Tuloksena todettiin kaulainfektioiden olevan lisääntyvä ongelma ja hammasperäisten tulehdusten osuus oli kasvanut. Kuolleisuutta esiintyi vaikeasti sairastuneilla (1,4 %) ja komplikaatioita noin viidenneksellä. Kaulan magneettikuvauksen todettiin olevan käyttökelpoinen ja tarkka diagnostinen menetelmä kuvantamiseen myös päivystysaikana.

Lapsilla syvät kaulainfektiot ovat harvinaisempia ja yleisemmin nielu- ja imusolmuketulehdusten aiheuttamia kuin hammasperäisiä. Tutkimus osoitti, että nopeammin toteutettu leikkaushoito lyhensi merkittävästi sairaalahoidon kestoa. Riittävän tarkan diagnostiikan varmistamiseksi viiveetön leikekuvantaminen on usein tarpeen ultraäänen sijaan, kun epäillään syvää kaulainfektiota.

Tutkimuksen etenevässä osuudessa selvitettiin mahdollisia pahentavia ja ennaltaehkäistävissä olevia tekijöitä. Tutkimuksessa vahvistui huonon suuhygienian ja hammashoidon saatavuuden merkitys taustatekijöinä sairaalahoitoa vaativille infektioille. Erityisesti akuuttihammashoidon palveluita toistuvasti käyttävät potilaat olivat riskiryhmä. Koska karies ja sen eteneminen ovat ehkäistävissä, panostukset hyvään suun terveyteen, valistukseen ja riittävään hammashoidon saatavuuteen voivat auttaa vähentämään näistä infektioista johtuvia merkittäviä kustannuksia sekä komplikaatiota ja myös kuolleisuutta.

AVAINSANAT: Kaulainfektiot, kaulan syvät absessit, vaikeat hammasinfektiot, kaulan päivystyskuvantaminen

Table of Contents

Abbreviations

ADC	Apparent diffusion coefficient
AIDS	Acquired immune deficiency syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologists physical status
BMI	Body mass index
C	Celsius
CBCT	Cone beam computed tomography
CECT	Contrast enhanced computed tomography
CRP	C-reactive protein
CT	Computed tomography
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DNI	Deep neck infection
DNM	Descending necrotizing mediastinitis
DWI	Diffusion-weighted imaging
ENT	Ear, nose, and throat (specialty)
EUCAST	European Committee on Antimicrobial Susceptibility Testing
F.	*Fucobacterium*
FP	False positive
FN	False negative
GAS	Group A β-hemolytic streptococcus
HBO	Hyperbaric oxygen therapy
HDSWF	Hospital District of Southwest Finland
HIV	Human immunodeficiency virus
ICD10	The International Classification of Diseases 10th Revision
ICU	Intensive care unit
LRINEC	The Laboratory Risk Indicator for Necrotizing Fasciitis
LOS	Length of stay
MALDI-TOF	Matrix-assisted laser-desorption-ionization time-of-flight
MRI	Magnetic resonance imaging

MRSA	Methicillin-resistant *Staphylococcus aureus*
NF	Necrotizing fasciitis
NGS	Next-generation sequencing
OI	Odontogenic infection
OMF	Oral and maxillofacial
OPG	Orthopantomography
P.	Prevotella
PACS	Picture archiving and communication system
PCR	Polymerase chain reaction
PCT	Procalcitonin
PICU	Pediatric intensive care unit
PPV	Positive predictive value
RIS	Radiological information system
rRNA	Ribosomal ribonucleic acid
S.	*Streptococcus*
SAG	*Streptoccus anginosus* group
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SOFA	First ICU day Sequential Organ Failure Assessment
spp.	Species
Staph.	*Staphylococcus*
TE	Tonsillectomy
TN	True negative
UK	The United Kingdom
US	The United States
VAC	Vacuum-assisted closure
WBC	White blood cell count

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Velhonoja J, Lääveri M, Soukka T, Irjala H, Kinnunen I. Deep neck space infections: an upward trend and changing characteristics. *European Archives of Oto-Rhino-Laryngology*, 2020; 277: 863–872.

II Nurminen J, Velhonoja J, Heikkinen J, Happonen T, Nyman M, Irjala H, Soukka T, Mattila K, Hirvonen J. Emergency neck MRI: feasibility and diagnostic accuracy in cases of neck infection. *Acta Radiologica*, 2021; 62(6): 735–742.

III Velhonoja J, Lääveri M, Soukka T, Hirvonen J, Kinnunen I, Irjala H. Early surgical intervention enhances recovery of severe pediatric deep neck infection patients. *International Journal of Pediatric Otorhinolaryngology*, 202; 144:110694.

IV Velhonoja J, Lääveri M, Soukka T, Haatainen S, Al-Neshawy N, Kinnunen I, Irjala H. A prospective study of orofacial and neck infections with an emphasis on preventive and aggravating factors. *Manuscript.*

1 Introduction

Deep neck infections (DNIs) are severe bacterial infections occurring in the potential spaces of the neck. They usually have a rapid onset, and begin as cellulitis in the soft tissue close to the source of common upper aerodigestive tract infections. Orofacial infections are often related to odontogenic infections (OIs) and can potentially spread further via the fascial planes of the neck. The widespread use of modern antibiotics and improved dental hygiene and care are believed to be behind the decline of these infections over the decades of the last century. However, the downward trend may be coming to an end. According to a few recent reports from several different countries, the number of these infections is increasing (Fu et al., 2020; R. Hurley et al., 2018; Seppänen et al., 2010).

In 1836, a German physician, Wilhelm Frederick von Ludwig, described a condition now known as Ludwig's angina, "Angina Ludovici" (Ludwig, 1837; Wasson et al., 2006). Prior to this, this kind of condition was described in ancient Greek and Arab times, by Hippocrates, Galen, and Celsus, for example. It was characterized as a gangrenous induration of the neck, and as more fatal than comparable neck infections (T. T. Thomas, 1908). Its clinical presentation was a septic infection and a rapidly spreading swelling under the mandible and the floor of the mouth, causing respiratory distress, cyanosis and eventually death by asphyxiation. The odontogenic origin was widely accepted when T. Turner Thomas wrote his review on this entity in 1908.

The anatomy of the neck is challenging for surgery. The cervical fascia envelops the muscles and all the critical neurovascular structures. The deep layers of the cervical fascia predominantly surround the potential deep spaces of the neck. These spaces or compartments provide routes for the purulent infection to spread, usually towards lower resistance. Due to this, an ordinary peritonsillar abscess can enter the parapharyngeal space and from there the retropharyngeal space, extending to the mediastinum. Traditionally, incision and drainage have been the cornerstone treatment for pus, along with wide-spectrum parenteral antibiotics (Osborn et al., 2008).

Pediatric DNI is a relatively rare entity. It has its own typical features in terms of affected spaces and microbiological etiology. Odontogenic causes are rarely found, and infections originating from the lymph nodes are the most common cause. Surgical treatment is warranted in many cases, but the first-line period of non-surgical treatment seems to play a greater role in the treatment of uncomplicated and smaller abscesses than in adult cases (Lawrence & Bateman, 2017; Wilkie et al., 2019).

Infections cause edema, and swelling in the neck and the orofacial area, and can potentially threaten the airways. Prompt airway management with endotracheal intubation or a tracheostomy is often warranted (Tapiovaara et al., 2017). After securing the airways, correct utilization and timing of diagnostic imaging is crucial. Computed tomography (CT) has been the mainstay treatment but magnetic resonance imaging (MRI) is also a promising method for accurate diagnosis without ionizing radiation. Nevertheless, MRI of the neck in emergency settings has not yet been widely studied.

DNI is still a potentially lethal disease and requires aggressive diagnostics and therapeutic management. Diabetes (DM), older age, and immune deficiency are some of the known predisposing factors, although previously healthy patients may also encounter complications and have long hospital stays. The polymicrobial nature of these infections is well documented, but the more complex interactions and combined effects of these microbes are still not fully understood (Boscolo-Rizzo et al., 2012; Celakovsky et al., 2015; Parhiscar & Har-El, 2001). There is a lack of knowledge about why some cases escalate to severe clinical courses and have complex and even fatal consequences, and about how to prevent these.

2 Review of the Literature

2.1 Orofacial and deep neck infections

2.1.1 Pathophysiology and anatomy

The cervical fascia is a fibrous connective tissue which envelopes the structures of the neck, and its loose connections create potential spaces for infection to spread. Knowledge of the anatomy is crucial when planning surgical treatment and predicting the spread of the disease. The cervical fascia is commonly divided into superficial and deep layers. The deep layer is further divided into superficial (investing), middle (muscular, pretracheal, buccopharyngeal, visceral) and deep (prevertebral, alar) fascia (Oliver & Gillespie, 2010; Vieira et al., 2008). All the layers of the deep fascia are in contact with each other and form a carotid sheath that encases the common carotid artery, internal jugular vein, vagus nerve, and ansa cervicalis. The terminology for the spaces between the fascial layers in the face and neck vary somewhat in the literature, and other classifications have also been presented (Guidera et al., 2014).

The parapharyngeal space is also known as the lateral pharyngeal space or the pharyngomaxillary space. It is frequently described as an inverted pyramid or cone, with its cranial part at the skull base and caudally delineated by a submandibular space at the level of the greater cornu of the hyoid bone. It is medially outlined by pharyngeal constrictor muscles, and anterolaterally by the pterygoid muscles, the parotid gland, and the mandible. The prevertebral muscles and fascia limit the space posteriorly, and include the carotid sheath, depending on the definition. Some subdivisions have been proposed, but free communications between many of them have also been described, questioning their clinical significance (Guidera et al., 2014).

The retropharyngeal (retrovisceral) space is situated posterior to the pharynx and the esophagus (Figure 1). The space is laterally formed between the anterior alar fascia, the posterior buccopharyngeal fascia, and the carotid sheaths. The retropharyngeal space is united at the midline and has lymph node chains on each side. It extends from the base of the skull to approximately the level of the tracheal bifurcation where the alar and buccopharyngeal fascias fuse. The exact lower level varies in the literature between the sixth cervical (C6) and the fourth to sixth thoracic vertebrae (T4–T6) (Guidera et al., 2014). However, the retropharyngeal space provides a route for the infection to spread to the mediastinal level.

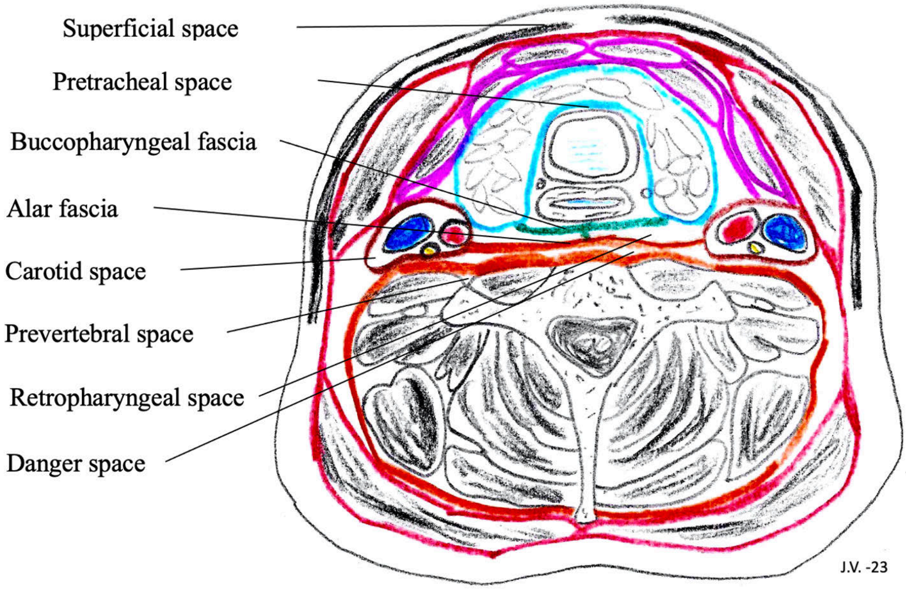

Figure 1. Anatomy of the neck spaces (cross section). Author's own drawing.

The danger space, also called the prevertebral space, is generally considered to lie posterior to the retropharyngeal space and anterior to the transverse processes of the vertebrae, extending from the skull base to the diaphragm or the coccyx. Two divisions of the deep layer of the deep cervical fascia (alar and prevertebral fascia) have loose areolar contents, which makes this space a potential route for life-threatening complications such as mediastinitis (Figure 2). (Oliver & Gillespie, 2010). The radiological distinction between a true retropharyngeal space abscess and a danger space abscess can be challenging or in some cases impossible in clinical settings (Hoang et al., 2011).

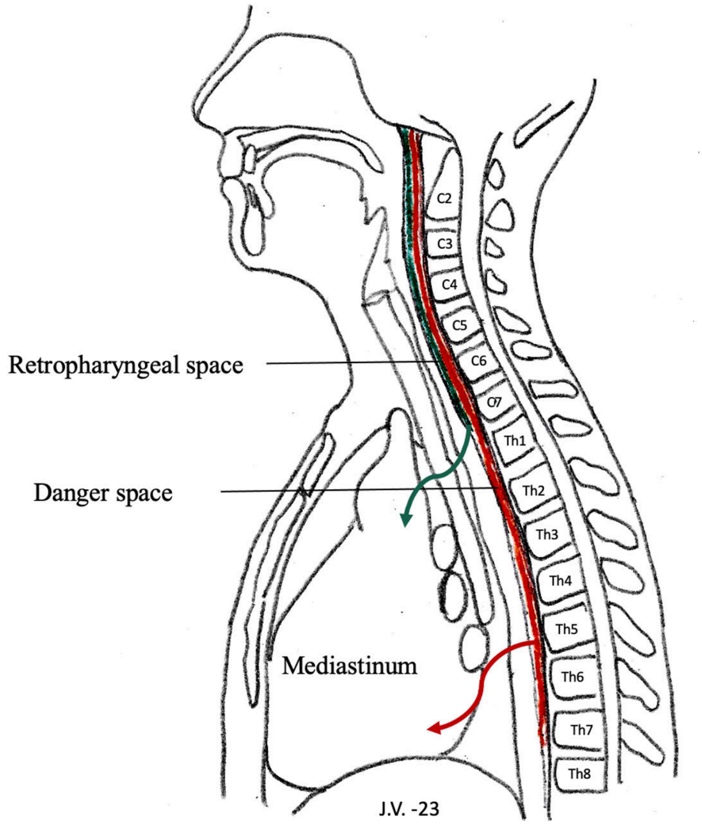

Figure 2. Anatomical relations and routes of spread from the retropharyngeal and danger spaces into the mediastinum. Author's own drawing.

The masticator space can be subdivided into the masseteric space, the pterygoid space and the temporal space and is enclosed by the divisions of the superficial layer of the deep cervical fascia. Its contents include these muscles of mastication and the mandibular divisions of the trigeminal nerve. Infections in the masticator space often originate from the third mandibular molars (Guidera et al., 2012; Vieira et al., 2008). Infections from the masticator spaces can spread into the infratemporal fossa or the orbit. Valveless venous communications between the maxillary, midface, and orbit regions with the cavernous sinus can enable a septic thrombophlebitis of the cavernous sinus which may lead to potentially fatal complications (Prabhu et al., 2015).

The buccal space is bordered by the buccopharyngeal fascia, which medially encases the buccinator muscle and laterally the skin of the cheek. The buccal fat pad is a direct continuation of the temporal fat pad and offers a route for the infection to spread. The classic picture of facial swelling typical in OIs arises from buccal space abscesses, which often originate from a periapical infection of the mandibular or maxillary premolars or molars.

The parotid space is formed by the superficial layer of the deep cervical fascia which encases the parotid gland lateral to the parapharyngeal space. The fascia around the deep lobe of the parotid gland is thin and a somewhat debatable functional barrier for preventing the spread of the infection into the parapharyngeal space. The parotid space contains the facial nerve, external carotid artery and retromandibular vein. Parotid space infections commonly originate from acute or chronic parotitis, sialolithiasis or occasionally from OIs of the masticator space (Guidera et al., 2012; Oliver & Gillespie, 2010; Vieira et al., 2008).

The submandibular space is often referred to as either sublingual (supramylohyoid) or inframylohyoid compartments. The sublingual space is above the mylohyoid muscle, but the spaces freely communicate over the posterior end of the mylohyoid muscle. The mucosa of the floor of the mouth forms the superior border and the hyoid bone the inferior border. The mylohyoid muscle line, as illustrated in Figure 3, in the medial aspect of the mandible forms a relative barrier between these two compartments. The roots of the second and third molars are located below this line, providing a direct route into the inframylohyoid compartment believed to contribute to severe infections (Flynn et al., 2006). This line also provides grounds for a surgical approach; an intraoral approach might be sufficient for a sublingual space abscess but an infection in the inframylohyoid submandibular space often requires an extraoral incision. Ludwig’s angina is a condition in which both supra- and inframylohyoid submandibular spaces are bilaterally affected by an abscess or fulminant cellulitis, typically causing a hard edema and an elevation of the tongue and often culminating in a compromised airway. The submental space lies between the anterior bellies of the digastric muscles and can also be seen as a medial subdivision of the submandibular space.

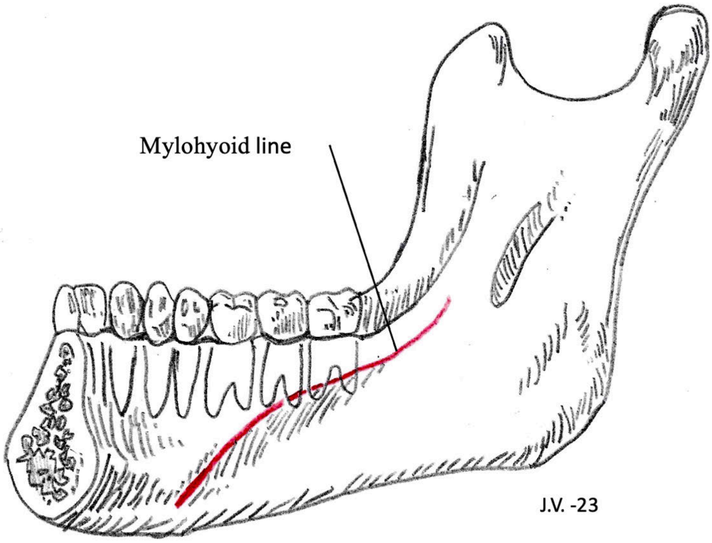

Figure 3. Mylohyoid line is shown in red. Author's own drawing.

The anterior visceral space (also pretracheal space) is formed by the structures coated by the middle layer of the deep cervical fascia. It extends from the thyroid cartilage to the superior mediastinum and contains the thyroid gland, larynx, esophagus, and trachea (Oliver & Gillespie, 2010).

The superior anterior mediastinum is a continuum of the pretracheal space and offers a route for the infection in the thyroid region to descend further into the thorax. The posterior mediastinum is characteristically affected when a retropharyngeal infection spreads to its lower limits of C6–T6 level. Several classifications have been proposed for descending mediastinitis. Based on computed tomography (CT) findings, superior infections above the tracheal bifurcation were defined as Type I, superior and anterior infections as Type IIa, and total anterior and posterior mediastinal infections as Type IIb (Endo et al., 1999). This classification does not include the solitary posterior mediastinum route. More recently, a modified classification has been suggested, defining anterosuperior infections as Type Ia, anterior infections as Type I, posterior mediastinum infections as Type II, and infection of the whole mediastinum as Type III (Guan et al., 2021).

2.1.2 Epidemiology

Many researchers state that DNIs are so much less common today due to the widespread use of antibiotics (Bottin et al., 2003; Marioni et al., 2010; Parhiscar & Har-El, 2001; Yang et al., 2008). However, in many Western countries, their incidence is increasing (Bottin et al., 2003; R. Hurley et al., 2018; Santos Gorjón et al., 2012; Seppänen et al., 2010; S. J. Thomas et al., 2008). It has been claimed that the causes for this increase are related to decreasing tonsillectomy (TE) rates and the rising number of dental abscesses (Lau et al., 2014; S. J. Thomas et al., 2008). Wang et al. (2015) described an increased incidence of DNIs among post-tonsillectomy patients, but whether patients with recurrent tonsillitis have a fundamental susceptibility to DNI remains unclear. An increased incidence of pediatric DNIs and retropharyngeal abscesses has also been reported (Cabrera et al., 2007; Novis et al., 2014). The overall incidence of DNIs is around 2.45 - 15 / 100 000 inhabitants per year (R. Hurley et al., 2018; Santos Gorjón et al., 2012).

Maxillofacial OIs that require hospital care are increasing significantly in many countries (Fu et al., 2020; Seppänen et al., 2010; Uluibau et al., 2005). Wennström et al. (2013) reported that edentulous women decreased from 18.2% to 0.3% in the 1968/69 and 2004/2005 Swedish cohorts, and this same trend has also been reported in Finland (Suominen-Taipale et al., 2008). Dementia is a growing problem in the aging Western population. Older people with dementia and full dentition, together with the increasing general population, may be behind the surge of infection cases (Delwel et al., 2017). Moreover, differences in accessing dental care services and the rising costs of these services have also been blamed for the increase in OIs (S. J. Thomas et al., 2008). Although odontogenic deep infections are less common among children than adults, these trends are worrying. A recent analysis showed that early childhood caries (among children under 5) is a growing burden in EU countries, with a prevalence of 37.2% (Bencze et al., 2021).

2.1.3 Special features of pediatric deep neck infections

Adults' and children's DNIs differ in clinical presentation, microbiology, and complications. Occasionally, the disease among children is stated to be its own entity (Baldassari et al., 2011; Maharaj et al., 2020).

The retropharyngeal lymph nodes are a chain of lymph nodes located on both lateral sides of the pharynx. They decrease in size with age, and in adults, the presence of retropharyngeal nodes can be a sign of a malignant disease (Ogura et al., 2004). Lymph nodes are part of the immune system; they filter substances, present new viral or bacterial antigens to the T-lymphocytes and produce specific immune cells as a response. In children, cervical lymphadenitis is a common disease and is usually believed to be due to pyogenic organisms such as *Staphylococcus aureus* or the *Streptococcal* species (spp.) being transported from the oropharyngeal mucosa or the skin to the lymph nodes (Nielsen et al., 2022). In general, these reactions can cause the lymph nodes to swell substantially, and can evolve into a significant distension, edema, or eventually necrosis. This necrosis can form an abscess, and in children a retropharyngeal abscess is one of the most common clinical presentations of DNI. Partly due to these anatomical differences, pediatric DNIs tend to primarily present with tonsillopharyngeal/upper respiratory tract symptoms and to involve one of the neck spaces, whereas among adults, multiple space involvement is more common (Coticchia et al., 2004; Maharaj et al., 2020).

Staphylococcus aureus, including methicillin-resistant *Staph. aureus* (MRSA), constitutes a significant part of bacterial culture findings among the pediatric population in many countries. The incidence of MRSA (3.2–66%) most probably reflects the general prevalence in the population (Cheng & Elden, 2013; C. M. Huang et al., 2017; Inman et al., 2008). It differs from adult DNIs, in which polymicrobial growth and the *Streptococcus viridans* group, together with anaerobes, play a much greater role (Klug et al., 2021). Complications may be rare among children due to their overall better healing tendency than that of adults (Baldassari et al., 2011).

2.2 Etiology and predisposing factors

2.2.1 Etiology

Before the era of modern antibiotics and dentist services, dental abscesses were listed as the fifth to sixth leading cause of death (Clarke, 1999). Moreover, at that time, 70% of DNIs were estimated to be of pharyngotonsillar origin (Parhiscar & Har-El, 2001). More recently, odontogenic origin (7.6–49.1%) has proven to be one of the most common etiologies of DNIs, alongside pharyngotonsillar causes (5–32.6%), of which bacterial and viral pharyngitis, tonsillitis, and peritonsillar abscess are common subgroups in the studies of 365 patients with DNI by Boscolo-Rizzo, and, of 106 by Daramola, then of 218 by Gehrke. Other frequently mentioned causes are sialadenitis, cervical lymphadenitis, otitis, sinusitis, epiglottitis, head and neck cancer, trauma, congenital neck cysts, intravenous drug abuse at the site of infection, and post-operative infection (Boscolo-Rizzo et al., 2012; Daramola et al., 2009; Gehrke et al., 2022). Ridder studied 234 patients and found that in 5.6% of patients, DNI was the first sign of a malignant disease, typically metastatic carcinoma of the head and neck or lymphoma, especially in the elderly population (Ridder et al., 2005). In Wang's material more than half of the cases they studied, the cause of infection remained unknown, but more recent studies report rates from 18.9% to 35% (Boscolo-Rizzo et al., 2012; Buckley et al., 2019; Daramola et al., 2009; Wang et al., 2003). A specific entity also worth mentioning is Bezold's abscess which is a deep neck abscess associated with mastoiditis and frequently concomitant cholesteatoma (40%). Typical features include bony erosion of the mastoid tip and the spread of the infection to the neck, between the sternocleidomastoid and digastric muscles (Valeggia et al., 2022).

2.2.2 Comorbidities

The majority of DNI patients have no significant underlying systemic diseases and the commonly mentioned diseases have varied in the published literature. Nonetheless, Boscolo-Rizzo (n=365) and T.T. Huang (n=185) have reported the frequency of associated diseases among DNI patients to be 22.5–34.1% in larger series (Boscolo-Rizzo et al., 2012; T. T. Huang et al., 2004). It is important to treat comorbidities as predisposing factors when exploring the reasons for the more severe and complex course of the disease.

2.2.2.1 Diabetes

Patients with DM are well known to be more prone to many infections. Their infections have more rapid and severe progression because of the immune dysfunction caused by hyperglycemia. DM is the most frequently (14.2–36.3%) reported comorbidity in DNIs and orofacial infections (Boscolo-Rizzo et al., 2012; Gujrathi et al., 2016). A higher risk of DNI has been reported in particular among patients with insulin-dependent DM (Chang et al., 2018). A meta-analysis by Hidaka et al. (2015) confirmed that DM is associated with complications and a more severe clinical course, supporting the claim of its role as a critical comorbid factor (Hidaka et al., 2015).

2.2.2.2 Obesity

Higher body mass index (BMI) is stated to lead to a more frequent need for intensive care (Riekert et al., 2019). Daramola et al. (2009) reported morbid obesity in 2.8% of DNI patients. Weise et al (2019) reported 16 patients with severe OI with septic progression, of whom six (37.5%) were also obese, although exact BMI was not mentioned. The current literature provides even stronger evidence that obesity is a risk factor for cervical necrotizing fasciitis (NF) (Gunaratne et al., 2018). The mean BMI of 26.9 kg/m^2 has been reported in DNI patients, which is within the definition of overweight (Gehrke et al., 2022). The strong association between obesity and the higher risk of hyperglycemia is well described, but the significance of obesity as an isolated risk factor for DNI remains undetermined.

2.2.2.3 Immunocompromised patients

Immunocompromised patients are generally considered more prone to infections. Studies have reported 4.6%–12.1% of DNI patients as immunocompromised (R. Hurley et al., 2018; Santos Gorjón et al., 2012). In a study by Furuholm et al. (2021), 19% of the patients hospitalized for severe OI were categorized as immunocompromised (DM was included). However, the hypothesis regarding more intensive care unit (ICU) treatment in this group was not confirmed. The pus samples of immunocompromised patients seem to have a wider spectrum of potential pathogens (Daramola et al., 2009). Moreover, immunocompromised patients have a five-day longer length of stay (LOS) on average (Santos Gorjón et al., 2012). Rheumatoid arthritis, which often requires immunosuppressive medication, has recently shown to be an independent predisposing factor (Chang et al., 2020). Some studies in the United States (US) have reported human immune deficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS) (0.9–15.2%) as a significant comorbidity (Daramola et al., 2009; Parhiscar & Har-El, 2001).

2.2.2.4 Other systemic diseases

Vascular diseases (7.3–14.5%) and hypertension (9.4–15%) have been repeatedly reported as associated systemic diseases, as have pulmonary (2.1–3.8%), liver (3.5–4.8%) and renal (0.8–9.5%) diseases (Boscolo-Rizzo et al., 2012; Daramola et al., 2009; T. T. Huang et al., 2004; Marioni et al., 2010).

2.2.2.5 Psychiatric morbidity and dementia

One meta-analysis of 334 503 patients has shown a link between poor oral health and psychiatric morbidity (Kisely et al., 2016). Psychiatric illness (10.4–13%) was among the most common comorbidities when this link was observed (Daramola et al., 2009; Seppänen et al., 2010). Dementia and the severity of cognitive decline also appear to affect the oral health of older people, with more plaque-related and oral disease among people with more cognitive decline (Delwel et al., 2018; Syrjälä et al., 2007) Nevertheless, the link between dementia and DNI has not been widely studied.

2.2.2.6 Alcohol, tobacco, and substance abuse

Intravenous substance abuse (12–22%) is a significant comorbidity in several series (Barber et al., 2014; Daramola et al., 2009; Parhiscar & Har-El, 2001). Tobacco smoking is a common habit among DNI patients, varying from 35.8%, as reported by Daramola; through 42%, as reported by Buckley; to 64.4%, as reported by O’Brien (Buckley et al., 2019; Daramola et al., 2009; O’Brien et al., 2020). This exceeds the percentage of smokers in the general population reported in Buckley’s study (Buckley et al., 2019). Smoking has also shown to be associated with acute teeth removal because of infection (Rautaporras et al., 2022). A few studies have found that excessive alcohol consumption and alcohol abuse (9–24.8%), frequently associated with smoking, is also a preceding factor (Furuholm et al., 2021; Gujrathi et al., 2016). From a broader perspective, excessive alcohol consumption has been found to generally impair the immune system through various molecular mechanisms, making it a risk factor for infections and wound healing (Trevejo-Nunez et al., 2015).

2.2.3 Sociodemographic factors

Male predominance in DNI patients is widely recognized in previously published literature and approximately two thirds of the patients are male (Boscolo-Rizzo et al., 2012; Eftekharian et al., 2009; L. Huang et al., 2015). A recent study of 4 741 patients which used data from the US national database, has confirmed that males have poorer oral health and oral hygiene habits, which may contribute to this gender difference in infection complications (Su et al., 2022). Since comorbidities tend to increase with age, it is reasonable that the prevalence of DNIs and orofacial infections is higher in older age. The median age has been reported as 49.5–52 years (Boscolo-Rizzo et al., 2012; T. T. Huang et al., 2004). Low level of education has also been associated with severe DNI (Barber et al., 2014). It is notable that socioeconomic inequalities affect the prevalence of caries in highly developed countries and the distribution of caries lesions is increasingly concentrated among a smaller proportion of disadvantaged individuals who have several other problems. Low socioeconomic position is also related to a higher risk of caries lesions, which could eventually lead to more severe infections (Bencze et al., 2021; Schwendicke et al., 2015).

2.2.4 Dental health-associated factors

Severe OIs are primarily caused by caries and an inflammatory reaction in the necrotic dental pulp causing a periapical infection that progresses to a periradicular disease such as a periapical abscess or a periradicular cyst. Pericoronitis, periodontitis and post-extraction infections are mainly localized in the lower molars and are recognized sources of infection (Boffano et al., 2012; Furuholm et al., 2022; Seppänen et al., 2011). As previously stated, anatomical reasons, such as the roots of the second and third lower molars extending below the mylohyoid line, are behind the unrestricted spread of infection to the submandibular space and further to the neck in these cases. Lower molars are the most frequent cause of OI, accounting for 26.6–36.5% of all cases (Cachovan et al., 2013; Haug et al., 1991; Katoumas et al., 2019; Sánchez et al., 2011).

Poor dental hygiene and a lack of routine dental care is common among patients with severe odontogenic infections. (Uluibau et al., 2005). Restricted access to preventative dental care is also believed to be behind the currently increasing number of OIs (Salomon et al., 2017). Many of the patients have previously obtained health care for the infection, but treatment is often inadequate, as 50–60% of patients only receive antibiotics (Gams et al., 2017; Uittamo et al., 2020). A multivariate analysis has shown that pre-admission antibiotics increase LOS, perhaps only briefly alleviating the symptoms and delaying definitive treatment (Gams et al., 2017). The aging of the population and today's elderly having full dentitions are also a challenge to oral health care.

2.2.5 Factors associated with severe infection

Australian researchers compared a cohort of severe OIs who were taken to operation theatre in 2003–2004 with a cohort treated in 2013-2014. Data from a total of 291 patients suggest that the severity of orofacial and deep neck infections is increasing (Fu et al., 2020). In 2014, Barber et al., analyzed 258 DNI patients in two tertiary hospitals in Canada. Those with a low level of education, living more than one hour from a tertiary care center, with their tonsils still intact, and with a *Streptococcus spp.* finding were at an increased risk of severe DNI (Barber et al., 2014). More recently, *S. anginosus* was found to be associated with more complicated clinical features of the disease (Furuholm et al., 2023). Age has also shown to be related to a more severe course of the disease, although not to the final outcome (Chi et al., 2014; Gehrke et al., 2022). Several risk factors for severe OIs have been proposed, such as an affected general health status, poor oral health, smoking, apical periodontitis, and HIV (Carey & Dodson, 2001; Furuholm et al., 2021, 2022; Seppänen et al., 2008, 2011).

Multispace or retropharyngeal location, ASA physical status (American Society of Anesthesiologists physical status) of III/IV, SAPS II (Simplified Acute Physiology Score) of >29, SOFA (First ICU day Sequential Organ Failure Assessment) of >2 were associated with severe diseases such as sepsis, mediastinitis, or NF in a retrospective study of DNI patients requiring ICU treatment (Garcia et al., 2012). ASA classification can be affected by the patient's septic state before the operation, whereas APACHE (Acute Physiology and Chronic Health Evaluation) II, SOFA and SAPS II take into account several diagnostic and laboratory parameters, and marginally also severe underlying diseases. In a Finnish retrospective cohort study of 60 hospitalized patients with OI, unfinished root canal treatments were found to enhance an infection spread (Grönholm et al., 2013). However, another study of 84 similar patients revealed that any dental treatment before hospitalization seemed to reduce the risk of severe infection (Seppänen et al., 2011). Moreover, infrahyoid involvement in non-odontogenic DNIs is considered a high-risk factor (Yuan & Gao, 2018).

In a multiple regression model, DM and vascular and pulmonary diseases were associated with mediastinal extension, as well as age of ≥55, C-reactive protein (CRP) of ≥300mg/l before treatment, a neutrophil to lymphocyte ratio of ≥13 (Celakovsky et al., 2014; Kimura et al., 2020). DM type 1 was proven to be an independent risk factor for longer hospitalization, mediastinal extension, and mortality in a population-based study (Chang et al., 2018). Other studies have found infection of the retropharyngeal, pretracheal and carotid space and initial CRP and procalcitonin (PCT) values to be the most sensitive predictors of necrotizing mediastinitis (Brajkovic et al., 2022; Gehrke et al., 2022). Moreover, immunocompromised status, DM, cirrhosis, arteriosclerosis, corticosteroid therapy, chronic renal failure, malignancy, intravenous drug abuse, obesity, alcoholism, and HIV are overexpressed in cervical NF patients (Gunaratne et al., 2018; Whitesides et al., 2000). A French study of 653 patients with severe OI, found that penicillin allergy, psychiatric disorders, oropharyngeal or floor-of-the-mouth edema, and trismus on admission were predictive of complex evolution (6% of patients), which was categorized as hospitalization for more than five days, ICU treatment, need for tracheostomy, or death. Further, alcohol abuse and infection in the mandibular molar were related to the need for revision surgery (Pham Dang et al., 2020).

2.3 Clinical presentation of orofacial and neck infections

2.3.1 Signs and symptoms

Knowing the common presentation of DNI is critical for optimal outcome and treatment. Patients may have unexpectedly mild symptoms in the early stages of the disease, but the literature emphasizes early recognition to achieve the best outcome (Osborn et al., 2008; Wang et al., 2003). Mild upper respiratory tract symptoms can be easily overlooked, as can preceding dental or gingival pain. Severe symptoms such as neck rigidity are alarming “red flags” and should raise suspicion of a progressing infection. On admission, neck swelling (69.6–95.4%), odynophagia (49.7–80.4%), dysphagia (39.7–72.7%), and fever (44.7–70.4%) are the most common symptoms. Swelling of the larynx and the upper aero-digestive tract (26.3–59.7%), dyspnea (1.8–14.8%), trismus (14.0–72.3%), dysphonia (5.6–17%), and otalgia (2.7–9.6%) have also been frequently reported (Boscolo-Rizzo et al., 2012; Bottin et al., 2003; Eftekharian et al., 2009; Mejzlik et al., 2017; Staffieri et al., 2014). Dental pain has not been as widely reported, but a percentage of 24.07% has been published (Gujrathi et al., 2016).

2.4 Diagnostics and imaging

2.4.1 Clinical investigations and laboratory tests

A high level of clinical suspicion is key to the early diagnosis of DNI and severe orofacial infections. Primary evaluation should include evaluation of the airways, breathing and circulation. Thorough clinical status, including endoscopic evaluation of the larynx when necessary and odontologic assessment, is often required. Moreover, a systematic otorhinolaryngological investigation is useful for assessing the origin of the infection.

The use of laboratory tests, including white blood cell count (WBC), CRP and blood cultures has been widely encouraged (Alotaibi et al., 2015; Boscolo-Rizzo et al., 2012). PCT is also useful because of its prognostic value among septic patients and it also seems to distinguish systemic infection in odontogenic maxillofacial infections (Gehrke et al., 2022; J. K. Kim & Lee, 2021; Liu et al., 2015). Some evidence has also shown that it might be prognostic to successful surgical treatment of necrotizing soft tissue infections (Friederichs et al., 2013). The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has been proposed for early detection of NF. It takes into account CRP, WBC, glucose, hemoglobin, sodium, and creatinine levels, of which the three first seem to be the most significant in cervical NF (Sideris et al., 2021).

2.4.2 Contrast-enhanced computed tomography (CECT)

Plain lateral radiographs and clinical evaluation were utilized for decades, but recently, due to its good availability and relatively low cost, CT imaging has been the mainstay imaging for patients with clinical suspicion of DNI or severe orofacial infections (Miller et al., 1999; Opitz et al., 2015). CECT can be obtained quickly and localizes the infection fairly well (Freling et al., 2009). However, the general disadvantages of CECT scanning are exposure to ionizing radiation and possible allergy to contrast media. Limitations to reliably differentiating cellulitis from an abscess are also considerable, false positive rates of 18–20% have been reported (Freling et al., 2009; Vural et al., 2003). Fluid collection with rim enhancement has been considered a sign of a drainable abscess in clinical settings, although universally accepted criteria is lacking. In a recent meta-analysis and systematic review, complete or partial rim enhancement was present on average in 88% of patients with surgically confirmed abscesses. Other frequently reported signs include gas, a hypodense area, scalloping, and bulging (Hagelberg et al., 2022). In addition, imaging of the upper mediastinum has been advised for all DNI patients (Boscolo-Rizzo et al., 2012)

2.4.3 Magnetic resonance imaging (MRI)

MRI offers excellent soft-tissue delineation without ionizing radiation and is therefore assumed to resolve the challenges related to CT imaging of the neck infections described above. Normal soft-tissue anatomy is well visualized in T1-weighted images after an intravenous gadolinium-based agent, as is pathology in T2-weighted images. Fat-suppression techniques and diffuse-weighted imaging can assist in evaluating inflammation and abscess collections (M. C. Hurley & Heran, 2007). Moreover, dental fillings can cause artifacts in CT imaging, more rarely in MRI (Eggers et al., 2005).

MRI was considered superior in a comparison of 47 patients who underwent CT and MRI for an initial evaluation for neck infection (Muñoz et al., 2001). Nonetheless, longer scanning time, tissue warming, and possible airway problems have been specific concerns related to MRI. Moreover, lack of availability and higher cost may influence the general practice in emergency settings. MRI is not widely used for the primary diagnostics of acute neck infections nor has it been reviewed in the published literature on severe orofacial infections.

2.4.4 Dental imaging

Dental radiographs are important in the workup of all deep neck and orofacial infections. Panoramic radiographs, orthopantomography (OPG) are fast and easy to use for identifying possible dental foci of infection. Cone beam-computed tomography (CBCT), developed in the late 1990s, has been an advantage in dental imaging, offering detailed imaging of the bony structures. This low-dose technique enables more precise periapical imaging, also in more complicated clinical settings, than traditional plain radiographs (Lofthag-Hansen et al., 2007). However, its low-dose method makes soft tissue imaging impossible. High resolution CT scans of the dental area can be used in diagnostics when utilizing CECT to examine the neck (Gahleitner et al., 2003). Some data also support the use of information acquired from MRI scans for evaluating periapical lesions (Mendes et al., 2020).

2.5 Microbiology

2.5.1 Diagnostic laboratory methods

The most often used test in the bacteriological diagnostics of DNI and OI is a bacterial culture from the pus sample of the abscess. The samples are cultured under both aerobic and anaerobic conditions. Recently, identification of the bacteria on the species level is increasingly being done by MALDI-TOF (matrix-assisted laser-desorption-ionization time-of-flight) mass spectrometry instead of phenotypic or biochemical identification tests (Klug et al., 2021). Also automated analyzers are available and have been experimented for the identification of bacteria and their antibiotic susceptibility from DNI samples (Beka et al., 2019). In Finland, the susceptibility of the microbes is reported in accordance with the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (EUCAST, 2023).

In recent decades, it has become evident that bacterial culture-based methods cannot identify all possible causative agents. Gene techniques, such as polymerase chain reaction (PCR), have provided a method for quick and wider identification of causative microbes. After the extraction of deoxyribonucleic acid (DNA) from the sample, the 16S rRNA gene of the bacteria can be amplified using universal primers. The PCR amplicons obtained can be then sequenced and compared to the existing database. Targeted primers can also be used to enable the detection of only certain bacteria. Many difficult to culture bacteria have been identified (Beka et al., 2019; Flynn et al., 2012). Next-generation sequencing (NGS) has provided an additional efficient way to analyze large numbers of genes at the same time but has thus far only been used for research purposes of DNI and OI samples. These methods can justifiably replace "sterile", no bacterial growth, pus cultivation findings and allow the examination of pus microbiomes and identification of more than 30 genera of bacteria in the pus from an odontogenic abscess (Böttger et al., 2021). The high number of species found might be a limitation in the clinical use of PCR-/NGS-based methods, as may the current, although still partial understanding of the clinical importance of these findings.

2.5.2 Bacteriology of orofacial and neck infection

Although the course of infection is affected by the patient's underlying conditions and immunology, bacteria and possible antibiotic resistance also play a major role. A wide range of aerobic and anaerobic species have been isolated from DNI pus samples and many previous studies have reported polymicrobial etiology varying from 15.8 to even 70.4% (Boscolo-Rizzo et al., 2012; Santos Gorjón et al., 2012). The etiology of the infection affects the culture findings. In general, the microbiota of the oral cavity is widely expressed in cultivated samples especially in odontogenic infections (Siqueira & Rôças, 2013). Similarly, respiratory and pharyngeal pathogens such as *Streptococcus pyogenes*, are a common finding in abscesses of tonsillopharyngeal origin (Gavriel et al., 2015).

From aerobic gram-positive bacteria, the Streptococcus species, especially viridans group streptococci, are dominant in most reports. α-hemolytic viridans group streptococci include *Streptococcus anginosus* group (SAG), formerly known as *S. milleri* group, consists of species *S. anginosus, S. intermedius* and *S. constellatus*. Other subgroups of the viridans streptococci are *S. mitis*, *S. sanguinis*, *S. salivarius*, *S. mutans,* and *S. bovis* groups. Other infrequent aerobic oral bacteria have also been found, such as *Proteus mirabilis*, *Proteus vulgaris*, group F and C streptococci, *Acinetobacter baumannii*, *Corynebacterium* spp., *Gemella morbillorum,* and *Stenotrophomonas maltophilia* (Beka et al., 2019; Boscolo-Rizzo et al., 2012; Bottin et al., 2003; T. T. Huang et al., 2006; Klug et al., 2021; Rasteniene et al., 2021; Ridder et al., 2005). Viridans group streptococci, for example, SAG bacteria, have been thought to colonize the oral mucosa without causing much harm to humans, but evidence that these virulent bacteria are potent and can cause even more complex and severe diseases is increasing. Recently, higher CRP and WBC, ICU treatment, and longer LOS have been associated with SAG (Furuholm et al., 2023). Satellite abscess formation and the metastatic spread of infection have been a trademark of *S. constellatus*, a member of this group that often occurs in the head and neck region (Han & Kerschner, 2001).

Group A β-hemolytic streptococcus (GAS)*, S. pyogenes,* is one of the main cultivation findings (Beka et al., 2019; Celakovsky et al., 2015; Klug et al., 2021). Other species responsible for respiratory tract infections, such as *S. pneumoniae* and *Haemophilus influenzae* (gram-negative) are also found regularly. GAS is notable because it can produce a severe invasive infection as a single pathogen, causing significant morbidity and mortality (Carapetis et al., 2005). In the US, MRSA is significantly prevalent, especially in the pediatric population, due to its more prevalent lymphadenitis etiology (Beka et al., 2019; Inman et al., 2008). *Staphylococcus epidermidis* and coagulase-negative staphylococci have also been found.

Aerobic gram-negative microbes have been cultivated. Examples are *Aggregatibacter aphrophilus, Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Serratia liquefaciens*, *Neisseria* spp., *Escherichia coli*, *Salmonella* spp., *Providencia stuartii, Bartonella henselae* ("cat scratch" disease), and *Capnocytophaga* spp. (Beka et al., 2019; T. T. Huang et al., 2006; Klug et al., 2021; Ridder et al., 2005). *Klebsiella pneumoniae* is a frequent finding (26.7–40.2%) in the Asian population and is also significantly more prevalent among patients with DM, although it has not been associated with complications (Lin et al., 2014; Wang et al., 2003).

Anaerobic pathogens are key participants in DNIs and orofacial infections. In OIs, anaerobic bacteria are even more common because they are closely related to oral microbiota. Anaerobic species account for 26.6–34.6% of cultivation findings. Typically reported species are *Fusobacterium* spp. (*F. necrophorum, F. nucleatum*), *Peptostreptococcus* spp., *Bacteroides* spp., *Porphyromonas* spp., *Prevotella* spp. (*P. melaninogenica*, *P. Buccae*), *Actinomyces* spp., *Alloscardovia omnicoles*, *Eikenella corrodens, Eggerthia catenaformis*, *Lachnoanaerobaculum orale*, *Parviromonas* *micra*, *Clostridium bifermentans*, *Propionibacterium acnes* and, *Veillonella* spp. (Beka et al., 2019; Boscolo-Rizzo et al., 2012; Eftekharian et al., 2009; Farmahan et al., 2014; Klug et al., 2021; Ridder et al., 2005). Oral microbiota has a complex mix of microbial communities, especially in plaque. NGS findings have also confirmed a wide bacterial microbiome in OI pus samples (Böttger et al., 2021). Complicated coaggregation complexes and biofilms have also been found. For example, *F. nucleatum* plays a key protective role in enabling mixed species coaggregation to form, such as that formed by *Prevotella* spp. and aerobic bacteria (Socransky et al., 1998). It is likely that many synergistic molecular mechanisms exist and that SAG and anaerobes benefit from the coaggregation through improved survival or increased resistance to the immune system (Asam & Spellerberg, 2014). More research is needed to understand how these mechanisms may affect the disease processes in DNIs and severe orofacial infections.

Mycobacterium tuberculosis is a rare entity in developed countries (3.6%) but is a significant pathogen in endemic areas and should especially be considered in cases of "cold" neck abscesses (Bakir et al., 2012; Maharaj et al., 2020; Ridder et al., 2005).

2.6 Treatment

2.6.1 Management of the airway

The initial part of the treatment of DNI and orofacial infections is the evaluation of the airways. A significant proportion of patients develop swelling in the oropharynx and larynx, which frequently disturbs the anatomy at the level of the epiglottis or aryepiglottic folds (Boscolo-Rizzo et al., 2012; Cho et al., 2016). Edema in the floor of the mouth could also cause elevation of the tongue (Ludwig's angina). Evaluation of the airways via flexible nasoendoscopy is usually warranted. Moreover, trismus can make oral endotracheal intubation challenging. In these circumstances, video laryngoscope, fiberoptic-guided endotracheal nasal intubation while the patient is awake, or primary tracheostomy under local anesthesia during surgery, should be considered to secure the airways (Cho et al., 2016; Riekert et al., 2019). In a Finnish retrospective study of 202 patients with DNI, intubation (82%) was the most common form of airway management, but 17% of their study participants still needed a primary tracheostomy, of which 74% in local anesthesia. In addition, 15% subsequently underwent tracheostomies due to prolonged intubation (Tapiovaara et al., 2017).

2.6.2 Antimicrobial therapy

After securing the airways, the second most important issue is antimicrobial treatment. Intravenous antibiotics are used empirically and then later targeted according to susceptibility testing of the pus samples (Alotaibi et al., 2015; Boscolo-Rizzo et al., 2012).

Empiric antibiotics should cover the most common aerobic and anaerobic microbes in oral microbiota, such as *Streptococcus*, *Bacteroides*, *Fusobacterium*, *Prevotella*, and *Actinomyces* species. Penicillin combined with metronidazole is primarily advised for OI in Current Care Guidelines 2022 in Finland (*Acute Odontogenic Infections and Antimicrobial Treatments. Current Care Guidelines*, 2022). Recently, penicillin-type antibiotic treatment has been recognized as a protective factor against return to the operating room in OIs (Christensen et al., 2021). Moreover, cefuroxime, covering the staphylococcal species and streptococci, is a reasonable choice, particularly in cases of DNI of non-odontogenic origin. The considerably higher prevalence of *Staph. aureus* in pediatric neck infections reflects the need to use of cefuroxime combined with metronidazole or clindamycin among children (Lawrence & Bateman, 2017). Several studies have justified the use of piperacillin-tazobactam to treat more invasive infections (Boscolo-Rizzo et al., 2012; Fu et al., 2020; Roccia et al., 2007). Broader spectrum antibiotics (fluoroquinolones, aminoglycosides) have been proposed for immunocompromised patients (Daramola et al., 2009).

Antibiotic resistance is a growing concern in many countries. However, local, and national bacterial susceptibility analysis are the most important tools for evaluating the regional recommendations. For example, in oral samples resistance to metronidazole is low (0-3%), as is the incidence of MRSA (2-3%) in the area of Turku University Hospital (Rantakokko-Jalava, 2023). Sensitivity to penicillin and metronidazole (84%) has remain reasonably high in a British study, the resistant 14% being skin infections with *Staph. aureus* (Farmahan et al., 2014). Nevertheless, higher rates of resistance to clindamycin (17.5%) have been observed in a German study, and in these cases, reconsideration of empiric antibiotics has been suggested (Heim et al., 2021).

2.6.3 Surgical treatment

Surgical treatment of DNI and maxillofacial infections is gold standard when purulence is suspected. As previously stated, because of the high percentage of odontogenic etiology, the evaluation (OPG) and management of the dental foci is crucial (Heim et al., 2019; Kirse & Roberson, 2001; Osborn et al., 2008; Peterson, 1993). Basically, surgery is based on knowledge of the relevant anatomy and the incision should be planned on the basis of the imaging (Miller et al., 1999). Adequate exposure, blunt finger dissection, drainage, and irrigation of the abscess cavity with hydrogen peroxide and saline have been advocated. In cases of tissue necrosis, debridement is usually performed. Wounds can be left partially or completely open and large-pore drains in place for daily irrigation (Figure 4). In cases of large and multispace infections, more aggressive surgery is warranted. (Boscolo-Rizzo et al., 2012; Caccamese & Coletti, 2008; Osborn et al., 2008). Studies have shown that a neck incision was necessary for 81.3–87.4% of the patients who required surgery and that an intraoral incision was considered sufficient for 12.6–18.6% (Boscolo-Rizzo et al., 2012; T. T. Huang et al., 2004). Moreover, vacuum-assisted closure (VAC) after surgical debridement in the postoperative care of patients with cervical NF has been suggested as a potential means of enhancing wound healing and reducing the amount of excised skin (Balcı et al., 2018; Sukato et al., 2017).

Figure 4. Neck incision and large-pore drains applied to the wound for irrigation. Photo: Jarno Velhonoja.

A fairly large portion, 62%, of adult DNI patients, were managed non-surgically in a retrospective study of 365 patients by Boscolo-Rizzo (2012). Abscesses over 30 mm, clinically unstable cases (sepsis, airway obstruction), cases involving over two spaces, or patients with descending infection were operated immediately, others were observed for 48 hours. In the abscess group, 52.1% of the patients were treated surgically, and in the cellulitis group, 18.4%. Nonetheless, surgery still plays a central role, and a higher frequency of surgical treatment (91.5%) has also been reported among adults (Daramola et al., 2009). Especially when primarily diagnosed in the cellulitis stage of the disease, antibiotics could be the only treatment, although active follow-up with imaging is recommended (Boscolo-Rizzo, Marchiori, Zanetti, et al., 2006). However, non-surgical management with antibiotics has also provided comparable results in selected cases in other studies. In their retrospective study, a group from the US were among the first to demonstrate that intravenous antibiotics effectively treat pediatric abscesses (Nagy et al., 1997). Sichel et al. (2002) reported good results among a small prospective series of seven patients with a parapharyngeal infection of whom six were children. Patients with pus in other neck spaces shown by the CT scan, airway distress, or gross extension were excluded (Sichel et al., 2002). Later, 15% of pediatric DNIs with abscesses were successfully treated in a retrospective case-control study (Wong et al., 2012). Another study concluded in a meta-analysis of pediatric deep neck abscesses that medical management may be a safe alternative (Carbone et al., 2012).

In general, studies of pediatric patients have reported lower rates of surgical treatment (72.5–79.5%) (Eftekharian et al., 2009; T. T. Huang et al., 2004). Recent papers have also targeted defining the role of surgery in pediatric DNI. Pediatric patients with an abscess under 22–25 mm, in stable clinical condition, with no breathing problems and a single site infection have the option of first line non-surgical treatment for 48h. If clinical or radiological improvement is not observed, surgery should be considered (Cheng & Elden, 2013; Grisaru-Soen et al., 2010; Lawrence & Bateman, 2017; Wilkie et al., 2019). In their multicenter, prospective cohort study, Cramer et al. (2016) described that delayed surgery was related to increased morbidity and mortality among adults, but did not find this association between the timing of the incision and drainage among children. This result highlights two points: First, there are differences between adults and children and thus the data further support the 48-hour initial trial of medical treatment for children. Secondly, all these patients were treated surgically, which means that if there is a need for surgery, operation should not be delayed in the case of adults. Ultimately, however, the treatment decision is also based on individual clinical criteria and the surgeon's experience.

2.6.4 Hospital stay

DNIs and orofacial infections can be considered relatively common problems for on-duty head and neck and oral and maxillofacial (OMF) surgeons. A large proportion of patients with these infections can be managed using straightforward management protocols. With adequate treatment, most of these patients recover relatively quickly, within a few days, or less than a week. The average LOS of DNI patients was 5.6 days in a study by Buckley et al. (range 1–19 days), a median of three days (1–27 days) in a study by Daramola et al., and a median of seven days (2–80 days) in a study by Tapiovaara et al. (Buckley et al., 2019; Daramola et al., 2009; Tapiovaara et al., 2017). Nevertheless, some patients' disease progresses intensively despite therapy and the need for intensive care and repeated surgery can significantly prolong hospitalization (Gehrke et al., 2022). Prolonged LOS is one of the reasons for the rising costs in the health care system and thus it is understandable that several studies have tried to uncover its risk factors.

Patients with comorbidities, smoking, repeated procedures, or presenting with an airway compromise, seem to have longer hospital stays. (Barber et al., 2014; Daramola et al., 2009; O'Brien et al., 2020). DM in particular is repeatedly associated with longer LOS (Chang et al., 2018; Hidaka et al., 2015; O'Brien et al., 2020). Studies of patients with OIs have shown similar results (Peters et al., 1996; Seppänen et al., 2008). Multivariate analyses have also found that increased age, pre-admission antibiotics, DM, and OI severity score are significant predictors of LOS in severe OI cases, whereas tooth extraction early in the course of the disease could decrease LOS (Gams et al., 2017; Heim et al., 2019). CRP on admission is believed to predict LOS as well as the neutrophil to lymphocyte ratio and WBC (Bowe et al., 2019; Gallagher et al., 2021; Heim et al., 2018).

2.6.5 Intensive care

Many reports have advocated multidisciplinary treatment of severe DNIs. Airway support and surveillance are the main reasons for the need for intensive care, in addition to wound care and administration of vasopressors in septic progression (Garcia et al., 2012). ICU treatment is often required by 14–40% of DNI and severe OI patients. An average ICU stay varies between three and seven days (Jundt & Gutta, 2012; Tapiovaara et al., 2017). In recent decades an increase in the number OI patients and in the LOS in the ICU has been reported (Fu et al., 2020; Seppänen et al., 2010).

Infrahyoid involvement, smoking, dysphagia, lower third molar involvement, and high CRP can indicate a need for ICU treatment (Fu et al., 2018; Furuholm et al., 2023; Yuan & Gao, 2018). Moreover, retropharyngeal or multiple space location and several scoring systems (incl. ASA, APACHE II, SOFA) that measure increased general and previous health problems have been associated with ICU treatment (Garcia et al., 2012).

2.6.5.1 Hyperbaric oxygen therapy

In hyperbaric oxygen therapy (HBO), 100% oxygen is administered in a pressure chamber that exceeds the absolute pressure of one atmosphere. Gas bubbles decrease in size and dissolution accelerates, thus enhancing tissue oxygenation and inhibiting anaerobic bacteria. Strong scientific evidence supports the therapeutic use of HBO for decompression sickness, arterial gas embolisms, and carbon monoxide poisoning, for example. Theoretically, many of the cellular and biochemical effects of HBO, such as improving leucocyte function, killing anaerobes, reducing tissue oedema, promoting angiogenesis and collagen formation, and enabling better penetration of antibiotic therapy, could be beneficial in severe infections and wound healing. Barotrauma of the ears or sinuses, pneumothorax or pulmonary barotrauma, neurological symptoms such as oxygen toxicity seizures, and fire accidents have been described as side effects and complications of HBO therapy (Leach et al., 1998; Mathieu et al., 2017). Although HBO therapy has been used worldwide as an adjuvant for NF in centers able to provide patients also with ICU treatment, its benefit has only been shown in a relatively small number of patients, mainly in retrospective case series with control groups, leaving it unsolved in a Cochrane review in 2015 (C. Huang et al., 2023; Levett et al., 2015; Shaw et al., 2014; Thrane & Ovesen, 2019). The Tenth European Consensus Conference on Hyperbaric Medicine in 2017 made a consensus based opinion of experts Type 1 (strongly recommended) recommendation with Level C evidence for treating necrotizing soft tissue infections using HBO, however the level of the evidence have to be taken into account (Mathieu et al., 2017). Necrotizing infection in the head and neck area is a rare disease. HBO has been utilized as an adjunctive treatment, with mostly promising or mixed results, but definitive randomized studies are lacking (Elander et al., 2016; Flanagan et al., 2009; Krenk et al., 2007; Thrane et al., 2017; Wolf et al., 2010). A recent systematic review of cervical NF found that HBO improved patients’ outcomes (Acharya et al., 2022).

2.7 Complications

Modern medicine, widespread use of antibiotics, better dental care and developed surgical approaches are believed to decrease the incidence and mortality of DNIs (Clarke, 1999; Parhiscar & Har-El, 2001). However, severe complications still occur, the most common of which are presented in Table 1. Several factors have been proposed as contributing to these complications. Infrahyoid involvement and multispace infections have been identified as prognostically significant factors for complications (Staffieri et al., 2014; Yuan & Gao, 2018). One of the largest multivariate analyses found DM, evidence of colliquation, multiple space involvement, WBC, and body temperature to be independent predictors of complications (Boscolo-Rizzo et al., 2012). Age, DM and other underlying diseases have also been linked to complications, in addition to neck swelling, respiratory difficulty at admission, and delays in diagnoses and treatment (Boscolo-Rizzo, Marchiori, Montolli, et al., 2006; Cramer et al., 2016; T. T. Huang et al., 2004; Wang et al., 2003).

Internal jugular vein thrombosis or thrombophlebitis with septic emboli, also referred as Lemierre's syndrome, has an incidence of 1.1–3.0% among DNI patients (Boscolo-Rizzo et al., 2012; T. T. Huang et al., 2004; Ridder et al., 2005). Pharyngotonsillitis and DNIs in previously healthy young adults are typical etiology, and most often *F. necrophorum* is the most common micro-organism found in blood culture (Karkos et al., 2009; Nygren & Holm, 2020). Septic metastasis was most frequently reported in the lungs and joints, and the mortality rate was 5% in a systematic review by Karkos et al. (2009). A recent Swedish nationwide study by Nygren and Holm (2020) reported also a rising incidence rate, possibly partly due to more frequent imaging. Anticoagulation should be considered along with aggressive antimicrobial therapy, although evidence of specific anticoagulation protocols is lacking.

Table 1. Complications of DNIs.

Complication	**Huang T.T. et al. 2004 n=185 % (n)**	**Ridder et al. 2005 n=234 % (n)**	**Boscolo-Rizzo et al. 2012 n=365 % (n)**
Airway obstruction	10.3 (19)	-	8.5 (31)
Sepsis	2.2 (4)	2.6 (6)	6.0 (22)
Descending mediastinitis	2.7 (5)	5.6 (13)	4.4 (16)
Pneumonia	1.6 (3)	2.6 (6)	3.3 (12)
Jugular vein thrombosis	1.1 (2)	2.1 (5)	3.0 (11)
Pleural effusion	0.5 (1)	-	1.1 (4)
Disseminated intravascular coagulation (DIC)	0.5 (1)	0.4 (1)*	0.3 (1)
Mortality	1.6 (3)	2.6 (6)	0.3 (1)
Gastrointestinal bleeding	3.2 (6)	-	-
Vocal cord palsy	0.5 (1)	-	0.5 (2)
Total complication rate	16.2 (30)	15.4 (36)	18.4 (67)

*Multiorgan failure
Combined from articles by Boscolo-Rizzo et al. 2012, Huang T.T. et al. 2004, and Ridder et al. 2005.

NF in the head and neck area and descending necrotizing mediastinitis (DNM) could be categorized as their own entity. Nevertheless, DNM in particular is often a complication of DNI, and similarly NF can be a continuum of severe infection in deep fascial planes. In two meta-analyses, the mortality rate of cervical NF was 13.4% and of DNM 17.5% (Gunaratne et al., 2018; Prado-Calleros et al., 2016). Gas between the facias or under subcutaneous tissue is considered nearly pathognomonic to NF; however, only 56.8% of the CT scans showed gas bubbles, indicating that in nearly half of the cases, gas was lacking. Typical findings mentioned are ischemia, causing tissue-separating fat; fascia necrosis; "dishwater pus" described as foul odorous, clearer, or darkish exudate; purplish skin color changes; and obnoxious odor from anaerobic bacteria. Surgical debridement is encouraged until the bleeding edges are reached, after which it should be repeated when necessary (Gunaratne et al., 2018).

The surgical complications described in addition to scarring were skin defects, especially in NF cases; post-operative bleeding; and nerve damage (recurrent laryngeal nerve, facial nerve) (T. T. Huang et al., 2004; Tapiovaara et al., 2017). The worst complications such as major vessel ruptures, pseudoaneurysms of the internal carotid artery, and intracranial spread such as cavernous sinus thrombosis or an epidural abscess are rare, mostly mentioned in case reports or more often associated with NF (Blum & Mccaffrey, 1983; Gunaratne et al., 2018; Koivunen et al., 1998; Makeieff et al., 2010; Prabhu et al., 2015; Tapiovaara et al., 2017). Cranial nerve IX–XII palsies or ipsilateral Horner's syndrome could indicate complications within the carotid sheath (Reynolds & Chow, 2007). Other mediastinal complications such as empyema and pericarditis have also been described (Zachariades et al., 1988). Orbital cellulitis with an abscess could be caused by OI, although this is rare (Rothschild et al., 2020). A cerebral abscess of odontogenic origin should be suspected when SAG or anaerobic species are found in the intracranial bacterial sample (Burgos-Larraín et al., 2022).

Pediatric patients' complications are similar, but less common (Baldassari et al., 2011). Vessel narrowing of the jugular vein and/or carotid artery with no neurologic complications were a common finding (44.7%) in the retrospective analysis of 208 patients with pediatric DNI, but no evidence to support more aggressive surgical intervention or altered medical therapy was found (Carroll et al., 2019).

2.8 Outcome

The outcome after treatment for DNI and severe orofacial infection is often good (Gehrke et al., 2022; Neal & Schlieve, 2022; Tapiovaara et al., 2017). Overall mortality rates of 0.3–5.9% have been published (Bakir et al., 2012; Boscolo-Rizzo et al., 2012; Ridder et al., 2005; Santos Gorjón et al., 2012; Tapiovaara et al., 2017; Yang et al., 2008). Sepsis with disseminated intravascular coagulation (DIC), multiorgan failure, DNM are the leading causes of fatal outcomes (Gehrke et al., 2022; Ridder et al., 2005). Clearly higher mortality is associated with more complicated infections, such as in cervical NF, for which the mortality rate was 13.4% (Gunaratne et al., 2018). A German study recently evaluated DNM outcome and found a mortality rate of 9%, and a significant portion of survivors (67%) had persistent dysphagia (Reuter et al., 2023). Overall, long-term sequalae seem to be rare, but on the other hand, long-term follow up is seldom reported.

2.9 Prevention

As the main cause for neck and orofacial infections are odontogenic, maintaining dental health is the key to prevention. Many DNI patients have neglected routine dental care (Uluibau et al., 2005). The overall cost of these severe infections is significant, and avoiding them should be emphasized (R. Hurley et al., 2018; Jundt & Gutta, 2012). The level of patient education and oral health care services in Finland has been rising for many decades (Raittio & Suominen, 2022). However, limited healthcare resources present challenges and cause disparities in the Finnish population. For example, in large epidemiological studies, the share of preventive treatment for those in need of basic periodontal or restorative treatment has been lower than expected and the focus has mainly been on the treatment of caries and its consequences (Linden et al., 2020). Increasing admissions and the severity of OIs have also been associated with restricted access to dental care in a retrospective cohort study of 1 405 patients presented for odontogenic pain or infection in the US (Salomon et al., 2017). Effective treatment of OIs should always focus on dental treatment in the early stages of the disease, and this should be included in treatment protocol. In 81.4% of the cases in an epidemiological study of the management of severe OIs, the tooth causing the infection had not received any treatment prior to hospital referral (Katoumas et al., 2019). As claimed in the WHO's recent global oral health status report, much work needs to be done to promote overall oral health internationally. In addition to improving dental care services, the use of known caries-preventing measures are encouraged, such as reducing sugar consumption, favoring fluoride products, and adding fluoride additives to drinking water (Jain et al., 2023).

The role of TE in preventing abscess complications or hospital admission has been debated. Some reports have shown an increasing number of hospital admissions for tonsillitis and peritonsillar, parapharyngeal and retropharyngeal abscesses after a decline in TE rates in the UK and Germany (Mcleod et al., 2017; Windfuhr & Chen, 2019). Moreover, a report from the UK showed that previously implemented national guidelines to improve patient selection, reducing the rate of TEs, now appear to be associated with a rising number of DNIs and mediastinitis (Pankhania et al., 2021). Nevertheless, opposite results have also been presented. A national Korean cohort study, which matched TE groups and sociodemographic factors and especially a two-year pre-operative history of upper respiratory infection, found a 1.87-times higher risk (hazard ratio) of DNI in its adult TE group than among children (S. Y. Kim et al., 2018). The reason for this result is unclear, but it has been hypothesized that frequent upper respiratory infections could be a risk factor for DNI. A change in the immune system after TE has also been suggested, but despite many studies, no clear evidence has been presented to support this.

3 Aims

This study aimed to clarify the features, treatment, and outcomes of DNIs and orofacial infections and to investigate the role of MRI in the diagnostics of neck emergencies. The specific aims were:

1. to review the outcome and characteristics of DNI patients treated in Turku University Hospital between 2004 and 2015, to compare their data to previous results, and to investigate possible changes.
2. to investigate the use of neck MRI in emergency settings and to evaluate its feasibility and diagnostic accuracy.
3. to study the role of the timing of surgical interventions and outcome among children with DNIs.
4. to assess the relationship between the possible preventive and aggravating factors in the orofacial infections of hospitalized patients in a prospective setting.

4 Materials and Methods

4.1 Materials

4.1.1 Patients and data

4.1.1.1 Original publication I: Retrospective study of DNIs

In Study I, we analyzed and compared our experiences of DNIs in Turku University Hospital, patients' characteristics and outcomes to older data from our institute. Inclusion criteria for the analysis were defined as a DNI requiring intraoral or extraoral surgical treatment and admission to a ward or ICU. Patients who were managed merely conservatively or treated for ordinary peritonsillar abscesses without any complications were excluded.

Electronic patient records were only available from 2004, thus the data for the first article was collected between 1.1.2004 and 30.11.2015 at Turku University Hospital, which serves as a tertiary, referral, on-call hospital for the Southwest Finland and Satakunta districts, covering a population of 870 000 people. As Turku University Hospital is also the national center for HBO treatment of patients requiring ICU treatment, some patients had been referred from other parts of Finland. We used the several possible ICD10 (The International Classification of Diseases 10^{th} Revision) codes to find all the patients with DNI (including J39.0, L02.1, K11.3, J39.1, J39.0, J36, A48.0, M72.6, K12.2, K02.1, K04.1, K04.4, K04.5, K04.60–K04.63, K04.69, K04.7, K05.5, K05.22 and K05.32). In total, we found 2 588 patients with matching codes, of whom 277 patients met the inclusion criteria.

An ear, nose, and throat (ENT) specialist and OMF surgeon reviewed all the patient records. They noted the patient demographics, clinical and/or radiological evaluation of oral health, underlying diseases, airway management, treatment, operations, hospital and ICU stays, bacterial culture findings, HBO days, complications, and outcomes.

4.1.1.2 Original publication II: Retrospective cohort study on emergency neck MRI

Study II evaluated the feasibility and accuracy of MRI in an acute neck infection setting in a retrospective cohort of patients who had undergone a primary MRI of the soft tissues of the neck in the emergency department at Turku University Hospital during a five-year period between 1.4.2013 and 30.4.2018. Cases were identified from picture archiving and communication systems (PACS) and radiological information systems (RIS) using standard neck MRI codes. An unknown magnetizing foreign object or fever of >38 ° Celsius (C) were absolute contraindications of MRI. Gadolinium was administered to all the patients except three adults. From the 541 scans, we found 461 primary MRI scans, 334 of which had been performed due to a suspected infection. The mean age of the patients was 46 and 14% (n=65) were pediatric or adolescent patients (0–21 years) and 21% (>65 years) elderly adults.

The primary radiological reports were reviewed, and all suspected infections were re-evaluated by a fellowship-trained neuroradiologist, J. Hirvonen or J. Heikkinen. Any differences between the primary and retrospective reviews were noted. They also assessed the inter-observer agreement on the MRI diagnoses of an abscess: A third neuroradiologist, M. Nyman, read these with no previous knowledge of the clinical diagnosis or the primary radiologic report. A random sample of 50 patients with an infection and the presence or absence of an abscess was recorded. Imaging data were compared with the clinical information from the medical records. Infection was defined on the basis of the final clinical diagnosis from the patient data, and an abscess as the presence of purulence or an abscess cavity found during surgery that had been carried out within 48 hours of the MRI. Open surgery, drainage, or puncture of pus were included as indication of an abscess. Patients with no abscesses in imaging are unlikely to have undergone surgical interventions, thus partial verification bias was noted. Nevertheless, patients with uncomplicated recovery following conservative treatment were categorized as true negatives (TNs) on the basis of the gold standard previously utilized for CT scans (Freling et al., 2009).

Any significant high signal of fat-suppressed T2-weighted Dixon images consistent with edema, and high signal fat-suppressed post-gadolinium T1-weighted Dixon images consistent with abnormal tissue enhancement, were defined as evidence of infection. An abscess was defined as an abnormal non-enhancing, T2-hyperintense collection with a low apparent diffusion coefficient (ADC) indicating purulent fluid bound by abnormal tissue enhancement.

4.1.1.3 Original publication III: Retrospective analysis of pediatric DNIs

Study III focused on the timing of surgical treatment, imaging, and the outcome of pediatric DNI patients. Inclusion criteria was restricted to DNI patients aged ≤16 years requiring hospitalization and/or surgical intervention. DNIs are a relatively rare disease, thus the period of data collection was extended to 1.1.2004–30.9.2019 and patients treated non-surgically were included. We found 42 patients. As in Study I, peritonsillar abscesses were excluded and the parameters described above were reviewed. The length of preoperative parenteral antibiotic treatment was measured to estimate the length of the first line non-surgical treatment period.

4.1.1.4 Original publication IV: Prospective study of aggravating and preventing factors in orofacial and neck infections

In Study IV, the preceding etiological factors, dental treatment before hospitalization, and their effect on the outcome were evaluated. Adult patients (aged 18 or older) hospitalized for neck and orofacial infections between 15.8.2016–31.8.2019 at Turku University Hospital were recruited. They signed their informed consent and completed a structured interview form. In total, 96 patients were enrolled; however, two patients did not complete the questionnaire and were excluded. The patient data were reinforced by clinical data from electronic patient records. The patients' demographics, BMI, comorbidities, symptoms, treatment, operations, dental hygiene habits, recent dental treatment, smoking, alcohol consumption, LOS, ICU stay, complications, and outcomes were also analyzed.

4.2 Methods

4.2.1 Data management

Patient data were reviewed and the patients who met the inclusion criteria were selected for Studies I–III. In Study I, a subgroup of patients from 2006–2015 was formed to compare their results to previously published data with same inclusion and exclusion criteria from Turku University Hospital. Data from 2004–2005 were excluded from this comparative analysis, because of the overlapping time period with the previous study. In Study II, sensitivity and specificity were determined using 2 × 2 tables (MRI vs. surgery) and positive and negative predictive values were calculated. In Study III, three groups were formed: an early surgical intervention group (<2 days of intravenous treatment), a late surgery group (2 or more days of treatment) and a conservatively treated group. Study IV used continuous prospective data collection forms.

4.2.2 MRI scanners and protocols (II)

MRI was conducted by a Philips Ingenia 3-T system using dS HeadNeckSpine coil configuration (Philips Healthcare, Best, Netherlands). The routine protocols took around 30 min of scanner time. Details of the MRI protocol are listed in Appendix 1.

4.2.3 Outcomes

The main outcomes of Studies I and III, in addition to the descriptive information, were LOS, the need for and length of ICU treatment, complications, reoperations, and mortality. Moreover, in Study III, the timing of the primary surgery was a key measure. Imaging outcomes, such as the most common locations, a surgically confirmed abscess finding, and inter-observer agreement on the presence of an abscess were analyzed in Study II. In Study IV, the analysis outcomes were overall LOS, prolonged LOS (7 or more days), ICU treatment, prolonged ICU treatment (7 or more days), complications, and reoperations.

4.2.4 Statistical analysis (I–IV)

IBM SPSS Statistics for Mac versions 24–27 was used for the data analysis in all the studies. Descripted information, such as mean and median age, LOS, and ICU days were calculated. *Fisher's exact* test (an asymptotic 2-sided significance) was performed when the expected group size was under five. Otherwise, a *Pearson Chi-Square* test was used to compare the groups' categorical data. *A Mann–Whitney U* test was utilized to compare the two groups' continuous variables. Study I also used one sample *t* test to compare means. In Study II, the inter-observer agreement was assessed using Kappa values and percent agreement. In Study III–IV, we applied the *Kruskal–Wallis* test for independent samples to compare the continuous variables of the multiple groups. *A Spearman's rank-order correlation* was used when non-normally distributed continuous variables were compared in Study IV. In all the studies, p-values of <0.05 were considered statistically significant.

4.2.5 Ethics

The data for Studies I–III were gathered retrospectively under institutional permissions (T221/2015, T66/2019, TO6/040/19) from the Turku Clinical Research Center. For Study IV, informed consent was obtained from all the patients and/or their legal guardian(s). Ethical approval for the study protocol and forms (TO6/036/16) was acquired on 16.2.2016 from the ethics committee of Hospital District of Southwest Finland (HDSWF). The study adhered to the ethical standards of the Declaration of Helsinki. Participation in the observational prospective Study IV did not affect the treatment and patients had the option to refuse throughout the study. An encrypted data platform was utilized for collection and preservation of the data. Paper forms have been stored in locked cabinets and will be destroyed when the information has been transferred to electronic format. The data was pseudonymized before statistical analysis, and only researchers collecting the data had access to the original data. Pseudonymized data will be archived in the institutional database after the study is completed.

5 Results and discussion

5.1 DNIs as an increasing challenge (I)

5.1.1 Study population and demographics

In Study I, we a found rising trend of DNI patients. The annual numbers were 24 cases per year, in comparison to the 14 per year of the previous data between 1985 and 2005 (Aitasalo, 2008). Population growth is noticeable in study area and partially explains the increase in cases however, other previous studies have also observed an upward trend. The growing number of severe OIs has been a particular concern and improvements to outpatient dental care and prevention have been emphasized (Fu et al., 2020; R. Hurley et al., 2018; Seppänen et al., 2010). Our analysis of 277 DNI patients requiring surgical treatment found a predominance of males (64.6%), which has also been documented in several previous studies (Boscolo-Rizzo et al., 2012; Gujrathi et al., 2016; Maharaj et al., 2020; Tapiovaara et al., 2017). The reason for this gender disparity is unclear. Odontogenic etiology was also associated with males (p=0.016) as well as poor dental status (p=0.005). Generally, it has been speculated that males tend to refrain more from engaging in health protective behavior (Williams, 2003). Age varied between 0.5 and 92 and the mean age was significantly higher ($p<0.001$) in the 2006–2015 group (43.3 years) than in the 1985–2005 group (38.5 years). The elderly (>65 years) have been found to be more prone to complications, longer LOS, higher rate of multiple involved spaces, and repeated surgery (Chi et al., 2014). Given the overall increasing trends in numbers and severity, these infections continue to represent a significant financial burden to public health care systems.

5.1.2 Comorbidities

In Study I, the comorbidities were observed from a broader perspective than in the previous data from the same institute. This may explain the reasonably large difference in comorbidities between the time periods of 17.4% vs. 43.1%. This means that 58.8% of the participants in our study were otherwise relatively healthy. Psychiatric disorders and/or dementia, the most common underlying illnesses, were observed in 55 participants (19.9%). Daramola et al. (2009) reported psychiatric disorders in 10.4% of patients with DNI and Uluibau et al. (2005) in 19% patients with severe OIs. In our study, poor dental status was found to be as high as 50.1% among the patients in this subgroup and the difference was significant (*p*=0.013). The majority of infections (54.5%) were odontogenic. The relationship between poor oral health and psychiatric morbidity has been well described (Kisely & Najman, 2022). Antidepressants and psychoactive drugs may also promote oral problems, xerostomia, and cravings for candy (Friedlander & Mahler, 2001). Moreover, neurodegenerative disorders such as Alzheimer's disease, are known to associate with poor oral health (Delwel et al., 2017).

Overall, 11.2% of the patients were taking medication for DM and 6.1% of the patients received insulin therapy. DM is a well-known, most common comorbidity for DNIs and orofacial infections, as stated in a systemic review and meta-analysis by Hidaka in 2015 (Hidaka et al., 2015). In Study I, diabetic patients had longer LOS, at a median of eight days, and they needed ICU treatment (p<0.000) more often. Overall, 23 (8.3%) of our patients, were assessed to be immunocompromised for other reasons.

In Study 1, alcohol abuse was found in the history of 29 (10.5%) patients and six (2.2%) had a history of intravenous substance abuse. The use of intravenous drugs has been previously reported as a significant risk factor (12–15%) (Parhiscar & Har-El, 2001; Tamir et al., 2015). The significant rate of drug abuse (12%) in Parhiscar's highly-cited study in 2001 may have been influenced by the study population being located in a dense urban area (Brooklyn, NY). Excessive alcohol usage has been linked to DNIs and severe OIs (Gujrathi et al., 2016; Kinzer et al., 2009). Smoking is also considered a frequent comorbidity (Daramola et al., 2009).

Cardiovascular diseases (coronary artery disease, congestive heart failure, previous stroke, or transient ischemic attack) were found in 20 participants (7.2%). Eleven (4%) had malignancies and eight (2.9%) had a hepatic disorder. Similar rates of 14.5% for cardiovascular diseases and 3.5% for liver diseases have been published (Boscolo-Rizzo et al., 2012).

5.1.3 Etiology

In Study I, the most common etiology for DNI was odontogenic (44.8%) and the second most common reason was tonsillar or pharyngeal (37.5%). Odontogenic etiology has dominated as the origin of DNIs in several studies, varying between 24% and 37.8% (Boscolo-Rizzo et al., 2012; Cho et al., 2016; R. Hurley et al., 2018; Tapiovaara et al., 2017). Nonetheless, specific criteria for the diagnosis of dental infection have not usually been described. The variable origin of DNIs is specified in Figure 5. In 20 (7.2%) cases, the cause remained undetermined.

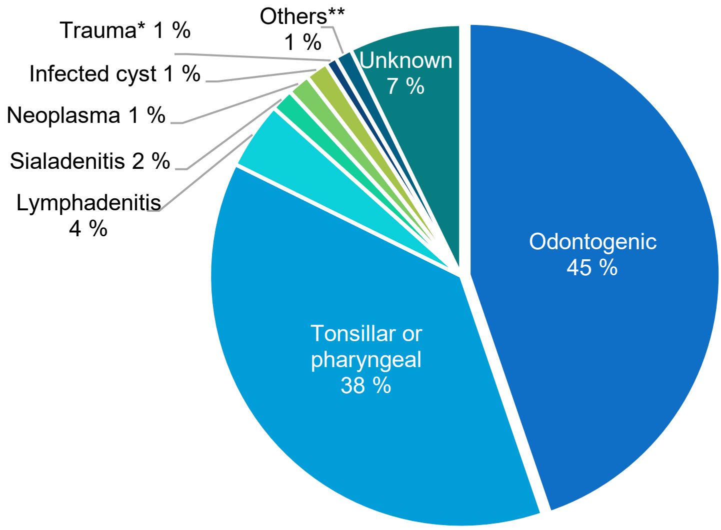

Figure 5. Etiology of DNI in 277 patients. *Two penetrating traumas to the cervical region ** Others: an otogenic, a foreign body, and a post-operative infection.

5.1.4 Diagnosis and treatment

In Study I, DNI was diagnosed after a systematic otorhinolaryngological investigation, including nasopharyngoscopy when required. OPG was performed on 147 (53.1%) patients. An OMF surgeon evaluated and treated odontogenic foci. CECT was performed on 174 (62.8%) and MRI on 37 (13.4%) patients, and both approaches were considered necessary for five patients. Although primary airway management with intubation was the most common way to secure airways, tracheostomy was required in 36 (13%) cases which is comparable to the 17% reported by Tapiovaara (Tapiovaara et al., 2017).

In Study I, surgical treatment was cervical incision and/or intraoral incision for 215 (77.6%) patients and intraoral for 62 (22.4%). Tonsil surgery was performed in 63 (22.7%) cases and dental extraction in 93 (33.6%) at Turku University Hospital, and on 113 (40.8%) of the patients in total. Other extractions were performed in the primary treatment facility prior to the admission. We showed that overall LOS significantly decreased from a median of seven days to five days (p=0.039) when extraction was performed immediately (the same day) with incision and drainage. Recently, it has been stated that simultaneous removal of the focus tooth is the best way to achieve the lowest LOS. However this idea was still considered controversial in recent decades (Heim et al., 2019).

Broad-spectrum parenteral antibiotics were administered and later targeted according to the susceptibility tests of the bacterial cultures. Cefuroxime combined with metronidazole (n=135; 48.7%) or penicillin combined with metronidazole (n=75; 27.1%) were the most common empiric antibiotics. Clindamycin with or without other regimen and carbapenems were initiated more infrequently, among 32 (11.6%) and 16 (5.8%) patients, respectively. These results reflect the reasoned practice to cover the most common pathogens in DNI and severe OI cases (Heim et al., 2021; Klug et al., 2021).

Revision surgery on the neck was required in 47 (17%) patients and seven (2.5%) patients needed mediastinal canalization or a thoracotomy. The odontogenic subgroup had undergone repeated surgery more frequently (p=0.022). The re-operation rate was comparable to the previously reported rate of 22% (Tapiovaara et al., 2017). Patients with at least one comorbidity also required repeated surgery (p=0.009) more frequently, which is in line with the report by Chi et al. (2014) that reported that elderly patients need more frequent revisions.

The median LOS was 6 days, the mean 8.5 (range 2–114 days, standard deviation, SD 10.1). For DNIs that have been surgically treated, a median LOS of 7 days and a mean of 16 days have been reported (Cho et al., 2016; Tapiovaara et al., 2017). As stated above, the DM patients had overall longer LOS. A significant proportion of DNI patients require ICU treatment, which usually means mechanical ventilation and/or vasoactive support. The mean ICU stay of 62 patients (22.4%) was 7.2 days, the median 5 days (range 1–36 days, SD 7.4). Nevertheless, patients with comorbidities had a more severe disease. They needed ICU treatment more frequently (p=0.020), and their ICU stays were longer, a median of 7 vs. 2 days (p=0.004). Garcia et al. (2012) showed an association between ICU treatment and several scoring systems measuring increased general and previous health problems.

HBO was utilized as an adjuvant therapy for 42 (15.2%) patients with a median of six days (range 1–15 days). It was administered once a day in general, but twice for two NF patients who were considered to be long-term, critically ill after multiple revisions. No immediate complications were reported. HBO treatment was initiated within 24 hours of the primary surgery in 23 (54.8%; range 0–12 days) of the cases. This delay may be due to the course of the disease. The first operation may have been limited to intraoral surgery and led to more aggressive treatment only as the patient’s condition deteriorated. The mortality rate of the mediastinitis patients (n=12) was 8.3% in our study, whereas Prado-Calleros reported 17.5% mortality in a systematic review of 480 patients in 2016. HBO treatment was used in nine cases (75%). Although HBO is used in our institute in severe and prolonged DNI cases, and is not limited to cervical NF or DNM, its greatest benefits are thought to emerge in the most severe cases as stated in a recent literature review of 77 patients with head and neck NF (Acharya et al., 2022). As cervical NF is an uncommon disease and large-scale studies are lacking, Shaw et al. (2014) examined all necrotizing soft tissue infections (n=1583) and found a significant survival advantage in HBO-capable centers (Shaw et al., 2014).

5.1.5 Complications

In Study I, we found complications in 61 (22.0%) patients, of which NF (6.5%) and descending mediastinitis (4.3%) were among the most common. Severe consequences often accumulate in the same patients, and 18 (29.5%) had multiple complications. The ones we found were pneumonia 16 (5.8%), sepsis (bacteria found in blood culture) 13 (4.7%), nerve damage 12 (4.3%), internal jugular vein thrombosis 6 (2.2%), total airway obstruction at primary presentation 4 (1.4%), orocutaneous fistula 3 (1.1%), DIC 2 (0.7%), iatrogenic tracheal stenosis 2 (0.7%), delirium 1 (0.4%), and pulmonary embolism 1 (0.4%). The mortality rate was 1.4% (n=4). Complications are frequently reported in different ways in literature, and the definitions and diagnostic criteria of sepsis, mediastinitis or NF are seldom explicitly mentioned. Moreover, acute and late complications are rarely separated, and follow–up times could vary. However, similar numbers have been found previously, such as mortality rates of 0.0–2.6% and complications in 11.3–20.8% of patients (Boscolo-Rizzo et al., 2012; Ridder et al., 2005; Staffieri et al., 2014; Tapiovaara et al., 2017).

Gas formation was present in 41 (14.8%) patients in the imaging. Significantly higher complication rate 46.3% ($p<0.000$), mortality ($p<0.000$), need for revisions ($p<0.000$), longer LOS ($p<0.000$), ICU treatment ($p<0.000$) and ICU days ($p=0.008$) were found. NF is frequently associated with gas formation and thus could explain the more severe course of the disease (Gunaratne et al., 2018). However, a subgroup of clinically non-NF patients with gas containing lesions (n=26) also had increased rates of complications ($p=0.002$), mortality ($p=0.003$), LOS ($p=0.001$), ICU treatment ($p=0.014$) and ICU days ($p=0.036$), but revisions did not differ ($p=0.084$).

5.1.6 Bacteriology

Pus samples were taken from 226 (81.6%) patients and 193 of these (85.4%) were positive by culture. SAG (35.8%) and the *Prevotella* spp. were the most common. The most often encountered bacterial findings are specified in Table 2. Cultivation was polymicrobial in most of the cases (n=115; 59.6%). Findings in other studies have confirmed that these are typical causative organisms (Beka et al., 2019; Celakovsky et al., 2015; Furuholm et al., 2023; Klug et al., 2021). The streptococcal and *Prevotella* spp. are frequently found together. In this study, only in one (0.5%) case was *Prevotella* spp. the only pathogen identified. SAG bacteria are known to promote the metastatic spread of infection (Han & Kerschner, 2001). Their interaction with aerobic bacteria should be further studied.

Table 2. Five most common findings in positive bacterial cultures. Modified from study 1.

Bacterial cultures	No. cases	% [a]
Prevotella species	70	36.3
Streptococcus anginosus group (SAG)	69	35.8
Fusobacterium species	29	15.0
Staphylococcus aureus	22	11.4
Streptococcus pyogenes (GAS)	15	7.8

[a]Percentage of positive cultures (n=193)

5.1.7 Comparison to previously published data from our institute

A review published by Aitasalo in 2008 analyzed 293 patients from between 1985 and 2005 and these results were compared to the current data in Study I (Aitasalo, 2008). The DNIs' main characteristics are specified in Table 3.

Table 3. Characteristics of deep neck infections in two time periods. Modified from Study I.

	1985–2005 (n=293)	%	2006–2015 (n=239)	%	*p*-value
Patients (n)	293		239		
Patients/year/mean	14		24 (15–32)		
Male	168	57.3	152	63.6	0.142[a]
Female	125	42.7	87	36.4	0.142[a]
Age distribution (mean)	38.5		43.3		**0.000**[b]
Age distribution (range)	4–91		0.5–92		
Intensive care unit (ICU) treatment	61	20.8	58	24.3	0.342[a]
Hyberbaric oxygen (HBO) treatment	36	12.3	41	17.2	0.112[a]
Complications	42	14.3	55	23.0	**0.009**[a]
Comorbidity	51	17.4	103	43.1	**0.000**[a]
Mortality	0	0.0	4	1.7	**0.040**[c]
Odontogenic	64	21.8	101	42.3	**0.000**[a]
prev. dental surgery	32	10.9	16	6.7	0.091[a]
Pharyngotonsillar	69	23.5	92	38.5	**0.000**[a]
Unknown	54	18.4	16	6.7	**0.000**[a]

[a] Chi-square test, [b] One sample T-test, [c] Fisher's exact test

The trend in total annual numbers and odontogenic etiology was increasing. Several studies have confirmed similar developments (R. Hurley et al., 2018; Lau et al., 2014; Santos Gorjón et al., 2012; Seppänen et al., 2010; S. J. Thomas et al., 2008). The percentage of DNI of unknown origin had decreased. One possible explanation may be the more frequent use of OPG (53.1%) and increased teamwork between ENT specialists and OMF surgeons. The rate for the former cohort was not available, but lower rates have been reported in similar studies (36.5%) (Staffieri et al., 2014). Another reason for this development could be that advances in imaging technology enable more accurate diagnoses. A recent study has shown that systematic radiological analysis of CECT scans can help evaluate odontogenic etiology and the routes by which infections can spread, and predict the need for mechanical ventilation pre-operatively (Rautaporras et al., 2023). Parapharyngeal (39.0/19.2%), submandibular (28/30.1%) and retropharyngeal (11/12.5%) spaces were the most often involved in both cohorts. The complication rate was higher in the later cohort, possibly due to differences in reporting.

5.2 Feasibility of MRI in cases of neck infection (II)

5.2.1 Feasibility, and comparison with computed tomography

In Study II, 334 (72%) of the 461 primary neck scans were performed because of a suspected infection. Other indications were postoperative spine imaging, head and neck tumors, neck traumas, and dyspnea. Due to insufficient imaging quality, five (1%) MRI scans were not suitable for diagnostics, mostly due to movement artifacts. Two of them required CECT instead for sufficient diagnostics of odontogenic DNI. The result was a 99% technical success rate. When failures to complete planned MRI scans (n=25) were also taken into account, the overall success rate of emergency MRI was 95%. Routine acute neck MRI has not been studied earlier. One hundred ninety-six primary neck CT scans from the same period were found, 118 for suspected infection and 78 for other indications. CT scans were usually done at night and MRI gradually replaced daytime examinations (Figure 6). Twenty-two CT scans were performed instead of primarily requested MRI. Patient-related causes for this change in modality included restlessness (n=4), high fever (n=3), and dyspnea (n=2). In four cases, the cause was limited availability of an MRI scanner and in five cases it remained unknown. Based on Study II, the feasibility of MRI in emergency settings was good. Relatively few of the MRI scans of these acutely ill patients were non-diagnostic, and only a few patients were primarily excluded and underwent CT.

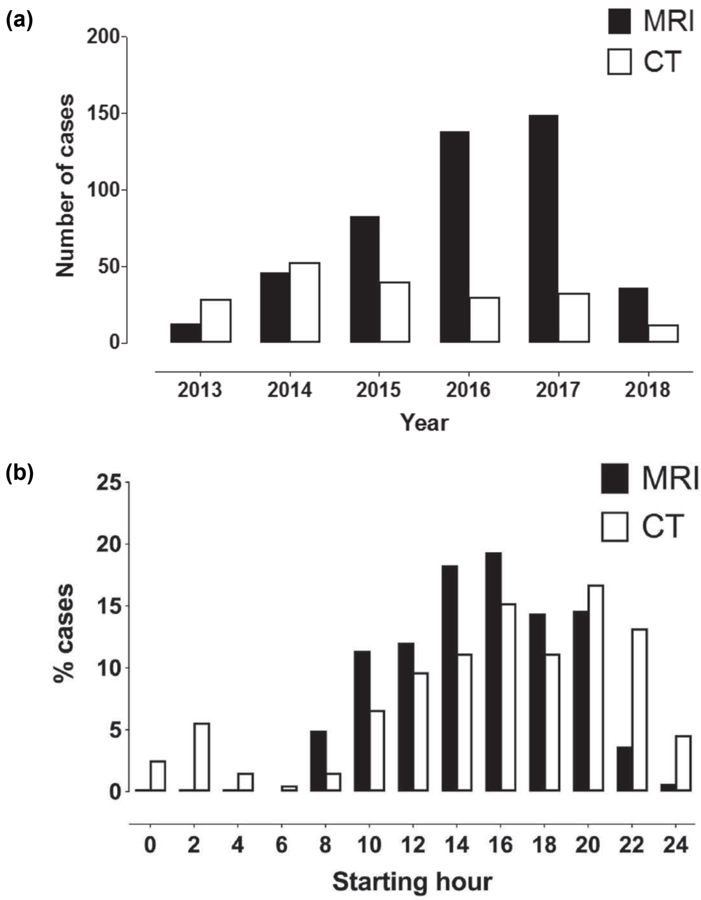

Figure 6. Comparison of numbers of primary studies of MRI and CT as annual totals (a), and in terms of cumulative distributions regarding time of day (b). Reproduced, with permission, from Study II.

5.2.2 Outcomes and diagnostic accuracy

The scans of the patients with suspected infections showed evidence of infection in 95% of cases. The main locations of the infections were the peritonsillar/parapharyngeal (43%) as well as the submandibular/sublingual and masticator/buccal (30%) sites. A total of 310 patients of the 317 suspected cases received a final clinical diagnosis of neck infection, rendering a positive predictive value (PPV) of 0.98 for infection. An abscess or multiple foci were found in 229 (72%) of the patients (Figure 7). One hundred ninety-three (84%) of these underwent a surgical intervention and purulence was found in 183 cases, producing a PPV of 0.95 and leaving 10 false positives (FP) in whom an abscess could not be found. In Study II, the PPV for MRI was higher than the 83–85% previously reported for CECT imaging (Freling et al., 2009; Hagelberg et al., 2022).

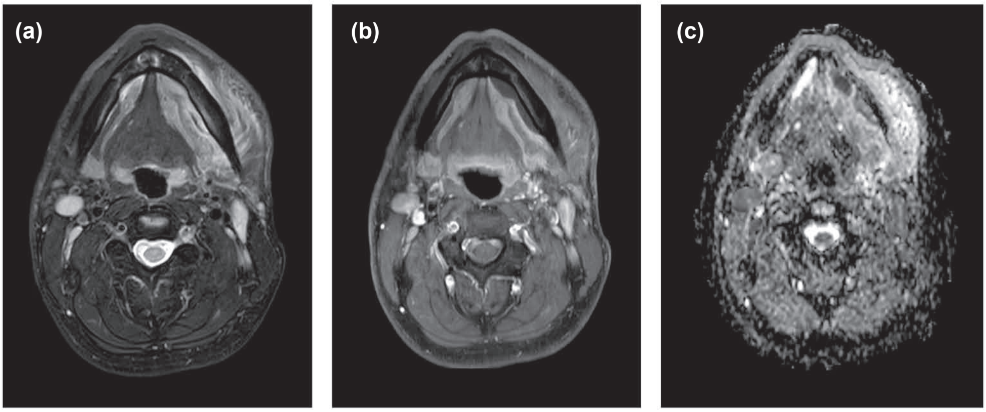

Figure 7. Submandibular space subperiosteal abscesses. A 32-year-old man presented with left submandibular space swelling and subsequent dental extraction. Axial MRI slices (a, T2-weighted Dixon water; b, gadolinium-enhanced T1-weighted Dixon water; c, apparent diffusion coefficient from diffusion weighted imaging) demonstrated non-enhancing collections with restricted diffusion surrounded by abnormal tissue enhancement on the medial aspect of the body of the mandible, consistent with subperiosteal abscesses. Modified from study II.

In addition, 22 patients underwent surgery (mainly TE) despite no MRI evidence of an abscess. Of these, 20 were true negatives (TN) and 2 were false negatives (FN). Among the neck infection patients without MRI evidence of an abscess (n=59), who had an uneventful recovery, i.e., TNs, we found a sensitivity of 0.99, a specificity of 0.89, and an accuracy of 0.96 for MRI diagnosis of an abscess. Thus, MRI had very high diagnostic accuracy and predictive value for both infection and abscesses. Moreover, the blind reader corresponded with the primary and secondary readings in 45/50 (90%) cases. Inter-observer agreement on the presence of an abscess was significant—the Kappa was 0.781, which is comparable to the absence of any intracranial hemorrhage (Kappa 0.78) in MRI found in a recent study (Van Der Ende et al., 2023).

Finding an abscess in DNI or severe OI is fundamental in decision-making when managing these infections (Boscolo-Rizzo et al., 2006). Low-density core, rim enhancement, bulging, and the presence of air have often been used as criteria to delineate an abscess in CT. However, none of the morphological criteria seemed to be highly accurate in a recent meta-analysis and the pooled estimated PPV was 0.83. The ability to differentiate phlegmon from an abscess may be difficult due to limited soft tissue contrast resolution (Hagelberg et al., 2022). Compared to the PPV of 0.95 of the MRI in this study, MRI could be an alternative to CECT as the primary modality in acute neck imaging. Moreover, it revealed infected neck spaces and abscesses more effectively than CT in a prospective series of 15 and 47 patients (Babu et al., 2018; Muñoz et al., 2001).

MRI has superior soft tissue discrimination, but the presence of purulent fluid can be misdiagnosed in cases of necrotic lymph nodes, as were the FPs we noted. In addition, small abscesses could be missed in surgery, which was used as a reference. More expensive costs, longer scanning time and contraindication for patients with severe dyspnea and restlessness or high fever are the drawbacks of MRI. Gas can be detected reliably in CT, whereas MRI may be less accurate and reveal intralesional gas (Muñoz et al., 2001). Nevertheless, avoiding ionizing radiation is a significant advantage of MRI, especially considering younger patients, and in cases of occasionally required repeated imaging. The high overall success rate, greater PPV value, and superior soft tissue discrimination support the use of MRI in the workup of acute neck infections.

5.3 Effect of timing of surgical intervention in pediatric deep neck infections (III)

5.3.1 Study population and clinical features

Of the 42 patients, 21 were male and 21 female. The age and gender distributions are shown in Figure 8. The mean age was 6.85 (SD 5.49) and varied between 0.5 and 16 years. Two patients had underlying illnesses. One had undergone radiotherapy to the head and neck area during early childhood and the other was on medication for juvenile rheumatoid arthritis.

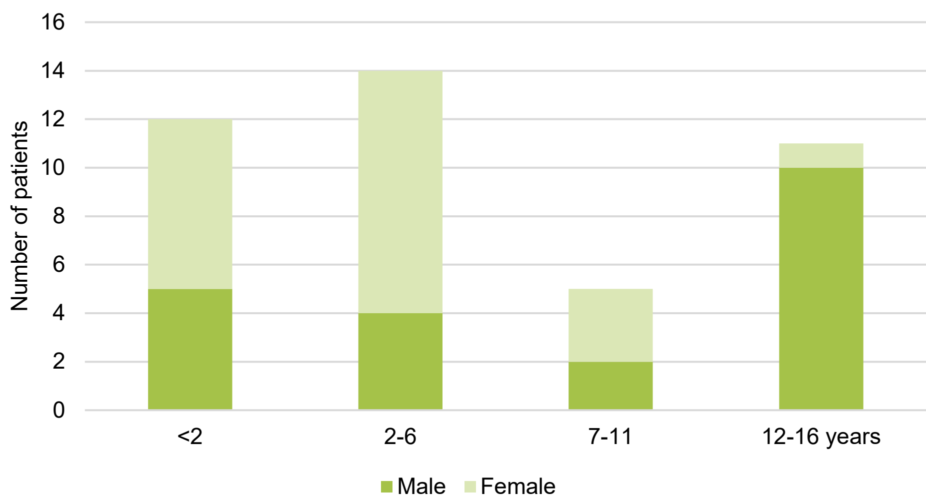

Figure 8. Age and gender distribution of pediatric DNIs. Modified from study III.

The mean duration of symptoms was 4.95 days (SD 3.19) varying between 1 and 14 days. Most of the patients presented with severe symptoms. The most common manifestations were neck swelling (n=39; 92.9%), neck pain (n=39; 92.9%), and fever (n=32;76.2). Twenty-two patients (52.4%) had limited neck movements (torticollis). The presenting signs and symptoms are specified in Figure 9. The symptoms described above—neck pain and swelling and limited movement—can be considered severe symptoms, but many of the other complaints may overlap with common upper respiratory tract infections. As DNI is a rare disease among children, vigilance is essential when treating patients with neck-related symptoms. Similar typical symptoms have also been previously identified (Donà et al., 2021; C. M. Huang et al., 2017).

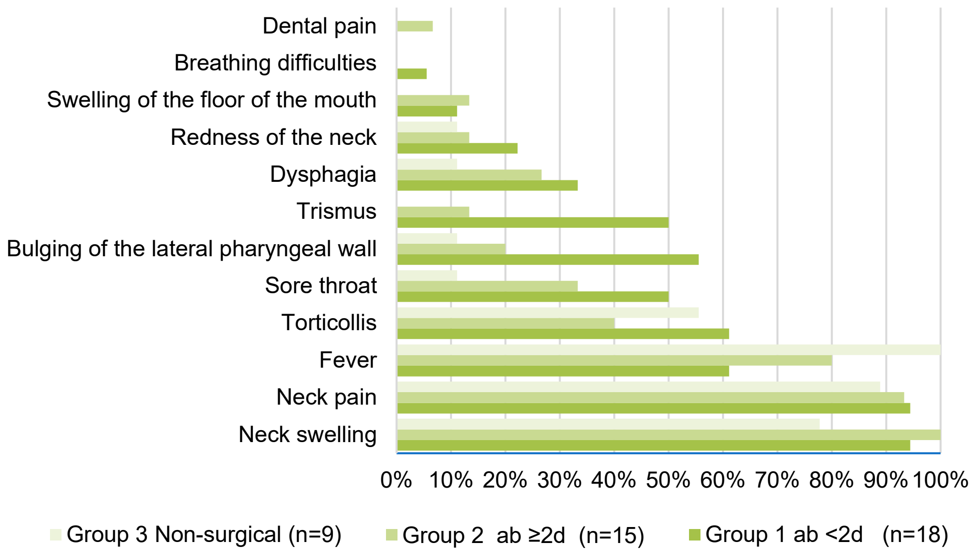

Figure 9. Presenting signs and symptoms of pediatric DNIs. Modified from study III.

5.3.2 Diagnosis and treatment

DNI was diagnosed using MRI in 24 (57.1%), CECT in 9 (26.2%) and ultrasound in 6 (14.3%) patients. The mean time lag between admission and the CECT or MRI scan was 1.26 days, varying between 0 and 6 days (SD 1.65). Twenty-two (51%) patients needed general anesthesia for imaging and the delay between admission and imaging was significantly longer in these cases (p=0.007). In 17 cases, MRI showed evidence of an abscess and in 15 (88.2%), purulence was found during surgery. An abscess was confirmed in CT in 9 cases and during surgery in 8 cases. Two FP were found in MRI and one in CT. According to Study III, MRI was utilized more frequently than the generally more commonly used CECT (Heilbronn et al., 2021; Virbalas & Friedman, 2021).

Mean CRP was 106 mg/L (range 4–380; SD 82.5) and mean WBC 19.4 E9/L (range 7.5–36.8; SD 7.57), and there was no difference between the groups (*p*=0.360, *p*=0.631). Intravenous antibiotics were initiated at admission to all patients. A cefuroxime–metronidazole combination 15 (35.7%), cefuroxime only 11 (26.2%) and cefuroxime combined with clindamycin 6 (14.3%) were the most frequently used treatment regimes, which is in line with former studies and reported microbiology (C. M. Huang et al., 2017). The need and time for surgery was individually evaluated on the basis of clinical and radiological examinations. A cervical incision was required in 23 (69.7%) and an intraoral incision in 10 (30.3%) cases. Moreover, seven patients had a concurrent TE and two an adenotomy or adenotonsillectomy. Dental extraction was performed in cases of OI (n=2).

Airway obstruction is a common reason for pediatric ICU (PICU) admission of children with retropharyngeal abscesses (Elsherif et al., 2010). In our cohort, 12 (28.6%) patients were treated in the PICU and their median age was 4.5 years. The mean LOS in the PICU was 4.3 days (range 1–17, SD 5.58) and the median 2.0 days. The mean overall LOS was 6.45 days (range 2–24 days, SD 4.36), and the median was 6.0 days, and 5.5 days for those managed surgically, similar to that reported by Wilkie et al. (2019), and the mean of 7.5 days reported by C. M. Huang et al. (2017). Younger children (<7 years) seemed to be admitted to the PICU more often (n=10; 38.5%, *p*=0.090) than older children (n=2), although the difference did not reach statistical significance. Elsherif et al. (2010) confirmed in an analysis of 130 pediatric patients with DNI that the mean age (3.7 years) of their PICU group was lower. Donà et al. (2021) investigated 153 patients and reported a median of 2.5 days in the PICU which is comparable to a median of 2.0 days in our study.

5.3.3 Microbiology

The microbiology of pediatric DNIs is specified in Table 4. According to Study III, *Staph. aureus* (n=7; 23.3%) and *S. pyogenes* (n=7; 23.3%) were most commonly found, which is consistent with several previous studies of pediatric patients (Cheng & Elden, 2013; Raffaldi et al., 2015; Wong et al., 2012). In addition, MRSA has also been mentioned as a significant pathogen in smaller (≤ 15 months) children in particular (Cheng & Elden, 2013; Inman et al., 2008). However, our Study III data showed only one case of MRSA (3.3%), which may be explained by the low local frequency of MRSA colonization in general (Rantakokko-Jalava, 2023; Tiemersma et al., 2004).

5.3.4 Outcomes and timing of operation

To assess the timing of surgery, we divided the patients into three subgroups. In Study III, Group 1 consisted of patients receiving intravenous antibiotics for less than two (<2) days (n=18; 42.9%), Group 2 of those who had medication preoperatively for a longer time (n=15; 35.7%) and those who were treated with medical therapy only. This process enabled us to harmonize the onset of the antibiotic treatment, but it must be noted that the medical treatment may have been initiated before exact diagnosis.

Table 4. Organisms found in bacterial cultures of pediatric deep neck infections. Modified from study III.

Bacterial cultures	**No. of culture findings**	**%[a]**
Staphylococcus aureus	7	23.3
Streptococcus pyogenes	7	23.3
Mixed flora	4	13.3
Viridans group streptococci (incl. *Streptococcus anginosus* group = SAG)	3	10.0
Prevotella species	3	10.0
Eikenella corrodens	1	3.3
Fusobacterium necrophorum	1	3.3
MRSA (methicillin-resistant *Staphylococcus aureus*)	1	3.3
Propionibacterium acnes	1	3.3
Negative culture	8	26.7

The percentage of samples available (n = 30) exceeded 100% due to multi-bacterial growth in 3 (10.0%) cases.

The abscess size in the groups (p=0.075) did not differ, although the mean size was smaller in non-surgical treatment Group 3. The neck incision rate was similar in the surgical treatment groups (p=0.072). The complication rates were 5.2% in Group 1, 13.3% in Group 2, and 33.3% in Group 3, but were not statistically significantly different (p=0.154). The key finding was the differences in overall LOS. The hospitalization period was shorter in Group 1 than in the delayed surgically treated Group 2 (mean 4.4 vs. 7.2; p=0.009) but the surgical groups and conservative treatment Group 3 did not differ. The longest mean LOS of 9.2 days was in conservative treatment Group 3, which is in line with related results concerning adults, and medically treated patients' longer LOS in a study by O'Brien (O'Brien et al., 2020). The outcomes are listed in Table 5.

According to Study III, the mean age in Group 1 was 9.6 years (range 0.9–16.0, SD 5.53), 3.6 years in Group 2 (range 0.5–14.0, SD 3.55), and the difference was significant (p=0.004). However, the mean age in Group 1 did not differ from the mean age of 6.9 years (range 0.8–15.0, SD 5.48) in non-surgical treatment Group 3. The mean abscess size was 27.6 mm (range 9–56 mm, SD 10.7). As shown in Table 5, the mean size was slightly smaller in the conservative subgroup (21 mm). Nonetheless, the difference was not significant (p=0.075). Being under four years of age could make primary surgical intervention more favorable (Lawrence & Bateman, 2017). A lower mean age in delayed surgery is not advocated. Given the long delay between admission and imaging when anesthesia was necessary, it is possible that the threshold for imaging younger children was higher, contributing in turn to the overall delay of surgery. Moreover, six patients (40%) in delayed surgery Group 2 had also undergone ultrasound before MRI. This could raise the question of a developing abscess or FN in ultrasound, causing postponement in obtaining more suitable imaging. Although ultrasound has been established as the gold standard for distinguishing cellulitis from abscesses in the cervical lymphadenitis, the limitations to seeing deeper structures are unquestionable (Maroldi et al., 2012). Furthermore, the known challenges of the neck anatomy may in some cases limit the possibilities of primary surgery. Cramer et al. showed an association between delayed drainage and morbidity and mortality among adults. Nonetheless, in the pediatric group they found no difference, although >3 days delay in surgery significantly increased LOS among both adults and children (Cramer et al., 2016). In our study, the overall LOS median was 6.0 days.

Table 5. Outcomes of the pediatric DNIs. Modified from study III.

Variable	Group 1 ab <2d (n=18)	Group 2 ab ≥2d (n=15)	Group 3 non-surgical (n= 9)	*p*-value
Pediatric ICU admission	4 (22.2%)	6 (40.0%)	2 (22.2%)	0.611[a]
Mean overall length of stay (median) days	4.4 (4.0)	7.2 (7.0)	9.2 (6.0)	**0.009**[b]
Mean size of abscess (median) mm	28 (26)	30 (30)	21 (19)	0.075[b]
Neck incision rate (%)	12 (66.7%)	11 (73.3%)	-	0.722[a]

Significant p-value is shown in bold

[a]Fisher's exact test

[b]Kruskal–Wallis test: significant difference between overall length of stay of Groups 1 and 2 in pairwise comparisons (Bonferroni-adjusted p=0.009)

Several authors have addressed the question of the roles of surgical and conservative treatment of pediatric DNIs. Smaller abscesses (<20–25 mm) among older children with a stable clinical condition, no airway problems, and a single space infection could be especially good candidates for non-surgical treatment with antibiotics (Elsherif et al., 2010; Grisaru-Soen et al., 2010; Wilkie et al., 2019; Wong et al., 2012). A multivariate analysis of 112 children found that older age was independently associated with successful conservative treatment. For every one-month increase in age, the probability of needing surgery decreased by 1% (Bolton et al., 2013). In 2017 Lawrence and Bateman proposed an evidence-based algorithm in which signs of airway compromise, the presence of complications, no clinical improvement after 48 hours of intravenous antimicrobials, an abscess of >22 mm in CT imaging, and age of <4 years could be indications for surgery (Lawrence & Bateman, 2017). Although our study was in favor of active surgery (<2 days after admission) as a means of achieving lower LOS, the initial non-surgical strategy was logical. Although surgical complications are rare, it is reasonable to avoid them, if complete healing without surgery is possible. Nonetheless, another key message in Study III was related to reducing delays in appropriate imaging, which could help achieve lower LOS in addition to a more accurate diagnosis.

Six patients had complications (14.3%). One patient required re-canalization after two days, but the others' recovery was uneventful after primary surgery. One case of pneumonia and one of *Rothia mucilaginosa* sepsis was noted in the surgically treated group. The conservative treatment group had two severely ill patients, of whom one had clival osteomyelitis. One nine-month-old patient had streptococcal sepsis and a small retropharyngeal fluid collection. Ultimately, mediastinitis developed, which was managed by a thoracoscopy and pleural drainage. One teenager had a parapharyngeal abscess (23 mm in max. dimension), *F. necrophorum* sepsis and internal jugular vein thrombosis. The disease was complicated by DIC and thrombocytopenia at presentation, and surgery was considered contraindicated at that time. Finally, all the patients were discharged without sequelae, and the median follow-up time was 44 days, varying between 3 and 695 days (SD 135.6). Complication rates of 6.7–11.5% have also been reported previously (Baldassari et al., 2011; Cheng & Elden, 2013; Elsherif et al., 2010). In an analysis of 135 pediatric patients with retropharyngeal or parapharyngeal infections, younger age was shown to associate with complications and longer LOS (Bolton et al., 2013). Severe complications occurred in the non-surgically treated group, and this might have been affected by the restricted sample size and multifactorial decision-making in individual cases mentioned above. Moreover, we found a tendency towards increased morbidity in PICU admission (22.2 vs. 40%) and the complication rate (5.2 vs. 13.3%) of the surgical groups. However, because of the limited number of patients, this was not statistically significant.

5.4 Predisposing and aggravating factors for hospitalized orofacial and neck infections patients (IV)

5.4.1 Patient characteristics and diagnostics

Ninety-four patients enrolled and completed the survey. Of these, 64 (68.1%) were males and 30 females (31.9%), and their mean age was 46.4 (18–82 years). The patient characteristics and underlying diseases are specified in Table 6. Thirty-five

(37.2%) patients were smokers, which is considerably higher than the average (Terveyden ja hyvinvoinninlaitos, 2022). They had OI (*p*=0.025) more often than the non-smokers. However, their LOS was similar (*p*=0.084) as its median was four days for the smokers and five days for the non-smokers. The complication rate was also comparable (*p*=0.761). The participants were mostly employed (n=53.2%). Educational level was mostly upper secondary, which is higher than the average in the Finnish population (Suomen virallinen tilasto, 2023). Three responses were missing. Fifty-two (55.3%) patients had no comorbidities. The most often reported systemic diseases were hypertension (19.1%), psychiatric disorders (11.7%), and DM (9.6%). A BMI of over 30 kg/m^2 did not significantly correlate with ICU admission (*p*=0.135), complications (*p*=0.498), or LOS (*p*=0.304).

Table 6. Patient demographics and comorbidities. Modified from Study IV.

Variable	**No. of patients (n=94)**	**%**
Age (mean, range)	46.4 (18–82)	
Socioeconomics		
Employed	50	53.2
Retired	26	27.7
Unemployed	13	13.8
Student	3	3.2
Other	2	2.1
Education (highest)		
Upper secondary level	56	59.6
Higher education	19	20.2
Primary school	16	17.0
Missing	3	3.2
Smoker	35	37.2
BMI kg/m^2 (mean, range)	28.2 (15.4–57.3)	
BMI >30	26	27.7
Comorbidities		
Hypertension	18	19.1
Psychiatric diagnosis	11	11.7
Diabetes	9	9.6
Heart and vascular disease	7	7.4
Lung disease (exc. asthma)	7	7.4
Malignancy (inc. previous)	4	4.3
Excess alcohol consumption	3	3.2
Immunocompromised	3	3.2
Chronic renal failure	1	1.1
Intravenous substance abuse	1	1.1
Healthy	52	55.3
Some or several co-morbidities	42	44.7

The most common origin of infection was odontogenic (n=63; 67%), and 17% (n=11) were categorized as dental post-operative infections. Pharyngotonsillar infection was the second most common (n=22; 23.4%). Other causes included two sialadenitis and one lymphadenitis, a neoplasm, otogenic origins, and cervical penetrating trauma. Three cases remained unknown.

The diagnosis of an infection requiring in-patient treatment was made by an on-call ENT or OMF surgeon on the basis of clinical, laboratory, and imaging findings. In this study, 45 (47.9%) patients underwent MRI, 8 (8.5%) CECT, 18 (19.1%) both. One ultrasound and one cone-beam CT were utilized. Repeated imaging (CECT or MRI) was performed in 20 (21.3%) cases. The main affected space was recognized in 88 (93.6%) cases, which is shown in Table 7. More than one affected space was reported in 41 (43.6%) cases on the basis of imaging. According to this data, mandibular molar infections, mostly periapical, were the most common cause of OI, which is in line with previous findings (Flynn et al., 2006; Seppänen et al., 2011). Thus, the submandibular space was among the most common spaces affected, because, as previously explained it offers a direct route for the infection to spread, which is associated with a higher risk of severe infection (Reynolds & Chow, 2007).

Table 7. Affected spaces identified in patients hospitalized with orofacial and neck infections in study IV.

Main affected space	No. of cases	%
Submandibular	15	16.0
Sublingual	15	16.0
Parapharyngeal	14	14.9
Masticator	11	11.7
Buccal	10	10.6
Ludwig's angina	4	4.3
Submental	3	3.2
Carotid	2	2.1
Base of tongue	2	2.1
Parotid	2	2.1
Other*	3	3.2
Multilocular**	7	7.4

*Other = one clavicular fossa, paratracheal, and retropharyngeal space
** If main space could not be identified from the numerous spaces

OPG (n=78) was possible in most cases (83%). Dental imaging findings were scrutinized in 68 cases and periapical infection 54 (79.4%), caries 19 (27.9%), pericoronitis 7 (10.3%) were found. In addition, in 6 (8.8%) cases, teeth were decayed to the root and 22 (32.4%) of these patients had multiple findings. Forty-two (44.7%) patients had poor dental health according to the radiological and clinical findings examined by OMF surgeon, which was significantly more common in the odontogenic subgroup (n=37; p=0.002), as expected. The dental status of 11 (11.7%) patients remained undetermined due to incomplete records.

CRP and WBC on admission were analyzed. The mean CRP was 139 mg/l, the median 127 (range 3–339; SD 81.8) and the mean WBC 15.0 $x10^9$/l and the median 14.1 (range 4.0–27.0; SD 5.0). Higher CRP values on admission were linked to re-operation (p=0.006) and complications (p=0.005), whereas WBC was not (p=0.722; p=0.147). Moreover, CRP on admission (p=0.001) was associated with prolonged hospitalization (7 days or over), but WBC (p=0.198), age (p=0.473), sex (p=0.741), or comorbidities (p=0.195) were not. Thus, these results are in accordance with those of previous studies, associating higher CRP with longer LOS and more severe disease (Riekert et al., 2019; Stathopoulos et al., 2017).

5.4.2 Variables affecting severity and LOS

We compared the signs and symptoms at presentation of the patients with a more severe clinical course to those of the others. A severe clinical course was described as prolonged LOS (≥7 days) or ICU treatment. The clinical symptoms and signs are shown in Table 8. Bilateral neck swelling (p=0.005) and swelling or erythema on the chest (p=0.003) were associated with longer LOS in the univariate analysis. Bulging of the lateral pharyngeal wall (p<0.001) and laryngeal edema (p<0.001) were also related to ICU treatment. These are serious findings and indicate a progressive stage of the illness. Laryngeal symptoms (edema, hoarseness) were significantly associated with ICU treatment, which is logical given their clear relationship with potential airway compromise. Former publications have shown that breathing difficulties are often linked to ICU treatment (Garcia et al., 2012). The median duration of symptoms before admission was 3 days and the mean was 4.3 days (1–20 days, SD 3.32). This duration did not differ in terms of educational level (p=0.852) or employment status (p=0.594).

Table 8. Clinical presentation on admission and associations to more severe clinical course. Modified from study IV.

Signs and symptoms	No. of patients (n)	%	7 days or longer LOS *p*-value	ICU treatment *p*-value
Neck pain	72	76.6	0.066[a]	0.343[a]
Neck swelling	70	74.5	0.062[a]	1.000[a]
bilateral	6	6.4	**0.005[a]**	0.070[a]
Sore throat	70	74.5	0.222[a]	0.062[a]
Dysphagia	56	59.6	0.634[b]	**0.034[b]**
Trismus	53	56.4	0.823[b]	0.752[b]
Edema of the floor of the mouth	38	40.4	0.944[b]	0.634[b]
bilateral	7	7.4	0.334[a]	**0.019[a]**
Fever >38 ° Celsius (C)	36	38.3	0.778[b]	0.412[b]
Facial swelling	34	36.2	0.231[b]	*0.004[b]
Bulging of lateral pharyngeal wall	32	34.0	0.211[b]	**<0.001[b]**
Redness of the neck	32	34.0	0.211[b]	0.904[b]
Dental pain	30	31.9	0.163[b]	*0.011[b]
Laryngeal swelling	20	21.3	0.348[a]	**<0.001[a]**
Torticollis	17	18.1	**<0.001[a]**	**0.012[a]**
Dyspnea	7	7.4	0.109[a]	0.109[a]
Hoarseness	5	5.3	0.207[a]	**0.042[a]**
Swelling or redness on the chest	5	5.3	**0.003[a]**	**0.040[a]**

[a] =*Fisher's exact,* [b]= *Chi-Square,* *negative predictive value

Dental care appointments and oral health habits were charted using a questionnaire, as partly presented in Table 9. Information on treatment before (<1 month) hospitalization was also collected. Most of the patients (n=44; 46.8%) had seen a dentist, 24 (25.5%) had seen a general practitioner or other physician, 16 a nurse, and 6 answers did not specify which medical professional the patient had seen. The first health care contact with the dentist appeared to be linked to shorter LOS (p=0.014). However, some milder dental infections (local anesthesia procedures were needed in 29.8% of cases) were included in the analysis, suggesting a precedence over shorter hospitalization. The negative link to ICU treatment with faciobuccal swelling (p=0.004) and dental pain (p=0.011) suggests this same tendency to a good overall prognosis. Fifty-five patients (58.5%) reported previous health care appointments due to an acute dental problem. Although 54.5% of these (n=30) reported being advised to seek additional treatment after their emergency appointment, 19 (63.3%) patients confirmed that they did not seek the suggested treatment. The main reasons behind this were specified as fear of the dentist (n=9), financial issues (n=4), and difficulty or insufficient access to follow-up care (n=2), which are common explanations for neglecting regular dental check-ups (Table 9).

Daily tooth brushing was significantly less frequent among patients with OIs (*p*=0.035). Higher education was also associated with more frequent daily brushing significantly more often than primary (*p*=0.005) or secondary/intermediate educational level (*p*=0.004). This study confirmed that poor commitment to oral health and oral hygiene habits and difficulties accessing follow-up treatment after emergency dental care are associated with severe orofacial and neck infections. Previous national surveys have shown that education level is related to oral health. Those with basic education rated their teeth and oral health as poorer and were more likely to be admitted to hospital for OI. On average, 46% of the males and 77% of the females in Finland reported brushing their teeth twice a day (Suominen-Taipale et al., 2008; Uittamo et al., 2020). Fear of the dentist was one of the main reasons for avoiding dental care in our survey (Table 8). In this study, 29.8% of the patients had been for a dental check-up during the preceding 12 months, which is lower than the average (52%) reported in the national data and may contribute to poorer oral health and infections (Suominen-Taipale et al., 2008).

Table 9. Dental care appointments and oral health habits. Modified from study IV.

	No. of patients (n)	**%**	
1. Regular dental check-up			
Yes	43	45.7	
No	50	53.2	
2. If yes, frequency			
Every six months	3	7.0	% of 43
Once a year	25	58.1	
Once in every two years	9	20.9	
Rarely	11	25.6	
Never	0	0.0	
3. Reason for no regular dental care check-ups			
Fear of dentist	26	52.0	% of 50
Financial issues	12	24.0	
Difficulty accessing treatment	9	18.0	
Lack of time	7	14.0	
Other	9	18.0	
4. When was the last time you had a dental check-up?			
Less than a year ago	47	50.0	
1–2 years ago	19	20.2	
3–4 years ago	7	7.4	
more than 4 years ago	20	21.3	
5. How often do you make an appointment for dental care due to an acute problem?			
4 times a year or more frequently	2	2.1	
2–3 times a year	2	2.1	
Once a year	3	3.2	
Less than once a year	87	92.6	
6. Do you brush your teeth daily?			
Yes	69	73.4	
No	25	26.6	

In Study IV, we investigated whether active dental focus management before admission could decrease LOS (Table 10). Dental extraction was performed on 68 (72.3%) patients, of which 46 (48.9%) took place at the hospital and 22 (23.4%) had taken place before admission. A mean of 2.6 teeth (range 1–13, SD 2.82) and a median of one tooth were removed. A slightly shorter mean LOS was found (5.23 vs. 6.13 days), but it did not reach statistical significance, possibly due to the limited number of patients. In addition, the number of removed teeth was negatively associated with daily brushing habits (p=0.026). Non-odontogenic infection patients stayed longer in hospital (p=0.032), which has also been previously reported among DNI patients (Staffieri et al., 2014).

Table 10. Effect of variables on length of stay (LOS). Modified from Study IV.

Variable	No. of patients (n)	%	LOS days (mean)	LOS days (median)	*p*-value*
All	93		5.88	4	
Smokers	35	38.9	5.00	4	0.084[b]
Non-smokers	55	61.1	6.58	5	
BMI > 30	25		5.4	5	0.304[b]
BMI < 30	63		6.08	4	
Dental extraction at hospital	46	67.6	6.13	4	0.889
Extraction before admission	22	32.4	5.27	4	
Comorbidity	41	44.1	6.73	5	0.284
No comorbidity	52	55.9	5.21	4	
Odontogenic	62	66.7	5.13	4	**0.032**
Non-odontogenic	31	33.3	7.47	5	

**Mann–Whitney U* test, [a] 4 missing values, [b] 5 missing values

5.4.3 Treatment

Most of the patients received cefuroxime combined with metronidazole (46.8%) or penicillin combined with metronidazole (37.2%) as empirical antimicrobial therapy, which was later specified according to bacterial susceptibility findings. Surgical intervention consisted of a neck incision and drainage +/- intraoral incision in 39 (41.5%) cases. Fifty-three (56.4%) patients underwent an intraoral incision, of which 28 (29.8%) were performed under local anesthesia alone.

Multidisciplinary treatment at the ICU was required in 17 (18.1%) cases, which is comparable to the 21% reported by Buckley et al (2019), but significantly lower than the 45% reported by Gams et al. (2017) for severe OIs. The mean ICU stay was 4.9 days (range 1–12) and the median 5 days. Prolonged ICU stay (≥7 days) was more common among the elderly patients, as their mean age was 64.5 and median 45 years. In the odontogenic subgroup, five patients (29.4%) needed ICU treatment and in the non-odontogenic group, 12 (70.6%). Daily HBO was given as adjuvant treatment to 10 (10.6%) patients for a mean of six days (range 3–10 days).

An abscess was found in surgery in 79 (84.0%) cases, five of which had "dishwater" pus. Dishwater pus was described as darkish, serous exudate with a foul odor, which was divergent from the dense yellowish pus that was more commonly found. The dishwater pus finding seemed to be associated with ICU treatment ($p<0.001$), prolonged ICU stay ($p=0.031$), revision surgery ($p<0.001$), and longer LOS ($p<0.0019$), but not with a worse outcome in terms of complications ($p=0.503$). In these cases, tissue necrosis or impaired circulation were not mentioned, and NF was not diagnosed. The dishwater type of purulence has been related to cervical NF (Gunaratne et al., 2018). In these five patients, it was clearly associated with a more severe clinical course. In addition, four of these five patients received HBO treatment and all of them were discharged with no significant sequelae. Further studies should be conducted to assess whether more aggressive treatment methods should be used in such cases.

Older age and comorbidities have shown to be risk factors for complications and longer LOS (Boscolo-Rizzo et al., 2012; Gujrathi et al., 2016; O'Brien et al., 2020) The data in Study IV confirmed that age is a risk factor for complications ($p=0.001$) and prolonged ICU treatment ($p=0.024$). The aging population and rising number of dementia patients may promote the increasing costs of health care because of severe OIs. The oral health of people with dementia could be enhanced if more effort was made to educate carers about the importance of regular dental care. Obesity was hypothesized in contributing to more severe disease, as previously published literature has described a higher rate of ICU admission and septic progression of obese patients with OI (Riekert et al., 2019; Weise et al., 2019). Nevertheless, BMI did not correlate with the increased ICU treatment, complications, or LOS in our data.

Study IV confirmed the association between poor oral health and deficient oral hygiene habits and severe orofacial and neck infections. The subgroup in our study using emergency dental services appeared to be at higher risk of hospitalization. However, nearly two-thirds of those in need of further treatment did not apply for it. Among other preventive measures, ensuring sufficient access to follow-up care, especially for these patients, could reduce the significant costs of inpatient care and surgery. Moreover, dishwater pus was associated with more severe disease, and special attention should be paid to this when monitoring these patients for progressive disease.

5.5 Clinical aspects and discussion (I-IV)

Characteristics of patients with DNI and OI in this thesis are comparable to those described in the previous literature. There was male predominance in Studies I and IV. In pediatric population, the same overexpression has been reported earlier (Cheng & Elden, 2013; Côrte et al., 2017), however in our Study III, the gender groups were equal. As earlier discussed, poorer oral hygiene in adult males could be behind this, nevertheless some other mechanisms might be causing this difference in pediatric population. Sex differences in pediatric infections in general have been reported, and underlying immunological mechanisms have been proposed (Muenchhoff & Goulder, 2014). Smoking seemed to be overexpressed among hospitalized orofacial and DNI patients according to Study IV. Smoking could alter the oral microbiota and higher incidence of acute teeth removal has also been reported (Rautaporras et al., 2022). Moreover, smoking is the most important independent risk factor for head and neck cancer alongside with heavy alcohol consumption (Lewin et al., 1998). Special attention should be paid to these patients as DNI could be the first manifestation of head and neck malignancy (5.6%) and histopathological specimens are recommended at the time of surgery (Ridder et al., 2005).

Comorbidities were a predisposing factor for a more severe course of disease in this thesis. Moreover, higher age was shown to be a risk factor for complication and prolonged ICU stay. The rising trend of DNIs observed in Study I and increasing elderly population with underlying diseases, could lead to a cumulative need for healthcare (Fu et al., 2018). Clinicians should pay attention to the comorbidity burden of these patients, which is essential to determine prognosis and treatment optimization.

Empiric parenteral antibiotics used for the treatment of DNIs and severe OIs are chosen based on the frequent polymicrobial etiology. The most often used regimen are specified in Table 11.

Table 11. Empiric antibiotics commonly used in Studies I, III-IV.

Antibiotic regimen	**Study I No. of patients (n=277)**	**Study III No. of patients (n=42)**	**Study IV No. of patients (n=94)**
Penicillin + metronidazole	75 (27.1%)	5 (11.9%)	35 (37.2%)
Cefuroxime + metronidazole	135 (48.7%)	15 (35.7%)	44 (46.8%)
Cefuroxime + clindamycin	7 (2.5%)	6 (14.3%)	1 (1.1%)
Cefuroxime	16 (5.8%)	11 (26.2%)	3 (3.2%)
Clindamycin	14 (5.1%)	1 (2.4%)	1 (1.1%)
Carbapenems	16 (5.8%)	-	2 (2.1%)

The subsequent data from Study IV, show a preference for penicillin in combination with metronidazole, which may reflect the opinion of current antibiotic use guidelines (Acute odontogenic infections and antimicrobial treatments. Current Care Guidelines 2022). The higher use of cefuroxime and clindamycin in pediatric patients with DNI, is consistent with the differences in the most common bacterial etiologies in children shown in Study III (*Staph. aureus* and *S. pyogenes*). The use of piperacillin-tazobactam as primary treatment seems to be low, however in Study I, it was the second line treatment in 21 (7.6%) patients and in 10 (10.6%) in Study IV. Nevertheless, the use of broad-spectrum antibiotics is reasoned and should be kept in mind when treating critically ill patients requiring ICU treatment (Weise et al., 2019). Patients presenting with bulging of the lateral pharyngeal wall, laryngeal swelling, dysphagia, torticollis, bilateral swelling of the floor of the mouth, hoarseness, or swelling or redness on the chest area were shown to need ICU treatment more often in Study IV. Moreover, early detection of these signs could help in selecting sufficiently effective first-line antibiotics.

The increased use of preoperative CT imaging in the diagnostics of severe OIs, has been speculated to increase the need for intensive care, as inflammation of deep structures and changes in the anatomy of the upper airway are more visible (Fu et al., 2018). MRI has been shown to delineate more infected spaces than CT (Babu et al., 2018). In Study II, MRI was shown to be feasible and accurate imaging method to confirm suspected neck infection. MRI was also used in majority (57%) of the patients with pediatric DNI in Study III. Inflammatory changes and tissue swelling cause enhanced lesions, especially in MRI. Experience is warranted in interpreting these changes and clinicians should communicate pre-operatively with radiologists to achieve best consensus for treatment planning. Anatomically accurate imaging is crucial for optimal surgical planning, and by combining clinical evaluation of airway and other status findings with imaging, the fear of overuse of intensive care treatment could be overcome (Miller et al., 1999). Moreover, imaging could reveal gas bubbles, which were associated to a more severe course of infection in Study I. In Study III, we emphasized the timely use of imaging to reduce delays and eventually overall LOS. The diagnosis of DNI is confirmed by cross-sectional imaging and ultrasound is not usually sufficient to visualize deeper structures (Maroldi et al., 2012).

One aim for this thesis was to investigate the possible factors to promote healing process. In Study III, surgical treatment early in the course of the disease, was associated with decreased LOS in children. In adults, surgical management of an abscess is usually a more straightforward decision, and when surgery is needed, delays should be avoided. Delay in surgical drainage has been proven to increase morbidity and mortality (Cramer et al., 2016). However, we found in Study I, that early extraction of the dental foci was related to a lower LOS. Dentists and doctors in primary care should be aware and trained to treat localized infections according to etiology. Antibiotics alone should not be given for primary treatment of OI without treatment of dental foci (Uittamo et al., 2020). In Study IV, the challenges in implementing the additional follow-up treatment after the emergency dental appointment became clear for this subgroup of patients in high risk for hospitalization. Focusing resources on care protocols of these patients could reduce admissions.

5.6 Limitations

DNIs and severe OIs are relatively rare diseases, and the literature has been dominated by retrospective study designs in order to obtain a sufficient study population. The retrospective nature of Studies I–III sets certain limitations to the patient data due to the inaccuracy or missing data of the medical records. All the data collected for chart review is prone to misclassification bias. Moreover, the groups may have had other risk factors that were not considered. The time periods of the studied retrospective cohorts were 5 to 16 years. To overcome the limitation of the restricted number of patients in single center studies, we had a longer time, which allowed us to analyze more cases, especially in pediatric Study III. One disadvantage of this approach is the risk of a lack of homogeneity, because so many different people are involved in patient care. In addition, a long study period may include differences in diagnostics and treatment practices. In addition, the follow-up time in Studies I and III varied, which could bias the results.

In Study II, the estimation of diagnostic accuracy was based on the reference standard of surgery. Obviously, patients with an abscess are more likely to undergo surgery, forming a partial verification bias. Basically, for the same reason, because the proportions of TNs and FNs are uncertain, sensitivity was overestimated, and specificity underestimated. However, this drawback also concerns previous studies that have used CT. From a clinician’s point of view, we could argue that patients who have recovered uneventfully with non-surgical treatment are TNs. Moreover, improvement of PPV with more precise diagnostics by MRI could prevent unnecessary surgery.

In Study III, the small sample size in the different groups and the exact diagnosis at the time of the initial parenteral antibiotic therapy were clear shortages. The progressive nature of this disease and the different imaging methods create uncertainty, but the groups’ measures of the clinical symptoms, laboratory values, and imaging findings appeared to be comparable.

Study IV had clear selection bias because not all patients treated during that period participated in the study. Only patients with written consent were included. Nevertheless, the prospective study design strengthened the equality of the data.

5.7 Future perspectives

The management of DNIs and severe OIs is a relatively common challenge in every major hospital. The increasing economic burden on health care services and the rising number of DNIs and severe OIs justifies future research on this topic. As in many areas of medicine, prospective research is limited to guide treatment. The prospective evaluations of treatment strategies could better answer the questions about, for example, the role of initial non-surgical treatment in selected cases. As it has been for decades, surgery is still the mainstay treatment for evacuating purulence, and it is likely to remain valid.

Extremely diverse bacterial flora is responsible for these infections, and we need to better understand their pathogenicity and synergism. Modern detection methods, such as NGS analysis with nearly incalculable bacterial findings, has brought new light to understanding the microbiota of odontogenic abscesses (Böttger et al., 2021). The limitations of culture-based techniques have become clear, increasing the importance of easier-to-grow bacteria, and probably underdetecting the more challenging anaerobes such as the *Prevotella*, *Parviromonas* and *Fusobacterium* spp. Thus, the relevance of current antibiotic susceptibility tests of DNI and OI samples may be questionable. Future studies could show how we can utilize novel techniques in clinical practice, especially when treating critically ill patients and possibly diagnosing and guiding treatment according to PCR- and NGS-based data. If we could overcome the higher costs, the need for massive data analysis, the management of the continuously ongoing evolution of bacterial resistance at the gene level and of genome sequencing-based methods, we might be able to update treatment strategies (Avershina et al., 2023).

The significance of HBO therapy in treating necrotizing soft tissue infections has been debated. A recent systematic review and meta-analysis by C. Huang et al. (2023), which included 49 152 patients with necrotizing soft tissue infections, of whom 1448 received HBO therapy, implies that HBO helps to reduce mortality and complications. HBO therapy in prolonged DNIs and severe OIs is more difficult to assess. Large patient cohorts are most likely needed to find the possible advantages. Due to the significant expenses of HBO treatment, cost-effectiveness would be an essential part of the analysis. Cervical NF and DNM are two subgroups of necrotizing soft tissue infections and particularly rare diseases. An increasing number of retrospective studies have suggested that the same benefits could apply to these diseases. However, multicenter studies, preferably prospective, would be optimal for clarifying this issue (Acharya et al., 2022).

The cornerstones of the successful treatment of DNIs and severe OIs are early diagnosis, prompt management strategies to secure airways, antimicrobial therapy and surgical treatment, including treatment of possible dental foci in the early stage of the disease (Heim et al., 2019). Technical advancements in the field of imaging and the better availability of acute MRI have promoted the use of MRI in neck infections in our practice. More precise imaging with MRI, or dual-energy CT combined with enhanced image reconstruction, could lead to better identification of abscesses and to the detection of possible prognostic factors. Future research is needed to study these aspects.

The aim of preventing rising costs of the health care system is well-grounded. As stated in this thesis, many DNIs are preventable by promoting good oral health. In future studies, the emphasis should be on prevention, and on promoting early recognition and timely and efficient treatment.

6 Conclusions

We can draw the following conclusions on the basis of the clinical studies presented:

1. There is a clear upward trend in the annual numbers of DNIs with odontogenic etiology being the main origin. DNIs continue to cause fatal complications; the mortality rate was 1.% and overall complications occurred in 61 (22.0%) patients.

2. MRI proved to be feasible. It has a high technical success rate in emergency settings, and it detects neck infections with a high accuracy (PPV for abscesses, 0.95). These results promote MRI as an alternative to CT as the first or only imaging modality in neck emergencies.

3. Early surgical intervention (less than two days after admission) was associated with decreased LOS among severe pediatric DNI patients.

4. Poor oral health and dental hygiene habits proved to be a risk factor for hospitalization, showing that access to professional preventive treatment and daily dental hygiene after urgent care must be improved. Higher age, underlying diseases, and dishwater pus contributed to complications, whereas laryngeal or parapharyngeal swelling contributed to more severe disease.

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Appendices

Appendix 1. Supplemental material for Study II, published online.

Detailed MRI protocol

MRI was performed on a Philips Ingenia 3 Tesla system using dS HeadNeckSpine coil configuration (Philips Healthcare, Best, Netherlands). In 84 of the 461 (18%) cases, we used an older protocol consisting of axial T2 TSE (slice thickness 3 mm, TE=80 ms, TR=3203 ms), coronal T2 SPAIR (slice thickness 3 mm, TE=80 ms, TR=3608 ms), sagittal T1 TSE (slice thickness 3 mm, TE=16 ms, TR=641 ms), axial DWI (slice thickness 4 mm, TE=86 ms, TR=4843 ms, b-value 1000 s/mm2), axial T1 SPIR after Gd (slice thickness 3 mm, TE=18 ms, TR=651 ms), and coronal T1 TSE after gadolinium (Gd) (slice thickness 3 mm, TE=16 ms, TR=604 ms). In the majority of the cases (377 of 461, 82%), we used a novel protocol consisting of axial T1 TSE (slice thickness 4 mm, TE=10 ms, TR=641 ms), axial T2 TSE Dixon (slice thickness 4 mm, TE=100 ms, TR=3021 ms), coronal T2 TSE Dixon (slice thickness 3.5 mm, TE=80 ms, TR=3210 ms), axial DWI (slice thickness 4 mm, TE=87 ms, TR=3981 ms, b-value 1000 s/mm2), and three T1 TSE Dixon sequences after Gd: axial (slice thickness 4 mm, TE=7 ms, TR=634 ms), coronal (slice thickness 3.5 mm, TE=14 ms, TR=560 ms), and sagittal (slice thickness 3 mm, TE=14 ms, TR=630 ms).

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