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Clinical examination of delayed-onset infection after surgical removal of lower third molars

PhD thesis

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List of Abbreviations

- AO - Alveolar Osteitis
- BMAF - Buccal Mucosal Advancement Flap
- BMI - Body Mass Index
- CT - Computer Tomography
- DM - Diabetes Mellitus
- DOI - Delayed-Onset Infection
- et al. - "et alii" = and others
- e.g. - "exempli gratia" = for example
- etc. - "et cetera" = and others
- HbA1c - Haemoglobin A1c
- IBM® - International Business Machines Corporation
- P-G - Pell and Gregory
- RPM - Revolutions per Minute
- SPSS® - Statistical Package for the Social Sciences
- TTF - Triangular Transposition Flap

1. Introduction

Wisdom teeth are the most commonly impacted teeth, with a frequency of up to 75% in the young adult population [1, 2].

The cause is linked to human evolution, as the neurocranium has developed at the expense of the splanchnocranium, whose dimensions have remained almost unchanged, rendering the third molars redundant [1, 3]. The eruption of wisdom teeth often occurs in anomalous positions due to lack of space, resulting in clinical symptoms such as recurring pain, otalgia, odynophagia, and dysphagia [1, 4]. As a result, the removal of these teeth, which in many cases takes place surgically, is one of the most common oral surgery procedures [1, 2].

The number of patients presenting with wisdom teeth issues at our clinic has been steadily increasing over the years. As a result, we have had to perform more operations that require significant professional and instrumental preparation. In 2007, we treated 1200 cases, while in 2017, we treated 2900. By 2022, we had treated over 3.000 cases annually [5].

The extraction of wisdom teeth is typically performed for several reasons, including acute or chronic pericoronitis, dental crowding, the presence of caries on adjacent teeth, periodontal problems, and the presence of a cyst or tumour [6, 7].

The average age of patients undergoing third molar extraction is decreasing due to the increased frequency of prophylactic procedures. As a result, we are increasingly seeing complications that are more typical of young people and that we rarely saw before. Delayed-onset infection (DOI) after lower third molar surgery can be one such complication. In addition, the patient who was thought to be cured comes back with complaints.

The fact that this complication is becoming more common and that the cause is often unknown is the reason for our study.

Research on this complication has been ongoing at our university since 2017. We first published our initial research results in 2018 [8]. The latter study investigated novel

parameters, including the role of the lower second molar tooth, *Nolla* stage, associated radiolucent lesions, and prior history of pain or infection, in addition to an increased number of cases. This thesis presents only the additional study, which expands on the first study only by including more cases and parameters [9].

When the investigation began, there was limited literature available on this complication. Although several articles have since been published on the subject, we aim to contribute to the body of knowledge related to this rare complication.

1.1. Classification - clinical aspects

For proper interpretation of the latter part of the thesis, it is important to present the fundamental clinical classifications in relation to the position of the lower third molar.

1.1.1. Orientation of the great axis of the tooth (*Winter*-classification)

G. B. Winter documented impaction types based on angulation - the inclination of the crown of an impacted third molar - concerning the angle formed between the long axes of the lower wisdom tooth and the adjacent second molar (Figure 1.) [10, 11].

The distinction between mesioangular, vertical, horizontal, distoangular, and inverted orientation may affect the surgical approach, in particular regarding the requirements for bone removal and tooth sectioning [12, 13].

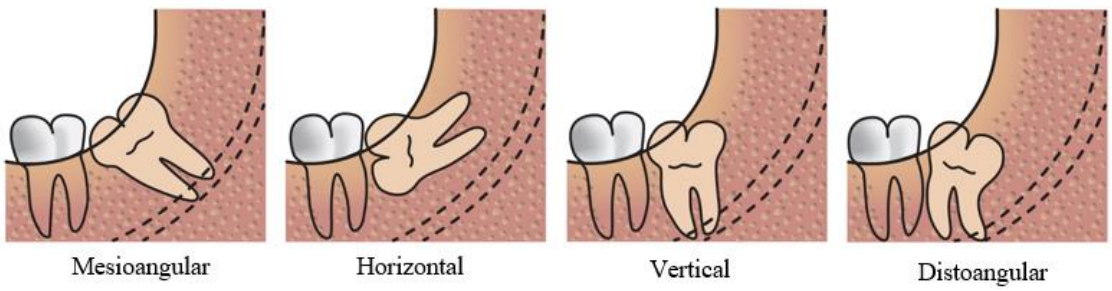

Figure 1. Diagram of the *Winter* classification [10,14]

1.1.2. Impaction depth according to *Pell and Gregory* classification

The *Pell and Gregory* classification (1933) is based on the relationship between the lower third molar to the ramus of the mandible and the second molar (based on the space available distal to the second molar, Figure 2.) [14, 15].

Ratio A: The highest portion of the mandibular third molar is on a level with or above the occlusal plane. The crowns of the second and third molars are at the same level [14, 15].

Ratio B: The highest portion of the third molar crown is located under the occlusal plane but above the cervical line of the second molar [14, 15].

Ratio C: The highest portion of the third molar crown remains under the cervical line [14, 15].

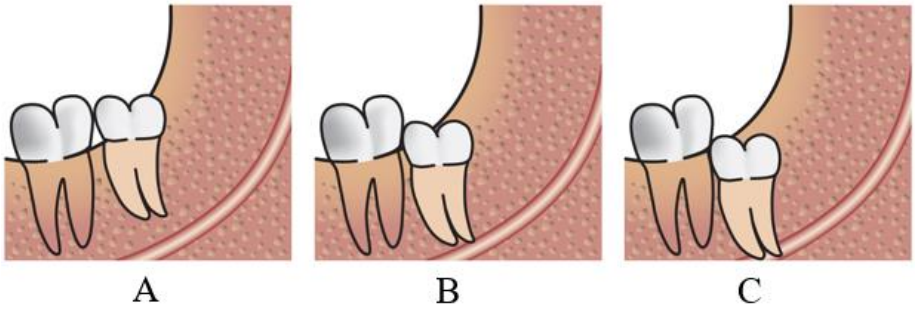

Figure 2. Impaction depth of the mandibular third molar according to *P-G* [13, 15]

1.1.3. The relationship of the tooth with the ramus according to *Pell and Gregory* classification

The *Pell and Gregory* classification (1933) is based on the relationship between the lower third molar to the ramus of the mandible and the second molar (based on the space available distal to the second molar, Figure 3.) [12, 15].

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Class I: The available space, at the level of the retromolar triangle, between the ramus and the distal aspect of the second molar is sufficient to expect that the wisdom tooth will erupt as far as the occlusal plane. None of the third molar crown is in the ramus of the mandible [12, 15].

Class II: The space between the ramus of the mandible and the adjacent second molar is less than the mesiodistal diameter of the crown of the third molar, and therefore the tooth will not be able to erupt. Less than half of the third molar crown is in the ramus [12, 15].

Class III: The temporal crest of the ramus of the mandible is placed against the distal aspect of the adjacent second molar, and there is no space for the eruption of the third molar. More than half of the third molar crown is in the ramus [12, 15].

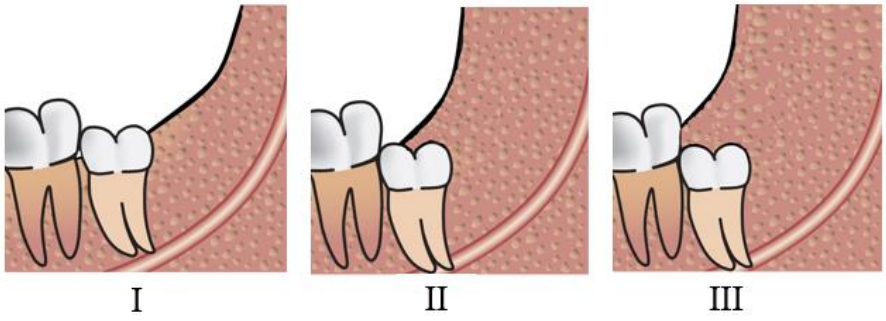


Figure 3. The relationship of the mandibular third molar with the ramus according to *P-G* [13, 15]

1.1.4. The relationship of the tooth with the ramus according to the *Ganss* ratio

The relationship between the space available in the retromolar region and the mesiodistal width of the third molar crown can be analysed on panoramic radiographs (Figure 4.).

Using the panoramic radiograph, the ratio of retromolar space to the width of the crown of the third molar can be calculated using the method originally described by *Olive and Basford* (1981) and later modified by *Ganss et al.* (1993) (known as the '*Ganss* ratio') [16, 17, 18].

Calculation of the *Ganss* ratio could assist investigations into the development of dental arch crowding and help determine the indications for third molar removal [16, 17, 18].

Ganss ratio: The ratio of line A to B, that is, available space/crown mesiodistal width.

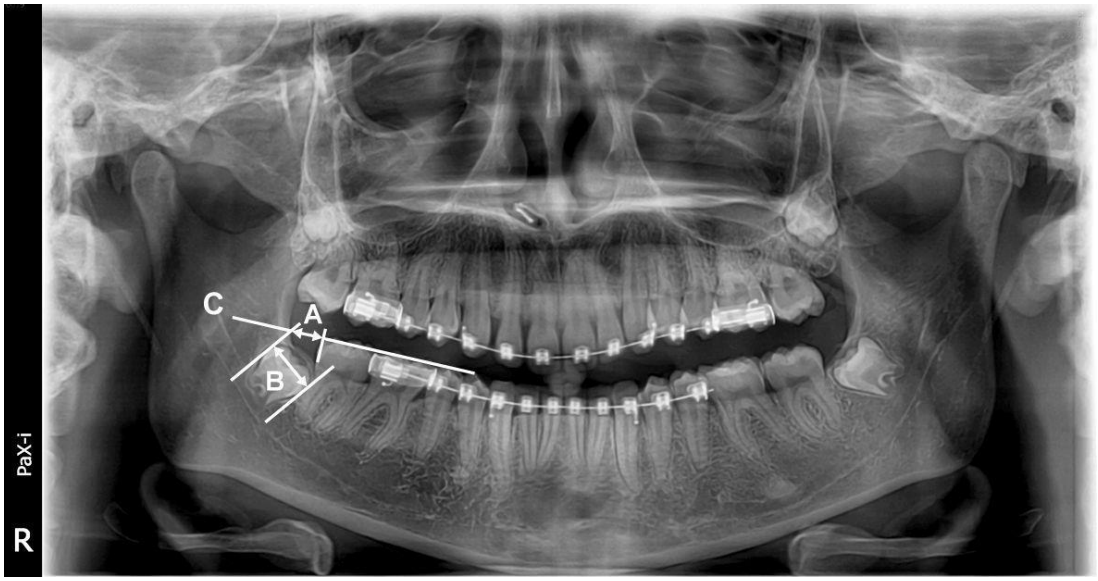


Figure 4. Panoramic radiograph measurement for assessment of the third molar space. A Distance between distal border of second molar crown and anterior border of ramus measured on occlusal plane, B width of third molar crown, C occlusal plane. The *Ganss* ratio = A/B [9]

1.1.5. *Nolla* classification

The third molar originates from the primitive dental lamina, and the crypt formation begins at 3 to 4 years of age. Calcification starts at 7 to 10 years of age and is complete by 12 to 16 years of age. Eruption of the teeth begins between 17 and 21 years of age. The formation of roots is completed between the ages of 18 and 25 years of age [19, 20. 21].

Nolla evaluated the development of the permanent teeth and in 1960 published her study. Dental development can be graded according to *Nolla*'s stages of tooth calcification (Figure 5.).

The stages are as follows: stage 0: absence of crypt, stage 1: presence of crypt, stage 2: initial calcification, stage 3: one-third of crown completed, stage 4: two-third of crown completed, stage 5: crown almost completed, stage 6: crown completed, stage 7: one-third of root completed, stage 8: two-thirds of root completed, stage 9: root completed and apex open, stage 10: apical foramen closed [19, 20. 21] .

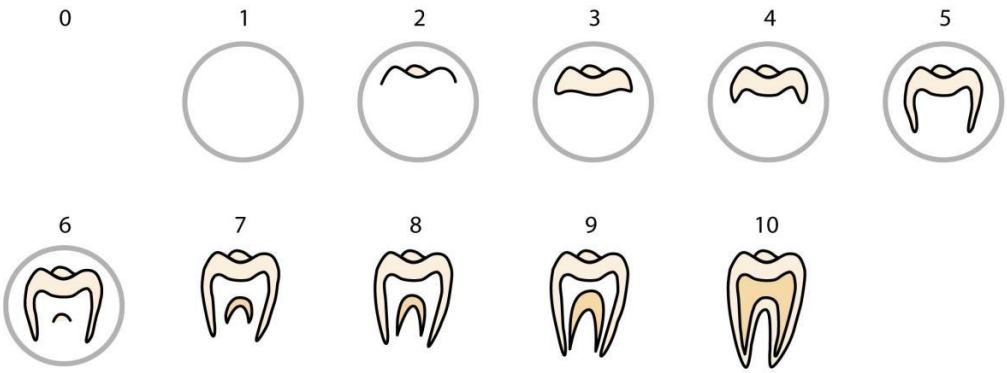


Figure 5. *Nolla* classification [9, 20]

1.2. Wound healing disorders after third molar surgery

Following the surgical removal of impacted third molars, postoperative symptoms lasting a few days are considered natural during the wound healing process. Pain, swelling, and trismus may occur to varying degrees depending on the duration of the surgery, the anatomical position of the molar, and other factors [8, 9, 22].

However, wound-healing disorders have a relatively high probability of occurrence (0.8%-7.8%). The most frequently occurring disorders are alveolitis and surgical site infections. Many studies have been carried out on complaints in the early post-operative period and predisposing factors have been identified. However, most clinical studies have focused only on inflammatory complications until the point of suture removal and have subsequently ceased to monitor patients. Among patients considered to have made a full recovery, post-procedural complications may occur weeks later. Delayed-onset infection (DOI) can cause swelling, jaw stiffness, moderate pain, pus formation, and fever. Symptoms typically appear 3-4 weeks after the procedure [9, 22, 23, 24].

1.2.1. Alveolar osteitis (dry socket)

Dry socket is a clinical diagnosis characterized by the development of severe, throbbing pain several days after the extraction of a tooth and often is accompanied by halitosis. The alveolar socket is often filled with debris and is conspicuous by the partial or complete loss of the blood clot. Alveolar osteitis (AO) was classically thought to be infectious in nature, is now understood to be associated with malformation, disruption, or other loss of a newly formed blood clot from a tooth alveolus [22, 25].

The reported incidence varies widely in the literature, but according to a Cochrane Review, it is most reported to be between 0.5% and 5% for routine tooth removals. But the same review reports the incidence of dry socket following lower third molar removals to be over 30% [26, 27].

Recognition of dry socket is based on the presence of new-onset severe pain, typically 3–5 days postoperatively, at which point pain and swelling associated with the operation

should be beginning to subside. The lack of constitutional symptoms (fever), significant swelling, or purulent discharge may help to distinguish AO from a surgical site infection [22, 25].

Physical examination findings may include a crypt-like socket with exposed bone and erythematous soft-tissue margins, occasionally food debris, or other detritus in the alveolar socket and extreme tenderness to palpation. Radiographs should also be obtained to rule out the presence of a retained root structure or other surgical site complication, such as alveolar fracture [22, 25].

As the condition is self-limiting, the therapy is mainly supportive, with pain control being the primary goal. Therapy typically consists of gentle irrigation of the wound area with warm saline and application of medicated packing to the area and, if necessary excochleation of the socket [22, 25].

The main risk factors for dry socket are a mandibular location of the extracted tooth, poor oral hygiene, difficult extraction, and a history of dry socket [22, 28].

Thorough surgical site irrigation, the use of topical medications and antibiotics, clot stabilisers, platelet-rich plasma, and medicated mouthwashes have been suggested to prevent dry socket [26].

1.2.2. Wound infections

Because the oral cavity is home to a wide variety of bacterial flora, any intraoral wound will be exposed to a broad spectrum of aerobic, anaerobic, and facultative organisms with potentially pathogenic potential [22]. Wound infections after third molar surgery can be classified into early onset infections and delayed-onset infections. While early onset infections occur in the early healing phase, delayed-onset infections do not appear until a time of about three to six weeks after the procedure [35]. Delayed-onset infection is discussed in a separate chapter.

Postoperative infections following the removal of third molars have been reported to range from approximately 0.8% to 10% [22, 25].

Patients presenting with infections will typically complain of enduring pain and swelling that is not improving with time, a foul taste, drainage from the wound, and limitation of mouth opening (trismus). Fever is variable and depends on the magnitude of the infection process. Early recognition of an infection, typically a cellulitis, requires prompt treatment with an empiric course of broad-spectrum antibiotics. If symptoms persist for more than 2-3 days after the procedure, an abscess, or pus pocket, may have formed, in which case incision and drainage may be indicated, with collection of exudates for culture and sensitivity testing to guide proper antibiotic therapy. Prompt recognition and management are necessary to prevent the spread of infection into the submandibular, sublingual, submental, retropharyngeal spaces, and spaces of the deep neck, which can result in airway compromise and the need for emergency airway management [22].

Immediate or early complications have been researched extensively and include factors related to the patient (age, sex, oral hygiene, etc.), the tooth (partial or complete impaction, impaction depth, previous pericoronitis, extractions needing bone removal, type of impaction, tooth sectioning), antibiotics, drugs taken (therapy before and/or after extraction), and the surgeon and surgical technics (experience or flap design, use of rotary or piezoelectric instruments) [23, 25, 29, 30, 31, 32, 33].

As with other common complications, careful tissue management, debridement/curettage of necrotic/ infected tissue, and thorough irrigation of the wound site and antibiotic prophylaxis with the right indication will help to reduce the bacterial inocula within the wound site and reduce the possibility of infection [22, 33].

Delayed-onset infection is discussed in the next chapter.

Other less common wound healing disorders like osteomyelitis, osteonecrosis, etc. are of special importance, but they do not form the topic of this thesis.

1.3. Delayed-onset infection (late-infection)

1.3.1 Signs and symptoms

Post-operative infection after tooth extraction occurs mainly in the mandible and rarely in the maxilla. Delayed-onset infections typically appear three to six weeks post-surgery and are usually seen in the lower jaw at the third molar site (Figure 6.) [34, 35].

This type of wound infection, also referred to as late secondary infection by *Osborn et al.*, can cause a variety of symptoms occurring several weeks after suture removal and discharge, affecting both hard and soft tissues [36, 38].

Delayed-onset infections after third molar extractions are relatively rare postoperative complications characterised by swelling, usually with purulent discharge at the surgical site. In the early stages of infection, swelling (intra- and/or extra-oral), jaw stiffness and moderate pain may be present without purulent discharge. It is sometimes associated with fever [23, 37].

Figueiredo et al. defined it as an inflammatory swelling of the operated area accompanied by pain or the presence of suppuration, starting at any time after suture removal 1 week postoperatively [38].

Osborn et al. reported that most secondary infections (66%) occurred between 15 and 60 days after surgery [36]. The occurrence of DOI has been described as most common at 1 month after extraction [6, 34, 38, 39, 40]. In a study by *Christiaens and Reychler*, 75% of infections developed earlier (after 2-3 weeks), but most sources in the literature 4-10 have reported a period of 25-35 days [6, 34, 39, 41].

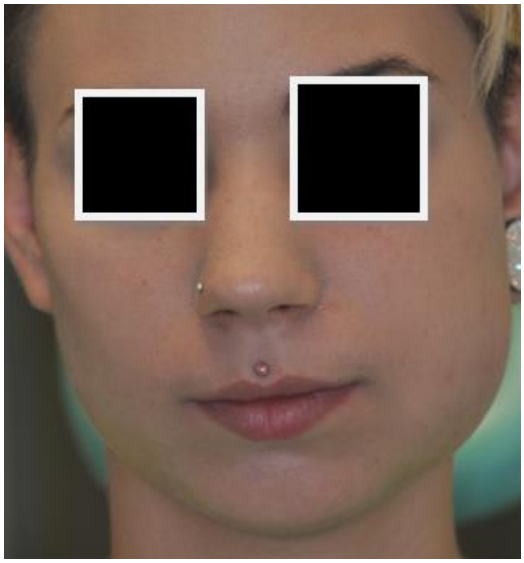


Figure 6. The patient presented at our clinic with swelling on the left side of their face 31 days after the removal of tooth 38 (Source: Personal)

1.3.2. Incidence

Many articles focus on postoperative complications, but only a few studies have investigated the incidence of delayed-onset infections [6, 34, 39, 40]. Most of the studies are retrospective [23, 34, 39] and three [36, 37, 42] are presented as prospective studies.

Osborn et al. [36] reported a 3.4% rate of late infections in a prospective study of 9.574 patients who underwent a total of 16.127 mandibular third-molar extractions. Another prospective study on postoperative complications after lower wisdom tooth extraction reported a wound infection rate of 2.2% at 4 weeks [42].

In their retrospective study of 1.213 upper and lower third-molar extractions, *Christiaens and Reychler* found that infection was the most common complication, with a secondary infection rate of 1.7% and 3.6% for mandibular third molars extracted under general and local anaesthesia, respectively [37, 41].

In a retrospective study of 958 tooth removals, the reported incidence of delayed-onset infection was 1.5%. However, the authors noted that a more conservative estimate could

be as high as 2.4% if only patients who had undergone surgery and had further follow-up after suture removal were included [37, 39].

The study by *Monaco et al.* found a high rate of delayed-onset infection, which may be attributed to their examination of all critical factors (lack of distal space, complete impaction, and asymptomatic teeth) in a selected cohort of patients within a narrow age range (12-20 years) [23,24].

1.3.3. Possible cause and involved bacteria

The cause of these infections is often unclear [6, 35, 39].

Monaco et al. found that almost every patient with DOI had first intention healing after suture removal. This method has the advantage of better control of reactionary bleeding during the postoperative period [23, 43]. However, it could also result in the „one-way valve effect that allows food debris to enter the socket but not easily escape", as stated by *Waite and Cherala*. This situation can increase the likelihood of socket infection [44].

Figueiredo et al. concluded that the reason for the association between the position (total soft tissue coverage, a lack of distal space, and a mesioangular tilt of the third molar) and the onset of infections is probably because the space left empty beneath the soft tissue can be colonized by bacteria across the gingival sulcus [39].

According to *Brunello et al.* (2016), more complicated surgeries may impair mucosal healing at the extraction site, even if it is not clinically evident 7-10 days after the extraction. This can be caused by several factors, including an inappropriate suturing technique that fails to juxtapose the epithelium on one or both sides of the surgical wound, failure of the epithelium to reattach at the cement-enamel junction of the second molar, and food or hematoma trapped under the flap [34, 37, 39, 45].

Sukegawa et al. explain that delayed-onset infection occurs due to the inability of a closed layer to completely prevent bacterial invasion. As a result, food may enter the tooth extraction cavity or dead space of the second molar, which is then rapidly healed by the

oral mucous, leading to the establishment of anaerobic bacterial infection approximately one month after the operation [6].

As an additional determining factor, the risk of delayed infection was found to be associated with the simultaneous extraction of both left and right mandibular third molars. This procedure can cause more swelling and trismus, which can lead to unsanitary conditions in the oral cavity. In particular, the retention of food residue in the extraction tooth cavities in the posterior molar section strongly supports the aforementioned infection mechanism [6].

Bacterial contamination of the surgical area's surroundings is inevitable, either from the patient's bacterial flora or oral environment [6].

In conclusion, food or debris can become trapped under the mucosa, which can then act as a substrate for bacteria. However, this material cannot be removed, and as a result, inflammation may develop at the surgical site [9, 39, 44, 45].

It is widely acknowledged that anaerobic bacteria have a significant impact on the development of orofacial infections. However, there is a lack of studies that specifically aim to identify the bacteria responsible for surgical wound infections through microbiological sample collections [46].

In 2012, *Figueiredo et al.* conducted a study that described the microbiological characteristics of delayed-onset infections following lower third molar removals for the first time.

Although the sample size may be considered small, the bacterial strains identified were similar in most patients with DOI. Another limitation of this study was that all patients received antibiotics (amoxicillin) after surgery [46].

This factor could have selected the identified bacteria and affected their sensitivity profiles. However, these amoxicillin-susceptible microorganisms are unlikely to be the cause of delayed-onset infections. Furthermore, the efficacy of postoperative antibiotics in preventing delayed-onset complications of this nature is uncertain. This is because, firstly, the majority of patients had completed their antibiotic course at least three weeks prior to diagnosis (with a mean time elapsed from extraction to infection of 39 days), and

secondly, because the alveolar socket can be easily recontaminated with oral bacteria [46].

Odontogenic infections frequently contain a mixed bacterial flora of anaerobic and aerobic microorganisms [47, 48]. Among these strains, viridans group streptococci and staphylococci are usually predominant. In this study, these bacteria might have been eliminated owing to the administration of postoperative antibiotics and the use of chlorhexidine mouthrinses. Nevertheless, most authors attribute a causative role to other anaerobic bacteria, such as Prevotella, Bacteroides, Fusobacterium, or Peptostreptococcus [47, 49, 50].

The result of the study entirely supports this opinion, showing that Fusobacterium species (present in 11 of the 12 samples analyzed), Prevotella species (found in 8 samples), and Peptostreptococcus species (present in 7 patients) were common in the samples when postoperative amoxicillin has been administered [46].

The study by *Böttger et al.* showed a new type of delayed-onset wound infection The causative organisms could only be identified through molecular methods, as standard culture and laboratory examinations were all sterile. The microbiome of the abscessing inflammation was analysed using 16S-rRNA gene analysis, revealing a mixed bacterial infection with a dominance of Delftia and Alcanivorax (subspecies), along with other bacteria from the normal oral flora. Delftia and Alcanivorax (subspecies) are water-affine environmental bacterial strains. The authors stated, that based on these results, utilizing 16S-rRNA-gene analysis, next-generation sequencing, and bioinformatics, a new type of chronic wound infection after third molar surgery was found [35].

1.3.4. Possible risk and influencing factors for delayed-onset infection

a, Attributes (sex, age)

Contrary to the findings of several studies [6, 37, 40], *Monaco et al.* reported that the male-to-female ratio was a significant predictor. Similar results were observed in studies by *Figueiredo et al*., where delayed infections occurred twice as frequently in female patients [23, 34]. However, due to the limited number of late infections, these data were not used in computing the discriminant scores. From a clinical perspective, it is challenging to explain these findings as several factors such as hormone levels and anatomical factors could influence the onset of infection [23].

Osborn et al. found that the late infection rate was 3.7%. However, in the younger age group (12-24 years), the rate was higher at 6.7% ($p=0.02$). The authors also noted that the incidence of secondary infection following third molar removal was three times greater in the younger age group (12-24 years) compared to the older age group (35-83 years) ($p<0.001$) [36, 39]. *This higher percentage is comparable to that found in the study by Monaco et al.,* in which the age of DOI patients ranged from 12 to 20 years (mean 15 years). *Osborn et al.* were the first to suggest that a higher percentage of delayed infection can be observed in the younger age group of patients. The study conducted by *Monaco et al.* in 2017 supports these findings [23, 36].

Monaco et al. observed a reduced space distal to the second molar in the younger age group, as documented by class III of *Pell and Gregory* classification. This anatomical condition could lead to difficulty in maintaining proper hygiene and an increased risk of food debris impaction. Additionally, the total bone and tissue impaction of the germ makes first intention closure by the operator easier. However, according to *Waite and Cherala* [44], healing by primary intention can result in a „one-way valve effect that allows food debris to enter the socket but not easily escape", increasing the likelihood of alveolar socket infection [24, 37].

In conclusion patient age seems to be one of the crucial points [23].

b, Physical status

-Body mass index (BMI)

A patient is considered obese when their body weight is 20% or more above their ideal body weight. Obesity can be measured using the body mass index (BMI), which is calculated by dividing the body weight in kilograms by the height in meters squared (BMI = Wt/ht2) [51]. The study by *Miyazaki* and the study by *Brunello* investigated the relationship between BMI and DOI. The development of DOI was not significantly associated with the BMI index [37, 40, 51].

- Hypertension

The study by *Miyazaki et al.* investigated the relationship between hypertension and delayed-onset infection. Hypertension was defined based on a physician's diagnosis and was found to be highly correlated with delayed-onset infection in *Miyazaki's* analyses, whereas the patient's perioperative blood pressure was not. It is generally considered that hypertension is a risk factor for tooth loss due to periodontal disease [40, 52]. It is believed that elevated blood pressure may contribute to the spread of inflammation and secondary damage to the vascular endothelium [53]. These factors could potentially impact the development of delayed-onset infections, although the exact mechanism remains unknown. It should be noted that patients with severe uncontrolled hypertension and cardiac diseases should ideally receive treatment for these conditions prior to undergoing extractions [51].

- Diabetes mellitus

Two studies, conducted by *Sukegawa* and *Miyazaaki*, investigated the relationship between DM and DOI. Diabetes was defined as having an HbA1c level greater than 6.5% [6,40]. The studies found that DM was not significantly associated with DOI. In general, uncontrolled metabolic diseases, such as diabetes, are a relative contraindication for tooth removal until they are brought under control [51].

- Bisphosphonate

In *Miyazaki et al.*'s study, bisphosphonate treatment did not show a significant association with DOI [40]. It is important to note that patients taking bisphosphonates or other antiresorptive medications should be closely monitored and treated according to the latest guidelines [51].

- Corticosteroids

Immunosuppressants and corticosteroids are used for various indications, such as autoimmune diseases and organ transplantation. They impair the function of lymphocytes and decrease immunoglobulin production. Patients on medication, such as corticosteroids, require extra attention and should be treated according to the latest guidelines [54].

According to *Sukegawa et al.* and *Miyazaki et al.,* taking corticosteroids is not associated with an increased risk of delayed-onset infection [6, 40].

- Contraceptives

The additional oestrogen in oral contraceptives might raise plasma fibrinolysis [55, 56].

Although oral contraceptive use is frequently cited as a risk factor for complications after wisdom tooth extraction, studies by *Figueiredo et al.* and *Miyazaki et al.* investigating the relationship between DOI and oral contraceptive use did not find any association [34, 40, 55, 57].

- Chronic hepatitis

In the study by *Sukegawa et al.,* they found no significant association between chronic hepatitis and DOI. It is important to pay extra attention to patients with hepatitis and treat them according to the recent guidelines. Consultation may be necessary [6, 51].

- Smoking habits

Smokers are at a greater risk of suffering alveolar osteitis and other postoperative complications [39, 58].

The causal mechanism behind the observed effects remains partly unknown. However, it is possible that cytotoxic substances, such as nicotine, carbon monoxide, cotinine, and hydrogen cyanide, may be among the culprits [55, 59]. Nicotine, for example, may increase the risk of microvascular occlusion and tissue ischemia by increasing platelet adhesiveness [55, 60]. Another possible association is with catecholamine release, which can lead to vasoconstriction and decreased tissue perfusion [55, 60]. Moreover, the suction, the heat, and contaminants of smoking byproducts might compromise the healing potential of wound [55, 61]. On the other hand, lower fibrinolytic activities in tobacco users might undermine mechanisms responsible for dry socket formation, and thus might confound its influencing role [55, 62, 63, 64]. In conclusion smoking might damage healing mechanisms, suction the clot, affect blood vessels, and contribute to poorly filling of the socket with blood [55, 65, 66, 67].

Figueiredo et al. (2005) found that most patients with delayed-onset infection in their study were nonsmokers, with only one being a heavy smoker [39]. The authors concluded that smoking is not a risk factor for delayed-onset infection, despite smokers being at a greater risk of suffering from dry socket and other postoperative complications [58,68]. Other authors, such as *Brunello* and *Miyazaki*, have also found no association between smoking and this complication in their studies [37, 40].

- Alcohol consumption

Miyazaki et al. investigated the association between the development of DOI and alcohol consumption and found that alcohol consumption is not a risk factor for DOI. The study did not provide a clear definition of alcohol consumption, which is a crucial factor in the development of oral carcinomas [40, 69].

- Any presence of systemic diseases, drug intake

Brunello et al. analysed the potential relationship between patient-related characteristics, such as systemic diseases, drug intake, and late infection, but did not find any significant correlation [37].

It is crucial to consider the patient's medical history, as specific medical conditions and drug therapies may necessitate special prophylaxis in accordance with current guidelines and consultation.

c, Anatomical variables

- *Winter*-classification

As described in a previous chapter, *Winter*'s classification provides information on the inclination of the third molar in relation to the longitudinal axis of the second molar [10, 70].

Figueiredo et al. found that in relation to the *Winter* classification, 8 mandibular third molars had a mesioangular inclination, 2 had a vertical inclination, 2 had a horizontal inclination and 1 had a distoangular inclination. of the 13 infections. They were the first to suggest that lower third molars with a vertical or mesioangular tilt may be more likely to develop delayed-onset infections [39]

In the study conducted by *Brunnelo et al*., the teeth extracted from sites where a DOI developed in their sample were mesioangular in 4 out of 8 cases, according to the *Winter* classification. These findings were confirmed by other authors, who reported that mesioangular third molars were more prone to DOI [34, 37, 40].

- Distal space according to *Pell and Gregory*

Figueiredo et al.'s study was the first to highlight the importance of lack of space for eruption and the position of the lower third molar as a crucial risk factor for DOI [34].

Impaction of the third molar in the ramus is associated with a reduction in the distal space and this situation can lead to food impaction and a greater difficulty in maintaining proper

oral hygiene [44]. The purpose of the retrospective study by *Monaco et al.* was to investigate the relationship between delayed infection after lower third molar germectomy and the absence of space distal to the second molar. The study aimed to determine whether there is a correlation between these two factors. The study demonstrated a significant correlation between the lack of space (as per *P-G* II and III) and DOI, which is defined as an infection that occurs between 2 and 8 weeks after surgery [23,24].

In contrast to *Sukegawa et al.*'s study, which did not find any significant association between digital space and DOI [6].

- *Ganss* ratio

The lower the *Ganss* ratio, the higher the value class (1 to 3) according to *Pell and Gregory*. Therefore, this aspect partially repeats what was described earlier. Different publications use one or the other.

In their retrospective study, *Monaco et al.* aimed to investigate the potential relationship between the incidence of delayed onset infection and the space distal to the second molar. The study obtained the ratio between the distal space and the crown width, measured according to the *Ganss* protocol on panoramic radiographs, for 218 surgical germectomies performed for orthodontic reasons in 134 patients [23].

In previous studies, other factors such as osteotomy, tooth position, and sectioning have been found to be related to this type of infection. These variables are also associated with early infections [23, 29, 31, 43, 71, 72]. However, they are difficult to eliminate in patients with fully formed third molars. This was the reason for investigating this anatomical condition only in third molar germectomy.

The study investigated the extraction of third molar germs to eliminate variables such as tooth angulation and position, patient age, root anatomy, and relationship with the inferior alveolar canal.

The mean *Ganss* ratio was 0.40-0.20 in the group with delayed infection and 0.53-0.21 in the group without delayed infection, with a statistically significant difference between the

groups. In 16 out of 20 cases of delayed infection, the ratio between the distal space and the crown width was less than 0.5, according to their findings [23].

In conclusion, the study by *Figueiredo et al.* and *Monaco et al.* suggests that when the space distal to the second molar is extremely reduced (*Ganss* ratio <0.5, corresponding to *Pell and Gregory* class III), there is a higher likelihood of developing delayed infection due to food impaction [23, 34].

On the contrary, some other studies could not confirm the relationship between the lack of space distal to the second molar and the occurrence of DOI [6, 37].

- Depth of inclusion according to *Pell and Gregory*

Sukegawa et al. and *Myazaki et al.* found a correlation between the risk of postoperative infection in the mandible and the depth of inclusion [6, 40].

Figueiredo et al. suggested that deeper third molars (total bone retention and *Pell and Gregory* Class II, III and B, C) are more likely to become infected, indicating a relationship between surgical aggression, the amount of ostectomy, and the incidence of delayed-onset infection. Although the study did not find an association between ostectomy and this complication, the authors suggest that the amount of bone removal may be a risk factor. They propose that the magnitude of ostectomy is better expressed by other variables, such as bone retention or tooth sectioning, as deeper third molars often require this procedure [6,40]. In contrast, other authors have stated that the depth of the inclusion of mandibular third molars does not appear to increase the risk of delayed-onset postoperative infection [23, 37].

- *Nolla* stage, stage of stage of root formation

As described in a previous chapter, *Nolla*'s classification is used to standardise the stage of development of the tooth (from 1st to 10th) [20].

In the study by *Figueiredo et al.*, *Nolla* developmental stages were similar in both groups, with a median of 9 for patients with DOI and 10 for patients without DOI, but the difference was not statistically significant [34].

Brunello analysed the relationship between the stage of root maturation (germ, developed more than 1/3 of root, developed root) and the occurrence of DOI but did not find any significant correlation, although younger age seemed to be more often associated with this complication [37].

In conclusion, several studies have investigated the relationship between *Nolla* stage and the occurrence of DOI, but none of them have found a significant relationship [37, 39, 70].

- Mouth opening

Brunello et al. found no difference in mouth opening between patients with and without DOI. The median value was 47 mm for patients without DOI and 45 mm for those with DOI, as measured before surgery [37].

- Type of mucosal and bone retention

In the study by *Figueiredo et al.*, only one lower third molar did not present any soft tissue retention. Two were partially covered by mucosa, and eleven were totally covered by mucosa. Out of these 11 cases, eight were partially and three were totally covered by bone. In previous studies [41, 45], it has been found that over 70% of infections in the third molar site occur when the tooth is surrounded completely by bone, although this was not observed in the study conducted by *Figueiredo et al.* [34]. Specifically, in their study, only 3 out of 14 mandibular third molars (21%) presented with total bony impaction. It was suggested that total mucosal impaction may be a more significant risk factor. One possible explanation for these cases is that the wound is tightly closed, allowing germs to penetrate through the gingival sulcus of the adjacent second molar and evade oral hygiene measures. All infected patients had their second molar present, which confirms this theory [34, 39].

Other reports have also suggested that both total mucosal retention and bone retention are risk factors for delayed-onset infections [23, 24]. *Monaco et al.* suggest that complete impaction of bone and tissue of the germ facilitates first intention closure [23]. However, as described above, first intention healing may result in the 'one-way valve effect' described by *Waite and Cherala*, which allows food debris to enter the socket but not easily escape, increasing the likelihood of alveolar socket infection [23, 44].

d, Pathological variable

- Radiolucent lesion

The study conducted by *Figueiredo et al.* 14 recorded delayed-onset wound infections. Out of these, 7 cases were associated with a radiolucent lesion by the third molar. In 6 of these cases, the lesion was compatible with a paradental cyst, while in the remaining case, it was compatible with a follicular cyst. The size of the radiolucent lesions varied from 3 mm to 21 mm in diameter. The study considered smaller radiolucent lesions as nonpathological [39].

In the study, radiolucent lesions associated with the third molar were observed in half of the patients. The authors suggested investigating the role of these lesions in delayed-onset infections in future research [39].

However, other studies did not find any association between DOI and radiotransparent widened follicle [6, 23, 37].

- Second mandibular molar, caries of neighbouring tooth

In their studies, *Figueiredo et al.* and *Monaco et al*, as well as other investigations with DOI, found that all cases of delayed-onset infections were associated with a lower second molar adjacent to the infected site [23, 34, 39].

Figueiredo et al. state that total mucosal impaction, combined with the presence of the second molar, may be a risk factor. This could be due to the surgical wound being tightly

closed, which allows germs to penetrate through the gingival sulcus of the adjacent second molar. It is difficult to maintain oral hygiene at the surgical site under these circumstances [39]. *Sukegawa* analysed the relationship between second molar caries and infection. However, none of the infected cases presented carious lesions on the adjacent molar [6].

- Previous experience with pericoronitis, pain, or related symptoms, as well as indications for removal

In the sample by *Figueiredo et al..*, over 70% of infected patients did not exhibit any symptoms related to the lower third molar prior to surgery. However, they found a similar proportion of asymptomatic third molars in both the control and delayed-onset infection groups, albeit slightly higher in the latter. In *Christiaens'* study, all patients who experienced a late infection after tooth extraction had undergone the procedure for either prophylactic or orthodontic reasons [41]. *Brunello et al.'s* study found that only one out of eight patients with late infection had previous pericoronitis [37].

Therefore, it can be concluded that previous pericoronitis, prior history of pain, and ongoing infection at the third molar site at the time of surgery are not associated with the development of DOI.

e, Operative variable

- Experience, education level of the surgeon

Farhadi argues that a surgeon's experience cannot be fully measured by their education level alone, but rather by the number of surgeries they have performed. However, education level can still be a partial indicator of a surgeon's experience, as measuring experience can be challenging [73].

Postoperative complications have been reported to be associated with a surgeon's lack of experience [42]. *Christiaens and Reychler* reported that complications were more

frequent when the surgeon had less experience [41]. *Blondeau and Daniel* also suggested a correlation between a surgeon's lack of experience and postoperative complications [42]. In contrast, this aspect was statistically insignificant in the study by *Brunello et al.* investigating the occurrence of late infection [37].

In the study by *Miyazaki et al*., no significant difference in the delayed-onset infection rate was detected between the extractions performed by the residents and those performed by the specialists. The authors suggest that this result may be because all tooth removals were performed under the guidance of highly experienced oral and maxillofacial surgeons in their department [40].

It is unclear whether the rate of delayed-onset infections is related to the surgeon's ability, as stated by *Figueiredo et al.* [39].

- Duration of the surgery

Two studies investigated DOI and recorded the duration of surgery, defined as the interval between initial incision and final suturing, in patient records [23, 37].

Brunello et al. found a strong correlation between the length of the surgical procedure and the onset of late infections. Longer procedures were generally associated with full impaction, making extraction more complicated. The only significant difference among the recorded features at the time of surgery was the duration of surgery, which was longer for patients who developed a late infection ($p = 0.02$) [37].

In contrast, *Monaco et al.* found no difference in the length of surgery between the group with and without DOI [23].

- Ostectomy, tooth sectioning

The findings of *Monaco et al.* [23] regarding the importance of the lack of space distal to the second molar partially contradict the reports of several authors [37, 40], such as *Figueiredo et al*., who described an increased incidence of late infection associated with the need for osteotomy and sectioning [34].

According to *Monaco et al*., when there is a greater amount of retromolar space (more favourable *Ganss* ratio), the germ is positioned distal to the second molar instead of vestibular. This anatomical condition requires a greater sacrifice of bone distal to the second molar. Additionally, in these situations, there may be an overlap of the mucosal incision and bone window performed for germectomy. However, their study did not observe an increased percentage of delayed infection in these anatomical conditions that require more complex bone surgery [23,24].

The study found that the more difficult surgical extractions, which require more complex ostectomy and are performed in older patients (25 cases had a close relationship with the mandibular canal), were not associated with an increased risk of delayed infection as hypothesized by *Figueiredo* [23,34]. According to *Monaco et al.,* the less invasive germectomy procedure is associated with an increased incidence of late infection compared to the more complex extraction of a fully formed tooth [23]. According to the authors, the rationale for this approach is that the germs can be divided into four fragments along two perpendicular lines, allowing for minimal bone removal that is consistent across all cases. Additionally, complete impaction in the ramus during germ removal does not necessitate further osteotomy, as a small cortical window of approximately 3 × 6 mm can be created distobuccally to the second molar [23].

- Type of flap

Two authors investigated the type of flap as a possible risk factor for DOI. Neither of them found an association between flap design (no flap, envelope flap, triangular flap) and the occurrence of DOI [37, 39].

- Type of wound closure

According to *Figueiredo et al*. and *Monaco et al.,* this complication could be amplified by first intention closure. In the study by *Monaco et al.,* all cases achieved first intention healing within the first week postoperatively, except for one case in which wound dehiscence occurred [23, 34]. This type of healing, as described below, could result in the „one-way valve effect' that allows food debris to enter the socket but not easily escape”,

as first stated by *Waite and Cherala* [23, 44]. This situation increases the probability of alveolar socket infection. On the other hand, second intention healing has the advantage of a self-cleansing wound, making it less likely to result in infection [23, 44].

Waite and Cherala analysed data from 1280 third molar extractions performed using a 'V'-shaped flap with a releasing incision placed distal to the second molar and no sutures at the end of the surgery. The authors reported that secondary closure facilitated drainage from the alveolar socket and reduced infections related to food impaction [44].

Monaco et al. had 102 cases of partially impacted third molars in the older age group, and in these cases, they did not achieve primary closure. Late infection did not occur in this group, which achieved secondary intention healing. The authors hypothesize that a second intention healing, combined with increased space distal to the second molar, allows for a self-cleansing of the wound, as noted by *Waite and Cherala* [23, 44]. This, in turn, enables patients to maintain good hygiene distal to the second molar, resulting in a lower risk of food impaction [23].

- Oral Hygiene

Several authors have emphasized the importance of satisfactory oral hygiene prior to surgical procedures. Poor oral hygiene is considered one of the most significant factors that can influence the incidence of complications after third molar removal [25, 74].

However, no studies have been conducted to investigate the role of oral hygiene in the development of delayed infection.

- Sterile cooling water

In a case report, *Böttger et al.* investigated a delayed wound infection after the removal of a third molar. The causative organisms were identified using molecular methods. The bacterial spectrum of the causative infection could not be detected by standard culture and laboratory examinations. The microbiome 16S-rRNA gene analysis revealed a mixed bacterial infection dominated by Delftia and Alcanivorax (spp.), alongside other bacteria from the normal oral flora. The results, obtained through 16S-rRNA-gene analysis, next-

generation sequencing, and bioinformatics, led to the discovery of a new type of chronic wound infection after third molar surgery. The water-affine environmental bacterial strains of Delftia and Alcanivorax raise suspicion of infection from contaminated water from a dental unit. Therefore, *Böttger et al.* recommend performing osteotomies of teeth only with sterile cooling water [35].

- Simultaneous extraction of mandibular third molars on both sides and extraction of maxillary and mandibular third molars.

Sukegawa et al. discovered that extracting both the left and right mandibular third molars at the same time is significantly linked to a higher risk of delayed-onset infection. The authors noted that this procedure can result in more pronounced swelling and trismus compared to extracting a single tooth, which can lead to unsanitary conditions in the oral cavity. Retaining food residue in tooth extraction cavities, particularly in the posterior molar section of the mouth, strongly supports delayed-onset infection [6]. This risk factor was only identified in the study by *Sukegawa et al.* A subsequent report by the same authors was unable to confirm the previously reported association between simultaneous extractions and DOI. [40]. *Miyazaki et al.* (2023) found no significant difference in the delayed-onset infection rate between cases with simultaneous maxilla and mandible extraction [40].

- Intraoperative haemostatic treatment

Sukegawa et al. (2019) discovered a significant correlation between haemostatic treatment during mandibular third molar extraction surgery and postoperative infections. The need for haemostasis may be due to the difficulty in extracting the tooth or operator technique. The gelatine sponge used for haemostasis in the study may take about 4-6 weeks to absorb, which could promote infection [6, 75].

Miyazaki et al.'s study confirmed previous findings that intraoperative haemostatic treatment is significantly associated with infection development, including DOI [6]. The study used oxidized cellulose as a haemostasis agent. Other studies have also reported

susceptibility to infection in relation to the use of oxidized cellulose, which takes 2 weeks to absorb [40, 76].

To confirm their findings, it is hypothesized that bacteria can attach to any remaining haemostasis agent, potentially causing a late infection. Therefore, the authors recommend using only the minimum necessary quantity of a haemostasis agent, such as oxidized cellulose or gelatine sponge, and removing any excess once the haemostatic effect has been achieved. *Miyazaki et al.* note that the higher occurrence of late infections caused by haemostasis agent use may be attributed to selection bias, such as extractions with preoperative infection or more difficult extraction [40].

- Antibiotics, chlorhexidine

Various therapies aim to minimise postoperative complications following third molar extraction surgery. One of them is the use of systemic antibiotic prophylaxis to prevent postoperative infections. However, the use of antibiotics for this purpose is controversial [6, 30].

Antibiotics are typically prescribed to prevent postoperative infections, with immunodeficient patients being prescribed more antibiotics [77]. Antibiotic resistance has become a serious public health issue worldwide [78]. Even short-term or single-dose amoxicillin administration can reduce the number of strains susceptible to amoxicillin [40, 79, 80]. The optimal timing of antibiotic administration (preoperative, postoperative, or both) is not well established [40, 81]. According to a recent review, the best available evidence suggests that while antibiotic use can reduce surgical site infections, the reduction is not significant enough to outweigh concerns about adverse effects and antimicrobial resistance. Therefore, routine use of antibiotics cannot be justified [30, 40].

In a study by *Miyazaki et al*., short-term intraoral amoxicillin administration was applied to study patients, but it did not prevent the occurrence of DOI.

The study conducted by *Figueiredo et al*. was unable to evaluate the impact of antibiotics on the incidence of delayed-onset infection of the lower third molars due to over 90% of the patients receiving the same postoperative antibiotic [34]. On the contrary, another

study found that the prophylaxis group, who received 2g of amoxicillin 1 hour before surgery, experienced fewer delayed-onset infections compared to the control group [82].

Chlorhexidine is commonly used as a rinse and gel to prevent complications, particularly alveolar osteitis [26]. However, its general use in the oral cavity can cause mild side effects. In addition, direct socket irrigation has recently been associated with fatal adverse reactions caused by hypersensitivity [83]. Due to the risk of hypersensitivity, many authors suggest using saline instead of chlorhexidine as the preferred intra-alveolar irrigant to prevent and manage inflammatory complications, such as alveolitis [26].

It should be noted that chlorhexidine and other antiseptic mouth rinses may also play a significant role in preventing late infections. However, since all patients in several DOI studies were prescribed chlorhexidine, it was not possible to draw any conclusions regarding its role in these infections.

The authors suggest that further research is necessary to determine the proper perioperative administration of antibiotics and antiseptics in wisdom tooth extractions [34, 40].

Several studies have investigated the possible association between various operative variables, such as sedation, proximity to the inferior alveolar nerve, postoperative paraesthesia of the inferior alveolar nerve, and postoperative cortisone, and the occurrence of DOI. However, none of these studies found any significant results [6, 37, 40].

f, Clinical features recorded at suture removal

- Dehiscence

  Dehiscence can be defined as "separation between buccal and lingual mucosa, after primary closure of the wound" [84].

  Mucosal closure under tension, failure to remove the sulcular epithelium around the wisdom teeth and lack of bony support below the suture line will result in wound

dehiscence. This explains why primary wound closure after removal of mandibular third molar leads to more pain and trismus in comparison with secondary healing, in which the surgeon intentionally creates 5-6 mm of gap in the mucosa distal to the mandibular second molar. According to *Rahpeyma et al.*, surgeons prefer to deal with an established large and self-cleaning dehiscence (intentionally creating a 5-6 mm gap in the mucosa distal to the mandibular second molar by secondary closure) rather than wound breakdown after soft tissue flap closure under tension, which may result in a small dehiscence (3-4 mm diameter). A large dehiscence has a greater chance of self-cleaning, whereas a small dehiscence may cause discomfort to the patient due to entrapment of food and bacterial fermentation products [84].

In the study conducted by *Monaco et al.*, all 20 cases of delayed-onset infection achieved first intention healing after suture removal (7 days after extraction) [23]. In the study conducted by *Brunello et al.*, only one out of the eight cases with delayed-onset infection had dehiscence at the time of suture removal [37]. Other studies did not analyse the association between DOI and wound dehiscence.

- Pus

In the study by *Brunello et al.* the presence of pus was recorded at the time of suture removal in one of the patients who developed DOI ($p = 0.04$). None of the other variables recorded at the time of suture removal were statistically different between patients who developed late infection and those who did not. Other studies have not found an association between pus recorded at the surgical site as a variable and the occurrence of DOI [37].

Brunello et al. also investigated the possible association between other clinical features recorded at the time of suture removal (e.g. lymph node enlargement, pain on palpation, bleeding and alveolitis) and DOI [37]. However, no association was found.

1.3.5. Treatment

The management of wound infection after lower third molar extraction is not well defined in the dental literature, with most studies focusing on the prophylactic use of antibiotics after third molar extraction rather than the management of established infections [47, 86]. However, it is widely accepted that oral antibiotics are usually the treatment of choice for such complications [23, 38]. According to *White et al*, only a small proportion of patients are expected to require additional surgical intervention, such as wound reopening (1%) or debridement (7%) (Figure 7.) [38, 85]. However, the study by *Figueiredo et al*. shows that delayed-onset infections should be considered as a separate entity, as one third of patients required such surgery. Nine out of 16 patients (56%) who had an infectious complication around 30 days after extraction required both pharmacological and surgical therapy. According to the authors, when antibiotics alone are ineffective, removal of granulation tissue from the socket, debridement of any bone particles, and removal of any foreign bodies are critical factors in the success of treatment. This study also claimed that amoxicillin/clavulanate and clindamycin had similar results in the treatment of delayed onset infections, being effective in two thirds of patients. Metronidazole could be considered a good option for the treatment of post-operative infections, especially when gram-negative anaerobic bacteria are involved. However, it should be noted that this antibacterial drug should be combined with another antibiotic, mainly because of its reduced activity against gram-positive aerobic bacteria [46, 87].

Figueiredo et al., in another clinical study, found that Fusobacterium species, Prevotella species and Peptostreptococcus species were frequently present in late infections after lower third molar removal when postoperative amoxicillin was administered. Based on the results of microbial susceptibility testing, clindamycin appeared to be the most appropriate antibiotic for the treatment of DOI [46].

Recent studies have also confirmed that the treatment of choice in most cases is systemic antibiotics (usually amoxicillin-clavulanate) and local antimicrobial mouthrinses (e.g. chlorhexidine 0.2%). If antibiotic treatment fails, surgical debridement of the extraction site is required [6, 40].

Figure 7. The drainage of purulent inflammation using a gauze strip impregnated with iodoform (Source: Personal)

1.3.6. Prevention

Infection control and prevention is one of the most important steps in surgery, but unfortunately, we do not find many well-defined measures for the prevention of delayed onset infections in the literature [73].

In the study by *Figueiredo et al*., all infected patients received prophylactic postoperative antibiotic treatment and chlorhexidine mouthrinses, which failed to prevent delayed-onset infections in 1.5% of cases. However, it was not possible to assess the effect of antibiotics on the rate of delayed-onset infection of the lower third molars because more than 90% of the operated patients received the same postoperative antibiotic. However, as all patients were discharged without symptoms and an infection developed after several weeks, antibiotics do not appear to be useful in preventing late infections, although antibiotics may be effective in preventing early type postoperative infections [30, 39]. The reason for this may be that the effects of the antibiotic and antiseptic have completely disappeared after 3 to 5 weeks [39].

Figueiredo et al. concluded that the probable cause of delayed infection is a dead space under the soft tissue. If their theory is correct, infection could possibly be avoided by not performing primary wound closure. Several authors have also suggested that leaving the extraction socket open or with a tube drain may reduce other postoperative complications such as swelling [38, 88, 89].

According to *Monaco et al.*, a second intentional healing may have the advantage of a 'self-cleaning' wound and therefore be less likely to result in infection [23,44]. The study by *Waite and Cherala* analysed data from 1280 third molar extractions performed with a 'V' shaped mucoperiosteal flap with a releasing incision placed distal to the second molar and no sutures at the end of surgery. The authors concluded that secondary closure facilitated drainage from the socket and reduced food impaction-related infections [44].

According to *Monaco et al,* considering the results reported by *Waite and Cherala,* it may be more appropriate to use a sutureless technique to achieve a more "self-cleaning" socket when distal space is lacking [23,44].

In addition, tight sutures, when the third molar is completely covered by the anterior border of the ramus, may result in tissue traction that determines partial coverage of the distal part of the second molar [23].

According to *Monaco et al,* in bilateral impaction cases, the surgeon should remove the second molar after a longer recovery period (45-60 days) to reduce the risk of late infection. When the space distal to the second molar is severely reduced (e.g. Pell Gregory class III), self-cleaning of residual food is particularly difficult and the recommendation to avoid chewing solid food on the operated side for at least 4-6 weeks may be useful to reduce the incidence of late infection [23].

2. Objectives

Immediate or early complications after third molar surgery have been studied extensively, but most clinical studies have focused on inflammatory complications up to the point of suture removal and then ceased to follow patients. Delayed-onset infection is a rare postoperative complication. Although DOI has been published by several articles, the literature is still incomplete and contains some contradictory information. The main aim of our present study was to determine the incidence and predisposing factors of DOI at Semmelweis University Faculty of Dentistry, Department of Oro-Maxillofacial Surgery and Stomatology. In addition, we aimed to review and supplement existing data on delayed-onset infections after third molar surgery.

Our specific aims were:

- To detect delayed-onset wound infections occurring after suture removal retrospectively in patient records

- To describe the main clinical features of infected patients

- To describe the management of patients with DOI

- To determine the incidence of DOI

- To identify the predisposing factors for DOI

- To revise and supplement existing data on DOI.

3. Materials and methods

3.1. Study design

The participants in the study were selected from among 1.102 outpatients who underwent surgical removal of lower wisdom teeth between January 2013 and June 2018 in the Semmelweis University Faculty of Dentistry, Department of Oro-Maxillofacial Surgery and Stomatology. There were patients who had both lower wisdom teeth removed during this period. Thus, in total, we reviewed the documentation of the removal of 1.349 lower wisdom teeth of these 1.102 outpatients, searching for the presence of late inflammation. All operations were performed under local anaesthesia by surgeons with the same professional experience (K.K., K.Cs., and A.J.-F.). Based on our preliminary results, late inflammation only occurred among healthy, non-smoking patients under the age of 26.

The case-control study revealing predisposing factors was therefore conducted among such healthy, non-smoking patients under the age of 26.

The case group consisted of 17 patients with late inflammation (there were no patients with this complication on both sides). The control group was narrowed down to healthy, non-smoking patients under the age of 26 who did not develop late inflammation. We identified 403 such patients, who had 622 lower wisdom teeth removed. The control group was further narrowed on the condition that only one side (the previously operated one) was included in the study control group for each patient, and the existence of appropriate patient documentation was a criterion (including that the patient's panoramic x-ray was found in the system). Thus, in the case-control study, we compared a total of 206 lower wisdom teeth of 206 patients with 17 lower wisdom teeth of 17 patients with late inflammation [9].

In DOI patients, we also described the clinical features of the late inflammation, as well as the treatment used.

The study protocol was approved by the local ethics committee of the Medical Research Council/Hungary (6428-1/2018/EKU) and was conducted in full accordance with the Declaration of Helsinki.

3.2. General protocol for care

All operations were performed according to the protocol of our clinic by surgeons with the same level of professional experience (K.K., K.Cs., and A.J.-F.). Before the intervention, an orthopantomogram was taken of the patients. They gave written consent to the surgery and to the use of individual data. If specific high-risk signs were observed on panoramic images, cone beam computed tomography was prescribed (Figure 8.) [9, 91, 92, 93].

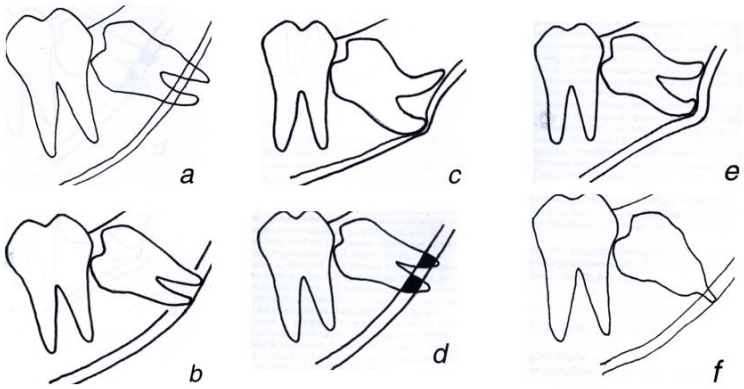


Figure 8. Specific panoramic high-risk signs [92, 93]

Based on the documentation, no inflammation was detected in the surgical area either in the 3 weeks before the surgery or during the surgery. If the patient had poor oral hygiene, the intervention took place after oral hygiene treatment. Only one lower wisdom tooth was removed at a time. The procedure was performed under local anaesthesia (2% lidocaine solution with epinephrine at a dilution of 1:100,000). The surgical field and all surgical materials were sterile. An L-shaped, full-thickness flap was prepared. Sterile, low-speed (40,000 rpm) handpieces and sterile saline were used to ostectomy and, if necessary, separate the tooth [9].

Wounds were closed with 3-0 or 4-0 Supramid sutures (B. Braun, Melsungen, Germany) by applying 3 simple sutures and 1 horizontal mattress stitch. If the crown of the wisdom

tooth was present in the mouth, no primary wound closure was performed at the place of this coronal part.

Nonsteroidal anti-inflammatory drugs (50 mg diclofenac, maximal dose 3 x 1) and mouthrinse (0.2% chlorhexidine digluconate every 12 hours for 7 days) were prescribed for all patients postoperatively. The indication and type of antibiotic was determined by the surgeons (300 mg clindamycin 4 x 1 for 4 days or 875 mg amoxicillin and 125 mg clavulanic acid 2 x 1 for 7 days). There was no standard protocol for this.

Patients also received standard postoperative recommendations regarding physical therapy, appropriate diet, and the avoidance of smoking [9].

Sutures were removed on postoperative day 7. Patients were requested to report any complaints in person at the clinic.

In case of late inflammation, a control panoramic X-ray was taken to rule out the presence of a residual root fragment (Figure 9.).

Figure 9. Panoramic radiography, 28 days after the removal of tooth 48 (Source: Personal)

For cases of purulent swelling, incision and iodoform drainage were applied (Figure 10., 11., 12., 13.). In the case of late inflammation, the indication and type of antibiotic were determined at the surgeon’s discretion (300 mg clindamycin 4 x 1 for 4 days or 1000 mg

amoxicillin and clavulanic acid 2 x 1 for 7 days). If the inflammatory complaints did not resolve within 7 days despite the previously detailed conservative therapy and, where applicable, incision and drainage, the surgical area was excochleated [9].

Figure 10. 20 days after the removal of tooth 48, the patient developed swelling, tension, and mild pain on the right side of her face. (Source: Personal)

Figure 11. When pressure is applied to the retromolar area, pus is discharged distally from tooth 47. (Source: Personal)

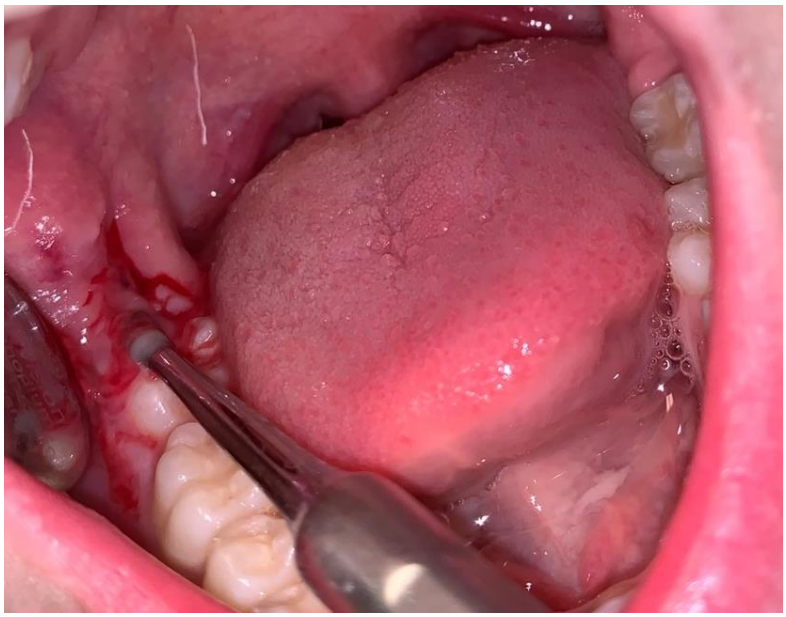


Figure 12. Incision, entering of the previous surgical site (Source: Personal)

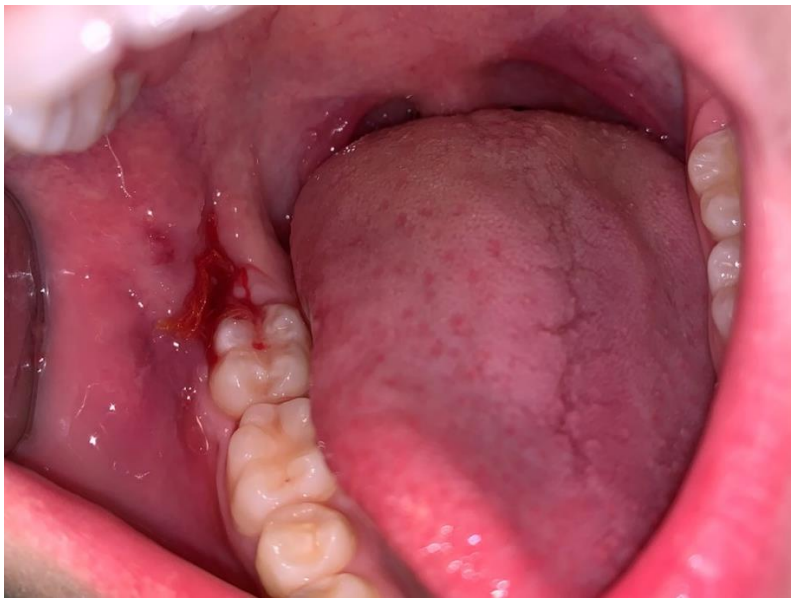


Figure 13. After irrigation, iodoform gauze strip was inserted. After 3 days of treatment, the patient became symptom-free, antibiotics were not needed in this case. (Source: Personal)

3.3. Data extraction

Clinical records were reviewed by 3 researchers (I.K., A.R.T. and A.B.). DOI was retrospectively diagnosed when swelling of the operated area or face, presence of purulent discharge, or trismus was recorded in the patient documentation that began at any time after suture removal (1 week postoperatively).

If DOI occurred, the following information was registered: the length of time between the surgery and the occurrence of complications, sufficiency of antibiotic therapy or application of drainage during the recovery period, and necessity of excochleation of the surgical site [9].

For all 223 surgeries of the case-control study, we collected data on sex, age, prior history of pain or infection, type of angulation (*Winter*'s classification [10]), depth of the impaction (Pell-Gregory classification [l5]), relationship of the tooth to the anterior border of the ramus of the mandible (Pell-Gregory classification, *Ganss* ratio; Figure 1 [16]), soft tissue coverage of the tooth (not covered, partially covered, or fully covered), bone coverage of the tooth (not covered, partially covered, or fully covered), development of the lower third molar (*Nolla* stage; Figure 2 [20]), presence of radiotransparent lesions measuring 3 mm or more associated with the lower third molar, presence of the adjacent lower second permanent molar, carious lesions of the adjacent lower second permanent molar, and the application and type of postoperative antibiotic prophylaxis. Data regarding surgeries were retrieved retrospectively from patient records and the panoramic radiograph database of the clinic and entered into an electronic database over the course of the study using Microsoft Excel (Microsoft, Redmond, Washington, United States) [9].

3.4. Statistical analysis

The normality of scale variables (patient age, *Nolla* stage of the extracted lower third molar, and time elapsed from extraction to infection onset) was assessed using the Shapiro-Wilk test. When normality was violated, medians were calculated. The Mann-Whitney U test and Fisher's exact test were used to compare groups. Values with $P < .05$

were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM, Armonk, New York) software. Statistical tests are indicated in the tables [9].

4. Results

DOI occurred after 17 surgeries (1.15% of 1349 outpatient wisdom tooth surgeries) performed by the 3 surgeons between January 2013 and June 2018. On average, 29.5 days elapsed before complications occurred. The number of days that elapsed after surgery ranged from 20 to 80. The youngest patient with DOI was 15 years old, and the oldest was 25 years old. The mean age was 18.1 (standard deviation, 2.5) years (Figure 14.) [9].

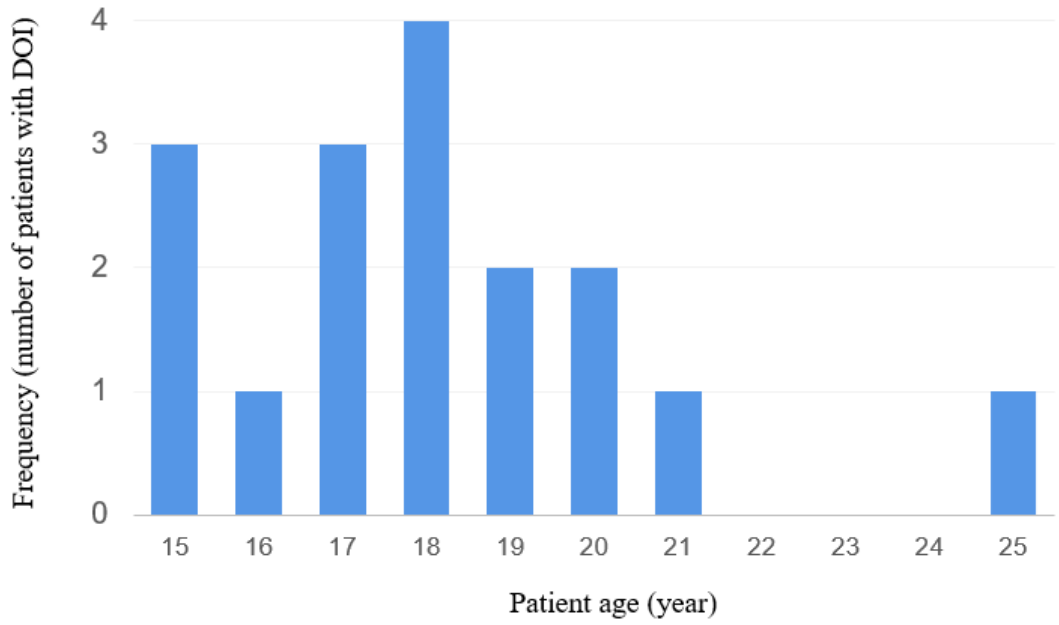


Figure 14. Relationship between patient age and DOI

DOIs were observed in 7 male patients and 10 female patients. During treatment for DOIs in cases of purulent swelling, intraoral opening of the abscess and iodoform drainage were applied. Transcervical drainage was deemed unnecessary. Ultrasound or CT was not needed during the diagnostical procedure, and there was no need for hospitalisation or emergency airway management. In 2 cases, opening of the local abscess at the previous surgical site, drainage, and daily lavage were sufficient for healing. For these patients, antibiotic treatment or excochleation was deemed unnecessary. The indication and type of antibiotic were determined according to the surgeon's discretion (300 mg clindamycin 4 x 1 for 4 days or 1000 mg amoxicillin and clavulanic acid 2 x 1 for 7 days). In 7 cases, antibiotic therapy (amoxicillin and clavulanic acid in 4 cases and clindamycin in 3 cases) alone proved sufficient [9].

In 6 cases, antibiotic therapy (amoxicillin and clavulanic acid in 4 cases and clindamycin in 2 cases) with intraoral drainage proved sufficient. In 2 patients, the complications persisted over 7 days after antibiotic therapy (1 case each after prescribing amoxicillin and clavulanic acid therapy or clindamycin therapy); in these patients, the surgical site had to be reopened, and excochleation was performed.

In the 15 to 25-year-old age group of the case-control study, complications tended to occur in younger patients. The mean age of patients with complications was 18.1 (standard deviation, 2.5) years. The mean age of control subjects was 21.0 (standard deviation, 2.7) years. The median age was significantly older in the control subjects (21 years) than in the patients (18 years) (Table 1.). No significant differences were observed regarding sex, associated radiolucent lesions, prior history of pain or infection, or administration of preventive postoperative antibiotics between patients with and without infection (Table 1.)[9].

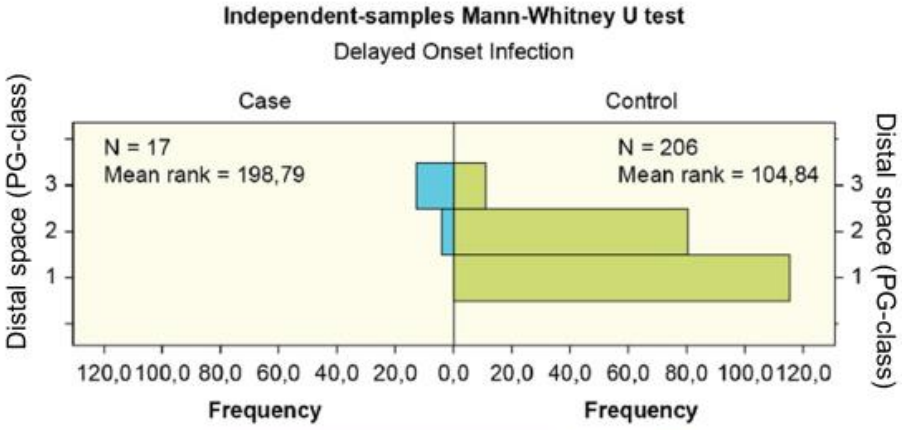
All cases in the DOI group presented with a lower second molar adjacent to the infected site, which did not exhibit caries lesions based on the panoramic x-rays. No significant differences between the case and control groups were observed in this regard (Table 1.) [9].

Table 1. Characteristics of groups with and without DOI [9]

		Case	Control	Bivariate (P)
Mean age (year)		18.1	21.0	<.001 *2
Sex	Male	7 (41,2%)	68 (33.0%)	.594 *3
	Female	10 (58,8%)	138 (67.0%)	
Radiolucent lesion	Present	2 (11,8%)	17 (8,3%)	.644 *1
	Absent	15 (88,2%)	189 (91,7%)	
Prior history of pain	Present	0	36 (17,5%)	.082 *1
	Absent	17 (100%)	170 (82,5%)	
Second molar	Present	17 (100%)	203 (98,5%)	1.000 *1
	Missing	0	3(1,5%)	
Second molar caries	Present	0	9 (4,4%)	1.000 *1
	Absent	17 (100%)	197 (95,6%)	
Postoperative Antibiotic	No	2 (11,8%)	38 (18,4%)	.622 *1
	Amox.-clav. or clindamycin	15 (88,3%)	168 (81,5%)	
	Amox.-clav.	7 (41,2%)	60 (29,1%)	
	Clindamycin	8 (47,1%)	108 (52,4%)	

*1: Fisher's exact test, *2: Mann-Whitney test, *3: χ^2 test

Lower third molars with a mesioangular direction were more prone to developing complications (Fisher's exact test, 13.178; P = .002) (Table 2.). The frequency of complications was higher for cases in which the molar was fully covered with soft tissue (P < .05). The soft tissue impaction ratio was greater for cases (median, 3, fully covered) than for control subjects (median, 2, partially covered) (Table 2.). Complete bony impaction was more frequent in cases with complications than in control subjects (P < .05) (Table 2.). Patients with *Pell-Gregory* class III were more prone to developing complications (Figure 15., Table 2.) [9].



Total N	223
Mann-Whitney U	275,500
Wilcoxon W	21 596,500
Test statistic	275,500
Standard error	229,850
Standardized test statistic	–6,419
Asymptotic sig. (2-sided test)	,000

Figure 15. Distal space according to *Pell-Gregory* classifications among patients and control subjects [9]

Most cases belonged to class B, which indicated a deeper impaction ($P < .05$). The *Mann-Whitney* U test revealed that the depth was greater for cases (median, 2, *Pell-Gregory* B) than for control subjects (median, 1, *Pell-Gregory* A) (Table 2.). The mean *Ganss* ratios were 0.47 ± 0.17 and 0.96 ± 0.28 in the group with DOIs and the group without DOIs, respectively; the difference between groups was statistically significant ($P < .001$, *Mann-Whitney* U test) (Table 2.) [9].

The *Mann-Whitney* U test indicated that the *Nolla* stage was greater for control subjects (median, 8) than for cases (median, 7) (Table 2; Figure 16., Figure 17., Figure 18.).

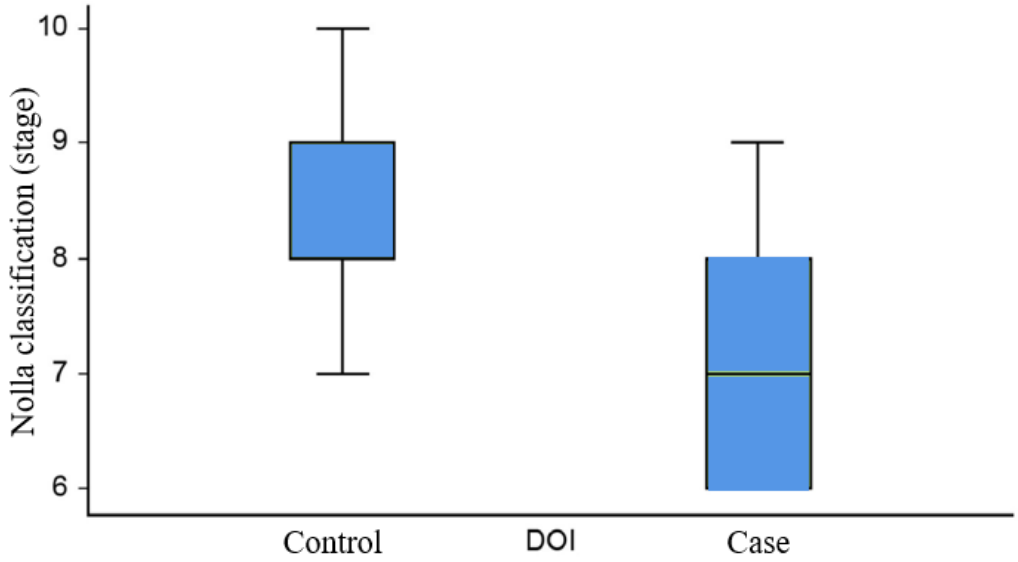


Figure 16. *Nolla* stages of control patients and patients with DOI [9]

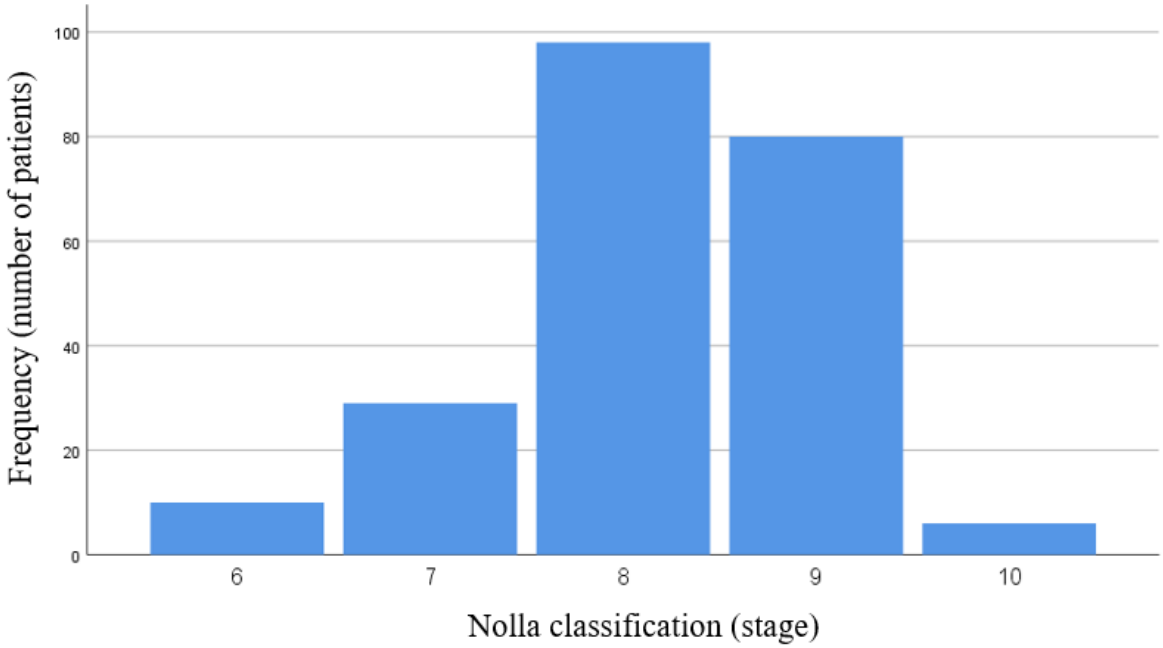


Figure 17. *Nolla* stages among patients without DOI

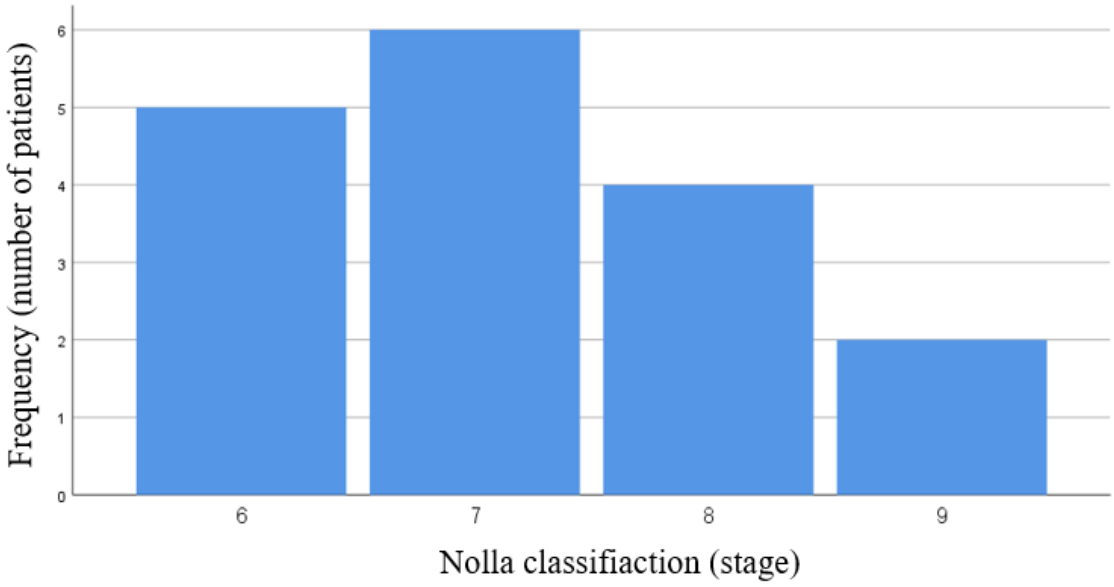


Figure 18. *Nolla* stages among DOI cases

Table 2. Results of the variables [9]

		Case	Control	Bivariate (P)
Angulation	Vertical	0	74 (35,9%)	.002 *1
	Mesioangular	13 (76,5%)	90 (43,7%)	
	Distoangular	0	12 (5,8%)	
	Horizontal	4 (23,5%)	30 (14,6%)	
Soft tissue retention	No	0	22 (10,7%)	<.001 *2
	Partial	0	105 (51%)	
	Total	17 (100%)	79 (38,3%)	
Bone retention	No	0	47 (22,8%)	.001 *2
	Partial	13 (76,5%)	153 (74,3%)	
	Total	4 (23,5%)	6 (2,9%)	
Depth of inclusion	A	2 (11,8%)	122 (59,2%)	<.001 *2
	B	14 (82,4%)	83 (40,3%)	
	C	1 (5,9%)	1 (0,5%)	
Distal space	I	0	115 (55,8%)	<.001 *2
	II	14 (23,5%)	80 (38,8%)	
	III	13 (76,5%)	11 (5,3%)	
Mean Ganss ratio		0.47 ± 0.17	0.96 ± 0.28	<0.001 *2
Nolla (median)		7	8	<.001 *2

*1: Fisher's exact test, *2: Mann-Whitney test, *3: χ^2 test

5. Discussion

A seminal study by *Osborn et al.* referred to delayed-onset complications as secondary infections. They reported that most secondary infections occurred in a group of patients between 12 and 24 years old [36]. In our study, the mean age of patients with DOIs (18.1 years) is in accordance with these data. The occurrence of late complications differed according to patient age. In our study, the 1.15% occurrence of late complications approximated the value of 1.5% reported by *Figueiredo et al*. but was lower than the value of 3.7% reported by *Brunello et al.* and the value of 9.17% reported by *Monaco et al.* [23, 37, 39]. *Monaco et al*. examined wound healing in patients after the removal of 134 lower third molar tooth germs [23]. Only 0.9% of young patients developed inflammatory complications within 1 week after the extraction. A high proportion (9.2%) of patients developed inflammation after suture removal. One reason for this discrepancy could be that only third molar tooth germ removal in patients with a mean age of 15 years was studied by *Monaco et al.* [23]. In our study, the mean elapsed time to the development of complications was 30 days. In a study by *Christiaens and Reychler* [41], 75% of infections developed earlier (after 2-3weeks), but most sources in the literature [23, 34, 37, 38, 39, 46] have reported a period of 25-35 days, which agrees with our work. In a large prospective study of 9574 patients who underwent a total of 16,127 mandibular third molar extractions, *Osborn et al.* reported that most secondary infections (66%) developed between 15 and 60 days after surgery [9, 36].

In contrast with our findings, *Monaco et al.* Reported that the male-to-female ratio was a significant predictor [23]. Similar results were observed in studies by *Figueiredo et al*., in which delayed infections occurred twice as frequently in female patients [34, 39]. We agree with the statement by *Monaco et al.* [23] that several factors such as anatomic factors or hormone levels could influence the onset of infection. Therefore, it is difficult to fully explain the findings based on sex [23]. All infected patients underwent surgical removal for prophylactic or orthodontic purposes. None of the patients had any previous episodes of pain or inflammation before extraction. This result is in accordance with previous reports [23, 34, 37, 38, 39, 46]. Patients with DOI risk typically do not have previous complaints such as pericoronitis due to total mucosal retention [23].

Figueiredo et al. reported that half of the patients with DOIs presented with radiolucent lesions associated with the third molar [39]. They suggested that the role of these lesions in DOIs should be investigated [39]. However, other similar studies did not confirm that the presence of radiotransparent widened follicles was a risk factor, in accordance with our findings [23, 34, 37]. Like previous authors [23, 34], we did not observe a significant difference in preventive postoperative antibiotic treatment between infected patients and control subjects. It has been suggested that changes in oral flora caused by systemic and topical antibacterial therapy may favour subsequent development of opportunistic infections [39]. *Piecuch et al.* investigated the infections occurring after third molar removals. When perioperative antibiotics were applied, 2.58% of patients developed delayed infections. In contrast, 1.2% of patients were diagnosed with DOIs when antibiotics were not applied [86]. Therefore, perioperative pharmacologic therapy does not seem to be a decisive factor in the development of late infections. Nevertheless, with the right indications, they may be effective in preventing early postoperative infections [9, 94].

Anatomic factors play a key role in the aetiology of complications [23, 34, 37, 38, 39, 46]. In cases of germectomy, the tooth is fully covered with bone. In such cases, the surgeon typically applies per primam closure of the wound. First intention healing has the advantage of better control of reactionary bleeding but concurrently determines a "one-way valve effect that allows food to enter the socket but not easily escape," as stated by *Waite and Cherala* [23,44]. This situation results in an increased risk of socket infection because food or debris may become trapped under the mucosa through a "one-way" door more easily, thereby acting as a substrate for bacteria. This material cannot be removed, and inflammation may develop at the surgical site [23, 34, 45]. A possible pathway for bacteria is the gingival sulcus of the adjacent second molar [34, 39]. In our study, all patients with DOIs presented with a lower second molar adjacent to the infected site, which supported this theory. In accordance with the results of *Figueiredo et al*., we observed that mesioangular third molars were more prone to develop late infections. This could also explain the theory described above, because the crown is in close approximation to the root of the adjacent second molar. *Figueiredo et al*. analyzed the *Nolla* stage of teeth with DOIs and obtained 8 as the median *Nolla* stage [39]. In our study, the *Nolla* stage of patients with infected lower third molars were significantly lower

than that of control subjects. Less developed tooth germ is covered entirely by the anterior border of the ramus in the most cases. This anatomic condition favours the development of DOIs after third molar removal. Previous studies have demonstrated that age and anatomic positions of teeth are the most decisive factors in the development of complications [23, 34]. We identified full soft tissue coverage, larger bone coverage, mesioangular direction, and a lack of space behind the third molar as the most important predisposing factors. These conditions play a major role in the aetiology of the theories described above [9].

Based on our data, we observed that antibiotic treatment and intraoral drainage for cases of purulent swelling were sufficient therapeutic modalities for 88% of patients. In the remaining 12%, complaints persisted after 7 days. Therefore, the surgical site had to be reopened, and excochleation was performed. Previous studies reported that surgical revision of infected sites was necessary in 10%-50% of cases [23, 34, 37, 46]. In 2 cases, intraoral drainage of the local abscess at the previous surgical site and daily lavage were sufficient for healing. For these patients, antibiotic treatment and/or excochleation were unnecessary. In general, we can establish that patient age, and thus the anatomic situation of the impacted third molar, seems to be the crucial points in the development of DOIs [9].

Owing to the increase in frequency of prophylactic procedures, the mean age of patients undergoing third molar removal is decreasing. Third molar development is typically incomplete by the age of 20 years because teeth tend to attain their final positions later in life. During early development, the third molars are located deeper, and the retromolar space increases only at an older age (>20 years). If the third molars are removed during this period, wound healing is adversely affected, and cleaning of the wound becomes more complicated. Because of the anatomic position, oral hygiene measures (especially chlorhexidine mouthrinses) for that area are not sufficiently effective. This does not pose problems during the early postoperative period but may be a causative factor of delayed infections [9, 23, 24, 34, 39].

Infection control and prevention is one of the most important steps in third molar surgery [73]. We could not study different methods to prevent DOI, if such exits at all, but we

could study the literature and think about how to contribute to the prevention of such infections, even if only theoretically now.

First, we would like to emphasise that oral hygiene must be adequate before wisdom tooth surgery, as with other elective surgical procedures [25]. In our study, the patients had good oral hygiene; if not, the surgery was performed after oral hygiene treatment in another department.

The fact that postoperative infections are more likely to occur in deeply impacted third molars was also demonstrated in our study. This may indicate that surgical invasion and the amount of alveolar bone ostectomy are related to the incidence of postoperative infection. Infections can be reduced by using proper surgical techniques [73]. One of the tools could be tooth sectioning, which aims to reduce the amount of bone surgery, making the procedure more minimally invasive (Figure 19.).

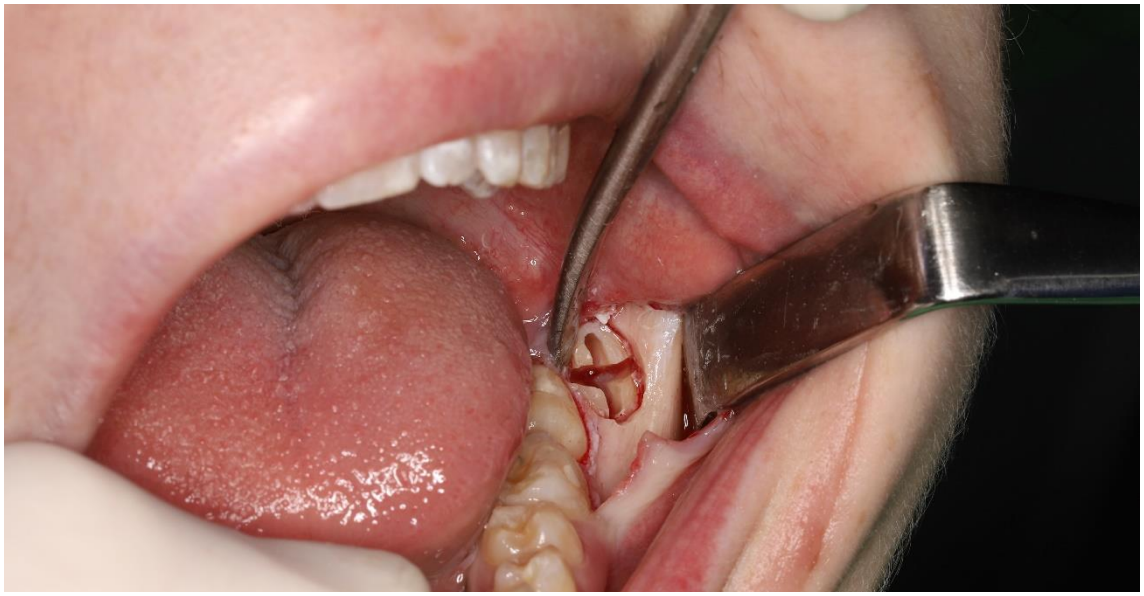


Figure 19. Minimally invasive tooth extraction (Source: Personal)

As mentioned above, antibiotics and antiseptics do not appear to be useful in preventing late infections, although they may be effective in preventing early postoperative infections [30, 39]. The effects of these antimicrobial agents may disappear after several weeks postoperatively [39].

Many authors suggest that the probable cause of delayed infection is a dead space beneath the soft tissue. If their theory is correct, infection could be avoided by not performing primary wound closure, leaving the extraction socket open, or using a tube drain [38, 88, 89]. The study by *Waite and Cherala* analysed data from 1280 third molar extractions performed with a V-shaped mucoperiosteal flap with a releasing incision placed distal to the second molar and no sutures at the end of surgery. The authors concluded that secondary closure facilitated drainage from the socket and reduced food impaction-related infections [44]. In conclusion, secondary intentional healing may be beneficial, creating a 'self-cleaning' effect that may be less likely to result in infection [23, 44, 46].

Additionally, tight sutures can result in tissue traction when the third molar is completely covered by the anterior border of the ramus (typically in tooth position *P-G* III), which may cause partial covering of the distal part of the second molar. This clinical situation may promote the development of delayed-onset infection [23]. Eliminating this „gingival hypertrophy" distally from the second molar may help prevent infection.

By performing gingivoplasty on the retromolar area or using a combined suture to stabilize the flap beneath the second molar's equator and counteract muscular forces, the surgeon may achieve this [70, 97].

In terms of flap design, it may be worthwhile to investigate the triangular transposition flap (TTF) or the buccal mucosal-advancement flap (BMAF) in studies that monitor patients after suture removal. To prevent food from getting trapped, these flap designs could be used to create a better seal over the socket [84, 98]. By TTF the vertical release is placed at distobuccal line angle of second molar. At the end of the operation, during the suturing, the TTF is not sutured to the initial site, but it is transposed to cover the extraction socket [84].

BMAF combines the advantages of both primary and secondary closure, as noted by some authors. The primary closure achieved by this flap design maintains a seal over the socket, preventing complications such as food accumulation and delayed healing. Preventing dehiscence requires adequate undermining and mobilisation of the flap and closure without tension. The patent vertical release facilitates adequate drainage and incorporates the advantages of secondary closure, such as reduced pain, oedema, trismus, alveolar osteitis, and infection [98].

The literature has been studied for filling the alveolus with a PRF clot, but no data was found regarding its effectiveness in preventing DOI [99]. Conducting a study on platelet-rich fibrin with patients at risk of DOI and monitoring them over the long term could provide further information in this context.

We also agree with *Monaco et al.* who suggest that, in cases of bilateral tooth impaction, the second germ should be removed after a more prolonged recovery period (45-60 days) to reduce the risk of late infection. For patients at risk of delayed-onset infection, it may be useful to follow the recommendation of not chewing solid food on the operated side for at least 4-6 weeks [23].

To gain a better understanding of delayed-onset infections, we recommend extending the observation time of clinical trials and properly document late inflammations. However, to gain insight into the prevention of complications, prospective studies investigating wound healing after third molar removal would be more appropriate. These studies should not exclusively focus on late inflammation but should monitor patients in the long term.

5.1. Limitation of the study

Limitations of our study include its retrospective nature, limited number of patients with this complication, and criteria used to define DOIs (predominantly based on clinical observations). Methods such as the measurement of acute-phase protein blood levels may provide more objective detection of infections [9, 95, 96]. Other limitations include the lack of specific protocols for antibiotic prescription and surgery duration, amount of bone removal, and tooth sectioning, which were not documented in patient records. However, there may be a correlation between these factors and the onset of late infections; a longer procedure is generally associated with fully impacted teeth, which renders their extraction more complex [9, 37].

5.2. New findings

- In our study, we were the first to conclude that, based on our study, the less developed germ state (lower *Nolla* class) is a significant predisposing factor for late inflammation [9].

- In our study, we did not use antibiotics in two cases during the treatment of late inflammation. Previous publications recommended antibiotic therapy in all cases. Based on our results and clinical experience, we do not recommend the unnecessary use of antibiotics in case of mild inflammatory symptoms by mild delayed-onset infections [9].

- This type of complication is significantly more likely to occur after the removal of *Pell-Gregory* III, class B, C teeth completely covered with mucosa. According to our study, its typical occurrence is 15-21 years of age [9].

- Based on our results and clinical experience, it is recommended to educate patients about late inflammation as a possible complication in the presence of risk factors [9].

6. Conclusions

In conclusion, although our research had certain limitations, we were able to achieve the objectives of the dissertation. We examined 1.102 clinical records and successfully detected 17 delayed-onset wound infections occurring after suture removal in extractions of the lower third molars. Data on the operations and the clinical characteristics and treatment of the investigated complication were obtained retrospectively from the patient records and the panoramic X-ray database. Delayed-onset infection was diagnosed when inflammatory swelling of the operated area occurred, generally accompanied by the presence of suppuration that began at any time after suture removal 1 week postoperatively.

The patient presented with swelling, jaw stiffness, and moderate pain. In some cases, there was pus formation and fever. Occasionally, an abscess or pus pocket distal to the second molar formed, requiring incision and drainage. Complications occurred on average 29.5 days after surgery, with a range of 20 to 80 days. The youngest patient with DOI was 15 years old, and the oldest was 25 years old. Our cases were relatively mild DOIs, and none of them resulted in airway compromise. Ultrasound or CT was not needed during the diagnostic procedure, and hospitalization or emergency airway management was not required.

Antibiotic treatment and intraoral drainage were effective therapeutic modalities for 88% of patients with purulent swelling. In the remaining 12% of cases, complaints persisted after 7 days and excochleation was needed. In two cases, intraoral drainage of the local abscess at the previous surgical site and lavage for three consecutive days was sufficient for recovery. It is important to note that for these patients, antibiotic treatment and/or excochleation were unnecessary for healing.

Delayed-onset infection occurred after 17 surgeries, resulting in an incidence rate of 1.15% among 1.349 outpatient wisdom tooth surgeries performed by the three surgeons between January 2013 and June 2018.

The case-control study part of our research found statistically significant that lower third molars with total soft tissue retention, lack of distal space, and mesioangular tilt were

more likely to develop DOIs, which is consistent with previous reports. Additionally, less mature tooth germs with lower *Nolla* stages were at a higher risk of developing DOIs.

We recommend longer observation periods for at-risk patients and increased oral hygiene maintenance. Furthermore, we recommend instructing patients to exercise caution and maintaining cleanliness of the surgical site even after suture removal. Patients should promptly report any complaints that arise.

To expand the knowledge about late complications, we recommend extending the observation time of clinical trials and properly documenting late inflammation. We encourage all researchers planning clinical studies to follow this approach.

7. Summary

Extraction of the third molar can result in infections either early (within the first postoperative week) or delayed (after one week). Early complications have been thoroughly studied, and all factors related to the patient and procedure have been well investigated due to their direct correlation with the procedure. Delayed-onset infections are more challenging to link to the surgical procedure and have received less attention in the literature. Late infection can be a serious medicolegal issue as it occurs when the patient believes that the healing process is complete. We found 17 cases of delayed infection in a sample of 1.349 surgeries, resulting in an incidence rate of 1.15%. Our statistical results suggest that lower *Nolla* stage, total soft tissue coverage, lack of distal space, deeper impaction, or mesioangular tilt significantly increase the risk of this type of infection. Based on the information available, it can be established that the age of the patient and the anatomical location of the impacted third molar are crucial factors in the development of delayed onset infections. The mean age of patients whose third molar is removed is decreasing, as prophylactic procedures are becoming more frequent. Third molar development usually is not yet complete by the age of 20 years. The teeth usually attain their final positions later. By the early development, the third molars are located deeper, and the retromolar space increases only at an older age (>20 years). The average age of patients undergoing third molar removal is decreasing due to the increasing frequency of prophylactic procedures. Third molar development is typically incomplete by the age of 20 years, with the teeth reaching their final positions at a later stage. Generally, during early development, the third molars are located deeper, and the retromolar space only increases at an older age (over 20 years). If they are removed during this period, wound healing can be more adversely affected, and the cleaning of the wound is more complicated. Due to the anatomical position, oral hygiene measures, especially chlorhexidine mouthrinses, are not effective enough in that area. This does not appear to be a problem in the early postoperative period, but it could be a causative factor of delayed infection. Thorough knowledge of potential post-surgery complications is crucial for both physicians and patients. This is particularly important for conditions that may be partially prevented through extra care, such as postoperative delayed onset infection after the removal of lower third molars.

8. References

1. Blasi A, Cuozzo A, Marcacci R, Isola G, Iorio-Siciliano V, Ramaglia L. Post-Operative Complications and Risk Predictors Related to the Avulsion of Lower Impacted Third Molars. Medicina (Kaunas). 2023 Mar 9;59(3):534.

2. Eklund SA, Pittman JL. Third-molar removal patterns in an insured population. J Am Dent Assoc. 2001 Apr;132(4):469-75.

3. Ramiro-Verdugo J, De Vicente-Corominas E, Montiel-Company JM, Gandía-Franco JL, Bellot-Arcís C. Association between third molar agenesis and craniofacial structure development. Am J Orthod Dentofacial Orthop. 2015 Nov;148(5):799-804.

4. Brickley M, Kay E, Shepherd JP, Armstrong RA. Decision analysis for lower-third-molar surgery. Med Decis Making. 1995 Apr-Jun;15(2):143-51.

5. Bogdán S, Bérczy K, Hardi E, Kaposvári I, Németh Z. A bölcsességfogak sebészete 2023-ban [Wisdom tooth surgery in 2023.]. Orv Hetil. 2023 Dec 3;164(48):1887-1894.

6. Sukegawa S, Yokota K, Kanno T, Manabe Y, Sukegawa-Takahashi Y, Masui M, Furuki Y. What are the risk factors for postoperative infections of third molar extraction surgery: A retrospective clinical study? Med Oral Patol Oral Cir Bucal. 2019 Jan 1;24(1):e123-e129.

7. Chiapasco M, De Cicco L, Marrone G. Side effects and complications associated with third molar surgery. Oral Surg Oral Med Oral Pathol. 1993 Oct;76(4):412-20.

8. Kaposvári I, Körmöczi K, Horváth F, Buglyó A, Turai AR, Joób-Fancsaly Á. Az alsó bölcsességfogak műtéti eltávolítását követő késői posztoperatív gyulladás (delayed-onset infection) vizsgálata [Incidence and case-control study of delayed-onset infection after lower third molar surgery]. Orv Hetil. 2018 Aug;159(31):1278-1283.

9. Kaposvári I, Körmöczi K, Csurgay K, Horváth F, Ashourioun AH, Buglyó A, Turai AR, Joób-Fancsaly Á. Delayed-onset infections after lower third molar surgery: a Hungarian case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021 Dec;132(6):641-647.

10. Winter G.B. Impacted Mandibular Third Molars. American Medical Book Co.; St. Louis, MO, USA: 1926.

11. Hashemipour MA, Tahmasbi-Arashlow M, Fahimi-Hanzaei F. Incidence of impacted mandibular and maxillary third molars: a radiographic study in a Southeast Iran population. Med Oral Patol Oral Cir Bucal. 2013 Jan 1;18(1):e140-5.

12. J.-M. Korbendau, X. Korbendau: Clinical Succes in Impacted Third Molar Extraction. Paris: Quintessence International, 2003. 39-49 p.

13. Karl-Erik Kahnberg, M. Anthony Pogrel, Lars Andersson: Essentials of Oral and Maxillofacial Surgery. New Jersey: Wiley-Blackwell, 2014. 77-100 p

14. James R. Hupp, Edward Ellis III, Myron R. Tucker: Contemporary Oral and Maxillofacial Surgery. Philadelphia: Elsevier, 2019. 161-183 p.

15. Pell GJ, Gregory GT. Impacted mandibular third molars: Classification and Impacted mandibular third molars: Classification and modified technique for removal. Dent Dig. 1933;39:330–8.

16. Ganss C, Hochban W, Kielbassa AM, Umstadt HE. Prognosis of third molar eruption. Oral Surg Oral Med Oral Pathol. 1993 Dec;76(6):688-93.

17. Olive R, Basford K. Reliability and validity of lower third molar space-assessment techniques. Am J Orthod. 1981 Jan;79(1):45-53.

18. Niedzielska I. Third molar influence on dental arch crowding. Eur J Orthod. 2005 Oct;27(5):518-23.

19. J.-M. Korbendau, X. Korbendau: Clinical Succes in Impacted Third Molar Extraction. Paris: Quintessence International, 2003. 7-17 p.

20. Nolla C. Development of the permanent teeth. J Dent Child 1960;27:254-60.

21. Massler M, Schour I, Poncher HG. Developmental pattern of the child as reflected in the calcification pattern of the teeth. Am J Dis Child 1941;62:33-67.

22. Karl-Erik Kahnberg, M. Anthony Pogrel, Lars Andersson: Essentials of Oral and Maxillofacial Surgery. New Jersey: Wiley-Blackwell, 2014. 53-61 p.

23. Monaco G, Cecchini S, Gatto MR, Pelliccioni GA. Delayed onset infections after lower third molar germectomy could be related to the space distal to the second molar. Int J Oral Maxillofac Surg. 2017 Mar;46(3):373-378.

24. Monaco G, Gatto MRA, Pelliccioni GA. Incidence of Delayed Infections after Lower Third Molar Extraction. Int J Environ Res Public Health. 2022 Mar 29;19(7):4028.

25. Bouloux GF, Steed MB, Perciaccante VJ. Complications of third molar surgery. Oral Maxillofac Surg Clin North Am. 2007 Feb;19(1):117-28.

26. Ghosh A, Aggarwal VR, Moore R. Aetiology, Prevention and Management of Alveolar Osteitis-A Scoping Review. J Oral Rehabil. 2022 Jan;49(1):103-113.

27. Daly B, Sharif MO, Newton T, Jones K, Worthington HV. Local interventions for the management of alveolar osteitis (dry socket). Cochrane Database Syst Rev. 2012 Dec 12;12:CD006968.

28. Taberner-Vallverdú M, Camps-Font O, Gay-Escoda C, Sánchez-Garcés MA. Previous dry socket as a risk factor for alveolar osteitis: A nested case-control study in primary healthcare services. J Clin Exp Dent. 2022 Jun 1;14(6):e479-e485.

29. Chiapasco M, Crescentini M, Romanoni G. Germectomy or delayed removal of mandibular impacted third molars: the relationship between age and incidence of complications. J Oral Maxillofac Surg. 1995 Apr;53(4):418-22; discussion 422-3.

30. Camps-Font O, Sábado-Bundó H, Toledano-Serrabona J, Valmaseda-de-la-Rosa N, Figueiredo R, Valmaseda-Castellón E. Antibiotic prophylaxis in the prevention of dry socket and surgical site infection after lower third molar extraction: a network meta-analysis. Int J Oral Maxillofac Surg. 2024 Jan;53(1):57-67.

31. Malkawi Z, Al-Omiri MK, Khraisat A. Risk indicators of postoperative complications following surgical extraction of lower third molars. Med Princ Pract. 2011;20(4):321-5.

32. Sortino F, Pedullà E, Masoli V. The piezoelectric and rotatory osteotomy technique in impacted third molar surgery: comparison of postoperative recovery. J Oral Maxillofac Surg. 2008

33. Cao Y, Jiang Q, Hu J. Prophylactic therapy for prevention of surgical site infection after extraction of third molar: An overview of reviews. Med Oral Patol Oral Cir Bucal. 2023 Nov 1;28(6):e581-e587.

34. Figueiredo R, Valmaseda-Castellón E, Berini-Aytés L, Gay-Escoda C. Delayed-onset infections after lower third molar extraction: a case-control study. J Oral Maxillofac Surg. 2007 Jan;65(1):97-102.

35. Böttger S, Zechel-Gran S, Streckbein P, Knitschke M, Hain T, Weigel M, Wilbrand JF, Domann E, Howaldt HP, Attia S. A New Type of Chronic Wound Infection after Wisdom Tooth Extraction: A Diagnostic Approach with 16S-rRNA Gene Analysis, Next-Generation Sequencing, and Bioinformatics. Pathogens. 2020 Sep 28;9(10):798.

36. Osborn TP, Frederickson G Jr, Small IA, Torgerson TS. A prospective study of complications related to mandibular third molar surgery. J Oral Maxillofac Surg. 1985 Oct;43(10):767-9.

37. Brunello G, De Biagi M, Crepaldi G, Rodrigues FI, Sivolella S. An Observational Cohort Study on Delayed-Onset Infections after Mandibular Third-Molar Extractions. Int J Dent. 2017;2017:1435348.

38. Figueiredo R, Valmaseda-Castellón E, Laskin DM, Berini-Aytés L, Gay-Escoda C. Treatment of delayed-onset infections after impacted lower third molar extraction. J Oral Maxillofac Surg. 2008 May;66(5):943-7.

39. Figueiredo R, Valmaseda-Castellón E, Berini-Aytés L, Gay-Escoda C. Incidence and clinical features of delayed-onset infections after extraction of lower third molars. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Mar;99(3):265-9.

40. Miyazaki R, Sukegawa S, Nakagawa K, Nakai F, Nakai Y, Ishihama T, Miyake M. Risk Factors for Delayed-Onset Infection after Mandibular Wisdom Tooth Extractions. Healthcare (Basel). 2023 Mar 16;11(6):871.

41. Christiaens I, Reychler H. Complications après extraction de dents de sagesse. Etude retrospective de 1 213 cas [Complications after third molar extractions: retrospective analysis of 1,213 teeth]. Rev Stomatol Chir Maxillofac. 2002 Nov;103(5):269-74.

42. Blondeau F, Daniel NG. Extraction of impacted mandibular third molars: postoperative complications and their risk factors. J Can Dent Assoc. 2007 May;73(4):325.

43. Bello SA, Adeyemo WL, Bamgbose BO, Obi EV, Adeyinka AA. Effect of age, impaction types and operative time on inflammatory tissue reactions following lower third molar surgery. Head Face Med. 2011 Apr 28;7:8. doi: 10.1186/1746-160X-7-8.

44. Waite PD, Cherala S. Surgical outcomes for suture-less surgery in 366 impacted third molar patients. J Oral Maxillofac Surg. 2006 Apr;64(4):669-73.

45. Goldberg MH, Nemarich AN, Marco WP 2nd. Complications after mandibular third molar surgery: a statistical analysis of 500 consecutive procedures in private practice. J Am Dent Assoc. 1985 Aug;111(2):277-9.

46. Figueiredo R, Valmaseda-Castellón E, Formoso-Senande MF, Berini-Aytés L, Gay-Escoda C. Delayed-onset infections after impacted lower third molar extraction: involved bacteria and sensitivity profiles to commonly used antibiotics. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Jul;114(1):43-8.

47. Poeschl PW, Spusta L, Russmueller G, Seemann R, Hirschl A, Poeschl E, Klug C, Ewers R. Antibiotic susceptibility and resistance of the odontogenic microbiological spectrum and its clinical impact on severe deep space head and neck infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Aug;110(2):151-6.

48. Rajasuo A, Perkki K, Nyfors S, Jousimies-Somer H, Meurman JH. Bacteremia following surgical dental extraction with an emphasis on anaerobic strains. J Dent Res. 2004 Feb;83(2):170-4.

49. Kuriyama T, Karasawa T, Nakagawa K, Yamamoto E, Nakamura S. Incidence of beta-lactamase production and antimicrobial susceptibility of anaerobic gram-negative rods isolated from pus specimens of orofacial odontogenic infections. Oral Microbiol Immunol. 2001 Feb;16(1):10-5.

50. Kuriyama T, Williams DW, Yanagisawa M, Iwahara K, Shimizu C, Nakagawa K, Yamamoto E, Karasawa T. Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. Oral Microbiol Immunol. 2007 Aug;22(4):285-8.

51. Karl-Erik Kahnberg, M. Anthony Pogrel, Lars Andersson: Essentials of Oral and Maxillofacial Surgery. New Jersey: Wiley-Blackwell, 2014. 3-7 p.

52. Al-Shammari KF, Al-Khabbaz AK, Al-Ansari JM, Neiva R, Wang HL. Risk indicators for tooth loss due to periodontal disease. J Periodontol. 2005 Nov;76(11):1910-8.

53. Tada A, Tano R, Miura H. The relationship between tooth loss and hypertension: a systematic review and meta-analysis. Sci Rep. 2022 Aug 3;12(1):13311.

54. James R. Hupp, Edward Ellis III, Myron R. Tucker: Contemporary Oral and Maxillofacial Surgery. Philadelphia: Elsevier, 2019. 318-335 p.

55. Rakhshan V. Common risk factors of dry socket (alveolitis osteitis) following dental extraction: A brief narrative review. J Stomatol Oral Maxillofac Surg. 2018 Nov;119(5):407-411.

56. Norris LA, Bonnar J. The effect of oestrogen dose and progestogen type on haemostatic changes in women taking low dose oral contraceptives. Br J Obstet Gynaecol. 1996 Mar;103(3):261-7.

57. Muhonen A, Ventä I, Ylipaavalniemi P. Factors predisposing to postoperative complications related to wisdom tooth surgery among university students. J Am Coll Health. 1997 Jul;46(1):39-42.

58. Larsen PE. Alveolar osteitis after surgical removal of impacted mandibular third molars. Identification of the patient at risk. Oral Surg Oral Med Oral Pathol. 1992 Apr;73(4):393-7.

59. Al-Belasy FA. The relationship of "shisha" (water pipe) smoking to postextraction dry socket. J Oral Maxillofac Surg. 2004 Jan;62(1):10-4.

60. Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med. 1976 Sep 9;295(11):573-7.

61. Sweet JB, Butler DP. The relationship of smoking to localized osteitis. J Oral Surg. 1979 Oct;37(10):732-5.

62. Meechan JG, Macgregor ID, Rogers SN, Hobson RS, Bate JP, Dennison M. The effect of smoking on immediate post-extraction socket filling with blood and on the incidence of painful socket. Br J Oral Maxillofac Surg. 1988 Oct;26(5):402-9.

63. López-Carriches C, Gómez-Font R, Martínez-González JM, Donado-Rodríguez M. Influence of smoking upon the postoperative course of lower third molar surgery. Med Oral Patol Oral Cir Bucal. 2006 Jan 1;11(1):E56-60.

64. Haraji A, Rakhshan V. Single-dose intra-alveolar chlorhexidine gel application, easier surgeries, and younger ages are associated with reduced dry socket risk. J Oral Maxillofac Surg. 2014 Feb;72(2):259-65.

65. Cardoso CL, Rodrigues MT, Ferreira Júnior O, Garlet GP, de Carvalho PS. Clinical concepts of dry socket. J Oral Maxillofac Surg. 2010 Aug;68(8):1922-32.

66. Noroozi AR, Philbert RF. Modern concepts in understanding and management of the "dry socket" syndrome: comprehensive review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Jan;107(1):30-5.

67. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Creminelli L, Santoro F. Assessing postoperative discomfort after third molar surgery: a prospective study. J Oral Maxillofac Surg. 2007 May;65(5):901-17.

68. Berge TI. Complications requiring hospitalization after third-molar surgery. Acta Odontol Scand. 1996 Feb;54(1):24-8.

69. Rivera C. Essentials of oral cancer. Int J Clin Exp Pathol. 2015 Sep 1;8(9):11884-94.

70. D'Angeli G, Zara F, Vozza I, D'Angeli FM, Sfasciotti GL. The Evaluation of Further Complications after the Extraction of the Third Molar Germ: A Pilot Study in Paediatric Dentistry. Healthcare (Basel). 2021 Jan 25;9(2):121.

71. Adeyemo WL. Do pathologies associated with impacted lower third molars justify prophylactic removal? A critical review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Oct;102(4):448-52.

72. De Santana-Santos T, de Souza-Santos aA, Martins-Filho PR, da Silva LC, de Oliveira E Silva ED, Gomes AC. Prediction of postoperative facial swelling, pain

and trismus following third molar surgery based on preoperative variables. Med Oral Patol Oral Cir Bucal. 2013 Jan 1;18(1):e65-70.

73. Farhadi F, Emamverdizadeh P, Hadilou M, Jalali P. Evaluation of Infection and Effective Factors in Impacted Mandibular Third Molar Surgeries: A Cross-Sectional Study. Int J Dent. 2022 May 4;2022:8934184.

74. Consorti G, Monarchi G, Betti E, Balercia P. The Impact of Professional Oral Hygiene in Orthognathic Surgery. J Craniofac Surg. 2023 Oct 1;34(7):e646-e648.

75. Duenas-Garcia OF, Goldberg JM. Topical hemostatic agents in gynecologic surgery. Obstet Gynecol Surv. 2008 Jun;63(6):389-94.

76. Lebendiger A, Gitlitz G, Hurwitt E, Lord G, Henderson J. Laboratory and clinical evaluation of a new absorbable hemostatic material prepared from oxidized regenerated cellulose. Surg Forum. 1960;10:440-3.

77. Epstein JB, Chong S, Le ND. A survey of antibiotic use in dentistry. J Am Dent Assoc. 2000 Nov;131(11):1600-9.

78. Davies SC, Fowler T, Watson J, Livermore DM, Walker D. Annual Report of the Chief Medical Officer: infection and the rise of antimicrobial resistance. Lancet. 2013 May 11;381(9878):1606-9.

79. Chardin H, Yasukawa K, Nouacer N, Plainvert C, Aucouturier P, Ergani A, Descroix V, Toledo-Arenas R, Azerad J, Bouvet A. Reduced susceptibility to amoxicillin of oral streptococci following amoxicillin exposure. J Med Microbiol. 2009 Aug;58(Pt 8):1092-1097.

80. Khalil D, Hultin M, Rashid MU, Lund B. Oral microflora and selection of resistance after a single dose of amoxicillin. Clin Microbiol Infect. 2016 Nov;22(11):949.e1-949.

81. Lodi G, Azzi L, Varoni EM, Pentenero M, Del Fabbro M, Carrassi A, Sardella A, Manfredi M. Antibiotics to prevent complications following tooth extractions. Cochrane Database Syst Rev. 2021 Feb 24;2(2):CD003811.

82. Monaco G, Tavernese L, Agostini R, Marchetti C. Evaluation of antibiotic prophylaxis in reducing postoperative infection after mandibular third molar extraction in young patients. J Oral Maxillofac Surg. 2009 Jul;67(7):1467-72.

83. Pemberton MN, Gibson J. Chlorhexidine and hypersensitivity reactions in dentistry. Br Dent J. 2012 Dec;213(11):547-50.

84. Rahpeyma A, Khajehahmadi S, Ilkhani S. Wound Dehiscence after Wisdom Tooth Removal in Mandibular Mesioangular Class IB Impactions: Triangular Transposition Flap versus Envelope Flap. J Dent Res Dent Clin Dent Prospects. 2015 Summer;9(3):175-80.

85. White RP Jr, Shugars DA, Shafer DM, Laskin DM, Buckley MJ, Phillips C. Recovery after third molar surgery: clinical and health-related quality of life outcomes. J Oral Maxillofac Surg. 2003 May;61(5):535-44.

86. Piecuch JF, Arzadon J, Lieblich SE. Prophylactic antibiotics for third molar surgery: a supportive opinion. J Oral Maxillofac Surg. 1995 Jan;53(1):53-60.

87. Maestre JR, Bascones A, Sánchez P, Matesanz P, Aguilar L, Giménez MJ, Pérez-Balcabao I, Granizo JJ, Prieto J. Odontogenic bacteria in periodontal disease and resistance patterns to common antibiotics used as treatment and prophylaxis in odontology in Spain. Rev Esp Quimioter. 2007 Mar;20(1):61-7.

88. Pasqualini D, Cocero N, Castella A, Mela L, Bracco P. Primary and secondary closure of the surgical wound after removal of impacted mandibular third molars: a comparative study. Int J Oral Maxillofac Surg. 2005 Jan;34(1):52-7.

89. Cerqueira PR, Vasconcelos BC, Bessa-Nogueira RV. Comparative study of the effect of a tube drain in impacted lower third molar surgery. J Oral Maxillofac Surg. 2004 Jan;62(1):57-61.

90. Greene JC, Vermillion JR. The Simplified Oral Hygiene Index. J Am Dent Assoc. 1964 Jan;68:7-13.

91. Winstanley KL, Otway LM, Thompson L, Brook ZH, King N, Koong B, O'Halloran M. Inferior alveolar nerve injury: Correlation between indicators of risk on panoramic radiographs and the incidence of tooth and mandibular canal contact on cone-beam computed tomography scans in a Western Australian population. J Investig Clin Dent. 2018 Aug;9(3):e12323.

92. Szalma J, Vajta L, Lovász BV, Kiss C, Soós B, Lempel E. Identification of Specific Panoramic High-Risk Signs in Impacted Third Molar Cases in Which Cone Beam Computed Tomography Changes the Treatment Decision. J Oral Maxillofac Surg. 2020 Jul;78(7):1061-1070.

93. Szalma J, Lempel E, Csuta T, Vajta L, Jeges S, Olasz L. A jellegzetes panorámaröntgen-jelek szerepe a nervus alveolaris inferior sérülések várható megítélésében alsó bölcsességfogak eltávolításakor [The specific panoramic radiographic signs and their relation with inferior alveolar nerve injuries after mandibular third molar surgery]. Fogorv Sz. 2011 Mar;104(1):27-32.

94. Rodríguez-Pérez M, Bravo-Pérez M, Sánchez-López JD, Muñoz-Soto E, Romero-Olid MN, Baca-García P. Effectiveness of 1% versus 0.2% chlorhexidine gels in reducing alveolar osteitis from mandibular third molar surgery: a randomized, double-blind clinical trial. Med Oral Patol Oral Cir Bucal. 2013 Jul 1;18(4):e693-700.

95. Bulut E, Bulut S, Etikan I, Koseoglu O. The value of routine antibiotic prophylaxis in mandibular third molar surgery: acute-phase protein levels as indicators of infection. J Oral Sci. 2001 Jun;43(2):117-22.

96. Bagul R, Chandan S, Sane VD, Patil S, Yadav D. Comparative Evaluation of C-Reactive Protein and WBC Count in Fascial Space Infections of Odontogenic Origin. J Maxillofac Oral Surg. 2017 Jun;16(2):238-242.

97. Korbendau, X. Korbendau: Clinical Succes in Impacted Third Molar Extraction. Paris: Quintessence International, 2003. 73-81 p.

98. Balamurugan R, Zachariah T. Comparison of primary and secondary closure with a buccal mucosal-advancement flap on postoperative course after mandibular impacted third molar surgery. Oral Maxillofac Surg. 2020 Mar;24(1):37-43.

99. Zwittnig K, Mukaddam K, Vegh D, Herber V, Jakse N, Schlenke P, Zrnc TA, Payer M. Platelet-Rich Fibrin in Oral Surgery and Implantology: A Narrative Review. Transfus Med Hemother. 2022 Dec 22;50(4):348-359.

9. Bibliography of the candidate's publications

9.1. Related to the dissertation

1, Kaposvári I, Körmöczi K, Horváth F, Buglyó A, Turai AR, Joób-Fancsaly Á. Az alsó bölcsességfogak műtéti eltávolítását követő késői posztoperatív gyulladás (delayed-onset infection) vizsgálata [Incidence and case-control study of delayed-onset infection after lower third molar surgery]. Orv Hetil. 2018 Aug;159(31):1278-1283. IF: 0,564

2, Kaposvári I, Körmöczi K, Csurgay K, Horváth F, Ashourioun AH, Buglyó A, Turai AR, Joób-Fancsaly Á. Delayed-onset infections after lower third molar surgery: a Hungarian case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021 Dec;132(6):641-647. IF:2,538

9.2. Unrelated to the dissertation

1, Kaposvári I, Körmöczi K, László ZB, Oberna F, Horváth F, Joób-Fancsaly Á. A preoperatív antibiotikus és antiszeptikus kezelés hatása a műtéti úton eltávolított alsó bölcsességfogak sebgyógyulására – prospektív randomizált vizsgálat [Prospective randomized study regarding the effect of the preoperative antibiotic and chlorhexidine rinse on wound healing after mandibular third molar surgery]. Orv Hetil. 2017 Jan;158(1):13-19. IF:0,322

2, Bogdán S, Bérczy K, Hardi E, Kaposvári I, Németh Z. A bölcsességfogak sebészete 2023-ban [Wisdom tooth surgery in 2023.]. Orv Hetil. 2023 Dec 3;164(48):1887-1894. IF: 0,6 (according to the IF of 2022)

3, Hermann P, Nagy K, Cziriák N, Kaposvári I, Joób-Fancsaly Á, Windisch P, Mikulás K. Az Emberi Erőforrások Minisztériuma egészségügyi szakmai irányelve fogászati implantátumok behelyezésének diagnosztikájáról, sebészi irányelveiről: Klinikai egészségügyi szakmai irányelv. EGÉSZSÉGÜGYI KÖZLÖNY 72 : 6 pp. 1017-1086. (2022)

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