UNIVERSIDADE FERNANDO PESSOA

SEPSIS AS A RESULT OF ODONTOGENIC INFECTIONS. IS THERE A REASON FOR CONCERN? A NARRATIVE REVIEW

[Sepse como resultado de infecções odontogênicas. Há razão de preocupação? Uma revisão narrativa]

Dissertação de Mestrado Integrado em Medicina Dentária

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Orientador:

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“Se não puder voar, corra. Se não puder correr, ande. Se não puder andar, rasteje, mas continue em frente de qualquer jeito.”

Martin Luther King

DEDICATÓRIA

Dedico ao meu filho Leo. Você foi e será a razão de tudo, TE AMO.

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A Deus por permitir essa conquista.

Aos meus pais por estarem presentes nesse caminho escolhido por mim e por terem me ajudado a chegar ao destino.

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RESUMO

A odontologia enfrentou desafios consideráveis com a ascensão da "Era da Infecção Focal", que levou à prática generalizada da extração dentária e dificultou o progresso da endodontia, devido à crença de que bactérias e toxinas nos túbulos dentinários poderiam causar doenças sistêmicas. Embora essa teoria tenha sido posteriormente refutada, pesquisas contemporâneas têm reavaliado a relação entre periodontite apical, tratamento endodôntico e saúde sistêmica, investigando a possibilidade de que doenças endodônticas possam impactar a saúde geral. Estudos indicam que doenças orais comuns, como cáries e periodontite, causadas por bactérias presentes na cavidade oral, podem levar a bacteremia durante procedimentos dentários ou devido à má higiene oral. Esse cenário motivou investigações sobre a associação entre periodontite apical e condições sistêmicas, incluindo doenças cardiovasculares, diabetes, desfechos adversos na gravidez e doenças autoimunes. Evidências sugerem que a bacteremia e a inflamação sistêmica de baixo grau associadas à periodontite apical podem ter um impacto negativo sobre a saúde sistêmica. Adicionalmente, a literatura aponta um aumento nas infecções sistêmicas originadas de fontes odontogênicas, possivelmente devido ao aprimoramento nos métodos de detecção ou à ocorrência de intervenções tardias. O aprofundamento científico sobre a disseminação de infecções odontogênicas localizadas e as complicações associadas a essa disseminação, com os possíveis locais envolvidos, demonstra a gravidade dos casos e o desenvolvimento de sepse e/ou choque séptico. O objetivo desta revisão foi realizar uma análise da literatura existente sobre o assunto. A revisão narrativa foi elaborada com base em uma pesquisa bibliográfica nas bases de dados “PubMed”, “LILACS” e “BMC”, utilizando palavras-chave combinadas com os operadores Booleanos “E” ou “OU”. Os critérios de inclusão foram artigos com texto completo em português, inglês ou espanhol, publicados entre 2013 e 2024. Os artigos foram inicialmente selecionados pelo título, seguidos pelo resumo, e, posteriormente, lidos na íntegra. Foram incluídos artigos de revisões, pesquisas clínicas e básicas, estudos randomizados, revisão sistemática e meta-análise, estudos comparativos, experimentais e não-experimentais, além de relatórios e séries de casos. Artigos não diretamente relacionados ao tema ou que não estavam disponíveis em texto completo foram excluídos. Em síntese, esta revisão conclui que condições não tratadas podem se disseminar rapidamente pela corrente sanguínea, resultando em infecções graves que necessitam de cuidados intensivos. Apesar dos avanços médicos, essas infecções continuam a representar um risco significativo, especialmente para indivíduos imunocomprometidos, podendo levar a sepse e aumento da mortalidade. Frequentemente originadas de problemas preveníveis, como cáries dentárias, essas infecções ressaltam a necessidade urgente de medidas de saúde pública mais eficazes para mitigar seu impacto.

Palavras-chave: Infecção odontogênica, infecção dentária, sépsis.

ABSTRACT

Dentistry has faced significant challenges with the rise of the "Focal Infection Era," which led to the widespread practice of tooth extraction and impeded the advancement of endodontics due to the belief that bacteria and toxins in dentinal tubules could cause systemic diseases. Although this theory has since been refuted, contemporary research has re-evaluated the relationship between apical periodontitis, endodontic treatment, and systemic health, investigating whether endodontic diseases could impact overall health. Studies have shown that common oral diseases, such as caries and periodontitis, caused by bacteria present in the oral cavity, can lead to bacteraemia during dental procedures or due to poor oral hygiene. This has prompted investigations into the associations between apical periodontitis and systemic conditions, such as cardiovascular diseases, diabetes, adverse pregnancy outcomes, and autoimmune diseases. Evidence suggests that bacteraemia and low-grade systemic inflammation related to apical periodontitis may negatively affect systemic health. Furthermore, the literature highlights an increase in systemic infections originating from odontogenic sources, possibly due to improved detection methods or delayed interventions. Scientific exploration into the dissemination of localized odontogenic infections and the complications resulting from such dissemination, including potential affected sites, demonstrates the severity of the cases and the development of sepsis and/or septic shock. The aim of this review was to analyse the existing literature on the subject. The narrative review was conducted based on a bibliographical search in the databases “PubMed,” “LILACS,” and “BMC,” using keywords combined with Boolean operators “AND” or “OR.” The inclusion criteria were articles with full text available in Portuguese, English, or Spanish, published between 2013 and 2024. Articles were initially selected by title, followed by the abstract, and then read in full. Included were review articles, clinical and basic research, randomized studies, systematic reviews, meta-analyses, comparative, experimental and non-experimental studies, as well as case reports and series. Articles not directly related to the topic or those not available in full text were excluded. In summary, this review concludes that untreated conditions can rapidly spread through the bloodstream, leading to severe infections that require intensive care. Despite medical advancements, these infections continue to represent a significant risk, especially for immunocompromised individuals, potentially resulting in sepsis and increased mortality. Often originating from preventable issues such as dental caries, these infections underscore the urgent need for more effective public health measures to mitigate their impact.

Keywords: Odontogenic infection, dental infection, sepsis.

INDEX

ABBREVIATIONS LIST

AD-HIES: Autosomal Dominant Hyper-IgE Syndrome

AHA: American Heart Association

AIDS: Acquired Immunodeficiency Syndrome

ARDS: Acute Respiratory Distress Syndrome

BM: Bacterial Meningitis

CFI: Cervicofacial Infection

CNF: Cervical Necrotizing Fasciitis

CRP: C-reactive Protein

CST: Cavernous Sinus Thrombosis

CT: Computed Tomography

DNI: Deep Neck Infections

DNSI: Deep Neck Space Infections

DNM: Descending Necrotizing Mediastinitis

HIV: Human Immunodeficiency Virus

ICU: Intensive Care Unit

IE: Infective Endocarditis

MRSA: Methicillin-Resistant Staphylococcus Aureus

mNGS: Next-Generation Metagenomic Sequencing

NASH: Non-Alcoholic Steatohepatitis

NLR: Neutrophil-to-Lymphocyte Ratio

NSTI: Necrotizing Soft Tissue Infections

OFC: Odontogenic Facial Cellulitis

OI: Odontogenic Infections

PCT: Procalcitonin

PSEP: Presepsin

qPCR: Quantitative Polymerase Chain Reaction

SII: Systemic Immuno-Inflammatory Index

SIRS: Systemic Inflammatory Response Syndrome

SPE: Septic Pulmonary Embolism

SS: Symptom Severity Index

TMD: Temporomandibular Dysfunction

WBC: White Blood Cell Count

I - INTRODUCTION

At the end of the 19th century and beginning of the 20th century, dentistry suffered a violent clash with the spread of the "Era of Focal Infection in Dentistry" which resulted in the widespread implementation of tooth extractions and limited the progress of endodontics. It was believed that bacteria and toxins trapped in dentinal tubules could spread systemically to remote parts of the human body, resulting in many types of degenerative systemic diseases. This theory was later refuted due to lack of evidence (Niazi & Bakhsh, 2022).

However, as new data emerged, there has been increasing interest in analysing, based on the current literature available, the dynamic associations between apical periodontitis, endodontic treatment and systemic health to investigate whether endodontic disease could have an impact on overall health (Niazi & Bakhsh, 2022).

Caries and periodontal disease are common oral diseases caused by bacteria indigenous to the oral cavity, and studies have shown that these oral bacteria can invade blood vessels during surgical procedures, such as tooth extraction and tartar removal, causing bacteraemia. Even poor oral hygiene is highly likely to cause bacteraemia (Takizawa et al., 2022).

Following this line of investigation, many studies point to evidence on the theory of infection focus related to bacteraemia and inflammatory markers, others argue the associations of apical periodontitis with cardiovascular diseases, diabetes mellitus, adverse pregnancy outcomes and autoimmune diseases, along with the effect of immunomodulators on the prevalence of apical periodontitis and prognosis of endodontic treatment. There is emerging evidence that bacteraemia and low-grade systemic inflammation associated with apical periodontitis can negatively impact the systemic health of patients (Niazi & Bakhsh, 2022).

Over the decades, scientific literature has described cases of the spread of infections throughout the human body and even an increase in their occurrence (Robertson & Smith, 2021; Ranjbar et al., 2023). The increase in the number of cases may be due to improved detection and diagnosis methods (Ranjbar et al., 2023). Another reason for the increased occurrence of this spread, giving rise to more serious cases, would be mainly due to late interventions or poorly diagnosed complications, which is why odontogenic infections represent a frequent cause of maxillofacial interventions (Qu et al., 2017; Robertson & Smith, 2021; Rosca et al., 2023).

The point is that odontogenic infections are common in dental practice, as well as in the care of patients with chronic immunosuppressive systemic diseases. Approaching these patients

requires knowledge on the part of the healthcare professional, as this type of patient can develop serious complications (Martini et al., 2015). Thus, severe odontogenic infections can spread throughout the human body, causing cases of sepsis and/or septic shock with a potential threat to the individual's life.

However, despite advances in dental care for the population, the lack of patient information and/or unpreparedness of professionals to intervene effectively to combat odontogenic infections in the early stages can result in cases of great morbidity (Martini et al., 2015).

In the literature it has been reported that a high mortality rate remains, despite the fact of subsequent introduction of intravenous antibiotics, major improvements in anaesthesia, intensive care and the development of computed tomography, the joint work of several reference centres with integration of medicine and dentistry in the early identification and treatment of odontogenic infections (Ranjbar et al., 2023).

In this way, the scientific deepening of the possibility of dissemination of localized odontogenic infections and the complications caused by the dissemination of this focus of infection with the possible sites involved, indicating the severity of the case, leading to the development of sepsis and, or septic shock, are part of within the scope of this narrative literature review.

1. METHODS

1.1 Sources of Information and Research

This narrative review was designed based on a bibliographical search carried out in the following databases: “PubMed”, “LILACS” and “BMC”, using keywords, combined with Boolean markers “AND” or “OR” as follows:

PubMed (odontogenic infection OR dental infection OR periapical abscess OR apical periodontitis OR endodontic infection OR periapical infection) AND (sepsis OR septicaemia).

LILACS (odontogenic infection OR dental infection OR periapical abscess OR apical periodontitis OR endodontic infection OR periapical infection) AND (sepsis OR septicaemia).

BMC (odontogenic infection OR dental infection OR periapical abscess OR apical periodontitis OR endodontic infection OR periapical infection) AND (sepsis OR septicaemia).

The inclusion criteria applied were: available articles with full text written in Portuguese, English or Spanish. The filter was applied to select year of publication, from 2013 to 2024. The articles were selected first by title, followed by the summary, and then read in full. The types of article publications included were: reviews, clinical and basic research, randomized or randomized, systematic review and meta-analysis, comparative, experimental and non-experimental studies, reports and case series. All articles that were not directly related to the topic or those that were not available in full text were excluded.

II – DEVELOPMENT

1. Focal Infection

In 1891, Miller proposed, without scientific basis, that oral microorganisms and/or their byproducts could spread throughout the body, implying a relationship between oral and systemic diseases. Western Price, in 1925, expanding this theory, advocated tooth extraction to remedy many types of degenerative systemic diseases, believing that toxins and residual bacteria, trapped in necrotic root canals, acted as antigens, playing an etiological role in these diseases via the bloodstream and lymphatic system. Later, Easlick (1952) pointed out flaws in Price's methodologies and refuted any associations between endodontically treated teeth and systemic disease, leading to a decline in interest in this theory due to a lack of conclusive evidence (cited by Niazi & Bakhsh, 2022).

Recently, however, the “Focal Infection Theory” has gained new attention. Recent studies have explored how oral infections, especially apical periodontitis, may be associated with a variety of systemic conditions such as diabetes, hypertension, pregnancy complications, bone infections, and heart disease. Focal infection is defined as a localized or generalized infection, caused by the systemic dissemination of bacteria or their products, from distant foci of infection. An “infection focus” is a confined, chronically infected area (Niazi & Bakhsh, 2022).

This reassessment suggests that oral infectious foci, even asymptomatic ones, can play a significant role in general health, reigniting the debate about the relationship between oral and systemic health.

2. Odontogenic Infections

Odontogenic infections (OI), also known as dental infections, typically start localized around a tooth and remain confined to the vicinity of the alveolar ridge (Weise et al., 2019). However, they can sometimes spread to deep fascial spaces, causing distant complications in critical areas such as the skull, brain, and thorax (Dai et al., 2019).

OI can be related to autoimmune diseases. A report by Rowen (2018) describes the case of a 48-year-old male patient with an inflammatory crisis and a confirmed diagnosis of Dermatomyositis. He was receiving immunosuppressive drugs without satisfactory results to alleviate his severe muscle pain, weakness, and diffuse generalized symptoms, such as skin rashes, which incapacitated him from working. With the help of ozone therapy and the removal of OI foci, an improvement in his condition was observed, allowing the discontinuation of the immunosuppressive medication that had been initiated four years earlier. This indicates a possible link between oral infections and autoimmune conditions.

In a study by Furuholm et al. (2021), 303 patient records of those requiring hospital care for OI were investigated. Of these, 23% required treatment in an intensive care unit (ICU), with no significant distinction between those with pre-existing conditions and healthy individuals. However, smokers were more prone to severe forms ($p = 0.001$) and to a lesser extent, patients with excessive alcohol or drug consumption. The study highlighted that infections originated in the mandible presented a higher risk of serious complications. Elevated levels of blood infection parameters upon hospital admission indicated longer ICU stays. The mortality rate was 0.3%. Sepsis was the most common infectious complication, followed by pneumonia.

Silva et al. (2022) focused on the spread of OI and their complications. They analysed the fascial spaces frequently involved with OI using CT (computed tomography) scans in a study conducted on 66 patients from June 2017 to May 2018. They found a decreasing frequency of fascial space involvement as follows: submandibular, buccal, sublingual, submental, masseteric, canine, lateral parapharyngeal, pterygomandibular, and retropharyngeal. Significant differences were also found between blood laboratory tests, average hospitalization time, and ICU admission depending on the number of fascial spaces involved, as analysed by CT scans. There was a significant difference in absolute neutrophil counts, neutrophil/lymphocyte ratios, and C-reactive protein (CRP) levels relative to the number of involved fascial spaces; higher values correlated with more spaces involved. Comorbidities,

nutritional status, or the causal tooth did not influence the number of involved fascial spaces, but 47% of patients reported smoking or drug use. The causal teeth involved were, in descending order: lower molars in 48 patients, primary molars in 7, multiple foci in 4, upper premolars in 3, upper incisors in 3, and an upper molar in 1 patient.

During the first year of the COVID-19 pandemic in Germany, Grill et al. (2023) observed a significant increase in severe OI. They noted that the stages of odontogenic abscesses that year were much more advanced compared to the previous two years (2018-2019). They attributed this phenomenon to patients' reluctance to seek medical care due to fear of contracting COVID-19. The rate of patients with poor oral hygiene and incomplete dental records was significantly higher in the COVID-19 year than in the previous two years ($p < 0.001$).

3. Localized Odontogenic Infections

Localized odontogenic infections, also known as foci of infection, can under certain conditions lead to bacteraemia and severe systemic complications, including sepsis and death. The pathogenicity of microorganisms, the patient's immune status, and delays in treatment are critical factors influencing the progression of these infections.

3.1 Periodontal Infections or Periodontitis

Omura et al. (2016) reported a morbid case of an obese patient with cirrhosis related to Non-Alcoholic Steatohepatitis (NASH) who died of sepsis caused by an odontogenic infection from *P. gingivalis*. They emphasized the importance of oral care and eradication to prevent severe systemic complications.

Epidemiological evidence points to a significant connection between periodontitis and an increased risk of atherosclerotic cardiovascular disease. A 2020 workshop organized by the European Federation of Periodontology and the World Heart Federation recognized periodontitis not only as a risk factor for cardiovascular diseases, with implications in heart failure and increased mortality, but also associated it with conditions such as Type II Diabetes Mellitus, Parkinson's disease, chronic obstructive pulmonary diseases, pneumonia, adverse pregnancy outcomes, osteoporosis, and kidney disease (Niazi & Bakhsh, 2022).

3.2 Root Canal Infection

Research has confirmed the connection between teeth with infected root canals and systemic diseases, suggesting that odontogenic conditions can be hidden sources of autoimmune diseases and systemic inflammation (Rowen, 2018). Root canal infections, commonly resulting from advanced dental caries, lead to irreversible pulp inflammation and eventually to pulp necrosis and periapical infections. The absence of an epithelial barrier between the necrotic, infected root canal and the surrounding highly vascularized granulomatous tissue in periapical infections allows these areas, with significant bone resorption, to act as "reservoirs" of inflammatory biomarkers. These biomarkers accumulate, turning endodontic disease into a primary infectious focus capable of disseminating microorganisms and inflammatory mediators into the systemic circulation. (Niazi & Bakhsh, 2022).

Acute manifestations of endodontic infections involve the formation of abscesses in the periapical tissues. Although these lesions are typically confined to the oral region, they can extend to neighbouring tissues as well as distant areas of the body through anatomical pathways - maxillary sinuses, brain, cavernous sinuses, eyes, mediastinum - posing real life-threatening risks. Pulmonary infections can be caused by the aspiration of oral bacteria involved in endodontic infections (Marceliano-Alves et al., 2010).

3.3 Apical Periodontitis

Apical periodontitis is an inflammation at the apex of the tooth, typically caused by untreated odontogenic infections stemming from dental caries. Inadequate treatment, such as failing to remove the caries or perform endodontic procedures, can worsen the inflammation, leading to the formation of periapical abscesses. If left untreated, these abscesses can spread to the maxillofacial and cervical regions, causing severe complications such as facial cellulitis, Ludwig's angina, and septicaemia. Treatment includes antibiotics, incision and drainage of the abscess, pain control, and elimination of the infectious focus (Bogacz, et al., 2019).

Apical periodontitis results from a complex interaction between the microbiota of the root canal system, microbial virulence factors, and the host immune response involving both innate and adaptive immunity. It is characterized by the recruitment of various cell types and inflammatory mediators, leading to the destruction of periapical tissue near the apex. This condition increases the risk of bacteraemia, the translocation of soluble microbial compounds, active inflammatory

mediators, and haemostatic factors from the root canal into the systemic circulation, triggering systemic inflammation. Both symptomatic and asymptomatic cases are reported, with the latter often only identified through radiographs after several years (Niazi & Bakhsh, 2022).

3.4 Odontogenic Abscess

Odontogenic abscesses, often triggered by caries, trauma, or failed endodontic treatment, are common infections that can be underestimated in the oral cavity. Once the pulp chamber is exposed to the oral environment, a variable set of bacteria colonize the walls of the necrotic root canals, forming a specialized mixed biofilm. When these bacteria and their toxic products reach the periapical tissues through the apical foramen, they can induce acute inflammation and pus formation. The main signs and symptoms of this disease include pain, swelling, erythema, and suppuration, usually localized to the region of the affected tooth but potentially spreading and evolving into severe systemic conditions, including sepsis (Bertossi et al., 2017).

Bertossi et al. (2017) observed that the most affected teeth were the lower posterior teeth. Other teeth were involved at a much lower percentage, or multiple teeth were simultaneously affected. The microbiological pattern varied between aerobic pathogens, obligate anaerobes, combined aerobic/anaerobic bacteria (the majority of cases), and, in some cases, no microorganisms were detected. Just over 50% of the patients were hospitalized for 5 days or less, while a few stayed for more than 10 days due to the severity of their clinical condition. One patient with mediastinitis required a 37-day hospitalization. Five patients developed cervicofacial necrotizing fasciitis, and three patients had Ludwig's angina.

Regarding management, abscess drainage combined with the removal of the affected teeth and complementary medical care, including intravenous antibiotics and anti-inflammatory drugs, was the most common treatment. In more complex cases, procedures under general anaesthesia were necessary. Medical therapy and abscess drainage often delayed specific dental treatment, indicating the need for an integrated approach to managing these infections. One hundred eighteen patients underwent abscess drainage through the root canals, root canal medication, and antibiotic therapy (Pastorino & Tavarez, 2024).

3.5 Odontogenic Cutaneous Sinus Tracts

The pulpal infection progresses to a periapical abscess but can continue evolving, slowly spreading through the alveolar bone and into surrounding soft tissues, eventually breaking through the skin as odontogenic cutaneous sinus tracts. Most of these infections develop intraorally; however, when they break through extraorally, they commonly affect the chin or submental region for lower incisor infections, while lower premolars and molars tend to drain toward the posterior mandible or submandibular areas. Upper tooth infections can manifest in the nasal region. The primary treatment for most cases is conservative and non-surgical, focused on endodontic therapy, though extraction is necessary for severely damaged teeth or those associated with significant bone loss (Gimenez-Garcia, Martinez-Vera & Fuentes-Vera, 2015).

These conditions are often misdiagnosed and incorrectly treated, leading to unnecessary procedures and patient suffering. Diagnostic errors can result in multiple surgical excisions and biopsies, excessive antibiotic therapy, and even radiotherapy. Early and correct diagnosis, based on radiological evidence of periapical root infection requiring endodontic treatment, can reduce the possibility of further complications such as sepsis and osteomyelitis. Extraction may be necessary for severely damaged teeth or those associated with significant bone loss. Gimenez-Garcia, Martinez-Vera and Fuentes-Vera (2015) reported two cases of recurrent suppurative facial lesions initially misdiagnosed and treated with oral antibiotics without response. Radiological examination revealed chronic periapical periodontitis consistent with sinus tracts.

4. Bacteraemia

Bacteraemia is the transient, intermittent, or continuous passage of bacteria into the bloodstream, often observed following oral surgical procedures. Dental extractions lead as the procedure with the highest incidence of bacteraemia, closely followed by periodontal therapy, while dental implants show lower incidences (Lafaurie et al., 2019). Even lower incidence is noted with non-surgical endodontic treatment, which is less than that observed with surgical flap reflection and periradicular surgery (Reis et al., 2016). Therefore, for infected teeth in patients with a history of valvular heart disease, endodontic therapy should be the treatment of choice, as extraction has been associated with a higher incidence of bacteraemia.

Regarding antibiotic prophylaxis, studies have questioned its efficacy in altering the incidence or levels of bacteraemia. In this regard, Reis et al. (2016) conducted a study to investigate bacteraemia incidence following root canal preparation in teeth with necrotic pulps and apical

periodontitis, and the role of antibiotic prophylaxis. They divided patients at high risk for Infective Endocarditis (IE) into Group I (n = 21), who received prophylactic antibiotics, and Group II, without risk (n = 11). Blood samples were collected before (to confirm pulp infection), 5 and 30 minutes after endodontic treatment. Samples underwent aerobic and anaerobic culture and real-time quantitative polymerase chain reaction (qPCR) to determine total bacterial levels. Culture did not reveal bacteraemia in any individuals. qPCR analysis showed bacterial DNA in all root canal samples, with a similar incidence of bacteraemia between patients who received prophylactic antibiotic therapy and those who did not. Thus, antibiotic prophylaxis showed no influence on bacteraemia incidence and levels, as determined by qPCR, raising questions about the necessity of this practice before endodontic interventions in patients at risk of IE.

These findings underscore the importance of reconsidering antibiotic prophylaxis guidelines for endodontic procedures, even in patients at risk of serious complications such as infective endocarditis. Further research is needed to inform clinical practices in this context, aiming to optimize patient safety and treatment efficacy.

Niazi and Bakhsh (2022) discussed the increased risk of bacteraemia associated with root canal infections, emphasizing that both periodontal and endodontic diseases can contribute to bacteraemia. Recent research using qPCR has identified bacteraemia following endodontic treatments, suggesting that dental procedures can lead to bacteremic episodes regardless of the microorganism detection technique used.

5. Sepsis / Septic Shock

Sepsis or septicaemia was first defined in 1991 as part of the Systemic Inflammatory Response Syndrome (SIRS), caused by bacteria, which can lead to systemic tissue damage, organ failure, and death (cited by Mannan et al., 2021).

For the diagnosis of sepsis, two or more specified clinical criteria from SIRS can be used, including:

(1) Body temperature above 38 °C or below 36 °C,

(2) Heart rate > 90 beats per minute,

(3) Respiratory rate > 20 breaths per minute,

(4) White blood cell count > 12,000 cells/mm³ or < 4,000 cells/mm³ (cited by Kang & Lee, 2022, p. 1-2).

Sepsis is a deleterious systemic response of the body to infection, which can progress to severe sepsis (characterized by acute organ dysfunction) and septic shock (severe sepsis including hypotension and organ dysfunction persisting despite volume resuscitation). Once septic shock develops, the mortality rate is high, nearly 50%. Sepsis and septic shock are two overlapping conditions, with sepsis progressing to septic shock (Martini et al., 2015; Mannan et al., 2021).

In patients with hematologic malignancies undergoing chemotherapy, odontogenic diseases pose a significant risk due to chemotherapy-induced myelosuppression, which can range from mild to severe, emphasizing the need to eliminate all odontogenic foci before stem cell transplantation. Akashi et al. (2013) emphasized the importance of communication between physicians and dentists to ensure proper understanding of the patient's health status, proposing a simplified classification of chemotherapy based on the level of myelosuppression, ranging from mild (grade A) to severe with persistent immunodeficiency (grade D). Their analysis revealed that patients undergoing grade B and C chemotherapies are particularly at risk of developing severe odontogenic infections during the first round of chemotherapy, regardless of whether they underwent invasive dental treatments. Among the patients studied, 5.4% of those newly diagnosed with hematologic malignancies developed severe odontogenic infections with septicaemia after receiving grade B or C chemotherapy. These cases were associated with both dental extractions and advanced periodontitis exacerbated by thrombocytopenia. No patients developed severe odontogenic infections during grade D chemotherapy.

Tsuji et al. (2014) also emphasize the need for a well-informed and prepared dental team to manage these patients in collaboration with hematologists, highlighting the importance of specific care protocols that consider the impact of chemotherapy on the patient's oral and systemic health.

In their prospective study, Tsuji et al. (2014) sought to understand the relationship between the myelosuppressive intensity of chemotherapy in patients with hematopoietic neoplasms and the incidence of odontogenic complications. They established a dental intervention protocol that included clinical and radiographic examinations, oral hygiene instructions, and all necessary dental procedures performed swiftly and decisively to avoid any delay in chemotherapy. Patients were divided into two groups: those who completed dental treatment before

chemotherapy and those who did not but started chemotherapy due to the urgency of their malignancy treatment. They further differentiated between patients about to undergo their first chemotherapy and those who had already started chemotherapy. Patients were monitored, and there was a transfer between groups based on the need for new dental interventions before the next round of chemotherapy (appearance or worsening of oral clinical findings on the observation day).

The group that completed their dental treatment prior to chemotherapy showed better outcomes than the other group, with significant differences noted. They observed that systemic and oral inflammatory complications increased with the severity of chemotherapy. The full implementation of the pre-chemotherapy dental intervention protocol resulted in fewer odontogenic and systemic complications, highlighting its importance, as there were no cases of chemotherapy interruption or postponement of follow-up therapy due to odontogenic infection.

Current guidelines for the treatment of sepsis and septic shock recommend initial management within 6 hours through correct diagnosis, control of the cause/drainage, antibiotic therapy, and obtaining cultures and susceptibility testing. Empirical antibiotic therapy should be initiated as soon as possible, as delay is associated with higher mortality rates. Subsequently, treatment focuses on supporting organ function and preventing complications.

Although sepsis caused by odontogenic infections is rare, they are commonly encountered in clinical practice and, if not promptly diagnosed and treated, can rapidly spread to deep spaces of the face and neck and affect other structures, leading to serious complications with risk of death. Improper use of antibiotics, immunocompromising conditions, and the virulence of involved microorganisms can promote infection progression (Martini et al., 2015).

Fungal infections in severely burned patients, who naturally have increased inflammatory states and impaired immune responses, can contribute as a risk factor for developing morbidity and mortality leading to systemic infection or sepsis. Serio, Burgess and Voigt (2017) emphasized the importance of careful dental examination in severely burned patients, who have impaired immune responses making them more susceptible to odontogenic infections and complications. They presented two cases where severely burned patients developed sepsis due to fungal periapical abscesses, a source of infection rarely considered. In one case, blood, urine, faecal, and sputum cultures were negative, and panoramic images including chest CT abdomen and pelvis failed to reveal a source of infection. However, jaw CT scans revealed periapical lucencies adjacent to both lower and upper molars. The diagnosis of multiple periapical

abscesses was established. In the other patient, no source of infection could be identified through imaging and blood and sputum culture, but periapical abscesses were revealed by jaw CT scan. Both patients underwent extraction of the involved teeth which showed fungal infections in cultures. They were successfully treated with antifungal and broad-spectrum antibiotic therapy after correct diagnosis, highlighting the importance of accurate diagnosis and immediate intervention.

Allareddy et al. (2017) investigated the relationship between periapical abscesses and the risk of postoperative infectious complications in patients undergoing open-heart surgery with cardiopulmonary bypass. Out of 265,235 analysed patients, 431 had periapical abscesses, among whom 16% developed septicaemia, a significantly higher rate compared to 4.2% in patients without periapical abscesses. Additionally, patients with periapical abscesses had a higher incidence of overall infectious complications (30.2%) compared to those without abscesses (11.6%). The study also found that older age was associated with a lower risk of complications, and elective admissions had lower chances of complications compared to emergency admissions.

Lamenha-Lins et al. (2020) conducted a cross-sectional study with low-income Brazilian schoolchildren to assess the prevalence of odontogenic infections and their relationship with quality of life and dental pain. It was observed that 42.6% of the children had odontogenic infections and 80% reported dental pain, which was associated with odontogenic sepsis, highlighting a significant connection between dental infections, previous pain experiences, and negative impacts on emotional, social well-being, and overall quality of life.

Pregnancy emerges as a significant risk factor for the development of sepsis due to the close relationship between oral health and systemic health. Pregnant women with untreated periodontal diseases and other oral infections face an elevated risk of serious complications, such as sepsis, pre-eclampsia, spontaneous abortions, and adverse effects on childbirth, including prematurity and low birth weight (Agili, 2023).

A case of neonatal sepsis caused by *Actinomyces odontolyticus* in a premature newborn was reported by Rueda et al. (2021). The pregnancy was complicated by intrauterine growth restriction of unknown etiology. *Actinomyces* species are normal commensal flora of the human oral cavity, gastrointestinal tract, and female genital tract, presenting low virulence. In this case, the mother was healthy but had a dental infection before pregnancy, requiring oral antibiotics

and endodontic treatment. A week before delivery, she experienced pain in the same region, with a yellow-green fluid-filled blister. Clinically, a papular lesion was observed between the right upper first and second molars. This pathogen was transmitted vertically, and the maternal dental infection may have been a risk factor.

6. Disseminated Odontogenic Infections

6.1 Pyogenic Odontogenic Infection

Pyogenic odontogenic infections, characterized by being polymicrobial and involving the normal endogenous flora, have dental caries, pericoronitis, periodontitis, trauma, and complications from dental procedures as predisposing factors. A study conducted by Kityamuwesi et al. (2015) at Mulago Hospital in Uganda with 136 patients revealed that such infections are most prevalent in the buccal, submasseteric, and submandibular fascial spaces. Patients with immunosuppressive conditions other than HIV (Human Immunodeficiency Virus) /AIDS (Acquired Immunodeficiency Syndrome) were excluded from the study, leaving a sample of 130, including thirty-five HIV-infected patients, of whom twelve were women. Pain and swelling were universal symptoms, with fever, trismus, and dyspnoea also reported. Most infections originated in the mandible, with dental caries being the most common predisposing factor. The research highlighted bacterial resistance to common antibiotics like ampicillin and cotrimoxazole, emphasizing the importance of antibiotic susceptibility testing and the rational use of antibiotics in treating these infections.

Thirty-one patients, including eight with HIV infection, had post-extraction complications as the cause of the infection, but HIV infection was not a significant risk factor for developing these complications. Twenty-four patients presented with respiratory discomfort due to the infections, including five (three women and two men) who succumbed to death. Airway obstruction and the general condition at admission were significant predictors of complications. *Streptococcus viridans* and *Staphylococcus aureus* were the most frequently isolated bacteria. The study concluded that bacterial resistance to common antibiotics like ampicillin and cotrimoxazole underscores the importance of antibiotic susceptibility testing and the rational use of antibiotics in treating these infections.

6.2 Chronic Suppurative Osteomyelitis of the Jaws

Chen et al. (2013) investigated risk factors for recurrence and life-threatening complications in hospitalized patients with chronic suppurative osteomyelitis of the jaws, based on the premise that microorganism inoculation into the jaws, resulting from trauma or odontogenic infection, are the primary causes of this condition. They found that prior antibiotic administration, mandibular ramus injury, preservation of pathogenic teeth, and extreme age groups were risk factors leading to disease recurrence. For severe complications, high leukocyte count, ICU admission with high fever, pre-admission antibiotic administration, existing diabetes, respiratory difficulties in the elderly, fever above 39°C, and high leukocyte count were identified as risk factors.

6.3 Brain Infections

The transmission of microorganisms to the skull can occur through various routes: direct extension, hematogenous dissemination, lymphatic vessels, and indirectly via odontogenic infection. However, the blood-brain barrier and the body's immune response generally prevent infection (Brady et al., 2014). Therefore, odontogenic infections rarely spread intracranially to cause complications such as cavernous sinus thrombosis, sinusitis, abscess, or meningitis. Cellulitis in the floor of the mouth can lead to the diffusion of an odontogenic infection to the central nervous system. If the infection reaches the angular vein, it can trigger cavernous sinus thrombosis. The incidence of morbidity and mortality is high because the diagnosis is often unsuspected regarding the severe consequences that an odontogenic infection can cause (Cariati et al., 2016).

6.3.1 Brain Abscess

Although brain abscesses are potentially lethal, pyogenic brain infections of odontogenic origin are uncommon in the modern antibiotic era. However, Brady et al. (2014) reported a case of a 68-year-old man with no comorbidities, admitted for acute neurological symptoms initially suspected to be a stroke. A CT scan revealed a brain abscess. Further investigations revealed that the patient had recently lost a tooth, leading to the hypothesis that an odontogenic infection might be the source of the abscess. Cultures from the brain abscess and blood identified *Actinomyces actinomycetemcomitans*, a microorganism commonly associated with periodontal

infections. Subsequent dental evaluation confirmed significant periodontal disease, suggesting this as the original infection source. The patient underwent surgical treatment for the brain abscess and antibiotic therapy, resulting in the gradual resolution of the lesion. Dental cleaning of the maxilla and extraction of two teeth in the left mandible, which were primarily periodontally infected and had extensive dental caries, were performed under general anaesthesia. A follow-up CT scan showed a gradual resolution of the brain lesion.

6.3.2 Bacterial Meningitis

Cariati et al. (2016) described a case of bacterial meningitis and subdural empyema following a surgical tooth extraction of tooth 38 two weeks prior. The patient presented with pain and swelling in the left temporomandibular area and fever. Intravenous antibiotics were administered, and a CT scan of the neck and face was performed. The CT scan revealed an abscess in the mandible. The odontogenic infection spread, causing meningitis and subsequent neurological complications. Despite antibiotic treatment and surgical drainage of the infection, the patient required comprehensive care, including antifungal coverage. The patient was discharged three weeks later.

Yoshizawa et al. (2023) reported a rare case of a 77-year-old patient with a history of chronic obstructive pulmonary disease caused by long-term smoking. The patient presented with trismus after a pulpectomy, initially diagnosed as temporomandibular dysfunction (TMD) due to the need for increased mouth opening during the endodontic procedure on the upper second molar. However, it was later revealed to be an abscess in the pterygomandibular space, which was drained externally, and the causative tooth was extracted. Due to symptom overlap and delayed treatment, the patient developed serious complications, including meningitis, resulting from the spread of the odontogenic infection to the skull. Blood culture tests identified the presence of *S. constellatus*. Despite antibiotic therapy and medical care, the patient developed hydrocephalus and pyothorax, requiring necessary interventions. On the 88th day of hospitalization, a ventriculoperitoneal shunt was placed to treat recurrent hydrocephalus. The patient was transferred to rehabilitation on the 106th day of hospitalization. The authors concluded that during the pulpectomy, the bacteria causing pulpitis might have been pushed into the pterygoid plexus due to the mechanical stress of mouth opening and the instruments

used. The venous drainage around the apices of the upper molars connects to the pterygoid plexus, which, in turn, connects to the cavernous sinus and meninges.

Niemelä et al. (2023) conducted a retrospective study analysing 148 cases of bacterial meningitis (BM) in adults. In addition to culture and PCR of cerebrospinal fluid, they included cases with negative cultures but with laboratory parameters and imaging strongly suggestive of BM. They highlighted the differentiation between nosocomial BM (when the patient was already hospitalized when they developed it or had a history of surgery in the last 54 days) and community-acquired BM (when the patient had no history of surgery or hospitalization in the previous 54 days). Cerebrospinal fluid culture for bacteria showed positivity in 50 cases, although pre-diagnosis antibiotic use was frequent. The most common pathogens in culture were *Streptococcus pneumoniae*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Neisseria meningitidis*. Thirty-nine patients presented with the triad of fever, headache, and neck stiffness. A neuro-surgical procedure or an acute cerebral incident before BM was recorded in 74 patients, with dental infection cases in nine patients. They identified a surprisingly high prevalence of nosocomial BM, suggesting the need for more detailed investigation. The lethality rate was 8.8%, and an additional 40.5% had unfavourable outcomes, associated with hypertension, altered mental state, neurological symptoms, pre-diagnosis antibiotic use, high doses of oral antibiotics, and antibiotic resistance of microorganisms. Decreased consciousness was observed in 62 patients. They concluded that bacterial meningitis requires immediate treatment and intensive medical attention.

6.3.3 Cavernous Sinus Thrombosis

Cavernous sinus thrombosis (CST) can be fatal and presents with symptoms such as exophthalmos, chemosis, periorbital edema, cranial nerve paralysis, and typical signs of infection, including fever, pain, and swelling. CST can occur secondary to the spread of infections from the paranasal, ethmoid, and sphenoid sinuses. The introduction of antibiotics has reduced, but not eliminated, the mortality associated with CST, which remains significant (14%-30%). This condition requires early diagnosis and appropriate treatment. Even after treatment, cranial nerve dysfunction and intracavernous aneurysm can occur, making long-term patient follow-up imperative (Yeo et al., 2014).

Cathcart et al. (2020) presented a complex case requiring contributions from multiple specialties to achieve diagnosis and initiate treatment. A 60-year-old woman with multiple sclerosis presented with ptosis, sixth cranial nerve palsy, right-sided facial paraesthesia, and signs of sepsis. She was diagnosed with an odontogenic abscess involving the masseter muscle and retained root of the fractured upper right lateral incisor. She was managed in intensive care, underwent surgical drainage of the abscess, and had the root surgically removed. Microbiological samples collected during abscess drainage matched the organism cultured from blood cultures. The odontogenic abscess led to bacterial meningitis caused by Streptococcus intermedius and CST. The case was complicated due to a delayed diagnosis, as the patient's symptoms were initially attributed to multiple sclerosis. Only after a contrast-enhanced CT scan of the head showed right cavernous sinus thrombosis, as well as thrombosis in the internal jugular vein and thrombus in the right sigmoid and transverse sinus, was the correct diagnosis made. Anticoagulation was planned for six months.

6.4 Odontogenic Facial Cellulitis

Odontogenic infection is the most common in the cervicofacial region and originates from the structures that form the teeth and periodontium; its progression spontaneously affects the jaw bones in the periapical region and constitutes one of the most common emergencies in emergency care (Fernandes et al., 2014).

Odontogenic facial cellulitis (OFC) is a septic inflammatory process primarily caused by poorly treated dental abscesses and pericoronitis. This condition, which can range from mild to severe clinical presentations, can lead to serious complications, including death if not treated appropriately. It is common at all ages, primarily caused by caries, root remnants, or advanced periodontal disease. OFC is considered serious, requiring early diagnosis and medical-surgical treatment, including effective antibiotic therapy, interceptive surgical procedures, and appropriate physiotherapy. The treatment aims to eliminate the septic sources as quickly as possible, which can be achieved through the socket by dental extraction, incision and drainage, or through the root canal.

Fernandes et al. (2014) evaluated 75 patients with OFC, observing that molars are frequently the causative teeth, and the mandible is the most affected region. The causal factors were predominantly root remnants at 46.7%, followed by dental caries at 38.7%.

When OFC results from the progression of dental caries leading to a dental abscess, the infection spreads around the proximal periapical areas. This spread is influenced by the relationship of the root apex to the mucosal surface, tissue planes, muscle insertions, and systemic factors such as poorly controlled diabetes. The spread along the tissue planes often leads to pain, edema, trismus, dysphagia, and airway loss, along with signs and symptoms of sepsis. Severe odontogenic infections are emergencies that must be promptly treated with a combination of surgical (incision and drainage, tooth extraction, and airway protection) and medical management of the infection (potent antibiotics) and the symptoms of sepsis. However, the vast majority of localized dental abscesses respond to early local surgical interventions such as tooth extraction or endodontic treatment (Robertson & Smith, 2021).

6.5 Deep Neck Infections

Deep neck infections (DNI) are serious medical conditions due to the complex anatomy of the neck, which involves potential spaces, fascial planes, neurovascular structures, and the ease of infection spread from one space to another. The most common primary sources include odontogenic infections, tonsil and salivary gland infections, malignancies, and foreign bodies (Kataria et al., 2015).

Kataria et al. (2015) studied 76 patients with DNI, identifying cervical pain as the most prevalent symptom, followed by neck swelling, dysphagia, fever, odynophagia, toothache, and in smaller proportions, airway difficulty, trismus, and torticollis. Odontogenic infection was the main etiological cause. Diabetes was found as a comorbidity in 10.52% of cases. The most common clinical presentations were Ludwig's angina, peritonsillar abscess, and submandibular abscess. Most patients underwent CT and surgical intervention, with pus samples sent for culture and sensitivity analysis. Forty-six patients had positive culture results, with *Streptococcus* and *Staphylococcus* isolated in 50% of cases. No bacterial growth was found in 11 patients. All received broad-spectrum intravenous antibiotics, adjusted based on culture and sensitivity results. Complications included airway obstruction, septic shock, internal jugular vein thrombosis, skin necrosis, and mediastinitis. One patient died from an unrelated systemic complication. Surgical intervention was necessary in 89.47% of cases, with hospital stays ranging from 3 to 15 days. The study confirmed the importance of early diagnosis and appropriate treatment of DNI to prevent severe complications.

Das, Nath and Mishra (2017) conducted a prospective study with 45 patients from northern India, covering a wide age range, to investigate DNI. Odontogenic infection was the most frequent cause (64.11%) and diabetes, the most common comorbidity. Most patients presented with neck pain and swelling, with the submandibular space being the most affected, mainly with bilateral involvement, followed by the sublingual space and others in smaller proportions. Simultaneous involvement of multiple spaces was found in most cases. Treatment included medical and surgical approaches, resulting in complete regression in 77% of cases; however, 4.4% of patients died, and 2.2% showed progressive worsening. Early diagnosis and treatment were necessary for complete recovery and to prevent complications. Pus samples were aspirated from 30 of the 45 patients for culture and sensitivity testing. In 60% of cases, the samples were sterile after 48 hours of incubation. The authors emphasized the need for early diagnosis and surgical drainage and highlighted the prevalence of polymicrobial infections, with *Staphylococcus aureus* being the most identified microorganism. Initial treatment should be with broad-spectrum intravenous antibiotics, adjusted based on culture and sensitivity reports.

Sittitrai, Srivanitchapoom, and Reunmakkaew (2018) compared clinical characteristics, complications, and outcomes of DNSI in adults with and without HIV. Among 31 HIV patients, 68% had odontogenic abscesses, while in the non-HIV group (192 patients), the rate was 47%. Both groups commonly had the parapharyngeal, submandibular, and masticatory spaces affected. Ludwig's angina was common in the HIV group, causing airway obstruction. Initial treatment used empirical antibiotics, adjusted based on culture results. The HIV group had higher rates of airway obstruction, serious complications, and mortality. Surgical drainage was indicated for confirmed abscesses or those not responding to antibiotics.

Antibiotic therapy is very important and should be initiated as early as possible in patients with DNSI (deep neck space infections). However, bacterial culture results require at least 48 hours, and the positive rate is only 30-50%, indicating that the use of empirical antibiotic treatment for most patients should be done within these 48 hours or even throughout the treatment period (Gao et al., 2022).

In this context, a prediction model and an online calculator to estimate the risk of severe disease development in patients with DNSI were developed by Gao et al. (2022), which are fundamental for the rational choice of empirical antibiotics. Analysing 433 patients, they identified that 92 developed potentially fatal complications. In mild cases, 43.2% had positive culture results

(49% for Gram-positive strains and 51% for Gram-negative strains) and in severe cases, 63% (37.9% for Gram-positive strains and 62.1% for Gram-negative strains). Interestingly, the presence of diabetes influenced the predominance of Gram-negative strains in mild diseases, while gas formation and trismus were associated with Gram-positive strains in severe diseases. Furthermore, the rate of multi-resistant strains was significantly higher in severe cases. Metagenomic sequencing was used to identify anaerobic strains that made up a rate of 83.3%. The authors pointed out that metagenomic sequencing is a valuable tool to improve the detection of pathogenic bacteria, especially anaerobes, optimizing the selection of empirical antibiotics, which should be adjusted after culture and susceptibility test results.

6.6 Ludwig's Angina

Ludwig's angina is a rapidly progressing infectious complication affecting the floor of the oral cavity, usually originating from molar abscesses, which spreads to the submandibular, sublingual, and submental spaces. This severe cellulitis can develop into fasciitis and abscess, leading to gangrene of the neck's connective tissues. The spread occurs through the mylohyoid muscle until it reaches the submaxillary, sublingual, and submental spaces, forming the submandibular space. Without immediate and adequate treatment, it can result in airway obstruction and sepsis, posing a life-threatening risk (Soriano-Cueto & Reyna-Villasmil, 2022).

Soriano-Cueto and Reyna-Villasmil (2022) treated a 21-year-old pregnant woman at 27 weeks with severe mandibular pain, swelling, dysphagia, fever, and chills, originating from a four-month-old untreated cavity. Exams indicated Ludwig's angina, confirmed by tomography, while obstetric evaluations showed a healthy pregnancy. Broad-spectrum antibiotics were administered, and 72 hours later, the patient underwent submental and submandibular decompression and extraction of the infected lower molars, releasing 150 ml of purulent fluid. The culture showed a polymicrobial infection. She continued antibiotics until the 7th postoperative day and was discharged with outpatient follow-up. No complications occurred postoperatively or during the remainder of her pregnancy and delivery.

6.7 Cervicofacial Infection

Cervicofacial infection (CFI) of odontogenic origin is one of the most frequent reasons for patient hospitalization, as they typically present late and often meet sepsis criteria. Henry et al.

(2021) documented 1,002 cases of CFI hospitalizations in the United Kingdom between May and October 2017. Most patients (54.5% male, average age of 34 years) presented with trismus (46%) and dysphagia (27%), with 1.7% showing airway compromise. Surprisingly, 82% of infections were odontogenic in origin, and more than half of these patients (55.1%) had previously sought treatment, with two-thirds only receiving antibiotics. Alarmingly, nearly half of the CFI cases (43.6%) and odontogenic infections (45.5%) met the criteria for sepsis, highlighting the need for immediate and appropriate diagnosis and treatment to avoid adverse outcomes.

6.8 Cervical Necrotizing Fasciitis

Cervical Necrotizing Fasciitis (CNF) is an acute and severe condition characterized by the rapid spread of infection through the soft tissues of the neck, causing necrosis of the subcutaneous and fascial tissues, which can lead to widespread gangrene and deep abscesses. With high morbidity and mortality, this disease is often of odontogenic or pharyngeal origin, involving mixed aerobic and anaerobic flora. Complications include airway compromise, sepsis with multiple organ failure, and descending mediastinitis. Early diagnosis and emergency management, including airway protection, intravenous broad-spectrum antibiotics, and aggressive surgical debridement, are vital for patient survival (Gupta et al., 2022).

Bucak et al. (2013) highlighted the importance of oral health in preventing CNF, noting that the disease can develop even in patients without previous risk factors. The infection can spread rapidly to regions such as the mediastinum, exacerbated by conditions like inappropriate antibiotic use and environmental changes. CNF is rare, progresses quickly involving the skin, subcutaneous tissue, superficial, and deep fasciae, potentially causing complications with a 75% mortality rate if treatment initiation is delayed. Due to the extensive communication of fascia between the gums, neck, and mediastinum, odontogenic infections can spread rapidly to the mediastinum facilitated by gravity, respiration, and negative intrathoracic pressure. They observed that the infection spread to the temporal and mediastinal regions in 3 out of 5 patients with primary odontogenic infection who developed descending necrotizing mediastinitis. Two of these 3 patients had posterior mediastinal involvement and died due to septicaemia and multiple organ dysfunction.

Gupta et al. (2022) reviewed cases of patients hospitalized between 2015 and 2019 with CNF. Of the seven patients evaluated, six were male. All other cases of cervical abscesses without histopathological evidence of tissue necrosis were excluded from the study. The most common aetiology was odontogenic infection (5 cases), primarily from the second and third lower molars, as their roots extend below the insertion of the mylohyoid muscle, providing a direct route for odontogenic infection to spread into the submandibular space. Characteristic symptoms included tender cervical swelling, often involving the submandibular and carotid triangles. One patient developed sepsis with descending mediastinitis. The average hospitalization was 27 days, but all patients survived, highlighting the importance of early diagnosis, broad-spectrum antibiotic use, and aggressive surgical debridement as key management strategies to improve survival. Urgent CT of the neck and chest was performed before surgery in all patients. Additional procedures such as tracheostomy or skin grafting were required in two cases. Pus and necrotic tissue were sent for culture sensitivity testing and histopathological examination. All patients were started on empirical injectable broad-spectrum antibiotics, later switched to culture-directed antibiotics. Comorbidities such as anaemia and type II diabetes mellitus were common, and tobacco use was reported in more than half of the patients. Pus and blood culture results revealed multibacterial growth including *E. coli* and MRSA. MRSA isolated from five patients was found sensitive to linezolid. Therefore, this antibiotic was switched to after three days of empirical antibiotic therapy.

6.9 Necrotizing Soft Tissue Infection and Deep Cervical Abscess

Severe infections in the head and neck region, particularly necrotizing soft tissue infections (NSTI) and deep cervical abscesses of odontogenic origin, are potentially fatal due to delays in diagnosis and treatment. Clinically, it is often challenging to distinguish NSTI and deep cervical abscesses in their initial cellulitis stage, and the decision to perform contrast-enhanced CT scanning for detection is often a challenge, as CT is used to assess the presence of abscess areas in deep locations and is usually reserved for confirming more severe cases. Thus, the use of routine blood tests according to hematologic and inflammatory parameters can serve as an adjunct diagnostic tool for NSTI and deep cervical abscesses (Kusumoto et al., 2022).

Kusumoto et al. (2022) conducted a retrospective study (January 2012 to March 2022) on odontogenic NSTI, evaluating 271 patients and dividing them into four severity-based groups.

Apical periodontitis was the most common cause, mainly affecting the lower molars. For abscesses, incisional drainage and bacterial cultures were performed. Hematologic and inflammatory parameters (CRP, leukocytes, NLR, and CRP+NLR) were analysed to assess severity. Results showed progressive increases in these parameters from cellulitis (Group I) to NSTI (Group IV). *Streptococcus* and anaerobes were prevalent in severe cases. The study concluded that these parameters aid in early severe infection diagnosis, guiding CT scan decisions.

6.10 Descending Necrotizing Mediastinitis

Descending Necrotizing Mediastinitis (DNM) is a severe mediastinal infection originating from infections in the oral, pharyngeal, and cervical regions. As the infected area expands through deep cervical fascial planes into the mediastinum, the patient's overall condition deteriorates rapidly with sepsis and multiple organ failure. Despite advances in antibiotics, diagnostic accuracy of CT, and intensive care, the mortality rate remains high, underscoring the severity of the disease (Sakai et al., 2021).

DNM is considered a rare complication of odontogenic infection. It typically follows cervical necrotizing fasciitis, with common infection origins including odontogenic or periamygdaloid abscesses. Risk factors for DNM include diabetes, alcoholism, poor oral hygiene, immunosuppression, and low socioeconomic conditions (Glen & Morrison, 2016). The condition is characterized by polymicrobial infection involving Gram-positive, anaerobic bacteria, and to a lesser extent, Gram-negative bacteria. High rates of bacterial resistance, including carbapenem-resistant Klebsiella pneumoniae and MRSA, further complicate treatment (Pota et al., 2018).

Odontogenic origins account for 60% to 70% of DNM cases, often associated with lower second or third molars. Additionally, the incidence of DNM as a complication of impacted third molars extraction or dental implant surgery has been gradually increasing. The infection spreads from cervical spaces, originating in the oropharyngeal or submandibular region, descending to the pretracheal space or from the submandibular/pterygomandibular space to the mediastinum and posterior pleural space. This descent is facilitated by gravity, respiration, and negative thoracic pressure. DNM has a devastating course with potential risks for sepsis, pyothorax, pericarditis, multiple organ failure, and hence, high mortality rates. Despite technological

advances, DNM continues to be associated with mortality rates ranging from approximately 11% to 40% (Muños et al., 2021).

Successful DNM treatment depends on early diagnosis, appropriate antibiotic use, aggressive surgical intervention for drainage, and proper antibiotic use according to cultures to favour patient survival (Pota et al., 2018; Muños et al., 2021; Sakai et al., 2021). Positive correlation was found between severity of case with life-threatening; ICU admission time after diagnosis; severity of case at admission; ICU stay and duration of hospitalization until surgery, in the ICU. This way, immediate ICU admission to treat severe sepsis and/or septic shock, combined with early and aggressive surgery, can be crucial to reduce such a high mortality rate (Palma et al., 2016).

In a prospective study, Palma et al. (2016) evaluated 34 DNM patients with an average age of 46.8 years, more frequently in men (26 patients) than in women. Common risk factors included type II diabetes mellitus (29%), smoking (24%), and hypertension (18%). DNM was most frequently caused by odontogenic infections (65%), followed by periamygdaloid abscesses (26%) and paranasal sinus infections (9%). Microbiological cultures revealed a high percentage of aerobic/anaerobic coinfection and were obtained from 24 patients, including *Streptococcus* (*S. viridans, S. aureus, S. constellatus, S. sanguis, S. mitis*), *Prevotella spp., Peptostreptococcus spp., and Klebsiella pneumoniae*. No bacteria were isolated from cultures obtained from four patients, and coinfection (aerobic/anaerobic bacteria) was present in 12 cases. The mortality rate was 12%, with non-survivors statistically more likely to have a higher severity score at ICU admission and more advanced disease stage ($p < 0.01$). Surgical treatment ranged from transcervical drainage to thoracotomy with radical mediastinal surgical debridement.

In 2016, Glen and Morrison reported a 59-year-old man with acute odontogenic sepsis leading to diffuse necrotizing mediastinitis and pleural empyema. A CT scan revealed infection spreading from dental apices to the mediastinum via submandibular, submental, parapharyngeal, and paratracheal spaces. *Streptococcus intermedius* and *Candida albicans* were identified. The infection reached the lower mediastinum and perforated the lung's left lower lobe. Recovery was complicated by severe dysphagia, requiring gastrostomy feeding for six months. This case uniquely highlighted severe dysphagia post-necrotizing mediastinitis.

A study by Qu et al. (2017) on 81 patients with necrotizing mediastinitis from odontogenic infections found the cohort predominantly male (68 men) with a mean age of 57 years. Causes

included periapical periodontitis (66.7%) and other dental issues. Premolars and lower molars were often involved. Symptoms included toothache, swelling, and limited mouth opening. Mortality was 4.9%, mainly from multiple organ failure. Pre-existing conditions were common (65.4%). Only 23.5% of bacterial cultures were positive, mainly *Streptococcus spp*. and *Staphylococcus aureus*. Treatment involved antibiotics and surgeries, with transcervical drainage in 74 cases and thoracotomy in 7. Risk factors included severe sepsis.

Pota et al. (2018) reported a case of a 38-year-old man with septic shock from necrotizing mediastinitis caused by multi-drug resistant bacteria. Initially treated with amoxicillin for severe tooth pain, he was misdiagnosed with pneumonia. Despite being obese, he had no other comorbidities, and did not smoke or consume alcohol. Upon ICU admission, he had respiratory distress needing mechanical ventilation and severe septic shock. A CT scan revealed extensive abscesses. Immediate surgery involved thoracotomy and cervicotomy for drainage. Post-surgery, he was treated based on culture results. Due to conventional therapy failure, he received enriched IgM immunoglobulin and polymyxin B hemoperfusion. Despite limited data on these treatments, he improved and survived.

Sakai et al. (2021) retrospectively analysed six patients who underwent thoracic surgery for necrotizing mediastinitis. Five were male smokers with an average age of 62 years. The infections were pharyngolaryngeal in three patients and odontogenic in the others. At surgery, five had sepsis and four had disseminated intravascular coagulation. Polymicrobial infections, including *Streptococcus anginosus* (SAG) with gas bubbles on chest CT, were common. Mixed infections with SAG and gas bubbles on CT may indicate severe necrotizing mediastinitis, requiring broad-spectrum antibiotics and aggressive surgical drainage. All patients underwent cervicotomy, tracheostomy, and transthoracic mediastinal drainage and debridement, with an average hospital stay of 58 days. No fatalities occurred.

Quick identification of pathogens is key for treating DNM. Duan et al. (2021) emphasize that Next-Generation Metagenomic Sequencing (mNGS) improves diagnosis and treatment by detecting more pathogens than traditional methods. Immediate diagnosis, early drainage, antibiotic therapy, and teamwork are vital. mNGS enables rapid microorganism detection and antibiotic adjustment. With technological advances and cost reduction, mNGS is expected to become a standard approach for diagnosing DNM, crucial for successful outcomes.

Alejandro-Ibanez and Ortega-Martinez (2022) detailed the clinical case of a 39-year-old male diabetic patient who presented to the emergency room with evolving dental abscess over four days. Examinations confirmed an inflammatory process extending from the floor of the mouth to the mediastinum, diagnosed as DNM. The patient underwent multiple surgeries and intensive ICU management for over 30 days, with a favourable outcome. Cultures identified *Enterococcus faecalis, Acinetobacter baumanii, Stenotrophomonas maltophilia,* and *Enterobacter cloacae,* guiding antibiotic treatment. They emphasized the importance of early diagnosis, immediate use of broad-spectrum antibiotics, prompt surgical intervention, and multidisciplinary support for patient survival.

Ranjbar et al. (2023) conducted a retrospective study spanning 18 years (2002–2019), analysing hospital records to identify patients diagnosed with DNM. They identified 25 patients with the disease, suggesting that although severe, it is not uncommon, with a high prevalence among young individuals, especially those under 40 years old. Cervical infection was the most common cause of DNM (57%), followed by periodontal infections (32.1%) and mandibular abscesses (14.3%). They found no significant differences in terms of age or gender among the etiological groups.

6.11 Lemierre Syndrome

Lemierre Syndrome, classically described as septic thrombophlebitis of the internal jugular vein, is a rare and potentially fatal sequel of head and neck infection, predominantly affecting young individuals; 70% of cases occur in individuals aged 16 to 25 years old, with no relevant past medical history (Noy et al., 2015).

Before antibiotics, the mortality rate of this syndrome was 90%, but with the introduction of antibiotics, both the incidence and mortality have significantly decreased. However, over the past 20 years, there has been an observed increase in reported cases, including odontogenic infections, which although rare (representing about 4% of all cases), have survival rates similar to those of the syndrome with other etiologies. Noy et al. (2015) reported the case of a healthy 30-year-old Ukrainian sailor with a history of toothache for 5 days and dysphagia for solids, accompanied by fevers up to 40°C. On physical examination, he had left submandibular swelling and severely carious lower left posterior teeth with minimal vestibular fluctuation. CT scan revealed diffuse edema of the lateral epidermal tissues extending from the left ramus and

body of the mandible to the base of the neck. The patient underwent tooth extractions and productive transcervical drainage of the submandibular abscess. Blood culture was positive for *Staphylococcus capitis* and alpha-hemolytic *streptococci*. The condition progressed to a diagnosis of Lemierre syndrome, and the patient underwent all necessary surgical and medical interventions, eventually recovering.

6.12 Pylephlebitis with portal mesenteric vein thrombophlebitis

Pylephlebitis or suppurative thrombophlebitis of the portal mesenteric vein results from an infection in regions drained by the portal system. Kim, Kwan and Durey (2019) reported a case where odontogenic bacteraemia was suggested as a risk factor for pylephlebitis, a rare and potentially serious condition. The patient, a 49-year-old man with no significant medical history, presented with fever, chills, and persistent abdominal pain for two weeks. Contrast-enhanced CT scan identified a hypoattenuated thrombosis in the mesenteric vein and fatty infiltration in the mesentery. No abnormalities were found in the liver, biliary tract, pancreas, or intestines. Initial treatment involved empirical antibiotics, and a transthoracic echocardiogram ruled out endocarditis. Two blood cultures identified *Gemella sanguinis* and *Streptococcus gordonii*. Further investigation revealed that the patient had undergone dental extraction and subsequent implantation 8 months before symptom onset, followed by regular dental procedures. Based on this and culture results, antibiotics were adjusted, leading to the patient's recovery without subsequent symptoms and normalization of laboratory tests.

6.13 Infective Endocarditis

Infective Endocarditis (IE) is a severe inflammation of the endocardium, especially the heart valves, capable of causing bacteraemia, vascular embolism, and cardiac damage. It is a systemic septic disease with clinical symptoms. Despite advances in diagnosis and treatment, IE still leads to high rates of morbidity and mortality. Predisposed patients should be evaluated for antibiotic prophylaxis when undergoing medical and dental procedures that may cause bacteraemia. To confirm this premise, Reis et al. (2016) assessed the incidence of bacteraemia after root canal preparation in teeth with necrotic pulps and apical periodontitis, focusing on patients at varying risk of developing IE. They studied two groups: 18 patients with valve disease and high risk of IE requiring prophylactic antibiotic therapy, and 9 patients with

coronary artery disease, considered low risk for IE and not needing prophylactic antibiotics. Interestingly, none of the patients showed detectable bacteraemia by culture after endodontic treatment. Molecular analysis, however, revealed the presence of bacterial DNA in the blood of some patients, with no significant difference between those who received antibiotic prophylaxis and those who did not.

In line with this, Lafaurie et al. (2019) reviewed the effectiveness of antibiotic prophylaxis in reducing post-dental procedure bacteraemia, commonly used to prevent IE in high-risk patients. They compared antibiotic use with placebo or no treatment in randomized trials, focusing on AHA-recommended antibiotics (amoxicillin, clindamycin, cephalosporin, azithromycin) and non-AHA alternatives like intravenous amoxicillin-clavulanic acid and moxifloxacin. The review found that prophylaxis significantly reduced bacteraemia, with amoxicillin being the most effective. Clindamycin and azithromycin were also effective, but cephalosporin was not. Non-AHA antibiotics like intravenous amoxicillin-clavulanic acid were effective alternatives. For penicillin-allergic patients, azithromycin was more effective than clindamycin and cephalosporin, suggesting a need to reassess clindamycin's recommendation.

Takizawa et al. (2022) reported a case of a 51-year-old woman with IE, presenting with headache, fever, myalgia, erythema, liver dysfunction, and motor weakness. Elevated PCT levels indicated sepsis, and blood culture revealed *Streptococcus viridans*. Residual roots and osteosclerosis around molars were identified as infection sources. The patient was treated with antibiotics and required aortic valve replacement due to aortic valve perforation. Residual roots were extracted, and oral hygiene instructions were given. The patient recovered without complications. The authors emphasize that all infection sources should be extracted urgently to prevent mortality and caution dentists that headache can be a symptom of IE.

6.14 Pulmonary Infections

Septic pulmonary embolism (SPE) is a rare disease that typically presents with insidious onset of fever, respiratory symptoms, and pulmonary infiltrates. Periodontal disease has been reported as a significant cause of SPE, although uncommon and challenging to identify the causative pathogen, likely due to inadequate culture techniques and sample collection (Watanabe, Yokoe & Noguchi, 2019).

Shiota et al. (2013) conducted a 10-year retrospective study to investigate SPE induced by odontogenic infections, criteria including multifocal lung lesions consistent with SPE on chest CT, active dental infection as the source of embolism, and absence of other infectious sources. During the study period, they identified 9 patients with SPE induced by odontogenic infection, aged between 47 and 74 years, all without immunocompromise or relevant medical issues. Symptoms presented included fever, chest pain, and in some cases, cough, sputum production, and wheezing. Most patients showed moderate to severe periodontitis on panoramic radiographs, with some having apical periodontitis and others gingival abscesses. Patients received treatment with parenteral or oral antibiotics, and one required thoracostomy for drainage of infected pleural effusion. Hospitalization was necessary for seven patients, with an average duration of 15 days. In seven cases, cultures were negative, which the authors associated with prior antibiotic use or intermittent low-grade bacteraemia. All patients recovered, with improvements observed in computed tomography scans.

Abe et al. (2014) reported a 64-year-old patient with Cogan syndrome, presenting with high fever, chills, dizziness, hypoxemia, and heart failure. This autoimmune condition responded well to corticosteroids. Echocardiography showed pulmonary hypertension, and CT revealed bilateral pulmonary congestion, dilated pulmonary arteries, anaemia, and elevated inflammation. Blood culture identified *S. constellatus*, a normal oral microorganism, suggesting an odontogenic infection. The patient had an infection in the lower left first molar, with swelling and acute symptoms, potentially worsened by corticosteroid and alendronate use.

Watanabe, Yokoe and Noguchi (2019) described the case of a diabetic patient with fever, malaise, and multiple bilateral subpleural pulmonary nodules on chest CT, indicative of SPE. Transthoracic echocardiography showed no vegetation on the heart valves, and additional exams did not identify other infection sources. Blood culture isolated *Parvimonas micra*, and further investigation identified chronic apical periodontitis and an abscess in the infratemporal fossa as primary infection sources. *Parvimonas micra*, commonly found in infected root canals and associated with chronic apical periodontitis, is rarely identified as the causative pathogen of SPE.

Yang et al. (2024) reported a case of a 58-year-old patient with AIDS/HIV, under antiviral therapy, diabetic, with a history of alcohol abuse and smoking for 30 years, presenting with empyema caused by *S. constellatus*. They found 29 cases of empyema caused by *S. constellatus*

in the past 20 years, with few associated with AIDS/HIV patients. The infection source was not fully clarified, but the authors suspected an odontogenic source due to a recent dental extraction by the patient. Successful treatment included antibiotic therapy, thoracic drainage, and intrapleural fibrinolytic enzyme injection. According to the authors, *S. constellatus* is one of the *S. pyogenes* that can cause purulent infections in various human organs, especially in cases of immunosuppression or decreased organic resistance, becoming a significant pathogen in these circumstances.

7. Predisposing Factors and Causes of Immunodeficiency

Upon reviewing the collected articles described in this narrative review, it has been observed that predisposing factors are largely responsible for triggering the dissemination of localized odontogenic infections.

Certain predisposing medical conditions can exacerbate the risk of developing severe and potentially life-threatening acute odontogenic infections (Furuholm et al., 2021). Immunocompromising diseases, autoimmune diseases, and immunosuppression caused by therapies and medications have been identified as significant factors.

Lifestyle conditions and habits also play a role, such as smoking (Kataria et al., 2015; Palma et al., 2016; Pricop et al., 2022; Rosca et al., 2023; Silva et al., 2022; Yoshizawa et al., 2023; Niemelä et al., 2023) and alcoholism (Glen & Morrison, 2016; Weise et al., 2019).

7.1 Immunodepressive Diseases

The management of patients with immunodepressive diseases requires specialized knowledge from healthcare professionals, as these patients may develop severe complications (Martini et al., 2015).

In the literature reviewed here, cases were found involving patients with uncontrolled asthma (Rivas et al., 2023), a patient with a history of chronic obstructive pulmonary disease due to long-term smoking (Yoshizawa et al., 2023), immunocompromised patients with chronic conditions such as cardiovascular diseases (Glen & Morrison, 2016), immunodeficiency (HIV), obesity, hepatitis, liver cirrhosis, and systemic lupus erythematosus (Weise et al., 2019), active cancer, lower and upper respiratory infections, and skin infections (Niemelä et al., 2023).

7.2 Autoimmune Diseases

Cogan's syndrome, an autoimmune disease, was reported by Abe et al. (2014) to exacerbate the condition of an immunocompromised patient, leading to systemic infection by *S. constellatus*.

Job syndrome, also known as hyper-IgE syndrome, is a rare congenital immunodeficiency disorder, characterized by autosomal dominant inheritance, multi-organ involvement, and long-lived post-infectious damage. Longitudinal records are crucial for improving knowledge of the history and management of these rare disorders. Carraba et al. (2023) evaluated 30 Italian patients with AD-HIES (Autosomal Dominant Hyper-IgE Syndrome) through a cohort study conducted within the Italian healthcare service network specializing in primary immunodeficiency. Respiratory complications, particularly bronchiectasis (46.7%) and pneumatoceles (43.3%), were present at diagnosis. Cutaneous involvement was noted in 93.3% of patients, including eczema (80.8%) and abscesses (66.7%). Survival analysis showed that 27 out of 30 patients survived, while three patients died at ages 28, 39, and 46 due to pulmonary disease, lymphoma, and sepsis, respectively. The average diagnostic delay was 13.7 years, with disease onset occurring before 12 months of age in 66.7% of patients. Analysis of diagnostic delays revealed an improvement in the number of cases diagnosed after 2007, following the identification of the gene responsible for AD-HIES, especially among adults who were not clinically diagnosed in childhood.

General practitioners, pediatricians, pulmonologists, and dermatologists lacking awareness of primary immunodeficiencies often misdiagnose elevated IgE and eczema as signs of allergy or chronic urticaria, despite notable medical histories of recurrent infections as severe as skin abscesses and pneumatoceles. In patients with AD-HIES, skin prick tests often yield negative results and do not confirm food or inhalant allergies. Early diagnosis, appropriate management at specialized immunodeficiency centres, prophylactic antibiotics, and antifungal therapy improve outcomes and positively impact patient life expectancy. Many patients undergo surgical procedures, including surgical tooth extractions, drainage of skin or other abscesses, and biopsies of the gastrointestinal tract, lymph nodes, liver, and lungs. Odontogenic infections and complications were common in the study by Carraba et al. (2023) and resulted in severe outcomes.

7.3 Immunodeficiency

Careful management is necessary for patients with immunodeficiency because they become more susceptible to infections, resulting in an increased risk of infectious complications, including the development of severe septicaemia that can be fatal (Tsuji et al., 2014; Glen & Morrison, 2016; Grill et al., 2023). Several chemotherapeutic agents used in hematopoietic malignancies cause serious side effects, including myelosuppression and immunosuppression (Tsuji et al., 2014). Immunosuppression can also occur following organ transplantation and radiotherapy (Weise et al., 2019).

8. Risk Factors

Additionally, several risk factors were enumerated, such as smoking, alcohol abuse, pregnancy, age over 65 years, and previous surgeries (Grill et al., 2023).

8.1 Pregnancy

The decreased immune response in pregnant women allows for the more rapid progression of infections due to alterations in cellular immunity, neutrophil chemotaxis, and natural killer cell activity. Hormonal changes affect gum tissues, which become more sensitive and susceptible to irritation and inflammation. Dental plaque can accumulate on teeth, forming hard deposits with a large number of bacteria that constantly produce local infections. All these changes lead to the development of an exaggerated local inflammatory response, which can cause erythematous and edematous inflammation of the gums. Approximately 70% of pregnant women present with this type of condition, even those with routine oral care (Soriano-Cueto & Reyna-Villasmil, 2022).

Thus, physiological, hormonal, and immunological changes caused by pregnancy can predispose to an increased risk of infectious complications, especially those arising from odontogenic infections, one of which is Ludwig's Angina. Its occurrence during pregnancy is associated with an increased risk of severe perinatal morbidity, mostly due to tissue hypoxia. Treatment consists of broad-spectrum antibiotic administration and, in some cases, surgical decompression of affected areas; therefore, potential adverse fetal effects of management must be considered (Soriano-Cueto & Reyna-Villasmil, 2022).

Increased levels of progesterone and estrogen during pregnancy affect oral health and are associated with an increased prevalence of periodontal disease. Fluctuations in these hormones increase capillary permeability in pregnant women's gums and enhance prostaglandin production, resulting in an exaggerated inflammatory response of the periodontium to dental plaque. Pregnant women with untreated periodontal disease and oral infections are at an increased risk of developing sepsis, preeclampsia, spontaneous abortions, and adverse delivery outcomes such as preterm birth and low birth weight (Soriano-Cueto & Reyna-Villasmil, 2022; Agili & Khalaf, 2023).

Intra-amniotic infection has a strong causal association with spontaneous preterm birth and pre-labor membrane rupture. The most common route of intra-amniotic infection is ascending, whereby microorganisms from the vagina gain access to the amniotic cavity. However, distant microorganisms, such as those from the oral cavity, have been reported in intra-amniotic infection through hematogenous dissemination, and dental caries or chronic periodontitis can be a source of infection. Therefore, oral cavity examination should be included in prenatal care to ensure optimal oral hygiene control (Chaemsaithong et al., 2022).

Dental treatments, such as routine cleanings, crowns, tooth extractions, gum treatment, and continuation of any orthodontic treatment, can be performed during pregnancy, preferably during the second trimester. Although dental anesthetics can cross the fetal-placental barrier, they generally do not reach sufficiently high blood concentrations as they are used locally and in small doses during routine dental procedures. Obstetricians and dentists should collaborate to advise on the importance of maintaining optimal oral health during pregnancy (Soriano-Cueto & Reyna-Villasmil, 2022). Therefore, healthcare systems should implement efforts to educate and monitor pregnant women regarding maternal oral health care, thereby impacting both maternal systemic health and the health of their babies (Agili & Khalaf, 2023).

8.2 Sexual Differences

Sexual differences impact susceptibility to bacterial infections, with men being more prone to certain diseases compared to women, due to the effects of sex hormones and genetic differences. Generally, men are more susceptible to bacterial gastrointestinal and respiratory diseases, as well as sepsis, while women are more susceptible to bacterial infections of the genitourinary tract. The female protection against bacterial infections and their complications is attributed to

the inflammatory protective effect of estradiol, whereas male susceptibility to these infections is associated with testosterone-mediated immunosuppression, likely through its specific receptors. Additionally, the expression of sex steroid receptors and the location of immune genes on the X chromosome, providing women with a broader immune repertoire, are contributing factors (Vasquez-Martinez et al., 2018).

9. Current Strategies in Attempting to Prevent the Progression of Severity of Odontogenic Infections

9.1 Hematological Biomarkers Predicting Complications of Infections

Early identification of the severity of OI is crucial to prevent complications such as sepsis and systemic inflammatory response syndrome (SIRS). Pricop et al. (2022) explored the use of biomarkers, specifically the Symptom Severity Index (SS) and the Systemic Immuno-Inflammatory Index (SII), in 108 patients with OI categorized by infection severity. The most common odontogenic cause was abscesses in 50.9% of the sample, followed by abscesses associated with cellulitis in 37.9%. The proportion of patients with abscesses associated with cellulitis at admission was significantly higher in the high-severity group (Group B) compared to the low-severity group (Group A). They found that patients with severe OI had higher comorbidities such as diabetes and smoking, and that more severe infections were associated with longer duration from symptom onset to admission, longer hospitalization, and higher incidence of SIRS and sepsis. They concluded that odontogenic infections could result in sepsis and systemic inflammatory response syndrome, two potentially fatal complications resulting from an elevated immune response to infection. This can lead to tissue damage, organ failure, and ultimately death. Notably, the SII and SS scores were effective predictors of OI severity, suggesting that such biomarkers could aid in assessing risks of sepsis and SIRS early on admission. This study reinforces the importance of early diagnosis and appropriate management of OI to improve patient outcomes, advocating for the integration of these indices into clinical care.

Another approach to prognosticate severity in the progression of infections has been indicated by elevated levels of inflammatory serum markers, measured by the combination of CRP and neutrophil-to-lymphocyte ratio (NLR) (CRP-NLR). In a retrospective analysis of 108 hospitalized patients divided into 2 groups based on symptom severity scale, Rosca et al. (2023)

sought to determine if there is a significant correlation between increased levels of these inflammatory serum markers and severity of odontogenic infections. In Group A, odontogenic origin abscesses accounted for 70.4% of admissions, while in Group B, abscesses and cellulitis were associated in 55.6% of cases. Disease outcomes were more severe in Group B patients, where 22.2% developed sepsis compared to 7.4% in Group A patients. However, there was no significant difference in mortality rates. The SS and SII in Group B patients were substantially higher than those in Group A patients. All biomarker scores, including CRP-NLR ratio, were considerably higher in Group B patients. Patients with OI in Group B (higher severity) were more frequently associated with diabetes mellitus and smoking than those in Group A (lower severity). They concluded that the CRP-NLR biomarker is reliable and accessible for determining the severity of odontogenic infections and could be included in other prognostic models for dental infections, potentially improving disease treatment choices.

Following this line of research, Kusumoto et al. (2022) conducted a study calculating CRP+NLR (sum of CRP and NLR) as a new inflammatory marker to assess the severity of deep cervical abscesses and necrotizing soft tissue infections (NSTI). Hematologic and inflammatory parameters, including CRP, leukocytes, NLR, PLR, SII, and PCR+NLR, were used to identify the most severe cases and indicate the need for diagnostic complementation by contrast-enhanced CT. They considered these parameters as adjuncts for the diagnosis of NSTI and deep cervical abscesses.

9.2 Metagenomic Sequencing

The adoption of Next-Generation Metagenomic Sequencing (mNGS) represents an innovative strategy to address severe infections, allowing for rapid and comprehensive identification of pathogens, crucial for precise adjustment of antibiotic therapy. This advanced method stands out for its ability to detect a wide range of microorganisms in complex and rare infection cases, where traditional methods fail in about 40% of cases. mNGS has the potential to revolutionize the diagnosis and treatment of serious conditions such as DNM, by providing detailed knowledge of pathogenic profiles. With technological advancements and decreasing sequencing costs, mNGS is expected to become a routine tool, benefiting an increasing number of patients by enabling more effective and timely medical interventions, such as immediate diagnosis and evidence-based optimized antibiotic therapy (Duan et al., 2021).

III – RESULTS AND DISCUSSION

The discussion on the implications of caries, periodontal disease, and poor oral hygiene on systemic health has been expanding, highlighting the risk of bacteraemia and serious complications arising from dental procedures (Weise et al., 2019). Studies indicate that even minimally invasive interventions can be gateways for significant infections, including bacteraemia and more severe conditions such as bacterial meningitis, posing a life-threatening risk in odontogenic infections. This underscores the importance of clinical vigilance following dental procedures, especially given the possibility of symptoms of serious complications being mistaken for less severe conditions such as temporomandibular dysfunction (Yoshizawa et al., 2023).

The literature reinforces the need for a cautious approach and precise diagnoses, including laboratory and imaging tests, to prevent delays in treatment that could lead to fatal outcomes. This evidence affirms the potential of odontogenic infections to trigger severe systemic complications, including sepsis and life-threatening risks. Therefore, the importance of a closer focus on oral health is recognised, not only for the impact on the patient's quality of life and well-being but also for the potential of serious systemic complications associated with odontogenic infections.

Acute odontogenic infections represent significant causes of emergency visits and hospitalisations, standing out due to their potential to evolve from local conditions to severe systemic complications, including airway obstruction, multiple organ failure, and death. Studies indicate that although such infections can arise in patients without pre-existing comorbidities, there are specific risk factors that exacerbate the severity of these conditions. Smoking is frequently cited as one of these factors due to its role in increasing the risk of developing severe odontogenic infections and inducing complications. Besides smoking, alcoholism and hypertension are also mentioned as contributors to the aggravation of these infections (Kataria et al., 2015; Pricop et al., 2022; Silva et al., 2022; Yoshizawa et al., 2023; Niemelä et al., 2023).

Diabetes mellitus, in particular, is highlighted as a significant predisposing factor due to its influence on modulating the immune response and wound healing, which can complicate recovery from odontogenic infections and increase susceptibility to complications (Martini et al., 2015; Qu et al., 2017; Weise et al., 2019; Rosca et al., 2023).

The relationship between diabetes mellitus and odontogenic infections is complex. Studies show both the negative impacts of diabetes on periapical healing due to elevated pro-inflammatory markers and the contribution of chronic periapical disease to diabetic metabolic dysregulation, necessitating therapeutic adjustments, including insulin dosage. Additionally, diabetes and elevated blood glucose levels are linked to a higher prevalence of apical periodontitis and a negative impact on endodontic treatment outcomes, with a lower success rate. However, the literature still presents limitations regarding the effect of diabetes and autoimmune diseases on the prevalence of post-endodontic treatment failures.

On the other hand, current evidence emphasises that effective endodontic treatment can benefit systemic health by reducing the inflammatory burden, countering the obsolete focal infection theory that encouraged tooth extraction. Despite the evidence on the relationship between apical periodontitis and systemic health, more high-quality research is needed to strengthen the benefits of endodontic therapy on overall health (cited by Niazi and Bakhsh, 2022).

Pregnancy and the health and susceptibility of both mother and fetus have been addressed, highlighting the need for increased attention to oral hygiene throughout gestation to prevent complications including sepsis, pre-eclampsia, miscarriages, premature birth, and low birth weight (Agili, 2023; Agili & Khalaf, 2023).

Immunosuppressive, autoimmune diseases and immunosuppression due to therapies or medications have been identified as conditions that exacerbate the risk of severe complications in odontogenic infections (Weise et al., 2019; Grill et al., 2023; Carraba et al., 2023).

Male predisposition to severe bacterial infections has been raised by Vasquez-Martinez et al. (2018), attributed to hormonal and genetic differences between genders, with men showing greater susceptibility as verified in various studies (Bucak et al., 2013; Bertossi et al., 2017; Qu et al., 2017; Sakai et al., 2021; Gupta et al., 2022).

Healthcare professionals should be aware of the heightened risks when intervening in patients with immunocompromise, where the presence of caries, periodontal disease, and root canal infections can lead to bacteraemia and severe complications (Martini et al., 2015; Weise et al., 2019; Takizawa et al., 2022). Understanding how these conditions affect the progression and risk of odontogenic infections is crucial to preventing severe outcomes, including septicaemia.

However, there are persistent divergences in studies regarding the precise effects of periodontal disease and endodontic treatments on systemic health, reflecting the complexity of the impact of oral conditions on immunity and overall health.

Reis et al. (2016) highlighted the low incidence of bacteraemia after endodontic procedures in patients with either high or very low risk of developing infective endocarditis, regardless of antibiotic prophylaxis. For this reason, they recommend endodontic procedures for infected teeth over tooth extraction, which carries a higher risk of bacteraemia.

Conversely, Niazi and Bakhsh (2022) noted that more recent studies have observed bacteraemia after non-surgical root canal therapy in all cases previously negative for bacteraemia using culture approaches. However, both Reis et al. (2016) and Niazi and Bakhsh (2022) agreed that molecular methods, such as qPCR, demonstrated greater accuracy in detecting bacteria during bacteraemias, contrasting with traditional culture methods, which are known for their low sensitivity.

Regarding antibiotic prophylaxis, based on AHA guidelines, it should be restricted to high-risk patients for infective endocarditis (IE). Lafaurie et al. (2019) demonstrated that premedication with antibiotics significantly reduced bacteraemia rates after tooth extractions, with amoxicillin showing the highest efficacy among antibiotics. However, the impact of prophylaxis on preventing IE remains controversial, with studies varying in their results. A limited approach to prophylaxis use has been suggested, given the inconsistency of evidence regarding its efficacy and the need for future research focusing on new antibiotics not included in current protocols for patients with or without penicillin allergy.

Allareddy et al. (2017) conducted research observing a significantly higher risk of postoperative infectious complications in patients with periapical abscesses undergoing cardiac surgeries with extracorporeal circulation. The presence of a periapical abscess increased the risk of infectious complications to 30.2%, compared to 11.6% for patients without this condition, and sepsis developed in 16% of these patients, compared to 4.2% of those without a periapical abscess.

Takizawa et al. (2022) underline the importance of preventive dental treatment to reduce the risk of IE in critical phases, suggesting the extraction of potentially infectious teeth before critical cardiac procedures. However, the AHA (2007) advises a thorough preoperative dental evaluation focusing on the completion of necessary dental treatment, as evidence supporting the removal of dental infection foci before cardiac surgeries is limited and inconclusive, even

in heart transplant patients undergoing systemic immunosuppression (cited by Allareddy et al., 2017).

The indigenous oral flora, typically of low virulence, can trigger local or haematogenous infectious dissemination under certain predisposing conditions, leading to distant infections and serious complications such as sepsis and septic shock. Studies highlight a polymicrobial spectrum, both aerobic and anaerobic, of oral bacteria involved in these infections (Bertossi et al., 2017; Gupta et al., 2022).

Kataria et al. (2015) identified *Streptococcus* and *Staphylococcus* as the most common microorganisms in deep neck space infections (DNSI), while Lee et al. (2016) reported a rare case of bacteraemia caused by *Dialister pneumosintes* and *Slackia exigua*, both associated with periodontal diseases. In descending necrotizing mediastinitis (DNM), Palma et al. (2016) observed significant aerobic/anaerobic coinfections, and Qu et al. (2017) reported a variety of pathogens, including *Streptococcus spp.*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Pota et al. (2018) highlighted the involvement of Gram-positive, anaerobic, and occasionally Gram-negative bacteria in DNM.

Weise et al. (2019) emphasized the predominance of *Streptococcus viridans* in severe odontogenic infections, followed by *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Prevotella oris*. *Prevotella* is a common Gram-negative anaerobic pathogen in odontogenic infections. Other identified bacteria included *Actinomyces actinomycetemcomitans*, *Streptococcus anginosus*, *Staphylococcus aureus*, *Enterococcus spp.*, *Escherichia coli*, MRSA, and *Streptococcus constellatus*.

The prevalence of OI tends to be higher in the mandible, especially in the posterior region, as reported by Bertossi et al. (2017). This finding is corroborated by Fernandes et al. (2014), who noted that the mandible was the most affected anatomical region in 60% of cases, and by Kityamuwesi et al. (2015), who highlighted that 72% of patients had infections originating in the mandible.

The teeth most frequently associated with OI are the lower posterior teeth (Qu et al., 2017; Richards et al., 2020; Gupta et al., 2022). Das, Nath, and Mishra (2017) demonstrated that the submandibular space was the most commonly involved, followed by the sublingual space. Therefore, OI tend to occur more in the mandible, especially in the posterior teeth and the submandibular and sublingual spaces. The anatomical configuration of the floor of the mouth

influences the progression and spread of OI, with infections spreading along paths of least resistance in the soft tissues from the affected teeth to adjacent spaces.

Effective and immediate control of odontogenic infections is crucial to prevent their local or systemic spread. Early diagnosis and prompt intervention are essential for effective resolution and improving patient survival, as highlighted by various researchers (Kataria et al., 2015; Cariati et al., 2016; Qu et al., 2017; Gupta et al., 2022). Despite advances in diagnostic methods, such as the precision of CT scans, and the development of antibiotics, managing OI has become more complex. This complexity is partly due to an increase in patients with comorbidities and growing antibiotic resistance, which can lead to more severe infections. Delayed correct diagnosis and the indiscriminate use of antibiotics or anti-inflammatory drugs can mask symptoms without effectively treating the disease, thereby increasing its severity (Pricop et al., 2022).

There is consensus among researchers on the importance of early diagnosis and treatment, as well as the use of culture-based antibiotic therapy, which is fundamental for patient survival in cases of OI (Muños et al., 2021; Gupta et al., 2022). Immediate diagnosis and rapid surgical intervention are essential in managing severe odontogenic infections, requiring a multidisciplinary team of specialists in maxillofacial surgery, thoracic surgery, and head and neck surgery (Ranjbar et al., 2023). Educational training between medicine and dentistry often does not adequately address the management of these infections, resulting in a knowledge gap that can compromise care. Collaboration between these fields is crucial, especially in potentially fatal conditions such as deep cervical abscesses and DNM, which present significant mortality risks due to delayed diagnosis and treatment (Qu et al., 2017; Pota et al., 2018; Muños et al., 2021; Ranjbar et al., 2023).

Studies indicate an increasing incidence of OI originating from dental sources, with mortality rates still high, ranging from 11% to 40%, underscoring the importance of early diagnosis and appropriate surgical interventions to reduce these rates (Qu et al., 2017; Pota et al., 2018; Muños et al., 2021; Ranjbar et al., 2023).

The use of immunosuppressive medications and the presence of chronic immunosuppressive diseases are known risk factors for sepsis and septic shock, with a mortality rate approaching 50% once septic shock develops (Martini et al., 2015; Mannan et al., 2021). Inadequate antibiotic selection and the virulence of microorganisms involved in OI can accelerate

progression to these serious complications, emphasizing the importance of early diagnosis and appropriate management to prevent fatal outcomes (Martini et al., 2015; Kang and Lee, 2022).

Studies have also shown that the severity of complications from OI is directly related to the time until ICU admission, the severity of symptoms at admission, and the duration of ICU stay (Bucak et al., 2013; Chen et al., 2013). Electively admitted patients have lower risks of complications compared to emergency cases (Allareddy et al., 2017).

While initial treatment for head and neck infections often involves empirical antibiotics and removal of infected teeth, prolonged use of systemic antibiotics can impair host immune defences, promote antibiotic resistance, and hinder recovery, increasing the risk of lethal complications (Nandimath et al., 2018).

In managing complications from OI, early antibiotic therapy is crucial, although bacterial culture test results typically take at least 48 hours, with a success rate of only 30-50%. This suggests the need to initiate empirical antibiotic treatment, adjusting it as bacterial culture and susceptibility test results become available (Gao et al., 2022). Duan et al. (2021) propose mNGS as a solution, enabling rapid identification of all microorganisms and facilitating antibiotic adjustment.

Accurate diagnoses involving blood tests and CT scans are essential to prevent diagnostic errors and treatment delays, especially considering that the majority of head and neck infections originate from odontogenic causes (Yoshizawa et al., 2023). The intensity of the immune-inflammatory response is viewed as a key indicator of infection severity, with hematologic and inflammatory biomarkers proving useful for diagnosing and prognosticating odontogenic infections (Kang & Lee, 2022; Kusumoto et al., 2022; Pricop et al., 2022; Rosca et al., 2023).

Rosca et al. (2023) and Kusumoto et al. (2022) highlight the combination of C-reactive protein (CRP) and the neutrophil-to-lymphocyte ratio (NLR) as potential predictors of odontogenic infection severity. These biomarkers not only serve as severity indicators but also complement clinical diagnosis, underscoring the need for a comprehensive diagnostic approach, including contrast CT when necessary.

Kang and Lee (2022) emphasize the relevance of biomarkers such as CRP, white blood cell count (WBC), PCT, and presepsin (PSEP) in the initial assessment of inflammatory severity and sepsis in emergency department patients. They found a positive correlation between these biomarkers, especially between PCT and PSEP, with their increase associated with a higher

risk of sepsis, suggesting PCT and PSEP as significant indicators for sepsis diagnosis. This finding reinforces the importance of specific biomarkers in determining sepsis risk in patients with odontogenic infections.

Pricop et al. (2022) also emphasize the importance of assessing odontogenic infection severity for effective prognosis and therapeutic planning. In contrast to the traditional use of CRP and white blood cell count to assess infection severity, they propose the SII as a more accurate tool. Based on platelet, neutrophil, and lymphocyte counts, SII has shown promise as an indicator of prognosis in various inflammatory conditions. Its applicability in infectious diseases, including odontogenic infections, is still under investigation.

Thus, studies highlight the need for reliable biomarkers to assess infection severity and the risk of serious complications such as sepsis and SIRS. The use of severe symptom scores (SS) and the SII at admission can provide insights into the risk of developing sepsis and SIRS in patients with odontogenic infections, suggesting a more personalized and targeted approach to managing these infections.

The prevention of odontogenic infections, often overlooked as a secondary concern, deserves attention due to its relevance in promoting oral health and its impact on systemic health. Studies such as Agili and Khalaf (2023), which explored oral health awareness among Saudi pregnant women, demonstrate the existing gap in dental education during pregnancy. With only a fraction of women receiving adequate guidance from their dentists, the study underscores the need for effective interventions to promote integration and collaboration in oral health, emphasizing its impact on maternal and child health.

Additionally, oral health education targeted at children and adolescents emerges as a crucial pillar in preventing future odontogenic infections. Ground et al.'s (2015) research on the prevalence of odontogenic infections in German children reveals that untreated dental caries in primary teeth is a significant issue, with an alarming proportion of untreated cases leading to infections. This neglect in early life stages signals an increased risk of cavities and infections in permanent teeth, highlighting the influence of socioeconomic disparities on child oral health.

Conversely, studies like Lamenha-Lins et al. (2020) suggest a connection between pain from odontogenic infections and its impact on children's psychosocial development, underscoring the importance of a proactive approach in dental education and treatment. The lack of success

from previous public health programs indicates an urgent need to review and restructure oral health policies, aiming to reduce inequalities and promote more equitable access to dental care.

His review highlights the urgent need for a more robust and integrated preventive approach to oral health, focusing on both education and early treatment to mitigate the risk of odontogenic infections and their systemic complications. The inclusion of targeted educational programs and public health policies aimed at oral health could represent a significant advancement in reducing health disparities and promoting overall well-being.

Odontogenic infections, primarily caused by dental caries, remain a significant concern in the UK, despite being largely preventable with adequate oral hygiene and reduced sugar consumption. Despite their preventable nature, the rate of dental caries and odontogenic infections has remained high in the population, with a 3.5-fold increase in hospital admissions in England due to severe dental infections over the past 20 years. This increase points to underlying issues such as limited access and financial capacity for dental treatments, leading to neglect until serious complications arise (Robertson & Smith, 2021).

It is true that odontogenic infection is most commonly caused by the preventable condition of dental caries and its progression, which typically responds well to early surgical interventions such as early endodontic treatment, incision and drainage, or tooth extraction. It is also true that severe dental infections can escalate into a serious and potentially life-threatening condition, necessitating hospitalization for surgical interventions, airway support, and medical management. However, it is inconceivable that over the past 20 years, the number of hospital admissions in England due to odontogenic infections has more than tripled, especially in a developed country.

Furthermore, maintaining good periodontal health through oral hygiene and professional dental care measures will help prevent serious systemic odontogenic infections. Thus, there is an urgent call for research focusing on the relationships between periodontal and systemic diseases, emphasizing the importance of periodontal treatment not only for oral health but also for overall systemic health (Robertson & Smith, 2021).

Early and effective treatment of odontogenic conditions such as pulp, periapical, and periodontal diseases is crucial to avoid the development and aggravation of disseminated odontogenic infections. Prevention and education on oral health are fundamental aspects to

minimize the risk of serious complications, including sepsis, which can progress to septic shock and result in fatalities.

Literature review over the past 10 years reveals a clear connection between untreated dental problems and severe systemic diseases, underscoring the importance of healthcare professionals' awareness of the risks associated with odontogenic infections. This understanding reinforces the need for rapid diagnosis, immediate intervention, and promotion of oral health as vital strategies to prevent significant negative outcomes from odontogenic infections (Dai et al., 2019).

Finally, evaluating the literature reviewed in this narrative review over the past 10 years, a variety of systemic diseases affecting numerous patients with severe complications, including fatalities, have been exposed. Therefore, there is an urgent need for healthcare professionals' awareness of this issue: there is legitimate concern about sepsis as a complication of odontogenic infection, which can progress to septic shock and death.

IV- CONCLUSION

Based on the literature reviewed and considering the primary objective of this research, it is concluded that odontogenic infections:

- Can spread through the bloodstream, triggering bacteraemia of varying proportions;
- When not promptly treated, can progress and spread to other areas of the body, causing severe infections that, without immediate intervention, can advance to increasingly morbid and potentially fatal conditions;
- Depending on their progression and severity, require treatment by a multidisciplinary surgical team in intensive care units;
- Remain a significant concern due to their progression to sepsis/septic shock, which can result in fatalities;
- Contribute to an increased risk of sepsis and mortality despite advances in scientific research, technology, laboratory, and medications;
- In immunocompromised patients, can have a faster and more severe progression;
- Are often caused by preventable dental caries, representing an area that requires greater attention and intervention by public health authorities to maintain the overall health of individuals.

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