SEVERE ODONTOGENIC INFECTIONS

Studies on local and systemic odontogenic infections requiring hospital care

Lotta Grönholm

Academic Dissertation

To be publicly discussed, with permission of the Medical Faculty of the University of Helsinki, in the small auditorium of the Haartman Institute, Helsinki 30\textsuperscript{th} November, 2012, at 12 o’clock noon
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“Non, je ne regrette rien”

Edith Piaf
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This thesis is based on following original articles, which are referred to in the text by the Roman numerals indicated below:


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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>AP</td>
<td>Antibiotic prophylaxis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
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<tr>
<td>FPIC</td>
<td>Finnish Patient Insurance Centre</td>
</tr>
<tr>
<td>HHV-1</td>
<td>Human herpesvirus 1</td>
</tr>
<tr>
<td>HHV-2</td>
<td>Human herpesvirus 2</td>
</tr>
<tr>
<td>HHV-5</td>
<td>Human herpesvirus 5</td>
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<tr>
<td>HZV</td>
<td>Herpes zoster virus</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>HUCH</td>
<td>Helsinki University Central Hospital</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IE</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroid anti-inflammatory drug</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RCT</td>
<td>Root canal treatment</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>SSI</td>
<td>Surgical site infection</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
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ABSTRACT

Odontogenic infections can spread either locally causing cellulitis and abscess formation, or by dissemination causing distant site infections. The aim of this study was to analyse the course of infection and predisposing factors for local and systemic odontogenic infections requiring hospital care.

This retrospective cohort study consisted of four populations (Studies I-IV). To analyse the clinical picture and predisposing factors of local and systemic odontogenic infections requiring hospital care, patient material from the years 2000-2003 was collected from the Finnish Patient Insurance Centre (FPIC) comprising the first study population (n=35) (Study I). To analyse predisposing factors and the course of locally invasive odontogenic infection, patient material was gathered from the Department of Oral and Maxillofacial Diseases at Helsinki University Central Hospital (HUCH), which operates in the Surgical Hospital and in Töölö Hospital (Studies II-IV). The second study population was comprised of medical records from all cases of odontogenic maxillofacial infections that led to hospitalisation during the years 1994-1996 (n=71) and 2004 (n=101) (Study II). The third study population was comprised of medical records and panoramic radiographs of patient cases, which led to hospitalisation due to odontogenic maxillofacial infection (n=84) in 2004 (Study III). The fourth study population was comprised of medical records and panoramic radiographs of patients admitted to hospital due to odontogenic maxillofacial infection with periapical pathology as the source of infection (n=60) in 2004 (Study IV).

In Study I, medically compromised patients appeared to be more susceptible to developing systemic infection with longer hospital care and, occasionally, fatal outcome. Previously healthy patients, on the contrary, appear to develop local infection complications with cellulitis and abscess formation more commonly.

In Study II, the course of odontogenic maxillofacial infections requiring hospital care became more severe and the incidence increased from 5.3 to 7.2 per 100,000 inhabitants between the two study cohorts one decade apart. The need for intensive care increased from 15% to 32%. The maximal C-reactive protein
(CRP) levels were significantly higher in the latter study cohort (median 127mg/L) compared to the first cohort one decade earlier (median 104mg/L). The proportion of previously healthy patients had decreased from 83% to 65% between the studied cohorts, thus underlying systemic diseases became more prevalent. In particular, the number of patients with mental disorders hospitalised due to odontogenic maxillofacial infections had increased considerably from 0 to 13%.

Odontogenic maxillofacial infections requiring hospital care were complications that mainly developed after dental treatment (58%) (Study III). Ongoing primary root canal treatment (RCT) was the most common endodontic procedure preceding the spread of infection due to apical periodontitis (70%). Initiation of primary RCT with inadequate or incomplete RCT of acute apical periodontitis seems to open a risk window for the locally invasive spread of infection to adjacent structures with local abscess formation and systemic symptoms (Study IV). Thereafter, the quality of the complete RCT appears to have minor impact on the risk for flare-up. Although a dental procedure may provoke a flare-up of a pre-existing infection, leaving the potential source of infection untreated creates a considerable risk for severe infection complications.

Microbiological findings from pus samples showed considerable changes between the patient groups with different antecedent dental care history of the focus teeth (Study IV). Aerobic gram-positive bacteria were more commonly found in the pus cultures from patients with preceding endodontic treatment compared to those from patients without preceding treatment, where anaerobic gram-negative bacteria were predominant. Thus, RCT was shown to efficiently prevent the growth and reduce the number of anaerobic bacteria in the root canal system and subsequently in the periapical abscesses.

Finally, patients without preceding dental treatment in the near past had poorer overall dental health and more potential infection focus sites. In this study, the presence of multiple chronic infection sites led to stronger systemic response and more severe course of infection (Studies III and IV).
1 INTRODUCTION

The oral cavity has various fundamental functions. Besides playing an important role in ingesting, speaking, and breathing, it is an entry from the external environment to the gastrointestinal tract and the human immune system. In health, oral microorganisms and the host immune system are in ecological equilibrium, which is a premise for sustaining a barrier against ingested pathogens. Our knowledge of these oral microorganisms and their role in health and oral diseases has increased during the past decades. As the number of dentate people and preserved teeth have increased in time, potential sources of infection in the oral cavity, such as apical periodontitis, have become more prevalent (Rautemaa et al. 2007). As restorative or endodontic treatment of a tooth may be demanding and rarely permanent, the increasing number of teeth with restorative and endodontic treatment may be a ticking time bomb. Indeed, the quality of endodontically treated teeth when assessed as a distance from the root filling to the root apex (adequate distance ≤3mm) has been shown to need improvement, especially in molars (Huurnonen et al. 2012).

The nature of local infections, such as periodontitis and apical periodontitis, is usually chronic. The role of periodontitis in the development of various systemic diseases, such as cardiovascular diseases (CVD), has become apparent (Mattila et al. 2005). Acute infections, however, have been shown to influence lipoproteins and atherogenesis as well (Mattila et al. 1998, Khovidhunkit et al. 2000). Thus, odontogenic infections may have long-term effects on human health.

The presence of local or systemic risk factors predisposes for locally invasive spread of infection to adjacent structures, or dissemination as sepsis and/or by a haematogenous route to various sites in the organ system, such as in infective endocarditis (IE). The treatment of localised odontogenic infections with cellulitis and abscess formation is well established and the prognosis is usually good (Blomquist et al. 1988, Flynn 2000). If left untreated or treated with delay, locally invasive odontogenic infections may require hospital care (Saito et al. 2011). There is, however, limited knowledge on the preceding events before hospital admission as the scientific interest has mainly focused on surgical
aspects. In addition, risk factors for severe odontogenic infections are scantly surveyed and the knowledge is mainly based on case reports and extrapolations from other infection complications. The prognosis of disseminated infections may be unpredictable and patients are invariably in the need of hospital care. Although severe local and systemic odontogenic infections requiring hospital care are rare, they still constitute a major cause of morbidity and mortality in dentistry. This is especially true among the growing number of dentate patients with pre-existing medical conditions.
2 REVIEW OF THE LITERATURE

2.1 Oral microbiota

The oral cavity carries a unique and diverse community of various microbes that exist in equilibrium with the host immune system in the healthy state. Similar to the gastrointestinal tract and vagina, the oral cavity is densely colonised with microbes due to its exposure to the external environment. The oral cavity possesses a unique feature, which cannot be found elsewhere in the body: the presence of non-shedding surfaces, enamel and cementum of the teeth. These enable the formation of biofilm with substantial microbial diversity. These microorganisms colonising teeth, gingival sulcus, tongue, cheeks, hard and soft palate, have been referred to in the literature as the normal flora, microflora, microbiome, or the oral microbiota as in this study (Dewhirst et al. 2010). The oral microbiota consists of bacteria, viruses, fungi, and parasites, although bacteria are the predominant microorganisms found in the oral microbiota.

Our knowledge of the oral microbiota has emerged as the molecular methods and culture-independent taxonomy have developed. Nearly 300 bacterial species have been isolated by culture and identified from the oral cavity (Paster et al. 2006, Dewhirst et al. 2010). Using culture-independent methods, over 700 microbial species overall have been identified (Aas et al. 2005, Paster et al. 2006, Dewhirst et al. 2010). The identification of additional species has been achieved with recently adopted cloning and sequencing methods (Keijser et al. 2008). By these methods, however, only predominant species can be identified in a sample. Keijser et al. introduced a novel pyrosequencing method for detail analysis of oral microbiota. They reported 3621 species-level phylotypes in saliva and 6888 in plaque and estimated a number of 19000 species-level phylotypes in the oral microbiota representing significantly higher number than previously reported. In addition, by this novel method, the relative abundance of each species-level phylotype can be estimated. The majority (99.6%) of the sequences belonged to seven phyla: Actinobacteria, Bacteroides, Firmicutes, Fusobacteria,
*Proteobacteria, Spirochetes,* and candidate division TM7. Of these, *Actinobacteria, Fusobacteria,* and *Spirochetes* were overrepresented in plaque, while *Bacteroides, Firmicutes,* and *Proteobacteria* were abundant in saliva.

There are several classifications for different bacterial species. In clinical practise, gram staining, morphology, and growth patterns are used. Gram-staining characterises bacteria according to the structure of the cell wall. The thick layers of peptidoglycan in the gram-positive cell wall stain purple, while the thin gram-negative cell wall appears as pink. Bacteria are classified also by their morphology to cocci and bacilli (rods). Bacteria are further classified by their growth pattern to aerobic, anaerobic, and facultative metabolism, and by their pattern of haemolysis.

Different surfaces in the oral cavity inhabit specific bacteria. Viridans group streptococci (alpha/nonhaemolytic streptococci) are a heterogenous group of streptococci, which are commensal inhabitants of the oropharyngeal cavity, the gastrointestinal tract, and the genital tract (Maeda et al. 2010). These streptococci are categorised to four groups: the salivarius group (*S. salivarius, S. vestibularis*), the mitis group (*S. oralis, S. mitis*), the anginosus group (*S. anginosus, S. constellatus, S. intermedius*), and the mutans group (*S. mutans, S. sobrinus*) (Maeda et al. 2010).

*Streptococcus, Gemella, Granulicatella* and *Veillonella* spp. are common findings in the oral cavity (Aas et al. 2005, Paster et al. 2006, Keijser et al. 2008). *S. mitis* has been the most commonly detected species at all sites (Aas et al. 2005). In the supragingival plaque, several species of *Streptococcus,* such as *S. sanguinis* and *S. gordonii,* *Actinomyces spp., Rothia dentocariosa,* and *Abiotrophia defectiva* are common findings (Paster et al. 2006). In the periodontal pockets, anaerobic pathogens, such as *Porphyromonas gingivalis, Treponema denticola, Aggregatibacter actinomycetemcomitans,* and *Tannerella forsythia* are predominant in addition to *Streptococcus* and *Gemella* spp. (Aas et al. 2005, Socransky et al. 2005, Paster et al. 2006, Rautemaa et al. 2007).
Odontogenic abscesses are polymicrobial infections comprising aerobic and anaerobic bacteria. Viridans group streptococci (alpha/nonhaemolytic streptococci) are the predominant species in pus samples (Rega et al. 2006, Rautemaa et al. 2007, Al-Qamachi et al. 2010, Sánchez et al. 2011). In addition, staphylococci are frequently isolated (Rega et al. 2006, Rautemaa et al. 2007, Al-Qamachi et al. 2010, Sánchez et al. 2011).

Anaerobic bacteria in odontogenic abscesses comprise mainly gram-positive cocci and gram-negative rods. *Prevotella, Porphyromonas,* and *Fusobacterium* spp. are commonly detected anaerobic gram-negative rods (Stefanopoulos et al. 2004, Rega et al. 2006). Pigmented *Prevotella* spp., such as *P. intermedia* and *P. melaninogenica,* and non-pigmented *Prevotella* spp., such as *P. oralis, P. oris,* and *P. buccae* are frequently isolated in odontogenic abscesses (Stefanopoulos et al. 2004). Of the *Porphyromonas* spp., *P. endodontalis* is almost exclusively linked to abscesses of endodontic origin and *P. gingivalis* to periodontal origin (Stefanopoulos et al. 2004). In the head and neck region *F. nucleatum* and *F. necrophorum* are the two most important pathogens of the *Fusobacterium* spp. (Stefanopoulos et al. 2004).

Anaerobic gram-positive rods, such as *Eubacterium, Actinomyces, Lactobacillus,* and *Bifidobacterium* spp. and *Micromonas micros* are frequently isolated from pus samples (Stefanopoulos et al. 2004, Sánchez et al. 2011). Of these, *Eubacterium* spp. has been suspected to have an important role in abscess formation despite its low virulence (Stefanopoulos et al. 2004). Microaerophilic bacteria, *S. anginosus, S. constellatus,* and *S. intermedius,* of the anginosus group streptococci, are frequently found pathogens in odontogenic abscesses (Stefanopoulos et al. 2004).

Fungi are eukaryotic microorganisms, which may inhabit the oral cavity. The fungi present in the mouth are either saprophytic or facultative pathogens. *Candida albicans* is the most common opportunistic yeast of *Candida* spp. and belongs to the commensal flora of the mouth (Thein et al. 2009). Other clinically relevant *Candida* spp. are *C. tropicalis, C. glabrata, C. parapsilosis,* and *C. krusei.*
Although the mean colonisation rate of *C. albicans* in healthy individuals has been reported to be 17.7% with a wide range of 1.9-62.3% depending on the studied population, only a minority develop local infection as oral candidosis (Cannon *et al.* 1999). Higher colonisation rates are associated to medically compromised patients and hospital care (Cannon *et al.* 1999, Siahi-Benlarbi *et al.* 2008, Rautemaa *et al.* 2011). Oral candidosis may manifest as acute or chronic infection. Pseudomembranous (thrush), erythematous, and hyperplastic candidosis, in addition to angular cheilitis, are local forms of candidosis. Chronic mucocutaneous candidosis is a rare form of candidosis and appears as complex syndromes with systemic manifestations. Chronic candidosis is also related to oral cancer in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) (Rautemaa *et al.* 2007). Disseminated *Candida* infections are mainly seen in medically compromised patients (Rautemaa *et al.* 2011). Yeasts have also a significant role in the biofilm formation of dental caries and periodontitis (Thein *et al.* 2009, Rautemaa *et al.* 2011). Indeed, *Candida* spp. and oral bacteria have been reported to interact in biofilms (Thein *et al.* 2009). *Candida* infections are frequently found among bacterial and viral infections in oral mucositis developing after chemotherapy or radiotherapy. In addition, *Candida* spp. are occasionally isolated in odontogenic abscesses (Rega *et al.* 2006). The clinical significance of *Candida* spp. in odontogenic abscesses is not fully known.

Viruses can replicate only inside the living cells of an organism. Human herpesviruses and Herpes zoster virus (HHV-1, HHV-2, HZV) manifest usually as vesicles in the oral cavity (McCullough *et al.* 2005). Human papillomavirus (HPV) manifests as warts and Herpangina as ulcers in the oral cavity (McCullough *et al.* 2005). These lesions appear on the oral mucosa and can usually be distinguished from bacterial or fungal infections. Epstein-Barr virus (EBV) manifests as fever, sore throat, and lymphadenopatia, and is involved in various conditions, such as mononucleosis, oral hairy leukoplakia, non-Hodgkin’s lymphoma, Burkitt’s lymphoma, and nasopharyngeal carcinoma (McCullough *et al.* 2005). Cytomegalovirus (CMV, HHV-5) is usually asymptomatic in immunocompetent patients, but is frequently found in salivary glands (Ohyama *et al.* 2006). Viral
infections manifesting the oral cavity may be accompanied by systemic symptoms, such as malaise, fever, and chills. These infections usually cause lifelong colonisation as latent infection and may reactivate if the immunological status changes. Parasite infections in the oral cavity are extremely rare, but mucosal leishmaniasis can occur in the oral mucosa, for example (Palmeiro et al. 2011).
2.2 Infection immunity

The concept of immunity is defined as the resistance of the organism against pathogens. The human immune system consists of two main classes, the innate and the adaptive immunity, which constantly communicate with each other. The innate immunity is characterised by fast and stereotypic reactions. Innate immunity provides a natural resistance thorough several molecular (pattern recognition molecules), chemical (complement system, cytokines), and cellular (phagocytes, such as granulocytes, and monocytes, natural killer -cells) mechanisms in addition to non-specific defence mechanisms (skin, mucous membrane, secretion) (Meri et al. 2011). These mechanisms of action form the first line of defence against pathogens. Innate immunity has only a limited capacity to identify target structures and it does not develop any biological memory in contrast to adaptive immunity (Kantele et al. 2011).

Adaptive immunity is characterised by slow and specific reactions with great diversity. Adaptive immunity creates immunological memory and specificity against pathogens. Adaptive immune responses are mediated through lymphocytes, T cells, and B cells, which are produced in the bone marrow (Arstila 2011). Lymphocytes are activated through complex cascades, which eventually lead to inflammatory reactions and eradication of the pathogen. The innate and adaptive immune systems both contain humoral (antibody production, complement system) and cellular (antigen presenting cells, natural killer-cells) components (Jokiranta et al. 2011, Arstila 2011). The immune system is also an important part of the homeostatic equilibrium. Old and damaged cells of the host are phagocytised and their components are reused in contrast to foreign structures, which are processed and delivered to lymph nodes for presentation and activation of lymphocytes (Meri et al. 2011).

Disorders of the immune system can result in predisposition to infections, autoimmune diseases, such as systemic lupus erythematosus (SLE), reumatoid arthritis (RA), and diabetes mellitus (DM) type 1; inflammatory diseases, such as asthma; or cancer (Vaarala et al. 2011). Immunodeficiency can be classified as
primary, resulting from a genetic disease (Kainulainen et al. 2011), or secondary, arising from acquired conditions, such as Human immunodeficiency virus (HIV) and malnutrition (Seppänen et al. 2011), or due to use of immunosuppressive medication (Järvinen et al. 2011).
2.3 Potential sources of infection of the oral cavity

2.3.1 General aspects

The vast majority of colonising bacteria are harmless and/or beneficial to the host. Thus, relatively few bacteria in the oral cavity are highly virulent. In acute bacterial infections in the oral and maxillofacial region, the classic symptoms; localised redness, heat, swelling, and pain, can be detected. In the oral region, local bacterial infections generally comprise dental diseases, such as apical periodontitis, localised abscess formation, or cellulitis. Local factors, such as anatomic abnormalities and implants, or systemic immunosuppressive conditions, such as DM and haematologic diseases, may predispose disseminated infections, such as sepsis and IE (Hoen et al. 2002, Walpot et al. 2006, Lee et al. 2009).

Oral infections have been linked to various conditions of the human body. Chronic oral infections are increasingly common findings at the present, as teeth are preserved even beyond adequate restoration (Rautemaa et al. 2007). It is now widely accepted that chronic oral infections, such as periodontitis have systemic effects besides the local disease process (Rautemaa et al. 2007). Thus, oral microorganisms have been linked to various systemic diseases or conditions, such as CVD (Mattila et al. 2005), RA (Persson 2012), DM (Genco et al. 2005, Demmer et al. 2008), aspiration pneumonias (Scannapieco et al. 1999, Pace et al. 2010), preterm birth (Offenbacher et al. 1998, Buduneli et al. 2005, Moss et al. 2007) and acute myocardial infarction (AMI) (Willershausen et al. 2009). In addition, both acute and chronic infections have been shown to influence lipoprotein levels and, thus, atherogenesis (Mattila et al. 1998, Khovidhunkit et al. 2000).

2.3.2 Apical periodontitis

Apical periodontitis can be described as the host response to microbial invasion from the pulp cavity to the surrounding periapical tissue (Siqueira 2002).
Microbes can invade the pulp tissue through several routes; dental caries, enamel cracks, tooth and root fractures, periodontal disease, open restoration margins, and dental trauma (Love 1996, Abbott 2004, Kirkevang et al. 2007). The clinical findings include pain, tenderness, mobility of the tooth, and soreness of the surrounding gingiva. Destruction of bone and occasionally, the apex of the root, is a common finding. This can be detected as periapical radiolucency in radiographs. It appears that patients with large periapical radiolucencies appear to be more prone to developing clinical signs of infection (Brennan et al. 2006). The immune system cannot eradicate bacteria from the pulp cavity (Kirkevang et al. 2007). Thus, the treatment of apical periodontitis is either root canal treatment (RCT) or tooth extraction. RCT is usually preferred, especially if the tooth is important for maintaining normal function of the occlusion. Apical periodontitis can be divided into acute and chronic diseases. Chronic apical periodontitis (granuloma) is a low-grade infection usually following an acute infection that has not completely healed or was inadequately treated.

2.3.3 Pericoronitis

Pericoronitis is an acute infection of the gingiva and surrounding soft tissues of a partially erupted tooth. It is a common condition in young adults. Maxillary and mandibular third molars are the most common impacted teeth, followed by maxillary canines (Chu et al. 2003). When partially impacted, the soft tissue around the crown, the operculum, creates a shield for microbes. Usually a sensitive equilibrium prevails between the microbes and the host. If the host defences become compromised for example due to an upper respiratory infection, or the operculum is constantly traumatised due to the opposite tooth, local infection evolves. Mild symptoms, such as local pain and swelling are treated with antiseptic mouth rinse and/or antimicrobial therapy. Operculectomy may be an option in acute cases. Severe cases with difficulty in swallowing, enlarged lymph nodes, fever, limited mouth opening with cellulitis and abscess formation are treated with surgical intervention and antimicrobial therapy. If untreated or treated with antibiotics only, the symptoms generally return and therefore the only definitive treatment is surgical extraction.
Postoperative complications following third molar extractions include infection complications, nerve injuries, postoperative haemorrhage, postoperative pain, fracture of the jaw, and in general trauma to adjacent structures (Kunkel et al. 2007). Infection is the most common postoperative complication comprising local complications, such as surgical site infection and alveolar osteitis, and maxillofacial infections, such as deep space infections (Kunkel et al. 2006, Kunkel et al. 2007, Chuang et al. 2008). The level of impaction, pre-existing infection, and pathology have been shown to be associated with an increased risk for inflammatory complications following third molar surgery (Kunkel et al. 2006, Kunkel et al. 2007, Chuang et al. 2008).

2.3.4 Gingivitis and periodontitis

Periodontal diseases in the form of gingivitis and various types of periodontitis belong to the most common infectious diseases (Oh et al. 2002). Gingivitis can be induced by the presence of dental plaque, steroid hormones, or drug-influenced gingival overgrowth (Oh et al. 2002). Clinical findings are characterised by redness and swelling of the marginal gingiva without detectable loss of surrounding bone or connective tissue, and bleeding on probing. Gingivitis does not always progress to periodontitis, but periodontitis is always preceded by gingivitis. Periodontitis is an acute or chronic infection of the periodontal tissue surrounding the tooth, which clinically manifests as inflamed gingiva and progressive loss of periodontal ligaments and alveolar bone. This chronic infection of the periodontal tissue can be a source of infection for disseminated infections. In addition, periodontitis is strongly linked to various systemic diseases as previously described, such as DM (Lalla et al. 2011). Occasional flare-up of the existing chronic infection may occur and lead to locally invasive spread of infection (Ylijoki et al. 2001, Flynn et al. 2006).
2.3.5 Alveolar osteitis

Alveolar osteitis, also called the dry socket, occurs most commonly after tooth extraction. Its prevalence has ranged in the literature from 1% to 70% depending on the patient material (Torres-Lagares et al. 2005). The signs and symptoms of alveolar osteitis start with 3-5 days delay as pain, odour, and detritus. The tooth socket is found empty without the sheltering blood clot. There are several risk factors, which predispose for alveolar osteitis; difficulty in dental extraction, surgeons inexperience, use of oral contraceptives, inadequate peroperative irrigation, age, female sex, smoking, immunosuppression, and surgical trauma (Torres-Lagares et al. 2005). The possible benefit from antibiotics is not clear, and therefore not always recommended (Torres-Lagares et al. 2005). Thus, the treatment is mainly aimed at relieving the pain (Torres-Lagares et al. 2005).

2.3.6 Osteomyelitis

Osteomyelitis is an inflammation of the cortical and medullar bone (Eyrich et al. 2003). Various forms have been identified. Most commonly it results from bacterial infection, occasionally, however, the aetiology remains unclear (Eyrich et al. 2003, Suei et al. 2005). The two main entities, acute and chronic forms, are separated with a time limit of 1 month (Suei et al. 2005, Theologie-Lygidakis et al. 2011). Osteomyelitis is also classified according to its localisation to focal or diffuse distribution, primary or secondary course of infection, and according to the tendency to suppurate (Suei et al. 2005). Osteomyelitis is seen mainly in patients with a history of local and systemic predisposing factors, such as previous radiotherapy, immunosuppression, smoking, alcoholism, DM, corticosteroid therapy, malnutrition, and malignancy (Mouzopoulos et al. 2011). Bacteria can enter the bone though blood stream, trauma, local infection, or iatrogenic for example though RCT (Theologie-Lygidakis et al. 2011, Mouzopoulos et al. 2011). In the maxillofacial region, osteomyelitis results mainly from odontogenic origins, such as tooth extraction or periodontal infection (Eyrich et al. 2003, Theologie-Lygidakis et al. 2011). The mandible is
affected more frequently than maxilla, as the bone is much thicker in the mandible and, hence, the blood supply is comparatively lesser (Eyrich et al. 2003, Theologie-Lygidakis et al. 2011). The most commonly reported microorganisms in mandibular osteomyelitis include *Staphylococcus* and *Peptostreptococcus* spp. among others (Suei et al. 2005). Rare causes reported include fungal infections, mycobacterial infections, syphilis, and actinomycosis (Suei et al. 2005). Outside the maxillofacial region, the tibia, femur, humerus, and vertebrae are most commonly affected (Theologie-Lygidakis et al. 2011).

### 2.3.7 Actinomycosis

Actinomycosis is a rare, chronic, and slowly progressive bacterial disease usually caused by *Actinomyces* spp., most commonly *A. israelii* (Wong et al. 2011). *Actinomyces* spp. are part of the oral microbiota as well as oropharynx, gastrointestinal tract and female genital mucosa (Wong et al. 2011). Other normal commensals, such as *A. actinomycetemcomitans*, *E. corrodens*, *Fusobacterium*, *Bacteroides*, *Captocytophaga*, *Staphylococcus*, *Streptococcus* or *Enterobacteriaceae* spp., are often isolated with *Actinomyces* spp. forming a mixed infection (Wong et al. 2011). Due to their low virulence, they are harmless as long as they stay on the surface of oral mucosa. There are several risk factors, which have been associated to actinomycosis; male sex, DM, age 20-60 years, corticosteroid therapy, bisphosphonates, leukaemia with chemotherapy, HIV induced immunosuppression, lung and renal transplant, alcoholism, and local tissue damage caused by trauma, surgery, or radiotherapy (Wong et al. 2011). Thus, previous dental treatment, poor oral health, periodontitis, and tissue damage to oral mucosa, have been identified as predisposing factors in cervicofacial actinomycosis (Kaplan et al. 2009). Cervicofacial actinomycosis is the most common form comprising up to 55% of the cases (Kaplan et al. 2009), but abdominal, thoracic and cutaneous forms are also seen. Actinomycosis is characterised by the formation of painful abscesses with multiple sinuses.
2.4 Anatomic considerations of the jaws

2.4.1 Anatomy of the teeth and periodontal tissues

Human dentition is comprised of deciduous and permanent teeth. Ten deciduous teeth begin to develop in the jaws before birth. The first tooth usually erupts at six months after birth, but the normal variation of eruption period extends up to two months after or before. Deciduous teeth are normally shed between six and twelve years of age and replaced by permanent teeth. Eruption of the permanent dentition is usually complete in early adulthood. Adult dentition consists of 28 permanent teeth and 0-4 third molars, which usually erupt later in adulthood. The eruption of the tooth remains incomplete if the tooth is mal-positioned and/or impacted. This is a common condition for third molars.

Teeth are mainly composed of dentin and each tooth consists of three parts: crown, neck, and root. The visible part, the crown, is covered by enamel. The root is covered by cementum and is fixed in the tooth socket by fibrous periodontal ligaments. The pulp cavity inside the tooth contains connective tissue, nerves, and blood vessels. An apical foramen connects the pulp tissue to periapical tissue. Four incisors are located in the middle anterior part of the jaw. One canine, two premolars, and two to three molars are located posterior to the incisors on each side as a row along the dental arch. The number of roots varies normally from one to four depending on the tooth in question. Teeth with one root (incisors, canines, and upper second premolars) contain usually one root canal. The morphology of the root canal system in these teeth is normally straight and predictable, although the apical part of the root canal may diverge. The root canal system of teeth with two or more roots varies frequently (Cleghorn et al. 2007). The clinical significance of this diversity of the root canal system becomes apparent when RCT is performed. The outcome of RCT is poorer, if the complex anatomy of root canal system does not allow proper canal debridement and subsequent intracanal calcium hydroxide medication (Cleghorn et al. 2007).
Teeth are surrounded by soft tissue called gingiva. The gingiva is composed of fibrous tissue and mucous membrane and is attached to the margins of tooth sockets and necks of the teeth. Gingiva, periodontal ligaments, alveolar bone, and cementum create the periodontal tissue of the teeth.

Figure 1. Anatomy of the tooth and the surrounding tissues; enamel (1), dentin (2), pulp cavity and root canal (3), marginal gingiva (4), cementum (5), periodontal ligaments (6), alveolar bone (7), and apical foramen (8).

2.4.2 Anatomy of the jaws

Anatomy concerning odontogenic maxillofacial infections covers the bony structures of upper and lower jaw and the surrounding soft tissues down to mediastinum. The specific anatomy of the jaw is quite complex as there are several muscles, which take part in motor actions, such as eating, speaking, and swallowing. Fascial spaces are potential fascia-lined spaces between anatomical structures, which in healthy individuals cannot be detected. In maxillofacial infections, fascial spaces are eroded or distended by purulent exudate.
The submental space is situated between the anterior bellies of the digastric muscles under the chin (Peterson 2003). The roots of the mandibular incisors may occasionally extend into potential space. The mylohyoid muscle divides the sublingual and submandibular spaces, although the spaces communicate freely behind the posterior edge of the muscle. The sublingual space is bordered by the mylohyoid muscle and mucosa of the floor of the mouth. The roots of mandibular molars and sometimes premolars point towards this potential space. The submandibular space is bordered by the mylohyoid muscle, superficial fascia, medial edges of the mandible and the surrounding skin (Peterson 2003). As the sublingual and submandibular spaces are not restricted posteriorly, infection of these spaces may easily spread to deep cervical spaces, called the retropharyngeal and the prevertebral spaces.

The buccal space is located between the facial skin and the buccinator muscle (Peterson 2003). Both maxillary and mandibular posterior teeth can infect this space. The masseteric space lies between the masseter muscle and the ramus of the mandible (Peterson 2003). The pterygomandibular space is bordered by the medial edge of the mandible and the medial pterygoid muscle (Peterson 2003). The infratemporal space is the upper part of the pterygomandibular space (Peterson 2003). The canine space is located between the levator anguli oris and the levator labii superiorii muscles (Peterson 2003). The maxillary canine infects this space. The peritonsillar space is located around the palatine tonsil between the pillars of the pharynx (Peterson 2003).

The deep cervical spaces comprise the lateral pharyngeal, retropharyngeal and prevertebral spaces (Peterson 2003). They all extend from the base of the skull inferiorly to different levels. The lateral pharyngeal spaces lie lateral to the pharynx and are continuous with the retropharyngeal space. They extend from the base of the skull inferiorly to the hyoid bone. The retropharyngeal space extends to the level of vertebra C7 or T1 where the alar fascia fuses with the buccopharyngeal fascia. The prevertebral space is separated from the retropharyngeal space by the alar layer of prevertebral fascia. The prevertebral
fascia extends to the level of diaphragm. Retropharyngeal and prevertebral spaces are located near mediastinum.

### 2.4.3 Anatomic routes for local spread of infection

The local infection borders first as an acute alveolar abscess, such as in apical periodontitis. Thereafter it spreads through bone and periosteum producing a soft fluctuant swelling. Without treatment and/or when the host cannot border the infection locally, the abscess erupts spontaneously in the mouth. If the sinus remains open, it permits discharge of pus and the infection becomes chronic. The chronic infection may revert again to acute, if this discharge is interrupted. The lymphatic system is also involved and lymphadenitis is a common finding.

![Figure 2. Anatomy of a diseased lower molar with perforating caries lesion (1), pulp necrosis (2), periodontitis (3), and alveolar abscess (4).](image)

Local infections generally spread towards the least tissue resistance. The course of local infection from the tooth is determined by two factors, the thickness of the surrounding bone and the attachment of the muscles (Peterson 2003). If the
root points to deep structures, the infection spreads towards the potential fascial spaces described earlier. Maxillofacial infections have a tendency to spread to deeper spaces concomitantly leading to airway compromise and life-threatening complications.

Figure 3. Anatomic routes for local spread of infection; the palate (1), the sinus (2), the buccal space (3 and 6), the vestibular space (4 and 5), the submandibular space (7), and sublingual space (8).
2.5 Predisposing factors for odontogenic infections

2.5.1 General aspects

Infection complications can arise through several different mechanisms. Local and systemic risk factors, in addition to disorders in the immune system, may contribute to infection complications. In general, surgical site infections (SSIs) are the major cause of postoperative morbidity with a reported incidence of 2.1-7% (Haridas et al. 2008). They prolong hospital stay and their treatment increases total cost. Several risk factors have been found to predispose for SSI. Of the underlying medical conditions, obesity and DM have been frequently reported as risk factors for SSIs (Russo et al. 2002, Harrington et al. 2004, Pessaux et al. 2005, Kaye et al. 2006). In addition, underweight, age, cirrhosis and hypoalbuminemia, chronic obstructive pulmonary disease (COPD), other systemic disease, and corticosteroid therapy have been reported as risk factors (Russo et al. 2002, Harrington et al. 2004, Pessaux et al. 2005, Kaye et al. 2006, Haridas et al. 2008).

The number of dentate people has increased during the past decades. As oral health habits have improved, periodontitis and decayed teeth have become less common (Suominen-Taipale et al. 2008). Teeth with apical periodontitis and RCT have, however, become more prevalent and the number has been shown to increase constantly with age (Ainamo et al. 1994, Kirkevåg et al. 2006, Kirkevåg et al. 2012). Unfortunately, the quality of RCT has often been shown to be inadequate (Kirkevåg et al. 2007, Huomonen et al. 2012). In a recent study by Huomonen et al. the quality of RCT was poorest in molars (75%), followed by premolars (49%) and anterior teeth (29%) (Huomonen et al. 2012). In addition, there seems to be a significant risk that apical periodontitis persists despite the RCT (Ainamo et al. 1994, Kirkevåg et al. 2006, Kirkevåg et al. 2007).
2.5.2 Predisposing factors for odontogenic maxillofacial infections

Only a few studies concerning predisposing factors for odontogenic maxillofacial infections exist. Length of stay (LOS) is frequently used as an indicator for severe infection. Identified factors associated to longer LOS in odontogenic maxillofacial infections were DM, alcohol abuse, SLE, organ transplant, and HIV seropositivity in a study by Peters et al. (Peters et al. 1996). Underlying medical condition and location of the infection were found to be the best predictors of LOS (Peters et al. 1996). In a study by Lee et al., multiple space involvement and DM were also found to correlate with longer LOS (Lee et al. 2007).

DM is an increasing health problem worldwide. This trend has also been noted in studies on maxillofacial and deep space infections as it has been recorded more often as an underlying medical condition (Eftekharian et al. 2009, Hasegawa et al. 2011, Rao et al. 2010, Sánchez et al. 2011). The mechanisms in which DM predisposes for infections include impaired function of neutrophil bactericidal function, cellular immunity, and complement activation. Huang et al. concluded that underlying medical conditions and older age predispose for infection complications (Huang et al. 2004). DM, especially, was found to predispose for deep space infections (Huang et al. 2004, Huang et al. 2006). In addition, DM has been shown to be associated to Klebsiella pneumoniae, hyperglycaemic problems, and ketoacidosis in patients with deep space infections (Huang et al. 2004, Huang et al. 2006). In a study by Zheng et al. DM was linked to multiple space infection, longer LOS, and more frequent complications (Zheng et al. 2011). In this context, DM seems to be the major underlying systemic disease predisposing for locally invasive spread of infection.

Obesity has become a worldwide health issue. It has become clear that obesity alters immune function (Milner et al. 2012), although the mechanisms behind this are highly complex and not yet fully understood. Studies on the relationship between obesity and proinflammatory cytokines have shown that elevations of soluble tumor necrosis factor receptor 1 and 2 (sTNF-αRI and sTNF-αRII) can be found in obese patients (Genco et al. 2005). Adipocytes appear to produce
several proinflammatory cytokines, such as TNF, leptin, and IL-1 leading to a proinflammatory state associated with obesity (Cottam et al. 2002). Although obesity has not been recorded in studies on odontogenic maxillofacial infections, the potential risk impact of obesity can be extrapolated from other studies, such as in risk evaluation of SSIs (Russo et al. 2002, Harrington et al. 2004, Pessaux et al. 2005, Kaye et al. 2006). In addition, obese patients have increased intensive care unit (ICU) length of stay and mortality rate (Milner et al. 2012). Obesity, hence body mass index (BMI), should also be recorded in future studies on odontogenic infections.

There is some evidence that severe odontogenic maxillofacial infections are more common in lower socioeconomic classes (Moles et al. 2008, Bakathir et al. 2009). In developing countries, maxillofacial infections are strongly associated with lower socioeconomic status (Agarwal et al. 2007). In addition, poor dental health has been linked to lower socioeconomic status (Hobdell et al. 2003). In Finland, younger age, lower levels of education, being single, or being unemployed, were linked to lower number of oral health-promoting habits in a recent study (Tseveenjav et al. 2012).

### 2.5.3 Predisposing factors for disseminated odontogenic infections

The three most common mechanisms for how oral microorganisms can cause systemic diseases have been described: distant site infection by haematogenous spread of infection, metastatic injury related to microbial toxins, and metastatic inflammation due to immune injury (Gendron et al. 2000, Li et al. 2000). The reticuloendothelial system usually eradicates oral microorganisms rapidly from the blood within few minutes: it is an essential component of the immune system, comprised of phagocytic cells located in different organs of the human body. Phagocytic cells are capable of engulfing substances, such as bacteria and viruses, and to render them harmless. They also ingest abnormal cells and old cells, thus cleaning the body. Therefore, disorders in this system, either transient or continuous, are present when haematogenous spread from the oral cavity
occurs. In addition, metastatic infection may have local predisposing factors, such as artificial material and foreign bodies.

Disseminated odontogenic infections are rather scantily studied and the knowledge is mainly based on experience and case reports. The main focus has been aimed at understanding the mechanisms behind IE, leaving other distant site infections of oral source to minor interest. In a study by Lee et al. 2009, underlying conditions for septicaemia following tooth extraction were studied and the following predisposing factors were identified: DM, renal transplant, liver cirrhosis/hepatoma, head and neck irradiation, and hematologic diseases (acute myeloid leukaemia, aplastic anaemia, bone marrow fibrosis with trombocytopenia, agranulocytosis) (Lee et al. 2009).

In a recent study by Barrington et al. it was suggested, however, that the risk for haematogenous spread from an oral source has been overestimated in the past (Barrington et al. 2011). In addition, recent studies indicate that the immune system would be adjusted for eradicating bacteria from the blood, as no definitive correlation between chronic oral infections and bacteraemia has been detected in immunocompetent patients (Kinane et al. 2005, Bahrani-Mougeot et al. 2008). Thus, our knowledge of the risk factors for disseminated infections is still limited and mainly based on immunocompetent patients and cannot be directly extrapolated to immunocompromised patients. Further studies are therefore urgently needed in this field.
2.6 Clinical picture of odontogenic maxillofacial infections

2.6.1 Aetiology

Local odontogenic infections usually originate from apical periodontitis (66.7%-70.7%), or initially from dental caries (33.8%-80.6%) (Ylijoki et al. 2001, Flynn et al. 2006, Saito et al. 2011, Sánchez et al. 2011). Other dental diseases causing local infection complications are pericoronitis, alveolar osteitis, periodontitis, and cysts (Indresano et al. 1992, Ylijoki et al. 2001, Smith et al. 2005, Saito et al. 2011, Sánchez et al. 2011). Extraction of a healthy tooth may also constitute the source of infection, although in that case it is often linked to osteotomy (Kunkel et al. 2006). Mandibular molars, as single or multiple, are the most common sources of severe odontogenic maxillofacial infections, in more than half of the cases, as their roots often point beneath the mylohyoid muscle (Storoe et al. 2001, Flynn et al. 2006, Marioni et al. 2008, Handley et al. 2009, Kinzer et al. 2009, Saito et al. 2011, Sánchez et al. 2011).

2.6.2 Patient characteristics

although this correlation has not existed in all studies (Flynn et al. 2006, Sato et al. 2009).

2.6.3 Incidence

The incidence of these severe odontogenic infections requiring hospital care has unfortunately not been systematically recorded in the literature. There is some evidence, however, that the number of odontogenic maxillofacial infections is increasing (Carter et al. 2006, Thomas et al. 2008). Carter et al. reported an increase of 47% in severe odontogenic infections with sepsis between 1999 and 2004 (Carter et al. 2006). Thomas et al. reported that the number of dental abscesses almost doubled between 1998-1999 and 2005-2006 at their hospital (Thomas et al. 2008). Thomas et al. concluded that the increase would be a result of difficulties in access to routine and emergency dental care (Thomas et al. 2008).

2.6.4 Involvement of fascial spaces

Characteristics of odontogenic maxillofacial infections have become more complex during the past decades. The most common fascial spaces affected are the submandibular (20.3%-68%) and the buccal space (8.5%-96%) (Haug et al. 1993, Storoe et al. 2001, Rega et al. 2006, Marioni et al. 2008, Bakathir et al. 2009, Handley et al. 2009, Kinzer et al. 2009, Sato et al. 2009, Rao et al. 2010), followed by lateral pharyngeal space, submental space, sublingual space, and canine space (Storoe et al. 2001, Rega et al. 2006). Deep fascial spaces, such as the lateral pharyngeal space and the retropharyngeal space are affected more often at present (Haug et al. 1993, Storoe et al. 2001). Children have been shown to more likely develop maxillary infections than mandibular infections (Dodson et al. 1989, Wang et al. 2005, Lin et al. 2006). In addition, multiple space involvement (50.6%-61.2%) is currently more common than single space involvement compared to the past (Haug et al. 1993, Storoe et al. 2001, Rega et al. 2006, Marioni et al. 2008). There is some variation in the nomination of anatomic spaces, which may confuse the exact prevalence of affected spaces when comparing different studies (Flynn et al. 2006).
2.6.5 Signs and symptoms

The typical signs and symptoms of severe odontogenic maxillofacial infections have remained unchanged over the course of time. Trismus, fever, dysphagia, pain, swelling, airway compromise, and respiratory distress are common symptoms (Blomqvist et al. 1988, Peterson 1993, Storoe et al. 2001, Marioni et al. 2008, Sato et al. 2009, Saito et al. 2011). These are usually the criteria for hospital admission (Storoe et al. 2001). Elevated body temperature is a common finding in acute infections and has also been recorded in odontogenic maxillofacial infections (Storoe et al. 2001, Flynn et al. 2006). It is rather a nonspecific finding and easily affected by the use of common painkillers, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). Elevated body temperature has been linked to longer LOS (Peters et al. 1996).

2.6.6 Hospital stay

In previous studies, the mean LOS of patients hospitalised due to severe odontogenic maxillofacial infection has ranged from 3.69 to 8.27 days (Peters et al. 1996, Storoe et al. 2001, Handley et al. 2009, Sato et al. 2009, Sánchez et al. 2011). This is approximately the same worldwide, however a trend of increasingly longer hospital stay has been detected (Storoe et al. 2001). Underlying medical conditions, markedly elevated inflammatory parameters, and infection complications, such as deep space infections are associated with longer LOS (Peters et al. 1996, Wang et al. 2005, Flynn et al. 2006). Sepsis was also found to be associated with longer LOS in a recent study by Handley et al. (Handley et al. 2009). The mean LOS for patients with sepsis was 4.7 days (range 2-17), compared to patients without diagnosed sepsis, mean 2.9 (range 1-6). In the same study by Handley et al., patients with mandibular infection had longer LOS (mean 4.6 days) compared to patients with maxillary infection (mean 2.6 days) (Handley et al. 2009). Children, in general, have shorter infection course and LOS (Wang et al. 2005). The need for intensive care is rarely recorded separately. In a study by Ylijoki et al. the need for intensive care was 18% of the patients (Ylijoki et al. 2001), whilst Handley et al. reported that 9% of patients
required intensive care due to septic complications (Handley et al. 2009). In severe odontogenic deep neck infections the need for intensive care was as high as 60% in a study by Kinzer et al. (Kinzer et al. 2009). The mean time interval from the start of symptoms to hospital admission was less than seven days in 81.8% and more than seven days in 18.2% in a study by Sánchez et al. (Sánchez et al. 2011).

2.6.7 Inflammatory parameters

Patients admitted due to severe odontogenic maxillofacial infection have invariably elevated inflammatory parameters. White blood cell (WBC) counts on admission have ranged from mean 12.0 to 14.9 \( (10^3/\mu\text{L}) \) (Storoe et al. 2001, Flynn et al. 2006, Marioni et al. 2008, Kinzer et al. 2009). Kinzer et al. studied severe odontogenic deep neck infections and recorded the mean C-reactive protein (CRP) level on admission as high as 135.8 (mg/L) (range 4.4 – 453) (Kinzer et al. 2009). Monitoring of CRP has been shown to be a useful marker of infection, sepsis, and resolution of infection as it is more sensitive than other currently used markers, WBC and body temperature (Povoa et al. 1998, Povoa et al. 2005). Although other markers, such as procalcitonin and prealbumin have been studied, they have not yet reached common practice (Cunningham et al. 2006, Castelli et al. 2004). In odontogenic maxillofacial infections, elevated inflammatory markers, CRP and WBC, are associated with a more severe course infection and need for intensive care (Ylijoki et al. 2001). Thus, these parameters may be used, in general, as predictors for LOS, need for intensive care, and infection complications (Ylijoki et al. 2001, Wang et al. 2005).

2.6.8 Surgical intervention

2009, Sánchez et al. 2011). These surgical procedures are performed under local or systemic anaesthesia (Sato et al. 2009, Sánchez et al. 2011). Reoperation is seldom (0.7%-8%) needed (Flynn et al. 2006, Sánchez et al. 2011). In rapid infection progress and/or airway compromise, intubation or tracheotomy is an essential procedure. If the infection extends to the mediastinum, mediastinotomy and/or thoracotomy may be inevitable (Kinzer et al. 2009).

### 2.6.9 Antimicrobial therapy

Antibiotics are commonly used in the treatment of localised odontogenic abscesses (Dailey et al. 2001), although immunocompetent patients have been shown to receive no additional benefit from antibiotics in addition to surgical intervention (Matthews et al. 2003, Brennan et al. 2006). Antibiotics have long-term effects on the microbiota, reducing richness and lowering the prevalence of commensal bacterial families (Hilty et al. 2012). The selection of strains tolerant to the antibiotic starts rapidly, within days, and may persist for up to 12 months, peaking at one month. (Chardin et al. 2009, Costelloe et al. 2010).

In locally invasive odontogenic infections, antimicrobial therapy is justified, in contrast to localised abscesses. Antimicrobial therapy is selected empirically in acute situations (Al-Qamachi et al. 2010). Penicillins have been the drug of choice in odontogenic infections in many countries (Soukka et al. 2002, Sato et al. 2009, Richardson et al. 2011), although there is some variation between countries (Maestre Vera et al. 2004, Sánchez et al. 2011). Penicillins are effective, cheap, well tolerated, have minimal side effects, and are readily available. The local Finnish guideline takes the patients immunological status into consideration. Penicillin V, in combination with metronidazole, is recommended for previously healthy patients. For patients with increased risk for infection complications, amoxicillin in combination with metronidazole is recommended. If reduced susceptibility to penicillins exists, first generation cefalosporine, such as kefalexin in combination with metronidazole, or clindamycin is recommended. Patients with significant risk for infection complications are
primarily treated at the hospital with intravenous antibiotic regimens (Richardson et al. 2011).

Intravenous antibiotic regimens are preferred at hospital. Ampicillin or cefuroxime in combination with metronidazole are the first-line drugs of choice (Marioni et al. 2008, Kinzer et al. 2009). Broad-spectrum antibiotics are occasionally needed, however. If a poor response to surgical intervention and first-line antibiotics is evident, or in immunosuppressive conditions, piperacillin-tazobactam or carbapenems in combination with vancomycin, may be used (Kinzer et al. 2009).

### 2.6.10 Rare infection complications

Ludwig's angina is a bilateral cellulitis of the submandibular and sublingual spaces (Busch et al. 1997, Furst et al. 2001, Costain et al. 2011). It was first described by Willhelm Frederick Von Ludwig in 1836 (Busch et al. 1997). Odontogenic infections account for most (70%) of these cases (Busch et al. 1997, Costain et al. 2011). The second mandibular molar is a frequently reported source of infection (Costain et al. 2011). Ludwig's angina is polymicrobial and caused by the same spectrum of pathogens as severe odontogenic infections, namely staphylococci, group A streptococci, *Fusobacterium* and *Bacteroides* spp. (Costain et al. 2011). Atypical microorganisms, such as *Escherichia coli*, *Pseudomonas*, *Candida* spp., and *Clostridium* spp. are associated with medically compromised patients (Costain et al. 2011). Ludwig's angina progresses rapidly leading to airway compromise and has a mortality rate of 8-10% (Furst et al. 2001, Costain et al. 2011).

Mediastinitis is a rare, but potentially life-threatening outcome of spreading dental infection (Kinzer et al. 2009). The mortality rate is still high (25-40%)(Furst et al. 2001, Pappa et al. 2005). Craniocervical necrotizing fasciitis is a rapidly spreading soft tissue infection. Gas formation is its typical feature. It seldom affects the head and neck regions. In these cases, however, it spreads along the fascial planes of the neck and causes widespread tissue destruction
(Wong et al. 1999, Treasure et al. 2010). Craniocervical necrotizing fasciitis is seen more often in immunocompromised patients (Wong et al. 1999).

In cranial extension of the infection, orbital abscess, for example, is a severe complication that requires an aggressive approach as permanent visual loss may occur (Akhaddar et al. 2010, Zachariades et al. 2005). The infection may spread intracranially through the interconnecting venous system and cause cavernous sinus thrombosis (Colbert et al. 2011).

Subcutaneous emphysema, pneumomediastinum, and pneumothorax are uncommon, but regularly reported complications of dental procedures, most commonly after third molar surgery (Sekine et al. 2000, Yang et al. 2006, Arai et al. 2009, Romeo et al. 2011). This complication is usually reported after the use of an air turbine drill (Sekine et al. 2000, Yang et al. 2006, Arai et al. 2009, Romeo et al. 2011). Infection is usually not present, but antimicrobial therapy is recommended as the introduction of air and water contaminated with oral microorganisms may cause the spread of infection (Arai et al. 2009).

Mortality is a rare complication and is associated with multiple space infections, such as Ludwig’s angina as well as with systemic infection complications (Green et al. 2001, Carter et al. 2007, Sato et al. 2009). Predisposing medical conditions reported cover chronic lymphocytic leukaemia, DM, and liver cirrhosis (Wong 1999, Huang et al. 2004, Carter et al. 2007, Sato et al. 2009). If left untreated, even previously healthy and immunocompetent patients may suffer from death due to severe odontogenic infections. In these cases, mortality has been linked to poor patient co-operation and poor dental status (Green et al. 2001).
2.7 Bacteraemia

2.7.1 General aspects of bacteraemia

Bacteraemia is the presence of viable bacteria in the blood (Handley et al. 2009), which is an abnormal condition given that blood is normally sterile. Bacteraemia is typically transient rather than continuous, and under normal conditions the transient bacteraemia usually lasts no more than 11-30 minutes (Roberts et al. 2006, Lockhart et al. 2008). The transient nature of odontogenic bacteraemia has been, however, questioned, as bacteraemia following tooth extractions has been reported to persist up to an hour (Tomas et al. 2007). The reticuloendothelial system normally eradicates these bacteria, however bacteraemia may lead to sepsis and/or haematogenous spread of bacteria to distant organs in medically compromised patients (Lee et al. 2009). There are several factors affecting the detected incidence of bacteraemia including the time at which the blood sample is taken preceding procedure, degree of inflammation of the source of bacteraemia, virulence of the bacteria, individual variations in the function of immune system, and methodological aspects. Thus, it is difficult to compare different studies and separate evaluation should be preferred instead.

2.7.2 Odontogenic bacteraemia

Practically all dental procedures have been shown to cause bacteraemia (Hall et al. 1999). The prevalence of bacteraemia after dental procedures has ranged from 57.9% to 100% (Heimdahl et al. 1990, Okabe et al. 1995, Lockhart et al. 2004, Rajasuo et al. 2004, Rajasuo et al. 2004, Kinane et al. 2005, Takai et al. 2005, Dios et al. 2006, Roberts et al. 2006, Tomás et al. 2007, Lockhart et al. 2008). There is, however, variation in the incidence and intensity of bacteraemia depending on the invasiveness of the procedure (Kinane et al. 2005). Thus, tooth extractions seem to provoke the highest incidence of bacteraemia, followed by other dental procedures, such as periodontal, orthodontic, and/ or minor dental procedures (Gendron et al. 2000, Lucas et al. 2002, Rajasuo et al. 2004, Kinane et al. 2005, Takai et al. 2005, Roberts et al. 2006, Tomas et al. 2007, Lockhart et al.
2008, Sonbol et al. 2009). Debanding of the upper arch and gold chain adjustment on the other hand has shown no difference in the prevalence and intensity of bacteraemia between baseline and after procedure (Lucas et al. 2007). Moreover the placement of dental implants via the mucoperiosteal flap has failed to induce bacteraemia, thus chlorhexidine mouth rinse was recommended preoperatively by the authors instead of AP (Pineiro et al. 2010).

The presence of chronic infections in particular, such as gingivitis and periodontitis, provokes this entry of oral microorganisms to the blood stream through the damaged mucosa (Okabe et al. 1995, Gendron et al. 2000, Daly et al. 2001, Takai et al. 2005, Brennan et al. 2007, Tomás et al. 2012). Due to the chronic nature of periodontitis, the cumulative exposure to bacteraemia from daily oral activities has been shown to be even higher compared to dental procedures (Guntheroth 1984, Roberts 1999). Thus, even normal daily habits such as tooth brushing causes bacteraemia (Lockhart et al. 2008, Lucas et al. 2008, Lockhart et al. 2009). Chewing and flossing on the other hand failed to provoke bacteraemia in patients with periodontal diseases (Murphy et al. 2006, Tomás et al. 2012). Lucas et al. compared different tooth brushing techniques and reported a significantly greater intensity of bacteraemia after brushing with electric toothbrush with oscillating movement and after slow hand piece with rubber cup compared to an electric toothbrush with rotary movement and manual a toothbrush (Lucas et al. 2008).

Contradictory results do, however, exist. Tomás et al. concluded that the degree of oral health did not correlate with the intensity of bacteraemia following tooth extractions (Tomás et al. 2007, Tomás et al. 2008). Kinane et al. studied patients with untreated periodontitis and bacteraemia after periodontal procedures (Kinane et al. 2005). They reported that it was impossible to predict the intensity of bacteraemia according to severity of periodontal disease. In addition, they concluded that it is possible that the immune system is adjusted for eradication of periodontal pathogens. Bahrani-Mougeot et al. came to the same conclusion in their pilot study where they measured the levels of 12 different cytokines pre- and postoperatively after tooth extractions. They found no correlation between
the level of periodontitis and bacteraemia (Bahrani-Mougeot et al. 2008). However, these studies were conducted on immunocompetent patients. Thus, there is no evidence if or how this eradication of bacteria from the blood occurs in patients with different immunocompromised conditions.

### 2.7.3 Microbiology of odontogenic bacteraemia

A wide range of bacteria has been isolated in odontogenic bacteraemia. The effect of various dental procedures on bacteraemia has been studied, although most of the studies have concentrated on bacteraemia following tooth extractions.

Heimdahl et al. recorded the incidence of bacteraemia after various surgical procedures comprising tooth extraction (100%), third molar surgery (55%), dental scaling (70%), endodontic treatment (20%), and bilateral tonsillectomy (55%) (Heimdahl et al. 1990). Anaerobic bacteria were most commonly isolated in all patient groups with the exception of the endodontic treatment group where aerobic bacteria were the most common isolates. Viridans group streptococci (alpha/nonhaemolytic streptococci) were the most commonly isolated bacteria.

Okabe et al. isolated anaerobes (71.1%), facultative anaerobes (27.3%), and aerobes (1.6%) after tooth extractions (Okabe et al. 1995). *Eubacterium, Peptostreptococcus*, and *Propionibacterium* spp. were the most common facultative anaerobes and *Lactobacillus, Streptococcus*, and *Staphylococcus* spp. were the most common aerobes and microaerophils.

Viridans group streptococci (49%), *Prevotella* (9%), *Actinomyces* (5%), and *Fusobacterium* spp. (5%) were the most common isolated bacteria in blood samples after tooth brushing and tooth extraction in a study by Lockhart et al. (Lockhart et al. 2008). Viridans group streptococci (alpha/nonhaemolytic streptococci) (45%) were the most common isolates after various dental procedures in a previous study by Lockhart et al. (Lockhart et al. 2004).
Rajasuo et al. isolated predominantly anaerobic *Prevotella, Eubacterium, and Peptostreptococcus* spp. after surgical tooth extraction (Rajasuo et al. 2004). Of the patients, 88% had detectable bacteraemia. Of the aerobic species, viridans group streptococci (alpha/nonhaemolytic streptococci) and anginosus group streptococci were the most common isolates. All isolated species were also found in the oral cavity: 93% in the pericoronar pockets and 43% in the extraction sockets.

Slightly different species were isolated after third molar extraction and plate removal in another study by Rajasuo et al. (Rajasuo et al. 2004). Bacteraemia was detectable in 60% of the patients. *Actinomyces* spp, followed by *Campylobacter* and *Lactobacillus* spp. were the predominant anaerobic bacteria (85%). *Streptococcus* spp. were the most common aerobic bacteria found in 15% of the isolates.

In a study by Takai et al. viridans group streptococci (alpha/nonhaemolytic streptococci) (51.4%) were the most common isolated bacteria, followed by *Actinomyces* (25.7%), *Prevotella* (18.6%), and *Veillonella* spp. (14.3%) after various oral and maxillofacial surgical procedures (Takai et al. 2005). Díoz et al. studied bacteraemia after tooth extractions and isolated streptococci most frequently (Díoz et al. 2006). Roberts et al. most commonly isolated *Streptococcus, Actinomyces*, and *Staphylococcus* spp. after tooth extractions in children (Roberts et al. 2006).

Tomás et al. identified most commonly *Streptococcus* spp. (63.8%), with the predominance of viridans group streptococci (alpha/nonhaemolytic streptococci) and anginosus group streptococci (Tomás et al. 2007). Staphylococci were the second most common genus (11%).

Lucas et al. isolated *Streptococcus* spp. in 15% of the cases and coagulase-negative staphylococci (CNS) in 24% of the cases with the lysis filtration technique after tooth brushing. Other isolated bacteria included *Lactobacillus,*
Actinomyces, Neisseria, and Mircococcus spp. Obligate anaerobes were not detected (Lucas et al. 2008).

According to the literature, there is controversy regarding the correlation of frequency and intensity of bacteraemia and the degree of inflammation of the oral source and the dental procedure in question. In addition, isolated bacteria in blood samples showed great variation reflecting the broad diversity of the oral microbiota. The course of bacteraemia depends on various factors and their individual impact, including the state of odontogenic source, host defence mechanisms, and virulence of the pathogen(s) in question.
2.8 Clinical picture of disseminated odontogenic infections

2.8.1 Sepsis

Sepsis, or septicemia is the systemic inflammatory response of the host with the presence of infection (Handley et al. 2009). This immunological response causes activation of acute-phase proteins, affecting the complement system and the coagulation pathways. If left untreated, or occasionally even with immediate and aggressive treatment, sepsis causes damage to organs and may lead to multiple organ failure and eventually death. There are different definitions for sepsis and its complications. In Finland, positive blood culture is not essential for diagnosis. If sepsis is complicated by organ dysfunction, the term severe sepsis is used. Septic shock covers acute circulatory failure with hypotension of no other cause. SIRS is a systemic inflammatory response syndrome and that can be triggered by a variety of infectious and non-infectious processes (Levy et al. 2003). Sepsis is characterised by fever or hypothermia, elevated or low WBC counts, and elevated CRP level. Other symptoms and signs, such as elevated heart rate, high respiratory rate, malaise, and nausea are common.

The incidence of sepsis has been reported to be 3 per 1000 population per year (Lever et al. 2007). It has up to this day a mortality rate of 30 to 50 deaths per 100 000 population per year depending on the aetiology (Lever et al. 2007). Mortality increases with the severity of sepsis. In Finland, the incidence of severe sepsis in intensive care was 0.38 per 1000 adults per year in a recent study by Karlsson et al. (Karlsson et al. 2007). In this study population, 15.5% died in the ICU and 28.3% at the hospital (Karlsson et al. 2007). Most of the cases (58.3%) are community-acquired infections and a smaller (38.9%) proportion is nosocomial (Karlsson et al. 2007). The most common isolated pathogens include the gram-positive bacteria *S. aureus, S. pneumoniae, Enterococcus* spp., CNS, and betahaemolytic streptococci (Loisa et al. 2003, Opal et al. 2003, Vincent et al. 2006). Of the gram-negative bacteria, the most common isolated include *E. coli, Neisseria meningitidis, Klebsiella* spp. and *Pseudomonas* spp. (Loisa et al. 2003,
Opal et al. 2003, Vincent et al. 2006). Other microorganisms, such as fungi, are isolated only occasionally (Karlsson et al. 2007).

The oral microbiota is usually stable and consists of microorganisms with low virulence. Medically compromised patients, however, are more frequently colonised with atypical pathogens, such as *P. aeruginosa* (Gosney et al. 1999, Napenas et al. 2007). Thus, the oral cavity is a potential source of bacteraemia and sepsis due to a wide range of microorganisms provoked by the presence of infection and invasive procedures (Lee 1984). Sepsis can occur after tooth extraction with or without infection (Lee et al. 2009). Lee et al. reported an incidence of odontogenic sepsis of 1.48 per 100 000 inhabitants and a mortality rate of 21.2% (Lee et al. 2009). In a study by Handley et al., 61.2% of the patients that had been admitted due to odontogenic maxillofacial infection presented with sepsis on admission (Handley et al. 2009). Several oral microorganisms have been reported in blood cultures of septic patients: *Streptococcus* spp, *Klebsiella pneumoniae* in diabetic patients, anaerobes, such as *Actinomyces, Bacteroides, Prevotella, Enterococcus, Eubacterium*, and *Clostridium* genera among others (Lee at al. 2009).

### 2.8.2 Infective endocarditis

Endocarditis is an inflammation of the inner layer of the heart, the endocardium. It can be classified by its aetiology to infective or non-infective endocarditis. The heart valves have poorer blood supply compared to other structures of the heart. Therefore, if a microorganism attaches to the valve surface and forms vegetations, the host immune system and antimicrobes cannot efficiently reach the infected valve. Normally blood flows smoothly though these valves, however if they are damaged, for example due to rheumatic heart disease or previous IE, or the blood flow is disturbed due to underlying structural cardiac conditions, such as complex cyanotic congenital heart diseases, the risk for microorganism attachment is increased (Dajani et al. 1997). IE can be classified by its clinical course of infection as subacute or acute IE (Ito 2006). Microorganisms with low virulence such as viridans group streptococci (alpha/nonhaemolytic
streptococci) are generally linked to subacute IE (Ito 2006, Cunha et al. 2010). Acute IE, in contrast, is commonly caused by high-virulence microorganisms, such S. aureus (Ito 2006, Cunha et al. 2010). In addition, IE can be classified as prosthetic valve endocarditis and native valve endocarditis (Ito 2006).

The first studies on the aetiology of IE concluded that dental procedures were the major risk factor for odontogenic sources of IE. Recent studies have, however, questioned these results, as the knowledge of the cumulative exposure to oral bacteraemia has increased (Roberts 1999). The intensity of bacteraemia seems to play an essential role in the risk for IE (Roberts 1999). Indeed, the major risk factor for odontogenic sources of IE appears to be the cumulative burden of poor oral health and normal daily activities, such as tooth brushing (Okabe et al. 1995, Gendron et al. 2000, Daly et al. 2001, Takai et al. 2005, Lockhart et al. 2008, Lucas et al. 2008, Lockhart et al. 2009). Dental procedures, on the other hand, seem to be a minor risk factor for developing IE even in the presence of valvular abnormalities (Ström et al. 1998). Cardiac abnormalities, in general, have remained as high-risk underlying conditions for IE (Ström et al. 1998, Ito 2006). Dental procedures, however, cannot be totally overlooked as they increase the cumulative exposure (Al-Karaawi et al. 2001).

The incidence of IE has substantially remained the same over the decades ranging from 1.4-9.61 per 100,000 inhabitants (Walpot et al. 2006, Tleyjeh et al. 2007, Dzupova et al. 2012), although an increase in incidence has been observed in some countries (Dzupova et al. 2012). The most common causative organisms in all IE cases have been the viridans group streptococci (alpha/nonhaemolytic streptococci) ranging between 6.8-45%, although the incidence of S. aureus has increased recently ranging from 12.2-33.9% (Coward et al. 2003, Walpot et al. 2006, Tleyjeh et al. 2007, Dzupova et al. 2012). The mortality rate of IE still remains high, as it has ranged from 16.6% to 27.5% (van der Meer et al. 1992, Hoen et al. 2002, Dzupova et al. 2012).

Oral streptococci, such as S. mitis and S. oralis, are the most common causative microorganisms for IE downstream of oral problems, especially in patients with
prosthetic valves (Aas et al. 2005, Ito 2006). Hoen et al. reported a decreased incidence of oral bacteria as causative organism in 17% of cases (Hoen et al. 2002). The proportion of oral streptococci decreased from 7.8 cases per million to 5.1 cases per million and was compensated by the increased proportion of group-D streptococci and staphylococci. It should be noted that viridans group streptococci (alpha/nonhaemolytic streptococci) are frequently referred to as oral streptococci, although the oral cavity is not the only reservoir of these microorganisms (Carmona et al. 2007). In their recent study, Dzupova et al. reported that 6.5% of their cases derived from an odontogenic source, due to untreated periodontitis, (Dzupova et al. 2012). Staphylococcus spp. has also been isolated from the oral cavity and can subsequently cause IE of oral source (Carmona et al. 2007). Anaerobic bacteria can also, in rare cases, infect the endocardium (Carmona et al. 2007).

The predisposing factors for IE have changed during the decades. While the number of patients with rheumatic heart disease has decreased and is, at the present, significant mainly in developing countries, the number of patients with degenerative valvular changes and cardiac operations has increased (Hoen et al. 2002, Tleyjeh et al. 2007, Dzupova et al. 2012). Unfortunately, the immunological status of these patients has generally not been evaluated in the literature as the scientific focus has aimed at cardiological aspects. The most commonly reported predisposing factors, in addition to cardiac conditions, were pyogenic infections of the skin and soft tissue, and chronic haemodialysis in a study by Dzupova et al. (Dzupova et al. 2012). Underlying medical conditions were common findings in a study by Walpot et al., and comprised high incidence of DM (28.1%), chronic renal failure (28.1%), and COPD (21.9%) (Walpot et al. 2006). The increasing number of intravenous drug users forms a specific patient group, which is characterised by acute IE due to S. aureus (Hoen et al. 2002, Dzupova et al. 2012).
2.8.3 Brain abscess and other disseminated infections in the central nervous system

Brain abscesses are focal infections resulting from the spread of infection by haematogenous or lymphatic spread, by direct extension along fascial planes, or from direct inoculation through trauma or neurosurgery (Andrews et al. 1990, Gendron et al. 2000, Al Masalma 2011). The temporal lobe is the most common affected region (42%), followed by the cerebellum region (30%) (Azenha et al. 2011). Depending on the location, prevalence ranges from 1-8 per 100 000 population (Azenha et al. 2011). Early symptoms are general, such as headaches and fever. Depending on the size and the location of the abscess, seizures, nausea and vomiting, neck stiffness, or neurological changes may occur. Without treatment, brain abscesses may be fatal. Unfortunately, long-term neurological problems, such as seizures due to scarring, are common even after the abscess is removed and the infection is treated.

Brain abscesses are usually polymicrobial (Azenha et al. 2011). Gram-positive aerobes belonging to *Streptococcus* and *Staphylococcus* spp. are the most common isolated bacteria (Carpenter et al. 2007, Lakshmi et al. 2011). In addition to anaerobes, *Nocardia, Mycobacteria, Enterococcus* spp., and fungi have been reported (Carpenter et al. 2007, Lakshmi et al. 2011). A great variation can be seen as rare microorganisms are increasingly found as the number of medically compromised patients increases (Carpenter et al. 2007, Lakshmi et al. 2011).

As brain abscesses are rare infection complications, mainly case reports can be found on cases originating from the oral cavity. A wide range of dental procedures and various chronic dental diseases have been reported to precede these infections. (Andrews et al. 1990, Li et al. 1999, Heckmann et al. 2003, Rahamat-Langendoen et al. 2011). The most commonly reported microorganisms in brain abscesses from oral sources are aerobic gram-positive cocci, such as *S. constellatus, S. viridans, and S. aureus*, facultative *A. actinomycetemcomitans*, and anaerobic bacteria, such as *Bacteroides* and

2.8.4 Spondylodiscitis

Pyogenic spinal infections include spondylodiscitis, which is a term encompassing vertebral osteomyelitis, spondylitis, and discitis. These are considered as different manifestations of the same pathological process. Spondylitis affects the vertebrae. Discitis is an inflammation of the intervertebral disc space. A combination of these two is called spondylodiscitis. Although rare, it is the main manifestation of haematogenous osteomyelitis in patients over 50 years of age, covering 3-5% of all cases of osteomyelitis (Gouliouris et al. 2010). Depending on the location and the aetiology, incidence has ranged in developed countries from 4 to 24 per million per year (Gouliouris et al. 2010). A distant focus can be found in over half of the cases covering the genitourinary tract (17%), skin and soft tissue (11%), intravascular devices (5%), gastrointestinal tract (5%), and respiratory tract (2%) (Mylona et al. 2009). The oral cavity has been reported in 2% of the cases. Spondylodiscitis has occasionally been found to be associated with IE (12%) (Mylona et al. 2009). DM is the most common reported risk factor in addition to age, immunosuppression, and previous spinal surgery (Mylona et al. 2009). Despite treatment with antimicrobial therapy and surgery, the mortality rate has ranged from 0% to 11% (Gouliouris et al. 2010).

Spondylodiscitis is mainly a monomicrobial infection (Gouliouris et al. 2010). Bacteria, mycobacteria, fungi, and parasites have been reported as causative microorganisms (Gouliouris et al. 2010). S. aureus is the predominant pathogen as it has been reported in half (range 20-84%) of the non-tuberculous cases (Gouliouris et al. 2010). Other reported pathogens include Enterobacteriaceae (7-33%), CNS (5-16%), alpha/nonhaemolytic streptococci (5-20%), and P. aeruginosa in isolated cases among other rare pathogens (Gouliouris et al. 2010).
Oral microorganisms found as case reports in the literature cover *S. oralis* discitis of an edentulous patient, who developed IE (Renton et al. 2009). *S. mutans* discitis was also found in a patient with IE (Biswa et al. 2010). Morelli et al. reported three cases of spondylodiscitis with IE, who all had positive blood cultures with *S. viridans* of a plausible dental source (Morelli et al. 2001). In addition, rare oral microorganisms, such as *Peptostreptococcus asaccharolyticus* have been reported as the cause of spondylitis (Rousseau et al. 1998).

### 2.8.5 Septic arthritis

Septic arthritis is the purulent infection of a joint. The terms “pyogenic arthritis” and “suppurative arthritis” refer to the production of pus without necessarily implying sepsis. Septic arthritis has a rapid onset with classic symptoms of inflammation of the joint in addition to general symptoms, such as fever and malaise. Usually one joint is affected. Septic arthritis is usually a bacterial infection, but even viral, mycobacterial, and fungal arthritis may occur. Microorganisms can enter the synovial membrane of a joint through a penetrating trauma, iatrogenic way, or by haematogenous dissemination from a distant focus, such as skin infection. Patients with prosthetic joints, DM, immunosuppressive treatment or condition, intravenous drug use, age, and pre-existing joint disease, such as RA are known risk factors (Clerc et al. 2011). The incidence of septic arthritis has been reported to range from 2 to 10 per 100 000 patients (Clerc et al. 2011). However, the incidence has been estimated to be 10 times higher in patients at risk (Clerc et al. 2011). *S. aureus* is the predominant pathogen followed by streptococci (Clerc et al. 2011). Less common pathogens are usually found in patients at risk (Clerc et al. 2011).

Septic arthritis has been reported to occur following dental procedures (Edson et al. 2002, Sonsale et al. 2004, Papaioannides et al. 2006, Fe Marques et al. 2008, Mandac et al. 2010). As only a few case reports can be found in the literature, it is difficult to draw common features. Although several different pathogens have been reported, *S. sanguis* was the most common finding (Edson et al. 2002, Papaioannides et al. 2006, Mandac et al. 2010). According to the literature *S.
*sanguis* typically affects the knee, sternoclavicular, acromioclavicular, and
sacroiliac joints (Papaioannides et al. 2006). Other isolated bacteria with obvious
relationships to previous dental procedures reported were *Prevotella loescheii*
following tooth extraction (Fe Marques et al. 2008) and *F. necrophorum*
following dental abscess (Sonsale et al. 2004). Septic arthritis of the
temporomandibular joint is a separate entity, as it occurs either by local spread
or by haematogenous dissemination. The most common microorganisms
isolated from the temporomandibular joint are staphylococci, streptococci,
*Neisseria gonorrhea*, and *Haemophilus influenzae* (Sembronio et al. 2007).

### 2.8.6 Lemierre’s syndrome

Lemierre’s syndrome is a rare form of disseminated septic thrombophlebitis. It
was first described by a French bacteriologist André-Alfred Lemierre in 1936
(Albilia et al. 2010). Lemierre’s syndrome usually originates from the
cranio-cervical region; hence odontogenic infections can be the source of
infection (Albilia et al. 2010). It is characterised by thrombosis of the internal
jugular vein, and distant septic emboli in the lungs, central nervous system, liver,
and joints (Albilia et al. 2010). Thus, it is potentially a lethal condition that
primarily affects adolescents and young adults. *F. necrophorum* is the main (82-
85%) causative pathogen (Puymirat et al. 2008, Shah et al. 2010). In rare cases,
other *Fusobacterium* spp., such as *F. nucleatum*, or *Bacteroides* spp.,
*Peptostreptococcus* spp., *S. aureus*, *S. microaerophilic*, betahaemolytic streptococci,
viridans group streptococci (alpha/nonhaemolytic streptococci), *Eikenella
corrodens*, and *Enterococcus* spp. have been reported (Puymirat et al. 2008, Shah
et al. 2010). Polymicrobial infections are rare (Puymirat et al. 2008, Shah et al.
2010).

### 2.8.7 Other disseminated infections originating from the oral cavity

Other locations for distant site infections originating from oral the cavity, besides
those previously described, comprise liver abscess (*F. nucleatum*) (Kajiya et al.
2008, Lei et al. 2009) and abscesses in other parts of the body, such as the
2.9 Antibiotic prophylaxis

Antibiotic prophylaxis (AP) refers to the prevention of infection complications, both local and systemic, following medical procedures using antimicrobial therapy, commonly antibiotics. AP is given preoperatively so that the peak concentration is achieved when the procedure begins. AP reduces the risk for local odontogenic infection complications, such as alveolitis due to tooth extraction (Ren et al. 2007). The choice of AP is aimed at patients with elevated risk for infection complications, such as immunocompromised patients and those with local predisposing factors, such as a prosthetic valve. The basis for AP in dentistry is the acknowledged fact that practically all kinds of dental manipulation cause bacteraemia. There is evidence that the incidence and duration of bacteraemia can be reduced by a single-dose-prophylaxis. Single-dose-prophylaxis seems to have minimal effects on the human microbiota without long-term changes (Seppälä et al. 2004). Although AP has been shown to significantly decrease the incidence and duration of bacteraemia following dental procedures, a notable proportion of patients with evident bacteraemia despite the AP are recorded reflecting the multifactorial nature of bacteraemia (Brennan et al. 2007, Lockhart et al. 2008). Adverse drug reactions, potential risk for resistant strains if continued, problems in the use of antibiotics, economic costs, and the rather unpredictable effect of AP should be noted. In addition, there are significant differences in the effect of various antibiotics, which should be noted when evaluating different studies and guidelines (Coulter et al. 1990, Lockhart et al. 2004, Oliver et al. 2004, Dios et al. 2006, Lockhart et al. 2008, Oliver et al. 2008). Amoxicillin, for example, has been found to provide high efficacy in several studies in reducing prevalence and duration of bacteraemia following tooth extractions, if appropriately taken (Coulter et al. 1990, Lockhart et al. 2004, Dios et al. 2006, Lockhart et al. 2008).

Various national recommendations have been made for the identification and evaluation of the risks and “at risk” patients (Oliver et al. 2004, Gould et al. 2006, Wilson et al. 2007, Oliver et al. 2008). Antibiotic prophylaxis and IE is has been widely debated in the absence of evidence of prevention of IE as it has been
difficult to prove the actual causal relationship due to the low incidence (Duval et al. 2006). In addition, patients included in these studies have been immunologically heterogeneous and poorly defined. Thus, researchers have focused on cardiac anomalies and conditions. Previously, all cardiac defects were infrequently considered to predispose for IE, but over time the indications for AP have been reduced one by one. Patients with specific cardiac conditions, such as previous IE and prosthetic valves, are still considered to be at risk for developing IE with little variation depending on the guideline.

The recommendation for oral AP in dental procedures is a single dose of amoxicillin (2g) as the first-line drug of choice according to the American Heart Association (AHA) (Wilson et al. 2007). If allergy to penicillins or ampicillins exists, cephalexin (2g), clindamycin (600mg) or azithromycin/clarithromycin (500mg) is recommended. In patients with an inability to take oral medication, ampicillin (2g), cefazolin (1g), or ceftriaxone (1g) is recommended. If allergy to penicillins or ampicillin exists, cefazolin (1g), ceftriaxone (1g), or clindamycin (600mg) is recommended. National variations exist due to local epidemiology and resistance profiles of oral pathogens (Brincat et al. 2006, Carmona et al. 2007). In addition, local Finnish guidelines take immunological status into consideration (Richardson et al. 2011). The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom published a guideline in March 2008, stipulating that AP is no longer recommended for at risk patients undergoing dental procedures (Richey et al. 2008, Wray et al. 2008). In addition, preoperative chlorhexidine mouth rinses were withdrawn (Richey et al. 2008, Wray et al. 2008). After this guideline was published, Thornhill et al. reported that despite the decrease of described AP, no increase of IE was found over a two-year period (Thornhill et al. 2011). Thus, guidelines are based on very limited knowledge and understanding.

As the scientific focus of AP in dentistry has been mainly aimed towards IE, other distant site infections, and their potential risk factors have been less studied. The major problem seems to be targeting AP to the correct patients in the correct
situations. In this context, maintaining good oral health remains in the key approach to take in order to prevent IE and other distant site infections.
2.10 Dental clearance

Organ transplant recipients and patients undergoing stem cell transplantation are prone to infections due their immunosuppressive medications, and posttransplantation infection is the most common cause of mortality (Akintoye et al. 2002, Yamagata et al. 2006). Poor dental health and invasive dental treatment have been shown to predispose particularly to bacteraemia and sepsis, as the immune system cannot eradicate bacteria from the blood (Akintoye et al. 2002). Patients who receive stem cell transplantation are at increased risk for developing oral complications, such as mucositis, gingivitis, and ulcerations (Melkos et al. 2003). There is evidence that oral microbiota changes during and after immunosuppression predispose for infections by atypical microorganisms (Meurman et al. 1997, Napenas et al. 2007). Thus, dentist consultation should be provided preoperatively and active sources of infection eradicated (Bergmann 1988, Guggenheimer et al. 2003, Melkos et al. 2003). However, minimal dental intervention is recommended and radical clearance should be avoided. Thus, dental procedures, if possible, should be postponed to a later occasion (Melkos et al. 2003, Niederhagen et al. 2003, Yamagata et al. 2006, Öhman et al. 2010).
3 AIMS OF THE STUDY

The purpose of the present study was to investigate the infection course of local and systemic odontogenic infections requiring hospital care.

The specific aims of this study were:

I To analyse systemic and local odontogenic infections requiring hospital care,

II To study whether the incidence and clinical features of odontogenic maxillofacial infections requiring hospital care have changed over a 10-year period,

III To determine the impact of antecedent dental procedures and dental health on the course of odontogenic maxillofacial infections requiring hospital care,

IV To evaluate the role of periapical pathology and the antecedent root canal treatment of the source of infection in the course of odontogenic maxillofacial infections requiring hospital care.
4 PATIENTS AND METHODS

4.1 Study design

This retrospective cohort study was established with the aim of analysing local and systemic odontogenic infections requiring hospital care and their predisposing factors. To analyse the clinical picture and predisposing factors of local and systemic infection complications, patient material was collected from the Finnish Patient Insurance Centre (FPIC) (Study I). To analyse predisposing factors and courses of locally invasive odontogenic infection, patient material was gathered from the Department of Oral and Maxillofacial Diseases in Helsinki University Central Hospital (HUCH), which operates in the Surgical Hospital and in Töölö Hospital (Studies II-IV).

4.2 Study populations

This study consisted of four populations (Studies I-IV). The first study involved the collection of medical records for all patient cases of odontogenic infections which led to hospitalisation and which were adjudicated by the FPIC (n=35) during 2000-2003 (I). The FPIC oversees the compensation procedures of patient injuries that have occurred in Finland. The second study involved the revision of medical records from all cases of odontogenic maxillofacial infections, which led to hospitalisation, in the Helsinki and Uusimaa hospital district in the years 1994-1996 (n=71) and 2004 (n=101) (II). The third study population involved the revision of medical records and panoramic radiographs for patient cases leading to hospitalisation due to odontogenic maxillofacial infection (n=84) in the Helsinki and Uusimaa hospital district during the year 2004 (III). The fourth study involved the revision of medical records and panoramic radiographs of patients admitted to hospital due to odontogenic maxillofacial infection with periaipical pathology as the source of infection (n=60) in the Helsinki and Uusimaa hospital district during the year 2004 (IV).
4.3 Data collection and operative methods

In the first study (I), patients were identified from the FPIC data-bases by the initial search term "dental care" and were further defined with the additional inclusion criteria: "infection", "septicaemia", "hospital care", "endocarditis", and "intensive care". Cases of odontogenic infections, which led to hospitalisation, were included in this study. Only cases with an obvious causal relationship concluded by the FPIC expert committee were included.

In the second, third, and fourth study (II-IV) patients admitted to the Department of Oral and Maxillofacial Diseases in HUCH were identified in the hospital database by using the following WHO ICD-10 diagnoses (http://www.who.int/classifications/icd/en/): K04.7 (periapical abscess without sinus), K05.2 (acute periodontitis), K12.2 (cellulitis and abscess of mouth), K14.0 (glossitis), J36 (peritonsillar abscess), and J39.1 (other abscess of the pharynx).

4.4 Study variables

The characteristics studied included age, gender, stratification of occupational social class, dental status, source of infection, radiological findings of the source of infection in the preoperative panoramic radiographs, specific status of the source of infection, antecedent dental procedures, microbiological diagnostics, antimicrobial treatment, site of infection, number of fascial spaces involved, length of stay (LOS), need for intensive care, length of intensive care, need for reoperation, and outcome. The general health status and the presence of underlying systemic diseases were recorded. Inflammatory parameters were recorded for CRP level, WBC counts, and body temperature on admission and at maximum.
4.5 Definitions

The diagnosis of sepsis (I) was based on the criteria as presented at The International Sepsis Definitions Conference in 2001 (Levy et al. 2001). Patients with the following underlying systemic diseases predisposing for infections were referred as medically compromised patients (I); immunosuppression, cardiac conditions associated with IE, acute malignancy, and diabetes (Bergmann 1988, Peters et al. 1996, Wong et al. 1999, Huang et al. 2004, Donnelly et al. 2005, Gould et al. 2006, Yamagata et al. 2006, Wilson et al. 2007). The socioeconomic status of the patients was defined by the patient’s occupation according to the UK Registrar General’s classification (II). The criteria for stratification of occupational social class are presented in detail in the patients and methods section in study II (Skapinakis et al. 2006). Immunodeficiency was defined as a state in which the immune system’s ability to fight infection is compromised or entirely absent (Kainulainen et al. 2011).

4.6 Microbiology

Culture reports from the pus samples and blood cultures of the patients were analysed (Study I and IV). In the Study-I population, culture reports were obtained from the medical reports. Pus samples and blood cultures from the Study-IV population were analysed at the reference laboratory of the Oral Microbiology Unit of Helsinki University Central Hospital Laboratory Diagnostics (HUSLAB), Finland (EUCAST). If several culture reports were available, the sample yielding the largest number of microbial species was included. The proportion of aerobic, anaerobic, and microaerophilic bacterial findings, fungal findings, and negative findings were calculated from the sample reports. The positive bacterial findings were further classified on the basis of gram staining and shape (cocci and rods), and the incidence of the findings calculated.
4.7 Radiological imaging

Preoperative panoramic radiographs of the patients were taken on hospital admission in the emergency department at HUCH. These radiographs were analysed for the source of infection and overall dental health (III, IV). A digitalised (Video disc AGFA CRMD 4.0 general; Disc reader AGFA CR 75; Manufacturer AGFA-GEVAERT; AGFA IMPAX system, Mortsel, Belgium) PM 2002 CC panoramic radiograph device (Planmeca Oy, Helsinki, Finland) was used in the panoramic radiograph imaging of the patients. A maxillofacial radiologist, Kim K Lemberg, re-reviewed the panoramic radiographs in detail. The source of infection was confirmed from the medical records. Periapical pathology was graded as widening of the periodontal space, periapical radiolucency, and large well-defined lucency. The quality of RCT was classified from teeth with signs of RCT as adequate or inadequate (obturation missing in at least one root, poor quality, and/or more than 2mm short from apex). In addition, re-treatment (radiological findings indicating signs of removed root filling) and unfinished RCT (radiological findings indicating signs of intracanal medication) were recorded. The specific studied variables are found in detail in the patients and methods section in studies III and IV. Based on these findings, a grading of overall dental health was assessed as good (1), moderate (2), or poor (3) according to the radiologic classification by Mattila et al. (Mattila et al. 1989)

4.8 Statistical analysis

The Mann Whitney U test (I,II,IV) was used for comparison of independent samples without Gaussian approximation and the unpaired 2-tailed t test (II) for comparison of independent samples with Gaussian approximation. To compare more than two independent samples, Kruskal-Wallis one-way analysis of variance with Dunn’s Multiple Comparison Test (III,IV) was used for comparison of independent samples without Gaussian approximation and One-way Analysis of Variance (ANOVA) with Bonferroni’s Multiple Comparison Test (III,IV) for comparison of independent samples with Gaussian approximation. The Fisher’s Exact test (I-III) and the Chi-square test (II,IV) were used for cross-tabulations of
the samples. Data are presented as mean (± standard deviation), median (range), or number (%) (I-IV). Data was analysed by using GraphPad Prism version 4.0 (GraphPad Inc. San Diego, California, USA) (I-IV) and SPSS version 15.0 (SPSS Inc. Chicago, Illinois, USA) (III). Statistical significance was set at $P < 0.05$ in all studies.

4.9 Ethical aspects

Study I was approved by the Ministry of Social Affairs and Health. Studies II-IV were approved by the Helsinki University Hospital Research Board (Trial number 220363).
5 RESULTS

5.1 Predisposing factors for local and systemic odontogenic infections requiring hospital care (Study I)

In Study I, local and systemic odontogenic infections requiring hospital care in 2000-2003 were analysed. Of the 35 patients, 20 were females and 15 males with a mean age of 38.5 (range 16-67) years (Table 1, I). Most of the patients (25/35, 71%) were hospitalised due to locally invasive odontogenic infection with cellulitis and/or abscess formation and, for a rather high proportion of patients (10/35, 29%), due to disseminated infection (Figure 1, I). The submandibular space was the most common infected space according to the common distribution of infected spaces in the literature. The systemic odontogenic infections: septicaemia, IE, spondylitis, brain abscess, and severe diabetic complications, covered the usual sites of disseminated infections described in the literature.

The course of infection between local and systemic infections had different features. Patients with systemic infection required a longer LOS (mean length 30.2 days, range 2-81) compared to patients with odontogenic maxillofacial infection (mean length 8.0 days, range 2-34) \( (P = 0.0144) \). Patients with systemic infections also demonstrated a severe outcome more frequently, as three cases out of ten with systemic infections led to death. The outcome in odontogenic maxillofacial infection is usually good and in this study all patients with only local infection survived \( (P = 0.0183) \). Eight patients were found to be medically compromised. Patients with systemic infection were more often medically compromised compared to patients with local maxillofacial infection \( (P = 0.0028) \). The infection spread mainly locally in previously healthy patients \( (P = 0.0028) \). Clinical picture and course of infection are shown in Table 2 (I).

Source of the infection and antecedent dental procedure was recorded for this study. The mandibular molar was the most common focus tooth (21/35), as reported in the literature. Dental procedure preceded all of these patient cases as the study material was collected from the FPIC (Table 3, Study I). In the study
material, the primary indication for the performed procedure was a prolonged or previous infection, instead of an acute problem in both systemic and local infection groups (8/10 and 16/25 respectively). Poor dental status was a common finding as it was documented in 12 of the 35 patient cases.

Microbiological diagnoses in this study covered the usual findings of oral bacteria found in the literature (Tables 1 and 4, I). Microbiological findings in odontogenic maxillofacial infections were mainly mixed infections of anaerobes and streptococci, mainly of viridans and anginosus group streptococci. In two cases, Staphylococcus spp. were reported; S. aureus in one generally healthy patient and S. epidermidis in a medically compromised patient. The most common anaerobes reported were Fusobacterium and Bacteroides spp.. Rare microbes, such as P. aeruginosa, S. pneumoniae, and L. lactis, in addition to oral streptococci, were reported in medically compromised patients.

The use of antimicrobial treatment or prophylaxis was sparse. Only one medically compromised patient received single-dose-antibiotic prophylaxis with erythromycin one hour preoperatively. One immunocompromised patient was continuously administered clindamycin and additional prophylactic antibiotics were therefore omitted. In addition, one previously healthy patient received roxythromycin as antibiotic prophylaxis before operative tooth extraction. Postoperative antibiotic therapy was given to 14 of the 35 patients: 2 medically compromised patients and 12 previously healthy. Of the 35 patients, 20 underwent surgical procedures, of which 8 were prescribed postoperative antibiotics.

5.2 Changing clinical picture of odontogenic maxillofacial infections requiring hospital care (Study II)

In Study II, the characteristics and clinical features of two patient cohorts of odontogenic maxillofacial infections requiring hospital care one decade apart were analysed. The first cohort (1994-96) was comprised of 71 patients and the second cohort 101 patients (2004). The incidence of odontogenic maxillofacial
Infections requiring hospital care increased from 5.3 to 7.2 per 100,000 inhabitants in ten years in the Helsinki and Uusimaa Hospital District. The two cohorts did not differ in age (mean 37.2±13.4 and 41.5±16.9 years, respectively) or gender (59% and 63% males, respectively). The proportion of previously healthy patients, however, decreased between the cohorts (83% and 65%, respectively) (P = 0.0101), (Table 2, Study II). The proportion of patients with CVD and hypertension increased during the decade (4% and 14%, P = 0.0406 and 1% and 11%, P = 0.0160, respectively). The proportion of DM increased, but not significantly (Table 2, II). Interestingly, the proportion of mental disorders increased markedly from 0 to 13% (P = 0.0008), (Table 3, II). The patients in the second study cohort had more severe underlying diseases as indicated by need for intensive care and high infection parameters (Table 3, II).

Multiple space involvement has been found to be more common than single space involvement at the present. In this study, however, odontogenic maxillofacial infections were mainly single space infections in both study cohorts (Table 4, II). In addition, some variation in the affected fascial spaces was found. In the first cohort, the most common location of single space infection was the buccal space (63%) whereas in the latter cohort it was the submandibular space (47%) (P = 0.0011). The incidence of submandibular space as a single space infection did not change over one decade. The submandibular space was the most common fascial space involved in multiple space infections in both study periods (95% and 85%, respectively) as commonly described in the literature. Mandibular molars were the most common sources of infection (80% and 82%). All five patients requiring ICU-treatment had either submandibular or sublingual space involvement indicating the more severe course of infection in mandibular infections.

Patients admitted to the hospital had usually been treated in primary care. Thus, antimicrobial treatment was commonly ongoing on hospital admission. The primary antibiotics prescribed prior to hospital admission and the primary antibiotics administered during hospital stay are shown in Tables 5 and 6 (II). The proportion of patients who were prescribed antibiotics prior to hospital
admission remained the same (59% and 60%, respectively), although the number of medically compromised patients increased. The usage of penicillin V alone decreased from 31% to 17% ($P = 0.0291$). Other groups of antibiotics, e.g. macrolides, were used increasingly instead. The spectrum of primary antibiotics administered during hospital stay did not change.

It has been postulated that patients with odontogenic maxillofacial infections are commonly found belonging to lower socioeconomic classes. This was true also in the first cohort of this study. However, in the more recent cohort, infections were more equally distributed in all socioeconomic classes.

### 5.3 Significance of dental health and antecedent dental procedure in odontogenic maxillofacial infections requiring hospital care (Study III)

The third study population was collected for analysis of the impact of antecedent dental procedure and dental health on the course of odontogenic maxillofacial infections requiring hospital care. Preoperative panoramic radiographs and medical records were available for 84 patients in 2004. Patients were divided to patient groups according to the antecedent dental events. Dental procedure preceded the spread of infection in 58% of the cases. Antecedent endodontic treatment was the most common dental procedure ($n=22, 26\%$), followed by tooth extraction ($n=19, 23\%$), and minor first aid dental treatment ($n=8, 10\%$). Antimicrobial treatment alone was recorded in eight patient cases (10%). Local spread of infection occurred without any preceding dental or antimicrobial treatment in 27 (32\%) cases.

The mean age of the patients was 43.2 ($\pm 16.5$) years; 34 (40\%) were females and 50 (60\%) were males (Table 1, III). The median LOS of the patients was 3 days (range 1-26). Patients without preceding treatment had the longest LOS (median 5 days, range 1-13). Of the 84 patients, 13 (15\%) required reoperation, i.e. extraoral re-incision and revision of the infected fascial spaces. This was especially common in the group of patients without preceding treatment (22\%). Patients with preceding mandibular third molar extractions ($n=9$) were younger
(mean age 26.3 years, range 19-35) as third molars are usually extracted due to problems in eruption in early adulthood.

Infection parameters were at all points higher in the patient group without preceding dental procedure compared to other patient groups. The median CRP level on admission was 107 (mg/L) for all patients, and the median maximal CRP level was 137 (mg/L) (Table 2, III). The patient group without preceding treatment had higher CRP levels on admission (median 128 mg/L, \( P = 0.020 \)) and maximal CRP levels (median 178 mg/L, \( P = 0.011 \)) compared to the other patient groups. For all patients, the median WBC count on admission was 11.5 (10³/μL) and the median maximal value was 11.8 (10³/μL). The WBC counts on admission were higher in the patient group without preceding treatment than in the other patient groups (\( P = 0.011 \)).

Dental disease of the source of infection was analysed for this study (Table 3, III). Apical periodontitis was the most common source of infection in all patient groups (87%). Pericoronitis was the most common dental disease in the tooth extraction group (37%) and in the antimicrobial treatment alone group (25%) (\( P < 0.001 \)). Mandibular molar was the most common focus tooth in all patient groups with preceding procedure (86%), but least common in the patient group without preceding treatment (74%). Of the 19 patients with preceding tooth extraction, 9 had undergone mandibular third molar extractions in accordance with the younger age. The affected fascial spaces were mainly single space infections (71%), although multiple space involvement was slightly more common in patients without preceding dental procedure (Table 3, III).

Patients without preceding dental treatment had poorer dental health than other patients (\( P < 0.001 \)) (Table 4, III). In the patient group without preceding dental treatment, 20 (74%) had poor dental health while most of the patients in other groups demonstrated good to moderate dental health. The poor dental health of the patients without preceding dental procedure was comprised of multiple endodontic and carious problems (Table 5, III).
Good to moderate dental health was mainly found in the endodontic (41%-45%), tooth extraction (47%-26%), minor first aid (50%-38%), and antimicrobial (25%-50%) treatment groups. Again, endodontic and carious problems were common findings (Table 5, III).

Of all the pathologic findings in the panoramic radiographs, endodontic problems were the most common findings in 82% of the cases (Table 5, III). Periapical radiolucency was found in 75% of the cases and signs of RCT were present in 57% of the cases. Findings suggesting a cariologic problem such as carious pulp exposure (33%) or residual carious root (37%) could be seen in 50% of the cases.

Periodontal problems, such as horizontal attachment loss were a common finding in all patients (56%), but especially in patients without preceding dental treatment (74%). It may have contributed to the course of infection as increased bacterial burden of poor dental health.

A total of 48 (57%) patients received antimicrobial treatment before hospital admission. Antibiotics were prescribed equally for all patient groups (77-88%) besides the antimicrobial treatment only group (100%) and patient group without preceding treatment (0%). Prescribed antibiotics followed local Finnish recommendations at that time.

5.4 Role of periapical pathology and root canal treatment in odontogenic maxillofacial infections requiring hospital care (Study IV)

The Study IV population consisted of 60 patients requiring hospital care due to periapical infection. Radiologically confirmed periapical pathology was found in 59 patients and one patient had clinically diagnosed pulpitis as the source of infection. Underlying systemic diseases were rather rare. DM (four patients with DM type 2 and two patients with DM type 1) was the most common systemic disease being recorded in six (10%) patients. Other systemic diseases were found only in isolated cases.
Patients were divided into three groups according to the antecedent dental procedure: 1) endodontic treatment, 2) other treatment, and 3) no dental treatment (Table 1, IV). The number of infection foci per patient ranged widely from 0 to 14 with a mean of 1.6 foci per patient. Patients without preceding dental treatment had the highest mean number of infection foci, 2.1 (range 0-14) and most numerous periapical findings \( (P = 0.0118) \) (Table 2, IV). In this patient group residual carious roots as source of infection were a common finding \( (P = 0.0003) \) (Table 3, IV).

Unfinished RCT was the most common finding (Figure 1, IV). RCT had been initiated due to acute apical periodontitis before hospital admission for 16 of the 23 patients with preceding endodontic treatment. Re-treatment had been initiated in four patients, whilst completed RCT was found in seven patients. Of these seven completed RCTs, two were adequate and five inadequate.

All patients presented classical signs of odontogenic maxillofacial infection, such as pain, swelling, reduced mouth opening, or fever. LOS varied depending on the antecedent dental procedure. For all patients, LOS was a median of 3 days (range 1-14). Patients with preceding endodontic treatment had the shortest LOS (median 2 days, range 1-14) and patients without preceding treatment the longest LOS (median 5 days, range 1-13) \( (P = .0412) \). There were differences, although not statistically significant, regarding the requirement for intensive care, length of intensive care treatment, and reoperation between the patient groups. Inflammatory parameters, on the contrary, showed a distinct trend. CRP levels and WBC counts were significantly higher on admission and at maximum in the patient group without preceding dental procedure, compared to other patient groups (Table 4, Study IV).

Most patients (62%) were not receiving any antibiotic therapy at the time of hospital admission. When described, penicillin V in combination with metronidazole was the most common antimicrobial therapy in all patient groups (Table V, IV).
Pus samples for microbiological diagnostics had been taken in 73% of cases (Table 6a, IV). Anaerobic gram-negative bacteria were reported in 41% of the cases in the patient group without preceding dental treatment, and aerobic gram-positive bacteria were reported in 33%. The patient group with preceding endodontic treatment, in contrast, were reported with anaerobic gram-negative bacteria only in 17% of the cases. Aerobic gram-positive bacteria were commonly found in samples from patients in the endodontic treatment group and other dental treatment group (55% and 53%, respectively). Mixed flora was reported in 7 (58%) of the 12 cases in the endodontic treatment group, 6 (67%) of the 9 cases in other dental treatment group, and in 11 (48%) of the 23 cases in the patient group without preceding dental treatment. Of these, two samples in the patient group without preceding dental treatment were reported only as oral mixed flora.

The microbiological findings of the pus samples followed the normal prevalence reported in the literature, in general (Table 6b, IV). However, there were variations in the prevalence of microbes depending on the treatment group. Alpha/nonhaemolytic streptococci were more common in patients with preceding endodontic treatment and other dental treatment (67% and 89%, respectively) compared to patients without preceding dental procedure (17%) \((P = 0.0008)\). In addition, *Prevotella* spp. were reported significantly less often in the patient group with preceding endodontic treatment (17%) compared to the group without preceding dental treatment or the other dental treatment group (61% and 56%, accordingly) \((P = 0.0397)\). Interestingly, staphylococci were reported in over 30% of the cases and *S. aureus* in 9% of the cases. The possibility of these pathogens should be kept in mind in case of poor response to the recommended first line choice (penicillin and amoxicillin). Yeasts were reported without variation between the patient groups (25%, 33%, and 30%, respectively). In addition, two positive blood cultures were reported in the group of patients without preceding dental treatment: *Veillonella* spp. and *Lactobacillus catenaforme*. 

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DISCUSSION

The principal focus of this work was to analyse local and systemic odontogenic infections requiring hospital care and their predisposing factors. The findings reported here confirmed that systemic predisposing factors have a significant impact on the spread and outcome of infection. In addition, local predisposing factors in the oral cavity, such as dental disease and the antecedent dental procedure, or its absence, affect the course of infection. Local odontogenic infections requiring hospital care were characterised here by local abscess formation and/or cellulitis of the maxillofacial region with systemic symptoms, such as fever and malaise. Systemic odontogenic infections requiring hospital care comprised sepsis, IE, spondylitis, and brain abscess, which belong to the most commonly reported systemic odontogenic infections found in the literature (Lee et al. 2009, Dzupova et al. 2012, Mylona et al. 2009, Rahamat-Langendoen et al. 2011).

Generally healthy patients, without any major underlying systemic diseases, were observed here to most commonly have developed odontogenic maxillofacial infections. The course of local infection was quite predictable in most cases, without any permanent consequences or disability. Medically compromised patients with underlying systemic diseases, however, were susceptible to develop systemic infections requiring a longer period of hospital care coupled, occasionally, with a fatal outcome.

Invasive dental procedures, such as tooth extractions, are acknowledged to induce bacteraemia (Takai et al. 2005). Indeed, tooth extractions and surgery seem to provoke highest incidence of bacteraemia compared to minor or non-invasive procedures (Takai et al. 2005). However, all dental manipulation may cause bacteria with different incidence, intensity and duration (Takai et al. 2005, Lockhart et al. 2008). The presence chronic infection of periodontal tissue provokes the entry of microorganisms to the blood stream through damaged mucosa (Takai et al. 2005, Tomás et al. 2012). Contradictory reports, however, exist in which the degree of oral health with chronic infections did not correlate
with the intensity of bacteraemia (Kinane et al. 2005, Tomás et al. 2007, Tomás et al. 2008, Bahrani-Mougeot et al. 2008). In this context, the type of the preceding dental procedure constitutes only one determining part of the multifactorial nature of odontogenic bacteraemia. In the cases reported here to carry systemic odontogenic infections, preceding dental treatment varied from minor invasive treatment, such as removal of dental plaque and calculus to invasive tooth extractions. Thus, these results support the findings in the literature that invariably all dental manipulation can induce bacteraemia, which subsequently may lead to dissemination of the infection (Gendron et al. 2000, Lucas et al. 2002, Rajasuo et al. 2004, Kinane et al. 2005, Takai et al. 2005, Roberts et al. 2006, Tomas et al. 2007, Lockhart et al. 2008, Sonbol et al. 2009).

The relationship between oral source of infection and distant site infection is well recognised (Hoen et al. 2002, Lei et al. 2009, Renton et al. 2009, Biswas et al. 2010, Mandac et al. 2010, Antunes et al. 2011, Azenha et al. 2011, Dzupova et al. 2012). The use of antibiotic prophylaxis was, however, sparse in the first study population. Only one out of eight medically compromised patients received AP and one immunocompromised patient was continuously administered clindamycin and additional prophylactic antibiotics were therefore omitted. Six of eight medically compromised patients developed systemic infection complications and two developed local infection complication. Thus, taking the local Finnish guideline into account (Richardson et al. 2011), most of the medically compromised patients in this study did not receive antibiotic prophylaxis, which could have prevented the infection complications observed.

The clinical picture of odontogenic maxillofacial infections requiring hospital care changed according to the results of a two-cohort study population one decade apart (years 1994-96 and 2004; Study 2). The incidence increased from 5.3 to 7.2 per 100 000 inhabitants. This trend has been observed in previous studies as well (Carter et al. 2006, Thomas et al. 2008). The odontogenic maxillofacial infections seen here were most commonly single space infections, although a predominance of multiple space involvement has been previously reported (Storoe et al. 2001, Rega et al. 2006, Marioni et al. 2008).
Submandibular and buccal spaces were the most common affected spaces, followed by the sublingual space, which was in accordance with the literature (Rega et al. 2006, Marioni et al. 2008, Bakathir et al. 2009, Kinzer et al. 2009, Sato et al. 2009, Rao et al. 2010). Rare fascial spaces, such as the retropharyngeal space and the masseteric space were found more frequently in the latter study cohort, however. The course of infection was also more severe in the latter study cohort: the need for intensive care increased from 15% to 32% of the patients and the maximal CRP levels were significantly higher in the latter study cohort (median 127mg/L) compared to the first cohort one decade earlier (median 104mg/L). In addition, the number of underlying systemic diseases increased, particularly the prevalence of CVD and hypertension. Interestingly, there was a considerable increase in the number of patients with mental disorders from 0 to 13% of the patients. The number of previously healthy patients thus decreased from 83% to 65% of the patients in the latter study cohort. However, patients with immunodeficiencies were not found in these two study cohorts supporting the results of the first study population.

According to the literature, studies on odontogenic maxillofacial infections requiring hospital care have mainly focused on the surgical aspects and treatment alignments (Peters et al. 1996, Storoe et al. 2001, Wang et al. 2005, Flynn et al. 2006, Rega et al. 2006, Kinzer et al. 2009, Sato et al. 2009, Saito et al. 2011, Sánchez et al. 2011). Source of infection and dental disease have been identified, but no systemic analyses on the antecedent dental treatment and source of infection have been performed. The present study showed that these factors can have a significant impact on the course of infection. The primary dental treatment, or its absence, preceding hospital admission was recorded. Most of the patients (58%) had visited a dentist in the near past (during the past month). Endodontic treatment (26%) and tooth extractions (23%) were the most common dental events before hospitalisation. A minority of the patients had received only antimicrobial treatment without dental procedures (10%), or minor dental procedures (10%), such as restorative treatment, occlusal adjustment, or other symptom-related first aid. However, one third of the patients had not visited dentist in the near past (during the past month). These
patients without preceding dental treatment had the highest inflammatory parameters, CRP levels and WBC-counts, on admission (median 128 mg/L and median 15.2 $10^3$/μL, respectively) and at maximum (median 178 mg/l and median 15.2 $10^3$/μL, respectively) compared to all cases on admission (median 107 mg/L and median 11.5 $10^3$/μL, respectively) and at maximum (median 137 mg/l and median 11.8 $10^3$/μL, respectively). Thorough canal debridement or tooth extraction in the first treatment session lowers the risk for spread of odontogenic infection.

In addition, poor dental health was found significantly more often in this patient group (74%) compared to all cases (37%). These findings are in accordance with previous studies, where odontogenic maxillofacial infections have increased, especially amongst poorer people belonging to lower socioeconomic classes and where poor dental health was a common condition (Hobdell et al. 2003, Moles et al. 2008). As odontogenic infections originate mainly from oral sources of infection, and rarely from infection-free sites, the significance of maintaining good oral health is again emphasised. Although the antecedent dental treatment did fail to prevent hospitalisation in this study, it contributed to a less severe course of infection. Thus, these results suggest that poor overall dental health contributes to a stronger systemic response and more severe course of infection.

Apical periodontitis has been reported to be the most common dental disease behind odontogenic maxillofacial infections requiring hospital care, which is in accordance with previous reports (Ylijoki et al. 2001, Flynn et al. 2006, Saito et al. 2011, Sánchez et al. 2011). To understand the role of periapical pathology as the source of infection, clinical and radiological findings were evaluated. The antecedent dental treatment and microbiological findings of the pus samples were recorded. Ongoing primary root canal treatment (RCT) was the most common endodontic procedure preceding the spread of infection due to apical periodontitis (70%). The results indicated that initiation of primary RCT of acute apical periodontitis with inadequate or incomplete RCT seems to open a risk window for locally invasive spread of infection to adjacent structures with local abscess formation and systemic symptoms. Thereafter, the quality of the
complete RCT appears to have minor impact on the risk for flare-up. Instead, it is strongly associated with chronic infections and their effect on general health and systemic diseases. Completed RCTs were underrepresented in this study material, further supporting the results.

Microbiological findings from the pus samples showed significant changes between patient groups that had undergone different antecedent dental procedures. Aerobic gram-positive bacteria were more common in pus cultures from patients with preceding endodontic treatment compared to patients without preceding treatment, for whom anaerobic gram-negative bacteria were the most common finding. Thus, RCT seems to efficiently prevent the growth and reduce the number of anaerobic bacteria in the root canal system and subsequently in the periapical periodontal lesions. Two positive blood cultures were recorded for \textit{Veillonella} spp. and \textit{Lactobacillus catenaforme} in the patient group that had not undergone a preceding dental procedure. These microorganisms with low virulence belong to the normal oral microbiota. The role of these microorganisms may reflect the predominance of anaerobic bacteria in the course of infection in patients without preceding dental procedure.

There are some limitations in this study due to the retrospective study model. Firstly, the patient cases comprised only those with failed dental treatment or its absence. In addition, the Study I included mainly the most severe cases of odontogenic systemic and local infections requiring hospital care as the study population was identified from the FPIC registry. Finally, periapical radiographs would have provided a more precise radiological view of the source of infection compared to panoramic radiographs, which were taken on admission to hospital.

Several local and systemic predisposing factors affecting the spread, course, and outcome of the infection were identified. As the emerging infection is an end result of several factors, the focus should be aimed at the early phases of the infection. The importance of good oral health is emphasised in preventing and treating these infections. Dentists and clinicians should deepen their
understanding of the systemic manifestations of oral diseases and improve their cooperation. Although the course of local and systemic odontogenic infections differs, good oral health remains in the key position in odontogenic infections and other systemic manifestations. Dentists have a special opportunity to educate their patients about the importance of good oral health.

Special attention should be given to medically compromised patients, as the course of infection may be unpredictable in this patient group. In these challenging cases, cooperation between the dentist and the clinician is essential. As good oral health is especially important in this patient group, the clinicians should readily refer the patient to see a dentist.

In this context, good oral health continues to be critical in the prevention and treatment of severe odontogenic infections. Although it is quite simple as a solution, it requires more profound awareness by society and health care professionals. The results of this research will hopefully deepen our understanding of the nature of severe odontogenic infections, and that improved understanding could be applied in clinical practice.
CONCLUSIONS

Based on the results of this investigation, the following conclusions can be drawn:

1. Medically compromised patients were at an increased risk of systemic infection with longer hospital care (mean 30.2 days vs 8 days) and occasionally fatal outcome compared to immunocompetent patients. Previously healthy patients developed mainly local infection with cellulitis and abscess formation.

2. The clinical picture of odontogenic maxillofacial infections requiring hospital care changed between the studied cohorts that were 10 years apart. The number of these infections increased and the course of infection became more severe and complex. Characteristics of patients with odontogenic maxillofacial infections also changed between the studied cohorts. The number of previously healthy patients decreased and underlying systemic diseases became more prevalent. The number of patients with mental disorders hospitalised due to odontogenic maxillofacial infections increased considerably.

3. Odontogenic maxillofacial infections requiring hospital care were mainly complications developing after dental treatment. However, leaving the source of potentially invasive infection untreated creates a considerable risk for severe infection complications.

4. Patients without preceding dental treatment in the near past had significantly poorer overall dental health and more potential infection focus sites compared to those with various preceding dental procedures. The presence of multiple chronic infections led to a stronger systemic response and more severe course of infection.
5. The microbiological findings of the pus samples showed considerable changes between the patient groups with different antecedent dental procedures. Aerobic gram-positive bacteria were more common in pus cultures from patients with preceding endodontic treatment compared to those without preceding treatment, for whom anaerobic gram-negative bacteria were predominant. Thus, RCT seems to efficiently prevent the growth and reduce the number of anaerobic bacteria in the root canal system and subsequently in the periapical periodontal lesions.

6. Initiation of primary RCT with inadequate or incomplete RCT of acute apical periodontitis seems to open a risk window for locally invasive spread of infection to adjacent structures with local abscess formation and systemic symptoms. Thereafter, the quality of the complete RCT appears to have minor impact on the risk for flare up.
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