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*Review article*

# CRANIOFACIAL DEVELOPMENT OF THE CHILD

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## ABSTRACT

This article briefly describes the mechanisms of cranio-facial growth and the role of the forming functions (namely mastication, breathing, swallowing and speech) in achieving a harmonious development. Facial sutures are joints and important sites of bone growth with visco-elastic characteristics that distribute forces to the whole cranial structure that remain well into adulthood. An equally important role is played by the temporomandibular joint, which undergoes a major change in morphology during growth, constantly accompanying the changing oral functions (from suction to mastication and speech); the mandibular condyle is an important site of bone growth, with a large capacity to adapt or to compensate. The ability of this joint to compensate is a lifelong adaptive process that takes place in interplay with everchanging occlusal conditions. The temporomandibular joint's dramatic involvement in children affected by juvenile idiopathic arthritis is quite obvious, with or without signs or symptoms. Some malocclusions, and the cross-bites in particular, alter both the occlusion and the masticatory function, leading to an altered cranial development that is irreversible at the end of growth.

Recently, laboratory and clinical research have highlighted, in animal models of reduced mastication, an association between the experimental reduction of the masticatory function and a significantly reduced number of hippocampal neurons, neurogenesis in the dentate gyrus, synaptic density, and increased glial activity, as well as reduced memory and spatial orientation.

Mastication is, therefore, central to the craniofacial development of the child and the development of cognitive functions. Therefore, the treatment of malocclusions must be respectful of physiology and biology to re-establish all the functions of the growing stomatognathic apparatus and avoid traumatic treatments whose effects are impossible to anticipate and prevent, given the developing system's complexity and its importance for future functional and cognitive balance.

**KEYWORDS:** *Mastication, craniofacial growth, cognition, memory, malocclusion*

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## INTRODUCTION

Craniofacial growth does not end in a simple volumetric increase: it is a rather complex individual process influenced simultaneously by the genetic / family characteristics of the child and the functions of the stomatognathic system (1–5). The growth of the individual bones of the skull is achieved thanks to apposition and resorption processes, which simultaneously allow for the increase in volume and progressive structural remodeling, including repositioning in the three planes of space. Each bone is repositioned according to its growth and the growth of the surrounding bones and soft tissues (1, 6). The development of the skull is, therefore, the result of the integration of volume increases, regional remodeling, and repositioning, which, interacting with each other, adapt, in physiological conditions or compensate, in pathological conditions, the anatomical structure in response to the changing functional needs (7, 8). The soft tissues surrounding a bone (muscles, ligaments, vessels and nerves, teguments) represent the functional matrix capable of influencing growth through functional stresses, among which chewing plays a particularly important role (9). Therefore, the adaptation or compensation of craniofacial structures must be understood as a response to the genetic and family characteristics of the individual, in turn, influenced by the characteristics of the soft tissues and function (Fig. 1).

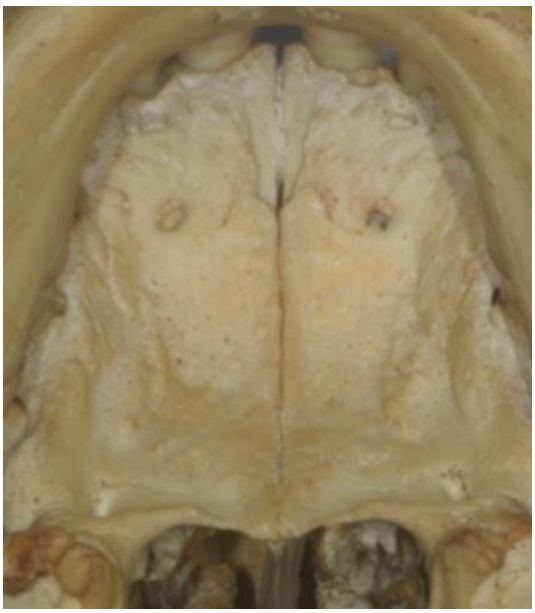

**Fig. 1.** *Median palatine suture at the age of 4: an important growth site in the course of development.*

It is important to remember that adaptation occurs in physiological conditions concerning anatomical conditions that change, for example, with aging. At the same time, compensation is a reaction to pathological structural conditions, which the system cannot self-correct to maintain the best possible function. The compensation, which immediately allows the most effective function, can trigger a chain of harmful pathological reactions, as occurs in cross bites.

Malocclusion is a pathology of the anatomical structure of the craniofacial complex that interacts with a cause/effect relationship with the genetic predisposition on the one hand, and functional conditions, on the other.

The chewing function plays a central role in the growth and development of the child's splanchnocranium, especially in early and second childhood. The forces of chewing and swallowing are necessary for growth, and their alteration significantly disturbs the development of the stomatognathic system; however, even in adulthood and during aging, they are important for health and quality of life. International research results have for some time now unequivocally highlighted the association between some malocclusions and the alterations/pathologies of chewing (10). Furthermore, recent basic and clinical international research results have also shown a link between chewing function and cognitive development (11). In fact, in animal model, the experimental reduction of chewing is significantly associated with alterations of the hippocampus, demonstrable both on a histological and behavioral level, which we will describe shortly.

Chewing, therefore, is not only of dental interest but also concerns the child's and adolescent's development. Traumatic orthodontic therapies during development, although widespread in the world, often act against functional physiological principles and require a biological price that is sometimes very important and worrying, as shown by recent studies in the field (12). The purpose of this article is, in the light of recent research results, to describe some fundamental evolutionary stages related to the functions of the masticatory organ, to facilitate the understanding of the etiopathogenesis of malocclusions as well as the importance of a correct therapeutic approach, in a logical and consistent path with the diagnosis and with the characteristics of craniofacial growth.

### *The role of facial sutures and the temporomandibular joint during growth*

Craniofacial growth, far from being the exclusive result of the expansion of a few growth centers, involves all the bones and joints of the skull (1). However, some structures play a particular role in growth, adaptation and/or compensation and deserve a particular description: the facial sutures and the temporomandibular joint.

The facial sutures have different characteristics and respond to different stimuli than the neurocranial sutures: while the latter is stimulated by the expansion of the brain, which mainly follows a genetically determined program, the facial

sutures are stimulated by the forces of the function of the stomatognathic system, i.e., chewing, swallowing, breathing and phonation. The presence of adequate stimuli is essential for developing and maintaining craniofacial sutures. In fact, they do not have intrinsic growth potential, and the deposition of bone on the two sides of the suture is stimulated by tensional, intermittent stresses (13). It is known from the basic research that the reduction of the masticatory function in the growing animal significantly decreases the bone apposition at the level of the sutures of the upper jaw, which become slightly patent and not very active (14,15). The reduction of muscle activity leads to morphological changes in the suture (16). Facial sutures, such as the fronto-maxillary, the naso-maxillary, and the zygomatic-maxillary, remain open for a very long time in physiological conditions until the seventh/eighth decade of life (17). The presence up to late age of the visco-elasticity characteristics of the sutures allows the loads generated by muscle function (chewing, swallowing, and speaking) to be effectively cushioned by the entire cranial structure. The trauma and the consequent premature ossification of the sutures, an inevitable consequence of traumatic and non-physiological therapies applied to the palatine suture and to many other facial and neurocranial sutures, do not allow the full performance of their growth function, nor their biomechanical distribution role of loads over the course of life.

The maxillary bone has an intra-membranous origin, and its growth occurs by sutural apposition and superficial remodeling at the periosteum. The median palatine suture (Fig. 1), an important growth site (18,19), along which the horizontal laminae of the palatine bones articulate posteriorly, and the palatine processes of the maxillary bones anteriorly, plays a primary role in the dimensional increase of the palate. It goes without saying that malocclusions due to insufficient growth of the upper jaw bones must be corrected by stimulating growth in a physiological and certainly not traumatic way, under penalty of an individual biological and functional price in the oral environment, present and future.

The growth of the mandible is different and peculiar: the condyle region develops through the enchondral route, while the rest of the mandible initially follows an external cartilage sketch (Meckel's cartilage, mantle ossification) and develops then by periosteal deposition (1). Unlike other cartilages of the skull, such as the synchondrosis of the skull base, or of the cartilage of the nasal septum, of direct mesenchymal derivation, particular attention must be paid to the condylar, which is a secondary cartilage. The growth of the temporomandibular joint is adaptive (or compensatory, in pathological conditions) and occurs in response to mechanical stimuli (20). The articular fibrocartilage that lines the head of the condyle is initially well represented and nourished by a rich vascularized connective tissue, which allows rapid growth during development. In fact, at birth, the temporomandibular joint is completely immature; over the years, the potential decreases, but continues to maintain a considerable capacity for adaptation or compensation for the entire duration of the individual's life (20,21). The temporomandibular joint actually changes during growth, constantly accompanying the evolution of its function: in the first years of life it has a flattened morphology, an expression of its function as a "flat" sliding joint suitable for sucking movement; subsequently, the joint eminence becomes progressively steeper and the condyle moves away from the occlusal plane (22, 23). Compensation of the temporomandibular joint is a lifelong adaptation process with respect to changing occlusal conditions.

The remarkable adaptability is demonstrated by studies on animal model, in which the application of a device designed to induce an asymmetrical lateral displacement of the mandible determines a different development of the two condyles (10). Similarly, in small patients with deciduous or mixed dentition presenting a crossbite-type malocclusion, which causes dislocation in the three planes of the mandible space, the two condyles are subjected to different stimulations during the course of function and their compensatory growth is asymmetrical, irreversibly at the end of growth (24). This is a predisposing condition to chronic craniofacial pain.

In light of the adaptive growth characteristics of the temporomandibular joint in the development phase, particular attention should be paid to a systemic inflammatory disease such as juvenile idiopathic arthritis (JIA). Due to the characteristics described above, the JIA involves the growing temporomandibular joint in an important and constant manner, even in the absence of obvious or reported signs and symptoms. In fact, it is rare for growing patients affected by JIA to report painful symptoms affecting the temporomandibular joint, although the latter is always affected by the pathological inflammatory process. It has been shown that, in the presence of JIA, the growth of the mandibular condyles proceeds asymmetrically, deviating significantly from the growth pattern of unaffected subjects (25,26). The asymmetry involves the condylar height and has repercussions on the vectoriality of the general cranial structure: in fact, cephalometric studies have highlighted a significant prevalence of hyperdivergence and postero-rotation of the jaw in patients with JIA compared to unaffected subjects. This is a type of cranial structure with a high risk of developing intrinsic asymmetries, occlusal instability and dysfunctions of the oral sphere: it is not surprising, since the condyle is an important site of growth and adaptation/compensation of the functions of the cranial structure (27). In growing patients affected by JIA, therefore, it is necessary to monitor and treat the temporomandibular joint function regardless of the

presence of signs and symptoms affecting it. Therefore, the orthognathic treatment must be of the gnathological type, that is, respectful of physiology, avoiding any traumatic mechanics whose side effects could add to the altered dynamic pattern of the skull structure, worsening it further.

*Shaping functions*

The dental arches are rigid structures that dominate the system and from which continuous proprioceptive signals depart, leading to the formation of patterns and motor memory. The oral functions of each functional period are forming functions; that is, they have a decisive influence on the morphology of the bone structures and the formation of functional motor patterns (28). Since the main motor of bone growth resides precisely in the functional matrices, an altered function or deforming influences such as malocclusions or spoiled habits, can, at any stage of the evolution of the chewing organ, but especially in the earliest ones, disturb the harmonious development of the craniofacial complex. Poor habits, oral breathing, atypical swallowing (with the interposition of the tongue or lower lip), prolonged use of the pacifier and sucking, especially of the thumb, can be responsible for disharmonic development (29). It would be a mistake to allow such dysfunctions and asymmetries to mature.

Starting from birth, many studies highlight the importance of breastfeeding in promoting the correct development of chewing muscles and jaw structures in the three dimensions of space (30). It should be remembered that the physiological sign of change and transition from sucking to swallowing is represented by the eruption of the first deciduous tooth which occurs on average at six months. From this moment on, the system begins its evolution towards adult swallowing and chewing. Prolonged breastfeeding beyond the first year of age represents an obstacle to the physiological evolution of swallowing and chewing function.

In addition to chewing and swallowing, respiration and speech are important functions in the growing subject: their functionality must be carefully monitored to detect anomalies early. Verbal communication, from the early stages of echolalia to fully developed language, involves neuromuscular activations that are less intense than chewing and swallowing but nevertheless important for development: phonation is also a shaping function.

Among the anatomical pathologies capable of significantly altering the chewing function and, therefore, the cranial bone growth irreversibly unbalancing it, there are certainly malocclusions, including open bites and all types of cross-bites. In particular, the rear unilateral cross-bite is the most common. This asymmetrical malocclusion has been defined as a neuromuscular syndrome because it causes pathological changes in the masticatory pattern and neuromuscular coordination, resulting in a severely asymmetrical function (31). International research studies have shown for some time that, in cross-bite conditions, abnormal dyskinetic and poorly efficient patterns develop during cross-biting, neuromuscular coordination between the sides is lost and the electromyographic amplitude reaches values about 50% lower than the unaffected side (32,33). Faced with such an important functional asymmetry, an asymmetrical development of the craniofacial structure will occur, primarily involving the joints, irreversible at the end of growth (34, 35). A peculiarity of this malocclusion is represented by the fact that it can manifest itself in deciduous dentition as early as 2-5 years of age, during the formation and fine-tuning of all neural motor schemes; therefore, its early diagnosis is important and the therapy becomes longer and at risk of relapse the later the intervention is carried out. Orthognathic therapy of the posterior cross-bite is not only aimed at repositioning the teeth within the arches in the correct occlusal relationship, but above all, through the teeth, to rebalance the chewing function between two sides. It goes without saying that it will not be possible to recover function with traumatic and anti-physiological mechanical therapies, but only with therapies that respect the physiology and biology of the system. The earlier this happens, the sooner the residual memory is corrected, the growth will become harmonious and the correction will easily remain stable over time.

*Recent research results: chewing function and cognitive development*

In recent years, it has emerged from studies on animal models that the experimental alteration of the chewing function causes alterations in the central nervous system, demonstrable from a histological and behavioral point of view (34,35). Animal studies are important for histological and biochemical demonstration; in fact, in the mouse model, the imposition of a soft diet right from weaning, in addition to the marked underdevelopment of the jaws (which is not reflected in the somatic development, which proceeds (36), is associated with the significant reduction in the number of neurons, reduction of neurogenesis in the dentate gyrus, reduction of synaptic density and activation of glial cells in the hippocampus, as well as a reduction in memory and spatial orientation. Furthermore, the chewing function is disturbed by a mechanical obstacle, such as a pre-contact inserted between the arches in the molar or incisal region that prevents any other occlusal contact (called bite-raise, nowadays widely used especially in adolescence), in addition to the neural alterations described

in the hippocampus. In that case, there is an activation of the hypothalamus-pituitary-adrenal axis, with an increase of corticosteroids. In fact, in the animal model the bite-raise creates a state of uncontrollable anxiety in the condition of new stressful stimuli, which persists even after the acute response is exhausted (37). In other words, occlusal stability is an important element for a child's harmonious psycho-physical development. Occlusal stability is the condition in which, during the closing movement of the mouth, the dental arches easily find the maximum intercuspation and the antagonist teeth face each other with a dense distribution of contact points, allowing the development of adequate forces to stimulate the bone growth (38). The unstable occlusion, on the contrary, does not allow adequate development of the functional forces necessary for the growth of the jaws and in addition, it has a negative influence on the cognitive development of the child. Achieving stable occlusion with adequate anterior canine guides is the aim of any orthognathic therapy (39-45).

There are therefore at least two distinct functional aspects to take into consideration: on the one hand, the occlusion, which can, if altered, be a source of stress for the body; on the other hand, the chewing function, which can, if exercised too little or altered by malocclusions or other congenital or acquired pathologies, negatively affect the trophism of the hippocampus and its functions. This has been demonstrated both during weaning and growth, and during aging. From clinical research, it is known that the presence of less than twenty teeth in the arch (considered the limit for efficient chewing) is associated with a reduction in cognitive performance in the elderly subject, which is completely consistent with the data from laboratory studies, as well as from clinical experience (46,47, 48). It must be emphasized that alterations in chewing and / or occlusion can lead to a reduction in the neuronal potential which otherwise allows aging to be faced with an adequate functional reserve necessary for maintaining a good quality of life. On the other hand, a full exercise of the masticatory function allows the complete expression of craniofacial development and could contribute to preserve intact a functional cognitive reserve through an adequate and necessary persistent stimulus to neurogenesis and to the differentiation of hippocampal neurons (11).

## CONCLUSION

In light of the complexity and characteristics of cranial growth intimately correlated to the oral functions described, it appears clear that the treatment plan for malocclusions must be aimed primarily at rebalancing the altered functions. The purpose of orthognathic therapy in the growth phase cannot simply limited to the alignment of the teeth but must be aimed at restoring the balance of functions and consequently of bone development. For this, a logical and consistent treatment plan with the diagnosis is needed, avoiding mechanical and traumatic therapeutic means. In fact, the mechanical and traumatic forces during cranial growth can determine unpredictable and unpredictable effects due to the complexity and individuality of the structure. The restoration of oral functions can only take place if the forces expressed by the therapeutic device have the characteristics of self-regulating and intermittent physiological stimuli, allowing the self-repositioning of the mandible in the three planes of space in a position of greater structural balance. Only in this way, in addition to the repositioning of the teeth inside the arches, will it be possible to guarantee the recovery of the neuro-muscular coordination of the entire cephalic and neighboring districts and a harmonious, stable and lasting function for the future life of the little patient.

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*Review*

# ORAL MANIFESTATIONS OF ERYTHEMA MULTIFORME AND COVID-19: A MINIREVIEW

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## ABSTRACT

Dermatological findings due to Coronavirus disease 2019 (COVID-19) have been reported in the last two years. This review aims to analyse the oral manifestations of Erythema multiforme (EM) in patients with COVID-19. On the 28th of June 2022, the search was performed in PubMed by including all English studies that reported oral injuries associated with EM and COVID-19. The search yielded 117, but only 12 studies were eligible. The main sites affected by EM are the tongue, buccal mucosa, palate, and lips. In most cases, oral and cutaneous lesions of EM appear at the same time. Autoreactive T-cells and massive production of cytokines are pathogenetic stages shared by either EM or COVID-19. Further studies are needed to evaluate the possible correlation between the onset of oral lesions linked to EM and COVID-19 due to the expression of the ACE2 receptor on keratinocytes.

**KEYWORDS:** *COVID-19, erythema, cytokine, interleukin, angiotensin*

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a zoonosis caused by a novel *Betacoronavirus* (SARS-CoV-2) which was first described in Wuhan, China (1). From March 2020 to nowadays World Health Organization (WHO) declared the COVID-19 pandemic (2).

Flu-like symptoms, such as myalgia, asthenia, fever, sneezing, and cough, are a spectrum linked to SARS-CoV-2 infection, and the most important complications are pneumonitis and sepsis because this virus has an elective tropism for epithelial cells of the airways and pneumocytes (3).

SARS-CoV-2, like other viruses, can represent stimuli to the innate and adaptative immune system whose consequences are cutaneous and mucosal implications (4). With the worldwide spread of SARS-CoV-2 infection, many authors reported

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cases of erythema multiforme (EM) linked to COVID-19 (5, 6).

EM is a dermatologic immune-mediated disorder, with or without mucosal involvement, triggered by viral and bacterial infections either or drugs (7). According to diagnostic criteria of Hebra, papules are the first manifestations of the disease, with a typical aspect of double concentric ring lesions and blisters: firstly, they appear symmetrically on the extremities of the body; then spontaneous healing occurs between one and four weeks, with desquamation or hyperpigmentation (8).

Mucosal injuries can precede or arise simultaneously or after the onset of cutaneous lesions, and they frequently affect the oral cavity and the oesophagus, pharynx and upper respiratory airways (8, 9).

Infections by Herpes simplex virus, Epstein-Barr virus, Cytomegalovirus, Hepatitis C virus, and influenza virus associated with EM have been described (10, 11). This review aims to describe the clinical aspects of oral manifestations of EM in patients with COVID-19.

## MATERIALS AND METHODS

PubMed was selected as the database to search articles that reported oral findings of EM related to COVID-19. The search strategy included the following terms joined with Boolean operators: "COVID-19" [Mesh] OR SARS-CoV-2 [tiab]) AND ("Erythema Multiforme" [Mesh] OR "erythema multiforme" [tiab]). The studies selected were all in English. Review articles and commentary were excluded. The selection of eligible studies was first performed after a screening based on the title and abstract, then reading the full text.

## RESULTS

On the 28th of June 2022, the search yielded 117 results, and one record was identified from a review article. After an accurate screening, 95 references were excluded. Twenty-two articles were evaluated to be included in this review. Finally, 12 studies were analysed for the qualitative synthesis (Fig. 1).

As reported in Table I, many people experienced widespread oral mucosa ulceration accompanied by intense pain. Oral and cutaneous lesions of EM appear simultaneously in most cases (12–15). Oral outcomes precede the onset of dermatological signs of EM and common symptoms of COVID-19 only in one case (16).

In these studies, cutaneous lesions associated with EM were acral target lesions that sometimes extended to the chest, upper back, legs, arms, and elbows. Rashes and irregular maculopapular lesions were also described. In two cases, the skin was spared (17, 18).

Other mucosal districts affected by ulcers akin to those found in the oral cavity were the conjunctiva, pharynx, and genitals. However, in four studies, the oral mucosa was the only mucosal site involved (12, 15, 16, 19).

## DISCUSSION

EM is a spectrum of mucocutaneous disease with or without spots, variable epidermal detachment rate, and typical either or atypical target lesions (20). Bastuji-Garin et al. identified five variants of EM: bullous EM, Stevens-Johnson syndrome (SJS), overlap SJS-Toxic epidermal necrolysis, Toxic epidermal necrolysis (TEN), the latter with or without spots (20). A new classification performed by Ayangco et al. distinguished two forms of EM (minor and major), SJS, TEN and oral EM: they can potentially have oral involvement, but the cutaneous injury is different (21).

The most important features of oral lesions linked to EM, also found in patients with COVID-19, are erosive vesicles, ulcerations with a fibrinous substrate that mimics aphthae, and target and crusty lesions associated with copious bleeding. The tongue, buccal mucosa, palate and lips are the primary sites affected by this condition. Hypersalivation and satellite lymphadenopathy completed the framework.

According to Eghbali Zarch et al., SARS-CoV-2 infection associated with a previous state of immunosuppression could lead to herpetic stomatitis, oral EM and enanthema (22). EM results from an immune system impairment elicited by antigens presented on keratinocytes (21). Aurelian et al. emphasised the role of INF-γ in Herpes simplex virus (HSV)-

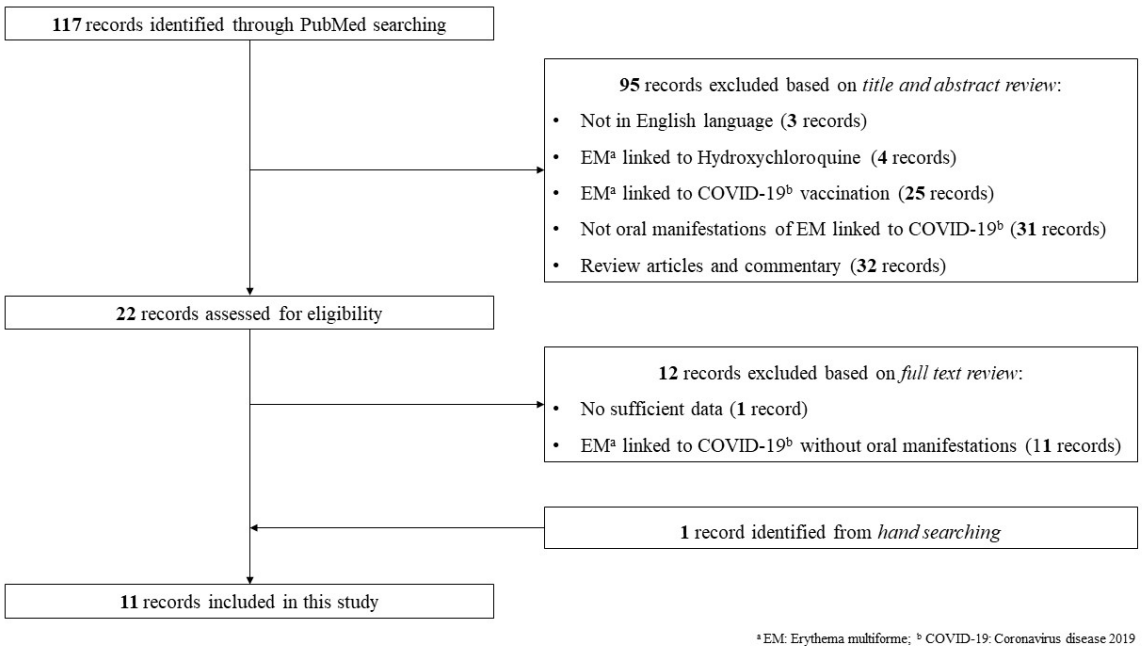


**Fig. 1.** *Oral manifestations in patients with COVID-19*

**Table I.** *Oral erythema multiforme in patients with COVID-19*

| Study ID | Publication year | Sample size | Age | M (%) | Erosions | Ulcerations | Blisters | Haemorrhagic crusting lesions | Target lesions | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| Palaia, 2022 | 2022 | 1 | 30 | 0 | - | Hard palate Lips | Buccal mucosa | - | - | EM[a] major (SJS[b]) |
| Erbaş, 2022 | 2022 | 4 | 50,00* | 25 | Tongue | Buccal mucosa Tongue | - | Lips | - | EM[a] |
| Narang, 2021 | 2021 | 1 | 53 | 0 | Oral cavity | - | - | Oral cavity | - | TEN[c] |
| Maden, 2021 | 2021 | 1 | 18 | 100 | - | Buccal mucosa | - | - | - | EM[a] major (SJS[b]) |
| Emadi, 2021 | 2021 | 1 | 30 | 0 | - | - | - | Lips | - | TEN[c] |
| Dalipi, 2021 | 2021 | 1 | 17 | 100 | Lips | Left labial mucosa | Tongue | - | Left labial mucosa | EM[a] |
| Binois, 2021 | 2021 | 1 | 57 | 100 | - | Buccal mucosa | - | - | - | EM[a] major (SJS[b]) |
| Abdelgabar, 2021 | 2021 | 1 | 23 | 100 | - | Buccal mucosa | - | Lips | Tongue | EM[a]/EM[a] major (SJS[b]) |
| Rolfo, 2020 | 2020 | 1 | 58 | 0 | - | Buccal mucosa | - | - | - | EM[a] |
| Labé, 2020 | 2020 | 1 | 6 | 100 | Lip angles Gingiva | - | - | Lips | - | EM[a] |
| Demirbaş, 2020 | 2020 | 1 | 37 | 0 | Lips Palate Tongue | - | - | - | - | EM[a] |

** Data are reported as mean; (-) Not stated, unclear, or unable to ascertain; a EM: Erythema multiforme; b SJS: Stevens-Johnson syndrome; c TEN: Toxic epidermal necrolysis*

associated erythema multiforme (HAEM): it promotes a huge production of cytokines to induce chemotaxis of leukocytes, monocytes, NK cells, and autoreactive T-cells lead keratinocytes to lysis (23). COVID-19 share the same increase of several proinflammatory cytokines, a condition known as a "cytokine storm" (24) and activation of local autoreactive B and T cells (4). It is known that SARS-CoV-2 binds angiotensin-converting enzyme 2 receptor (ACE2 receptor) to infect pneumocytes (3)due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, but this receptor is also localised and overexpressed in keratinocytes during Atopic Dermatitis (25). Studies to evaluate a possible correlation between the onset of EM oral manifestations and COVID-19 due to the expression of the ACE2 receptor on keratinocytes should be considered.

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*Case report*

# ORTHODONTIC MANAGEMENT OF MAXILLARY TOOTH TRANSPOSITION: A CASE REPORT

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## ABSTRACT

Transposition is an exchange of the position of two adjacent teeth, which can be incomplete or complete. The aim of this case report was to illustrate the non-extraction treatment of transposition between maxillary canine and first premolar using multibrackets fixed appliance. The treatment of this anomaly varies from acceptance to correction and should consider several aspects such as age, dental morphology, malocclusion, facial esthetics, stage of root development, the position of the root apices, and magnitude of the transposition. The patient, a boy, aged 11 years, had a class III malocclusion with narrow maxillary arch, crossbite from 1.2 to 1.5 and 2.2, with transposition of 2.3. The early diagnosis plays a significant role in considering esthetics and functional factors in deciding which treatment strategy should be followed to promote the patient's self-esteem. The key to a successful and stable result is precise treatment planning and careful orthodontic management.

**KEYWORDS:** *tooth, transposition, treatment, orthodontics, surgery*

## INTRODUCTION

Dental transposition is the interchange of the position between two teeth, which can be incomplete or complete (1). In

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the complete one, both the crowns and the entire root structures are parallel in their transposed positions. The crowns may be transposed in the incomplete transposition, but the roots remain in their regular positions (2). The prevalence of transposition is about 0.5% in the general population and presents no gender predilection (3, 4). Transposition can appear in both the maxilla and the mandible. However, it is more frequent in the maxilla than in the mandible and more unilaterally than bilaterally (5–8).

In the upper arch, the most frequent transposition is between the canine and the first premolar. On the contrary, the most common transposition in the lower arch is between the canine and the lateral incisor.

Transposition is characterized by a multifactorial etiology that is not entirely understood nowadays. Several theories have been proposed to explain this condition. Multifactorial genetic factors such as the inversion of the position of the dental lamina of the teeth involved have been suggested as one of the causes, as supported by Peck, et al. (9) and Nelson (10). Additionally, environmental factors such as deciduous trauma, retained deciduous whose roots can cause mechanical interference on the permanent teeth, severe rotations, malformation of adjacent teeth, dental malposition, the supernumerary teeth and the lacerations, can as well contribute to its establishment (6–8, 11).

A correct diagnosis is the basis of an effective treatment plan. It is necessary to identify the anomalous position of the dental elements and to evaluate their relationship with the adjacent anatomical structures and the possibility of recovery. The first level radiographic exam for a preliminary assessment is the panoramic x-ray. However, only the CT/Cone Beam can provide images useful for the evaluation of the 3D position of the affected roots, bone defects, and the involvement of the nearby structures (12–15).

The decision on whether to keep or correct the transposed teeth is crucial to the treatment planning for transposition and depends on various factors such as patient's age, diagnosis, teeth involved, degree and extent of transposition(16).

From an orthodontic perspective, the treatment can be performed by extraction or non-extraction. In the non-extraction option, the transposed teeth are aligned in their normal or transposed positions (12–15).

Generally, in medicine, it is mandatory to consider several approaches after formulating a correct diagnosis and then monitor the treatment results and their efficacy compared to other approaches used in similar clinical cases. Specifically, evaluating the advantages and disadvantages of these patients' two main treatment options remains necessary. The most significant advantages from an aesthetic and functional point of view are obtained by repositioning the affected dental elements. However, this option is not always possible considering the complications of the biomechanics and the risk of resorption of the adjacent bone structures, root resorption, and treatment time.

This case report demonstrates the management of a young patient's maxillary tooth transposition, canine-first premolar.

## CASE REPORT

*Diagnosis and etiology*

A male patient aged 11 years and came to the Orthodontic Program with his parents complaining of an ugly smile. He did not report any previous orthodontic treatment or trauma history. Extraoral examination revealed a symmetrical face, decreased lower facial height with a concave profile, increased Z angle, and accentuated labiomenton groove. Intraoral examination revealed a molar class III relationship bilaterally. The maxillary left permanent canine was partially erupted in an ectopic position, buccally to the first premolar. He had widespread diastemas, crossbite from 1.2 to 1.5 and 2.2, with overbite and overjet of 0 mm (Fig. 1). The panoramic x-ray showed an incomplete transposition of the crowns and the roots of the maxillary left canine (2.3) and the first premolar (2.4).

The lateral cephalometric analysis revealed that in this patient, there was a skeletal class III relationship (ANB angle = -1,5°) with upper and lower incisors compensation. In addition, the Cervical Vertebral Maturation (CVM) and the hand-wrist radiography (HWR) indicated that the patient was in the pubertal peak phase.

*Treatment objectives*

The main goal was to control the skeletal class III relationship and to achieve aligned and leveled teeth without compromising soft tissue and periodontal structure. For this reason, the treatment objectives were to improve the skeletal and molar class III relationships, achieve a functional molar occlusion, correct the transposition, maintain or improve overjet and overbite, and maintain the upper and lower incisor compensation. Based on the patient age and diagnosis, the best treatment option was an interceptive treatment with the following orthodontic correction treatment of the transposition. The interceptive treatment was carried out with a modified SEC III protocol with a rapid palatal

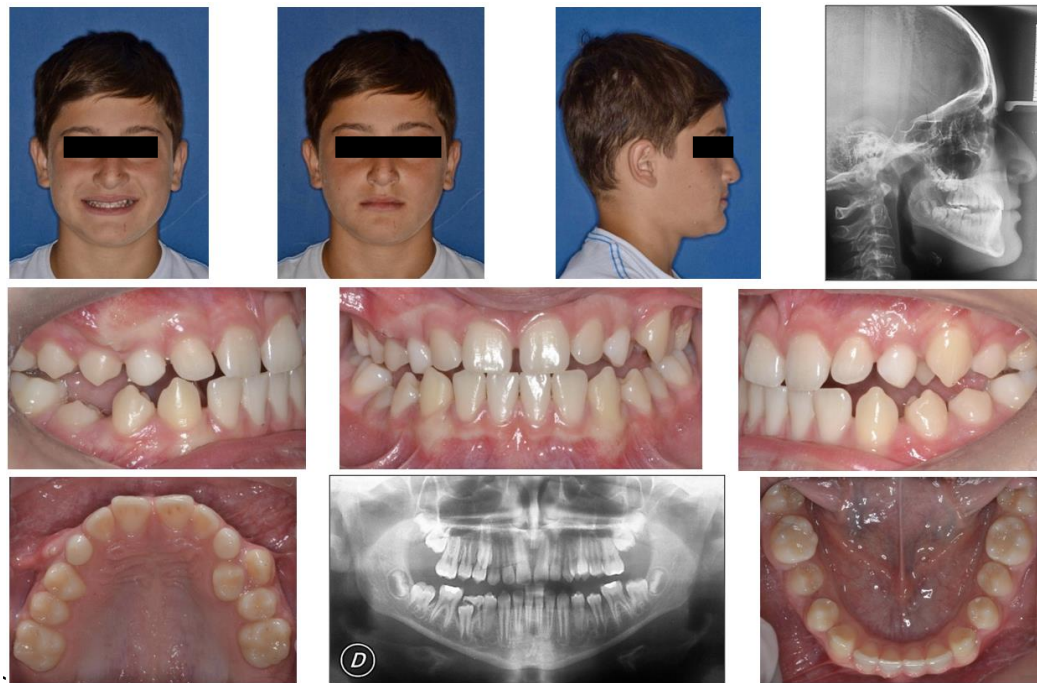

**Fig. 1.** *Pretreatment extraoral and intraoral photographs.*

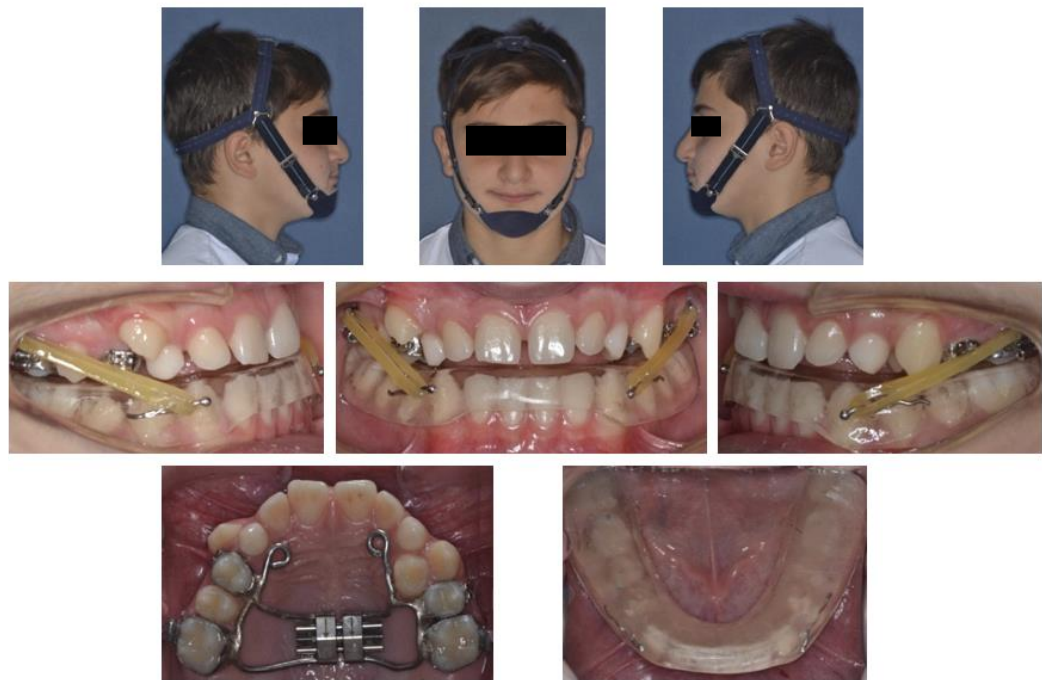

**Fig. 2.** *Modified SEC III protocol.*

expander (RPE) on four bands, a lower splint with class III elastics, and a chin cup (Fig. 2).

In the second phase, 7-7 upper and lower multibracket fixed appliances were used in the upper and lower arches.

*Treatment progress*

The first phase of treatment involves the modified SEC III protocol with:

- rapid palatal expander on four bands with arms extended up to the canines, with auxiliary eyelets to help cuspid reposition;
- lower splint with class III elastics;
- chin cup with a bilateral force equal to 450gr/side (16 oz) (Fig. 2).

The deciduous canines were extracted (5.3 and 6.3). The upper and lower arches were fully bonded with 0.022″ × 0.028″ MBT fixed appliances.

A sectional archwire 0.16x0.22 SS with contact omega loops and an open vertical loop for 2.3 mesialization were inserted (Fig. 3).

After a new sectional 0.16x0.22, SS with contact omega loops and an open vertical multi-loop for the mesialization of the 2.3 was applied (Fig. 4).

When 2.3 reached its correct position, we began repositioning 2.4 in the arch. In the upper arch, a .016 AA wire with two contact omega loops on 1.6 and 2.6 was positioned, with a Niti coil spring between 2.2 and 2.4 to gain space for 2.3 and to center the upper median. After, .017 × .025 Nickel-Titanium and .019 × .025 stainless steel wires were used in the upper and lower arches with class III elastic (1/4 oz per side) and the chin cup (for the mandibular control). After 36 months of active treatment, the maxillary and mandibular fixed appliances were removed, and the post-treatment records were taken to assess whether the treatment objectives were fully achieved.

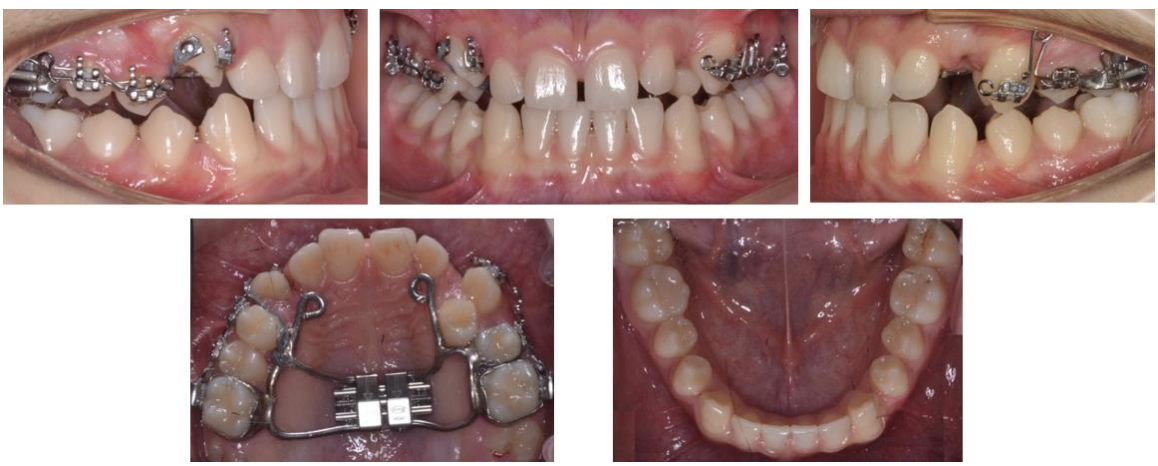

**Fig. 3.** *0.16x0.22 SS with contact omega loop and an open vertical loop.*

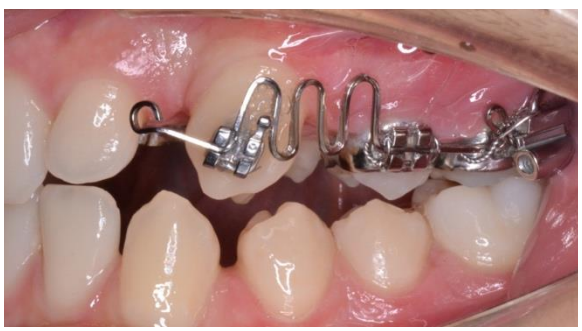

**Fig. 4.** *Activation of the open vertical multi-loop.*

## RESULTS

The treatment goals were correctly achieved, supporting and complementing the already published scientific information (15, 16). The skeletal relationship was controlled with a nice facial profile (Fig. 5). The occlusal, functional, and esthetic results were satisfactory; therefore, the patient and his family were happy with his smile. The patient presented class I molar and canine relationship and good intercuspation. All maxillary spaces were closed. The upper and lower dental midlines were coincident with good overjet and overbite. From a periodontal point of view, all the upper and lower teeth were well-positioned with no supporting dental tissue complications. The end-treatment panoramic x-ray showed that all roots were in good parallelism. The patient was also fully satisfied with the results.

## DISCUSSION

Dental transposition is one of the foremost challenging conditions in orthodontics, betting on which teeth are involved and their positions relative to the adjacent teeth.

The treatment strategy of transposition should be individual by considering various factors such as the patient's age, diagnosis, teeth involved, and degree and extent of transposition. For the observed transposition, many treatment modalities have been proposed in the literature depending on the degree of difficulty and age of the patient: (1) extraction of one of the transposed teeth that would reduce the time of treatment and make the correction easier; (2) non-extraction treatment including two different alternatives maintaining the transposed order or correcting the transposition. This case report decided to correct the transposition to obtain an ideal functional and aesthetic result. One of the main purposes was the control of the angulation and torque of the root of the first premolars and canines.

This therapeutic approach has certain limitations (17), for example, the role of periodontal inflammation in type 2 diabetes mellitus. This work presents a case report with a longer treatment duration (3 years) than usual orthodontic treatment, but this option should guarantee a symmetrical outcome without needing future restorative procedures.

## CONCLUSIONS

Dental transposition is a very challenging condition in terms of precise planning and management. The early diagnosis plays a significant role in considering esthetics and function factors to decide which treatment strategy should be followed. Therefore, treatment planning and well-designed treatment mechanics are mandatory, together with good finishing, to achieve a successful and stable result.

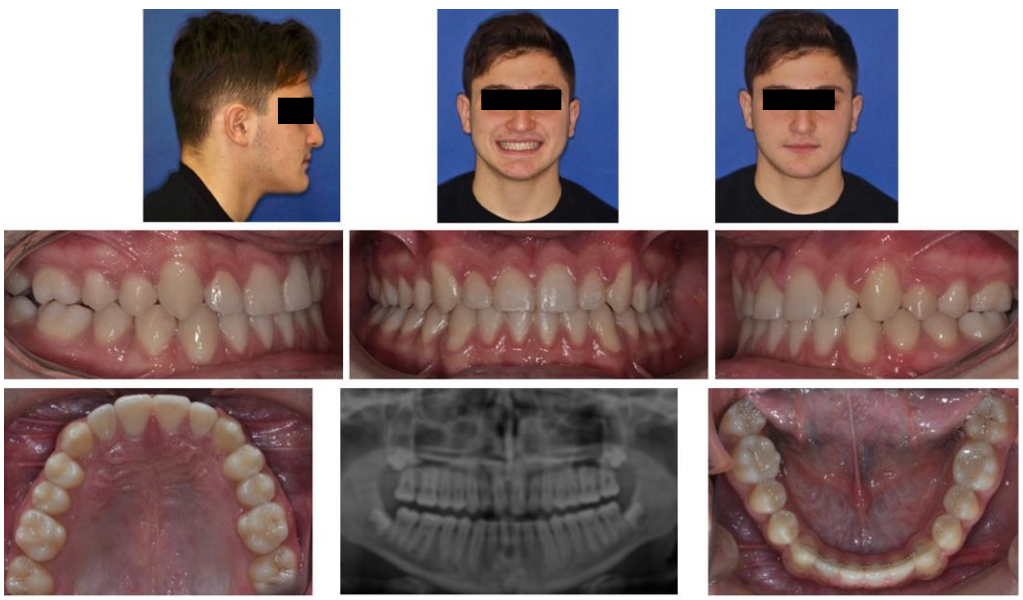

**Fig. 5.** *Post-treatment records.*

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*Case report*

# PERIPROSTHETIC KNEE INFECTION: A CASE REPORT

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## ABSTRACT

Periprosthetic joint infection (PJI) is one of the major complications resulting from prosthesis implantation. Staphylococci are responsible for more than 50% of PJI, 20% are polymicrobial, 15% are caused by gram-negative, and about 10% of cultures are negative. The complete eradication of PJI is challenging. For a correct treatment, it is helpful to perform clinical staging based on the anatomical location of PJI and the immune characteristics of the host. However, regardless of the area of infection, the surgeon's role is crucial, firstly in terms of timing and secondly in assessing the extension of the pathological process. The goal of the treatment is to eradicate PJI ensuring the maximum functional result. The reported case describes an extensive necrotic area on the right knee, with exposure to the prosthetic device, the treatment, and the available bibliography is discussed.

**KEYWORDS:** *joint, knee, infection, prosthesis, leg, bacteria*

## INTRODUCTION

Periprosthetic joint infection (PJI) is one of the major complications resulting from prosthesis implantation. The incidence of PJI is 1-2%, which reaches 4% in revisions (1-3).

There is no universally accepted definition of a PJI. Clinically, it manifests itself in multiple forms, while classical signs of a phlogistic process such as fever leukocytosis or local signs may be absent, thus making the diagnosis difficult.

Staphylococci are responsible for more than 50% of PJI, about 20% can be polymicrobial, 15% are caused by gram-negative, and about 10% of cultures are negative (4, 5). However, failing to identify the pathogen does not rule out the diagnosis. Pathogens differ depending on the onset of the infection and when the prosthesis was inserted (6, 7).

It has been observed that PJI that develop within the first 4 weeks after surgery (e.g., early infection) is caused by highly virulent microorganisms (such as Staphylococcus aureus), while those that develop after 3 months are caused by

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low virulence organisms (such as coagulase-negative Staphylococcus, Propionibacterium acnes and Enterococci). In addition, infection rates are higher in the first 2 years after surgery due to the greater vascularisation of the peri-implant tissues, which favours the hematogenous spread of PJI (8).

The complete eradication of the infection is challenging, mainly because the biofilm, a complex environment formed by bacteria within their extracellular matrix, can evade the body's immune defences, thus creating a resistance to antibiotics that is 1000 times higher than normal (9). The most relevant points on PJI were discussed during the International Consensus held in Philadelphia in 2018 to give indications deriving from the latest publications.

To apply a correct treatment, it remains mandatory to perform a clinical staging based on the infection's anatomical location and the host's immune characteristics. However, regardless of the area of PJI, the surgeon's role is crucial, firstly in terms of timing and secondly in assessing the extension of PJI.

Few articles have been published on the management of exposed prostheses, and it seems that adequate and early soft tissue coverage allows the prosthesis to be saved (10).

Skin complications are common following knee replacement surgery, although they do not always lead to exposure to the implant. In case of exposure, the simple suture is ineffective, and only a vascularised graft makes it possible to heal the wound and save the prosthesis. The gastrocnemius muscle flap is the technique of choice since it is simple and safe, allowing good-quality coverage. In addition, it can be performed in a single step, and low morbidity and no residual scarring are reasons for doing it early (11-13). Other advantages of this method are early mobilisation and hospital discharge (11). It also reduces the rate of the arthrodesis with better functional results.

Here, we describe a case of an extensive necrotic area on the right knee with implant exposure. Moreover, the available bibliography is discussed to support our clinical management and the technique employed.

## CASE REPORT

A lady, 74 years old, arrived at the hospital in February 2021 due to an evident and extensive necrotic area on the right knee that arose after a revision implant surgery in December 2020.

The patient reported a previous surgery for right knee arthroplasty in May 2017 as a result of a tri-compartmental arthrosis responsible for severe right knee pain, resistant to medical therapy and physiotherapy. After rehabilitation treatment, optimal knee range of motion recovery was reported, and recovery in normal daily activities. However, in August 2020, the patient had an accidental fall and presented a periprosthetic fracture on the right femur that was reduced and synthesised with a condyle plate.

In December 2020, due to a non-traumatic rupture of the implanted plate (Fig. 1), a second surgical treatment with implantation of mega-prosthesis revision (Fig. 2) was performed.

The patient was then admitted to a rehabilitation department where, about two weeks after admission, she reported an extensive wet necrotic ulcer on her right knee (7cmx7cm with 3 fistulous ulcers) with positive wound swab for Staphylococcus spp. (Fig. 3). Routine laboratory investigations showed C-reactive protein (CRP) 35 and erythrocyte sedimentation rate (ESR) 112.

On February 2021, the patient arrived at our hospital's emergency department presenting a wide skin loss on the implant (Fig. 3). Clinically, the patient was apyretic and in good general condition.

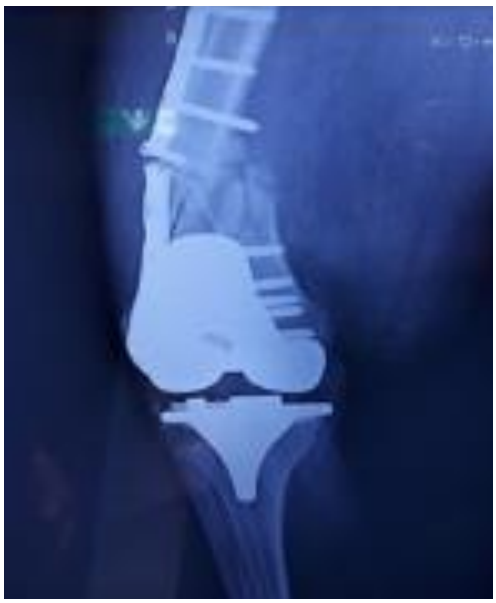


**Fig. 1.** *Non-traumatic rupture of the implanted plate.*

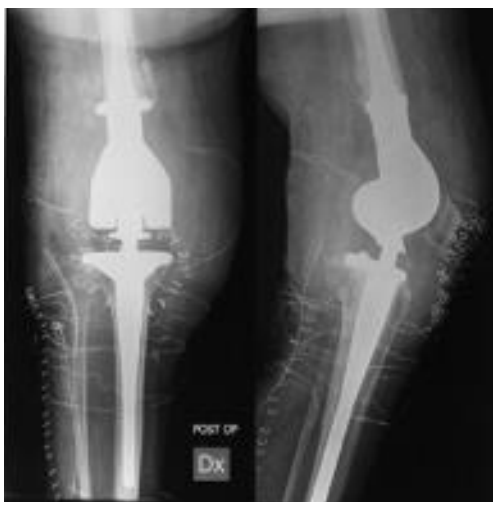



**Fig. 2.** *Second surgical treatment.*

On admission, intravenous therapy with Augmentin 2 gr x 3/day and Bactrim 60 mg 1 fl x 3/day was performed, as well as a new wound swab, while the advice from the plastic surgeon was to apply a tissue coverage of the wound after an accurate debridement and intraoperative evaluation of the depth extension of the necrotic area and the type of surface (e.g., bone or prosthesis) exposed.

The wound swab was positive for Proteus Mirabilis, so Augmentin was stopped, and Tazocin 4.5 gr x 3/day was administered. The radiographs showed no signs of detachment or mobility of the prosthetic components (Fig. 4).

Computed tomography (CT) scan revealed the presence of subcutaneous bullae at knee level with an abscess in the vastus intermedius muscle at the proximal third of the femoral prosthetic taproot; the positron emission tomography (PET) scan performed about one week after admission showed the presence of tissue with high glycidic metabolism compatible with a phlogistic process. During hospitalisation, CRP, ESR and presepsin values showed progressive improvement.

We discussed with the patient and relatives the possibility of amputation, but the patient refused. Finally, in agreement with the plastic surgeons, it was accepted to do Vacuum Assisted Closure (VAC) therapy in polyurethane foam to be replaced every 5 days and to continue the antibiotic treatment. On March 2021, the patient voluntarily resigned and continued antibiotic and medical treatment at home.

On May 2021, the patient returned to the hospital. She was apyretic, in good general clinical condition and with CRP values <2.9. Following medical treatment with VAC therapy, the necrotic area was reduced by at least 2 cm compared to those at previous admissions (Fig. 5).

CT scan showed the presence of minimal intra-articular effusion with a small collection on the lateral side of the knee extended in the subcutaneous region with a diameter of 4x2 cm. We discussed again with the plastic surgeon about therapeutic options, and the patient agreed to perform a surgical debridement of the wound and placement of a dermo-epidermal graft.

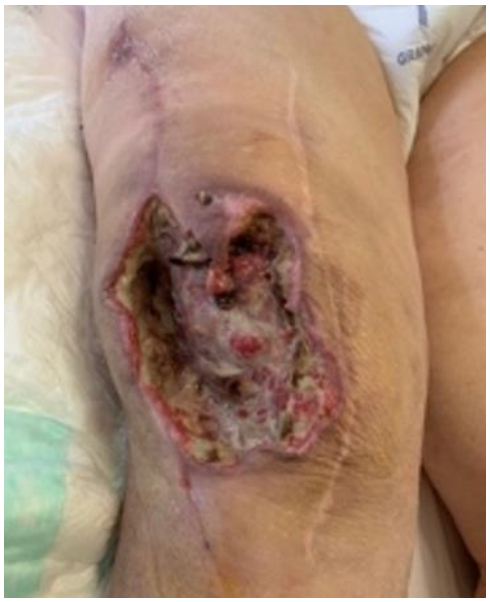


**Fig. 3.** *Skin loss on the implant.*

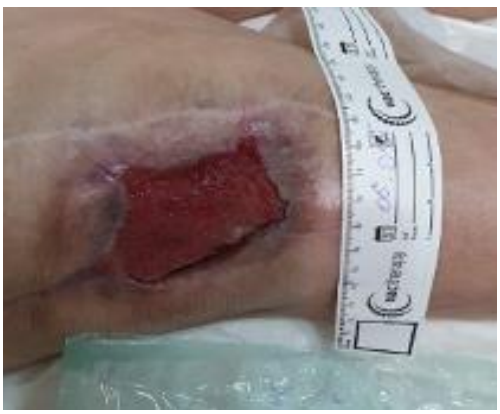


**Fig. 5.** *After medical treatment with VAC therapy, the necrotic area was reduced by at least 2 cm compared to those at previous admissions.*

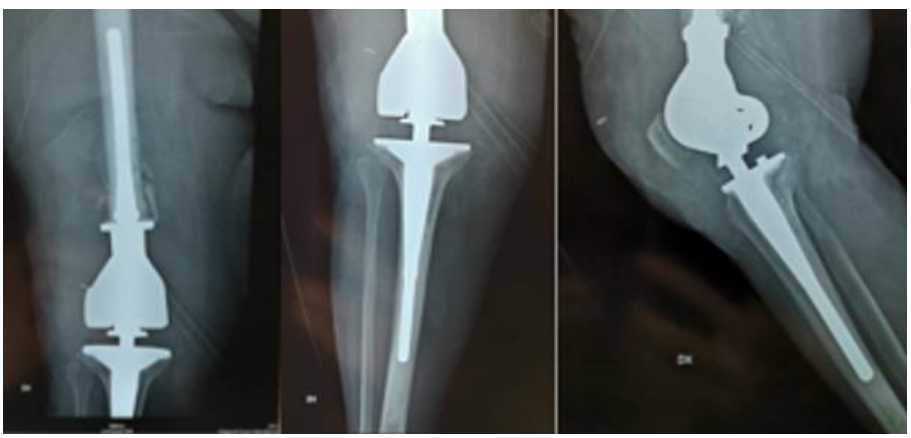


**Fig. 4.** *The radiograph of the prosthetic components.*

*First surgical procedure*

Two grams of Cefazolin were administered as antibiotic prophylaxis and 1 gram of Tranexamic acid to decrease bleeding. The patient was placed in the lateral position, and spinal anaesthesia plus sciatic nerve block was done. After 15 minutes, the patient was placed in supine decubitus, and a sterile surgical field with alcoholic chlorhexidine was done. The edges of the loss of substance were recentered, and medial parapatellar access was performed. Prosthetic components were exposed, and their stability was tested. Debridement of periprosthetic tissues was performed, and multiple samples were taken for microbiological evaluation. Washing with 4 litres of Bactisure ® solution and 2 litres of Ringer Lactate was performed as well as with 2 litres of saline solution. Finally, suturing of the arthrotomy was done.

*Second surgical procedure*

In ischemia, a skin incision was made cranially-caudally at the level of the lateral margin of the right leg. Identification of the body of the lateral gastrocnemius muscle, dieresis of the soft tissues and access to the vascular space between that muscle and the peroneal muscle was made. Detachment of the flap at the level of the insertion of the lateral gastrocnemius muscle, identification of the vascular peduncle was performed, and the flap was tunnelled (Fig. 6, 7). Finally, partial-thickness dermo-epidermal grafting was done from the ipsilateral thigh (Fig. 8). Two suction drains were placed at the level of the leg. Suturing and dressing were done.

Because of the size of the defect, we opted for a rotation flap of the lateral side of the gastrocnemius muscle, formed by two muscle bellies. The two heads originate respectively from the two femoral condyles, run in the posterior region of the leg divided by a median raphe and insert through their common tendon on the tendon of the soleus muscle forming the calcaneal or Achilles tendon. The lateral head is vascularised by the lateral sural artery that originates from the popliteal artery at the level of the articular surface of the knee. The lateral gastrocnemius rotation range allows it to cover an area up to about 5x12cm, unlike the medial wound area, which was about 7x7cm. It should be considered during lateral head rotation not to compress the peroneal nerve. The most significant disadvantage of using the lateral gastrocnemius is a cosmetic deformity from the donor site.

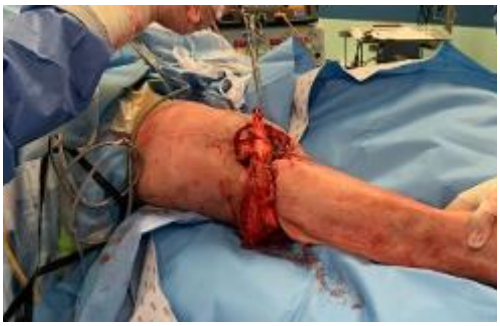


**Fig. 6.** *Detachment of the flap.*

In the post-operative period, there was a partial failure of the lateral skin flap with localised necrosis (Fig. 9-12); treated with VAC therapy. However, after 5 months, there was a complete healing of the wound and the normalisation of infection (Fig 10- 13).

Special attention was given to masks to control the COVID-19 infection during the surgical treatment (14, 15) and to the decontamination of the operating room (16).

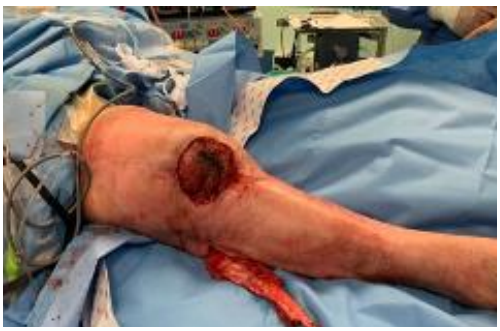


**Fig. 7.** *Tunnelling of the flap.*

## DISCUSSION

The diagnosis of PJI represents a challenge, although new criteria and scores have been developed to facilitate the diagnosis. Nevertheless, proper PJI diagnosis remains critical to choose the optimal treatment option (17). In 2011, the Musculoskeletal Infection Society proposed some criteria to standardise the diagnosis of PJI (18), which were revisited in 2013 during the International Consensus Meeting (19).

Recently, national and international workgroups have established standardised diagnostic protocols for suspected PJI. In 2018, a new evidence-based PJI definition was published, which improved performance for diagnosing hip and knee PJI (20). In addition, in 2020, the European Joint Infection Society gave the latest definition of PJI, a practical guide for clinicians based on a three-level approach (21).

In the presence of a fistula, or in case of prosthesis exposure, the total

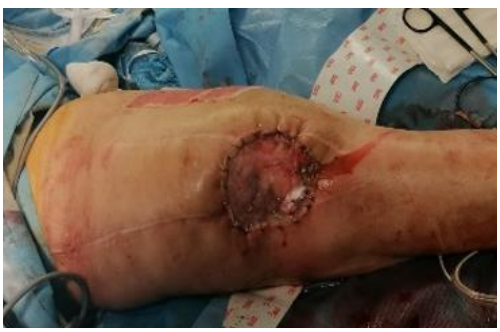


**Fig. 8.** *Dermo-epidermal grafting from the ipsilateral thigh.*

knee arthroplasty is considered infected. In occult cases, local signs of infection or fever can lead to suspicion of PJI, and pain is the most relevant symptom in over 90% of cases. X-rays in two projections, blood tests and arthrocentesis must be performed. X-rays may show prosthesis loosening and femoral or tibial osteolysis (radiolucent lines). To date, there is no clinical sign able to make a 100% diagnosis.

Usually, levels of CRP and/or D-dimers and ESR are increased, but recent studies on the sensitivity of CRP and ESR have demonstrated about 20% of false negatives (22). In case of fever (> 38 ° C), a blood culture is recommended to diagnose early-stage bacteremia and avoid worse complications such as septic shock, systemic inflammatory response syndrome,e or multi-organ failure. Another essential diagnostic step is knee arthrocentesis. If possible, any antibiotic therapy should be suspended for at least 14 days prior to sampling to increase the test's sensitivity (23).

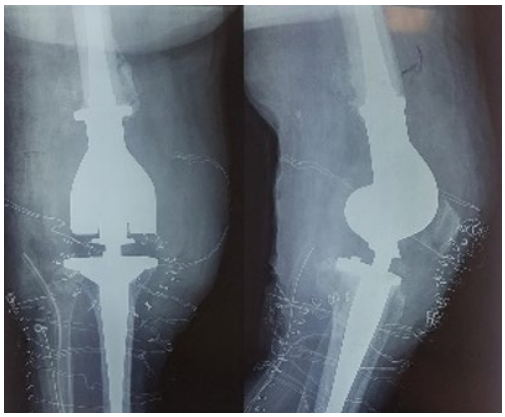
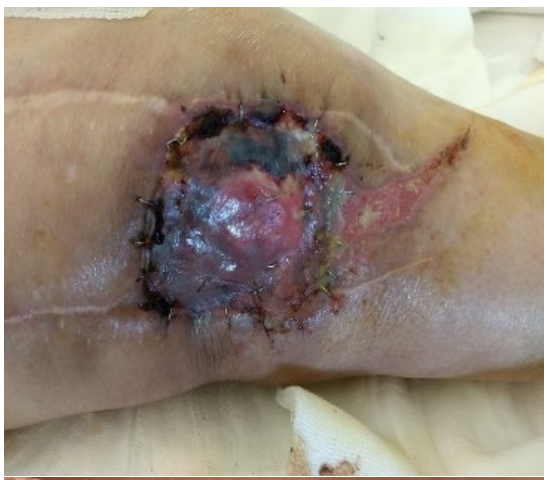


**Fig. 9.** *Post-operative X-ray.*



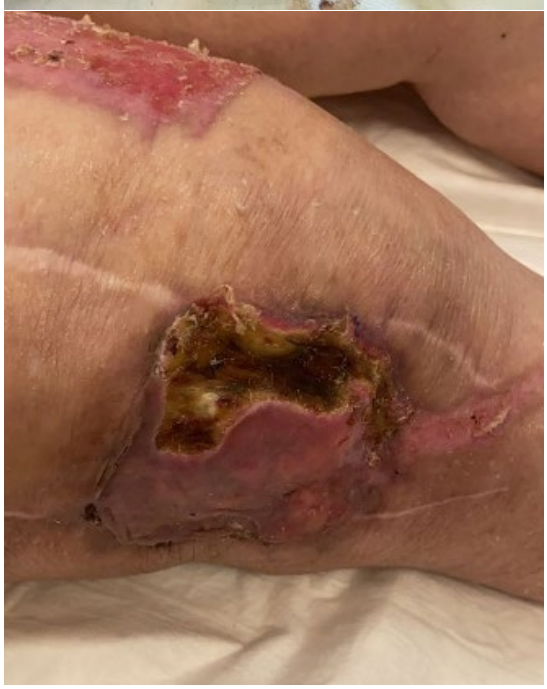


**Fig. 10.** *June 2021*

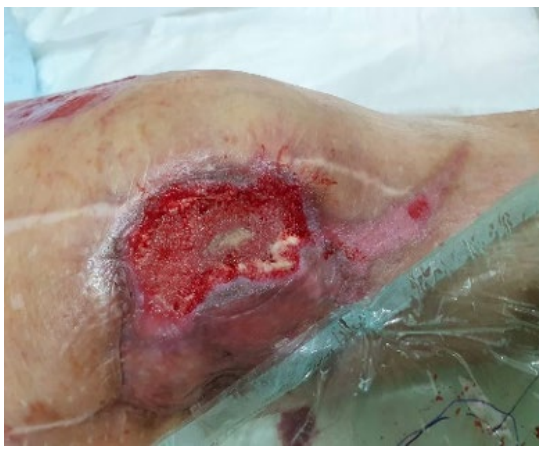


**Fig. 11.** *July 2021*

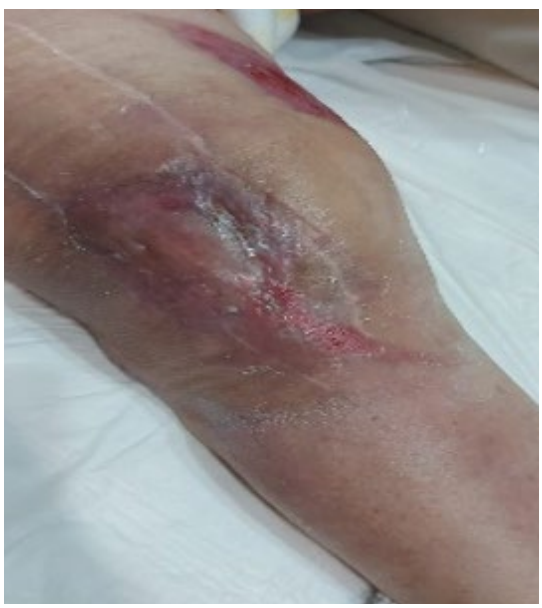


**Fig. 12.** *November 2021*

It would be recommended to take at least 2 mL of liquid to perform the various tests: alpha-defensin test and dosage of white blood cells (WBC), leukocyte esterase (LE), CRP and PMN in the synovial fluid.

Alpha-defensin is an antimicrobial peptide produced by neutrophils and, together with CRP, represents one of the new markers included in the diagnostic criteria. Alpha-defensin is a very sensitive test but presents some disadvantages, such as the high costs and the possibility of giving false positives for metallosis.

Stone et al. (24) proposed an algorithm combining the alpha-defensin test with the CRP assay to reduce false positives and negatives.

Tests can be done directly at the patient's bedside. The cheapest and fastest is the leukocyte esterase test (LET). A differential diagnosis should be made with other inflammatory arthropathies (e.g., gout, rheumatological diseases) if positive. In a meta-analysis of 1011 patients, a sensitivity of approximately 90% and a specificity of approximately 97% were shown (25**)**.

However, tests performed on synovial fluid samples, centrifuged to remove blood traces, are more reliable. In a recent study, the cut-offs considered for the diagnosis of PJI are 1630 leukocytes / microL (estimate sensitivity - SE 83.6%, specificity - SP 82.2%) and PMN (%) of 60.5% (SE 80.3%, SP 77.1%) (26). It is now recognised that swab culture tests provide a high percentage of false positives. The gold standard for diagnosing PJI is bacterial cultures, which should be grown in a microbiology laboratory for at least 14 days. Two positive cultures for the same microorganism are indicative of infection. Based on these tools, a scoring system for diagnosing PJI was created at an international meeting in Philadelphia in 2018 (Table I, II). This new score system facilitated the preoperative diagnosis and, compared to the Musculoskeletal Infection Society criteria, demonstrated an improvement in results with a sensitivity of 97.7% and a specificity of 99.5%. The last frontier for diagnosing PJI is represented by next-generation sequencing (NGS), a new application of genetic sequencing with lower costs and faster times than the classical techniques (27). NGS has proved extremely sensitive in detecting bacterial DNA (28).

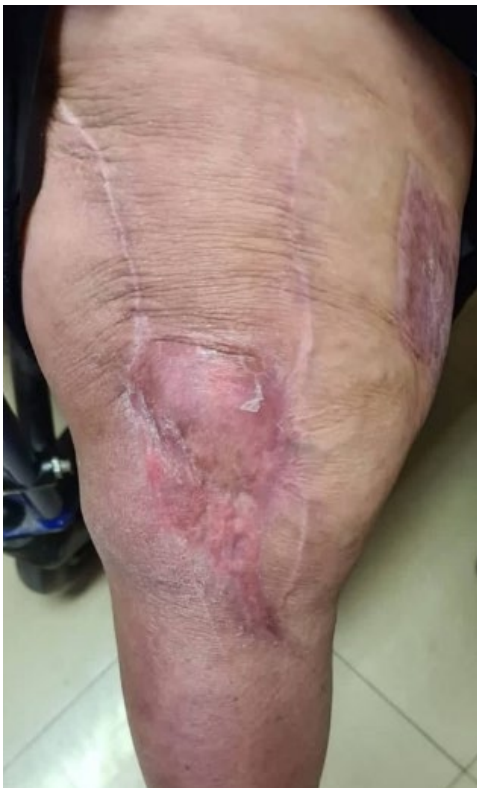


**Fig. 13.** *February 2022*

The treatment of PJI must take into account several aspects, such as the timing of the onset (early/ delayed/ late infection), the condition of the soft tissues and the clinical objectivity (i.e. the functionality of the extensor apparatus) (29, 30) the patient`s comorbidities, laboratory (i.e. inflammation indices) and microbiological data (i.e. the agent and relative antibiotic sensitivity), the stability of the prosthetic implant, the patient's expectations and the functional needs.

The treatment aims to eradicate the infection, ensuring maximum functional results. It includes antibiotic therapy as the only treatment or in combination with surgical therapy.

*Antibiotic therapy*

Antibiotic therapy is one of the two fundamental pillars in treating PJI. However, in the case of infection, the efficiency of eradicating the PJI with antibiotic therapy alone is limited, mainly due to the bacterial biofilm on the prosthetic implant. Therefore antibiotic therapy alone should be limited to specific circumstances, such as high operative risk, in the medically

**Table I.** *Scoring system for the diagnosis of PJI created at an international meeting held in Philadelphia in 2018.*

| **Major criteria (at least one of the following)** | **Decision** |
|---|---|
| Two positive cultures of the same organism | Infected |
| Sinus tract with evidence of communication to the joint or visualization of the prosthesis | |

**Table II.** *New scoring system definition for PJI (Philadelphia ICM 2018).*

| | | Minor criteria | Score | Decision |
|---|---|---|---|---|
| **Preoperative Diagnosis** | Serum | Elevated CRP or D-Dimer | 2 | ≥6 Infected<br>**2-5 Possibly Infected**<br>0-1 Not Infected |
| | | Elevated ESR | 1 | |
| | | Elevated synovial WBC count or LE | 3 | |
| | Synovial | Positive alpha-defensin | 3 | |
| | | Elevated synovial PMN (%) | 2 | |
| | | Elevated synovial CRP | 1 | |

| | Inconclusive pre-op score or dry tap | Score | Decision |
|---|---|---|---|
| **Intraoperative Diagnosis** | Preoperative score | - | ≥6 Infected<br>**4-5 Inconclusive**<br>≤3 Not Infected |
| | Positive histology | 3 | |
| | Positive purulence | 3 | |
| | Single positive culture | 2 | |

stable patient (absence of an ongoing septic picture), the presence of low virulence microorganisms sensitive to antibiotics and mechanically stable prosthesis (31). Based on the antibiogram, a specific antibiotic should be selected. Broad-spectrum antibiotics should be prescribed and used in case of an acutely PJI of the patient showing signs of sepsis (32).

Monitoring the patient during treatment and deciding the type and course of the antibiotic should be determined by specialists (e.g., microbiologists and virologists). A post-surgical protocol has to define the duration and route of antibiotic delivery.

*Surgical treatment*

Treatment must consider the degree of exposure of the prosthetic implant, in addition to PJI. In association with the antibiotic treatment, the surgical treatment has several options with different clinical outcomes: from rescue procedures (arthrodesis, amputation) to procedures with preservation of joint function (one/two-stage revision) and DAIR (debridement, antibiotic and implant retention).

*DAIR*

In early infection, the debridement and irrigation with antiseptic solutions, without implant removal, are usually the choices for surgical treatment in the absence of X-rays pictures of mobilisation of the prosthetic implant (to be confirmed intraoperatively) or of heterotrophic bone formation (radiographic signs of chronic infection) (31). The tissue removed during surgical debridement is sent to a microbiological laboratory. The application of a drain facilitates the expulsion of intra-articular blood/serum, and the local application of antibiotics in beads, in association with the systemic one, can ensure better post-operative antibiotic coverage.

In the presence of a moving prosthesis, the treatment should include replacing each modular component of the prosthetic system (32). DAIR is a valid surgical option even in the presence of mega-prostheses if sufficient covering tissue to ensure adequate post-operative wound closure is present. DAIR should be performed within 4 weeks after surgery before the biofilm is formed onto the prosthetic implant. Contraindications are chronic infections with signs of implant loosening, covering defects and patients not eligible for reoperation.

*Two-stage revision*

The prosthetic implant and any other foreign material are removed. Next, aggressive debridement of all necrotic tissues is performed, and an antibiotic spacer is implanted to allow the healing of the injured tissues and the total or partial preservation of joint motility. The second stage involves the removal of the antibiotic spacer and the implantation of a new prosthesis after the eradication of PJI (31).

The two-stage revision is indicated in the case of chronic infections with mobilisation of the implant and for infections caused by virulent organisms such as Methicillin-resistant Staphylococcus aureus (31).

*Single stage revision*

A single-stage revision is recommended in patients with a known aetiologic organism and sensitive to an antibiotic, when no abscess is present, when the patient is not immunocompromised, and if there is no radiological evidence of prosthetic implant loosening or ongoing osteitis (31). This type of revision is considered when the pathogen is sensitive to antibiotic treatment, and a specific antibiotic has to be given 2-3 weeks prior to surgery (33) when there is good coverage of healthy soft tissues onto the prosthesis and with little or moderate bone loss. Technically, the one-step revision procedure includes removing the implant and all foreign material and replacing with a new prosthesis.

*Rescue Operation*

Unfortunately, for some patients, it is not possible to perform a prosthetic re-implantation since it might lead to the patient death; thus, rescue surgeries such as arthrodesis, resection arthroplasty and amputation are needed (34). In addition, a rescue procedure is to be considered in case of a failure in the revision treatment, in case of a multi-operated knee or if the patient is debilitated (31).

*Arthrodesis*

The potential indications for knee arthrodesis are the failure of other surgical options, patients with extensive deformities, advanced alterations of the extensor mechanism, major soft tissue deficits, immunosuppression or infections with highly virulent bacteria. Arthrodesis stabilises the joint, irreversibly compromising its flexion-extension movement, allowing it to be loaded and making it painless. The surgical procedure can be performed using an intramedullary nail, a plate or an external fixator (31).

Arthrodesis is the most common rescue procedure in severe knee instability after removing a total knee prosthesis for infection. However, in some cases, it may not ensure joint stability, especially in cases where a constrained prosthesis has been explanted, which causes major bone resection. The arthrodesis's success also depends on the type of prosthesis.

Of 45 cases of arthrodesis, Brodersen et al. (35) recorded an 81% cessation following the failure of total knee arthroplasty with a condylar prosthesis, compared with a rate of 56% following the failure of a constrained implant. Similar results were recorded by Knutson et al. (36) out of a total of 85 cases of arthrodesis, the success rate after the removal of a semi-constrained knee prosthesis was 50%, compared with a success rate of 20% after the removal of a constrained prosthesis.

Furthermore, a stable arthrodesis is more challenging to achieve in those cases where implantation involves a more significant bone resection, such as in the case of the implantation of a mega-prosthesis.

*Resection arthroplasty*

Resection arthroplasty removes the implant and the cement associated with local debridement without re-implanting any device. This technique aims to create a false joint that ensures minimum mobility. The candidates for this type of treatment are patients with low functional demand (31).

After the resection arthroplasty, the limb is immobilised for three to six months. During this time, there is a retraction of the soft tissue at the level of the bone stumps subject to resection arthroplasty, which will ensure a certain degree of movement.

Resection arthroplasty can provide a viable alternative to arthrodesis, especially in severely disabled patients who may benefit from some degree of joint motility, especially if forced to be sedentary. A stiff knee in post-arthrodesis extension may be a factor that reduces rather than increases the chances of movement, especially in patients with severe disabilities (24).

*Amputation*

Amputation is a surgical rescue option to be considered when an uncontrollable local infection, reduced bone stock and significant loss of soft tissues that do not allow the wound to close are present (31).

Above-knee amputation also represents a valid alternative in those patients whose functionality of the extensor apparatus has been lost with consequent non-functional joint (27).

*Treatment of surgical wound complications*

After a knee arthroplasty, hemarthrosis can arise when drainage is reduced. The presence of persistent bleeding inside

the joint promotes bacterial growth. If bleeding is excessive, it can lead to a dehiscence of the surgical wound.

Rest and suspension of rehabilitation therapy can reduce the stress on the surgical wound and must therefore be considered in the presence of complications.

Surgical wound healing can be affected by several patient-related factors, such as nutritional status, pre-existing vascular disease, rheumatoid arthritis and/or diabetes mellitus, smoking and previous complications. In case of superficial dehiscence of the surgical wound after total knee arthroplasty and the absence of local signs and laboratory indexes of infection, the constant dressing of the surgical wound and its constant monitoring can represent the proper measures to ensure healing.

Much more serious is the presence of a large ischemic area around the surgical wound that can predict full-thickness tissue loss. A decision must be made on whether to surgically remove this area and then cover it with a skin graft, muscle flap or both. Timing is crucial in making this decision; surgery as early as possible ensures a greater chance of healing without further complications (27).

## CONCLUSIONS

Identifying the patient's risk factors, adequate preoperative planning and correct surgical execution, antibiotic prophylaxis and early management of the potential complications reduce PJI risk.

In the presence of signs and symptoms and/or laboratory tests suggestive of infection, early diagnosis and aggressive treatment increase the rate of PJI eradication.

The most important factors to be considered when choosing the best protocol for treating a PJI include the following:
the time between the first surgery and the development of the infection;
the nature of the patient's symptoms;
the radiographic findings;
the etiological agents involved and their sensitivity to antibiotics;
what type of prosthesis is present;
if the bone-cement and bone-prosthesis interface is involved in the infectious process;
whether the prosthesis has any mobilisation findings;
if replanting is possible;
how much healthy bone remains after prosthesis removal;
the presence of complications affecting the surgical wound and/or soft tissue;
the functional needs of the patient.

In consideration of these variables, rational management can be planned. Early diagnosis of PJI can ensure less invasive surgical management. In this case, surgical debridement associated with antibiotic therapy can ensure implant retention, especially in the presence of a low-virulence infectious agent.

When these criteria are absent, the prosthesis must be removed, and the implant must be replaced after debridement and local antibiotic therapy. In case the infection cannot be controlled or in the presence of important skin and soft tissue loss, arthrodesis may be the best approach. Resection arthroplasty and amputation are reserved when neither re-implantation nor arthrodesis is possible. However, it is possible to perform implant retention with DAIR in selected cases, as reported.

*Conflicts of interest*

The authors declare no conflict of interest.

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*Case report*

# SEVERELY IMPACTED CANINE: HIGH RISK OR GREAT CHALLENGE TO OVERCOME?

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## ABSTRACT

Canine impaction is a common issue in orthodontics. Canines play important functional and esthetic roles in humans, and altered eruption of these teeth is an important patient concern. Therefore, a sound diagnostic and therapeutic approach and clear knowledge of all prognostic implications are mandatory for timely diagnosis and appropriate treatment planning.

Early diagnosis and intervention are extremely important. Untreated impacted canines can result in various complications, including displacement and loss of vitality of the adjacent teeth, arch length discrepancy, dental midline shift, formation of follicular cysts, ankylosis, recurrent infections, pain, caries decay, internal resorption, external resorption of the canine and adjacent teeth, or combinations of thereof.

Due to advanced diagnostic techniques, an increasing number of patients with impacted canines are diagnosed early and referred for treatment, satisfying their increasing demands for oral health. Here, a case of an impacted maxillary canine in a young patient is reported, and the literature is discussed.

**KEYWORDS**: *cuspid, inclusion, surgery, orthodontics, tooth*

## INTRODUCTION

Impaction is defined as the failure of tooth eruption at its pre-determined site in the dental arch within its standard period of growth due to an obstacle in the eruption path or ectopic position of the tooth germ (1). Canine impaction is a

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common issue in orthodontics. Maxillary canines are the second most frequently impacted teeth after the third molars, with a prevalence ranging from 0.9 to 5%. It is more difficult to find clinical guidelines derived from studies based on large population sample allows the permanent canines to erupt normally and prevents their potential impactation (2-7).In orthodontics, dentistry, and, more generally, medicine, providing the patient with multiple options is mandatory to achieve better outcomes, solve problems, and improve the overall quality of life.

Early diagnosis and intervention are extremely important. Untreated impacted canines can result in various complications, including displacement and loss of vitality of the adjacent teeth, arch length discrepancy, dental midline shift, formation of follicular cysts, ankylosis, recurrent infections, pain, caries decay, internal resorption, external resorption of the canine and adjacent teeth, or combinations of thereof (1–7).

With advanced diagnostic techniques, an increasing number of patients with impacted canines are diagnosed early and referred for treatment, satisfying their increasing demands for oral health.

A detailed assessment of the impacted maxillary canine's location, angulation, and orientation is essential for planning treatment. A variety of radiographic assessment tools have been used for evaluation and classification. Two-dimensional (2D) panoramic X-ray has limitations, but three-dimensional (3D) cone beam computed tomography (CBCT) allows detailed localization of impacted canines and their relation to adjacent teeth (8, 9).

Impacted maxillary canines may present a wide three-dimensional range of variations with a corresponding difference in treatment difficulty.

The success of treatment is related to the complexity, duration, complications, and functional and esthetic outcomes. Therefore, evaluating the burden of care and treatment outcomes is paramount for case selection for specific interventions to improve the overall predictability and quality of treatment of impacted maxillary canines. In the literature, different treatment approaches are described:

1) extraction of the primary canine, allowing spontaneous eruption of the impacted permanent tooth;
2) extraction of impacted canine followed by implant placement on the site or orthodontic closure of the space;
3) orthodontic traction of an impacted canine, with or without the need for previous surgical exposure;
4) autotransplantation of impacted canine (7).

This case report describes the management of an impacted maxillary canine in a young patient.

## CASE REPORT

*Diagnosis*

A female, aged 13 years, came to the Orthodontic Department in July 2012 with upper and lower fixed appliances since she was already undergoing orthodontic treatment in a private office. Her request was to attempt the disinclusion of the upper right canine for which the extraction with subsequent implant-prosthetic rehabilitation was previously planned.

Extraoral examination revealed a symmetrical face with a reduced lower third and a harmonious smile arch. The profile was concave with an increased Z angle and a pronounced labio-mental groove (Fig. 1).

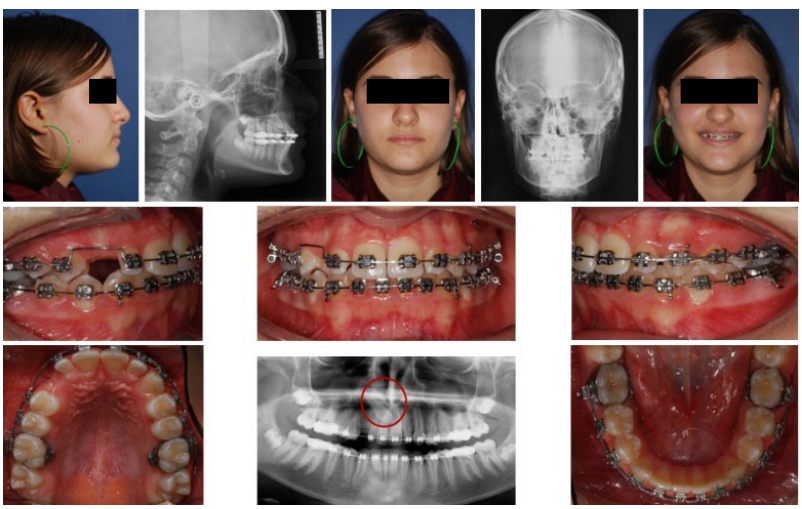

**Fig. 1.** *Pretreatment extraoral and intraoral photographs.*

Intraoral examination revealed in the frontal view a slight deviation of the upper right dental midline, microdontia of the upper lateral incisors, and an altered Bolton index. A normal OVJ and a bilateral class I were detected in the lateral view. In the occlusal view, the upper arch had diastema in the anterior sector with space in the right canine area by the previous fixed appliances. The lower arch had slight antero-inferior crowding and dental rotations.

The cephalometric analysis showed a skeletal tendency to class III malocclusion with mandibular protrusion and a hypodivergent growth pattern, and the proclination of the incisors.

The cervical vertebral maturation (CVM) analysis showed a skeletal maturation stage CS6, so the patient had passed the pubertal peak (Fig. 2).

The panoramic x-ray showed 1.3 impactions, so the angle formed between the axis of the canine and the midline was increased compared to the norm value, and the vertex of the canine cusp was positioned mesially (in sector 1 according to the classification of Ericson and Kurol, that corresponded to Lindauer's sector IV). As a result, the distance between the canine and occlusal plane was high - 15 mm (Fig. 3).

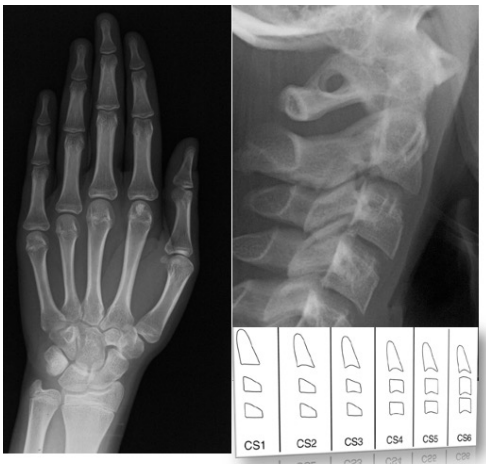


**Fig. 2.** *Radiographs showing hand-wrist (HW) and cervical vertebral maturation (CVM).*

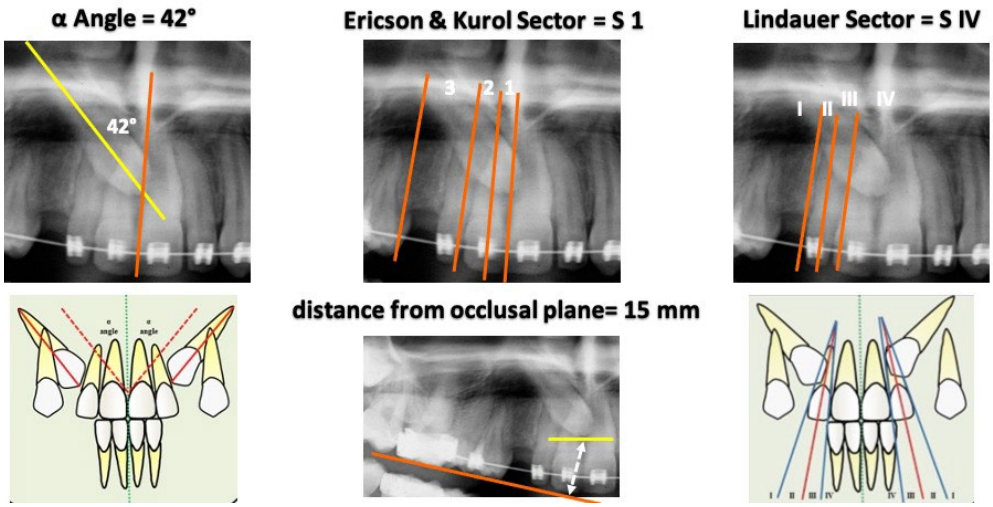


**Fig. 3.** *Panoramic x-ray examination.*

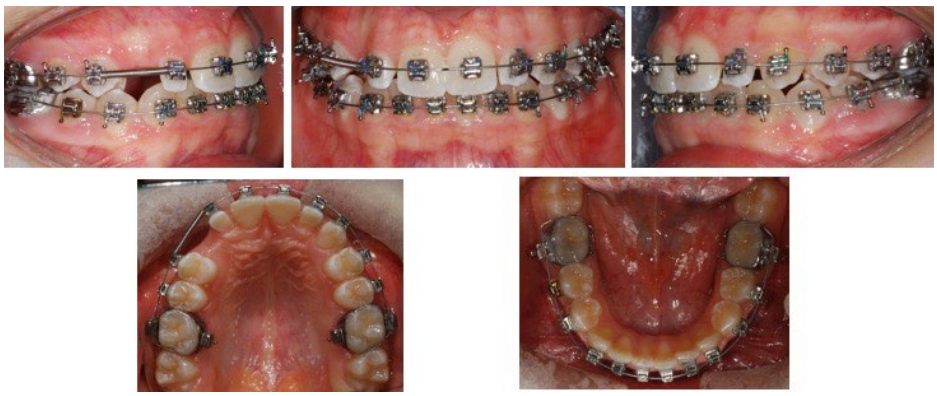

**Fig. 4.** *Initial treatment phase.*

*Treatment objectives*

The main treatment objectives were: surgical exposure and orthodontic repositioning of 1.3, correction of the upper midline, correction of the slight lower crowding, and control of the mandibular protrusion. The active treatment was carried out with a prodigy-type fixed self-ligating device, transpalatal arch, miniscrews, auxiliary sectionals, class III, and intercuspation elastics.

Moreover, the coronoplasty of 1.2 and 2.2 was performed during the recovery of the upper space. The retention phase included a Hawley retainer appliance in the upper arch and a cuspid-to-cuspid fixed retainer in the lower arch.

*Other treatment options*

Various therapeutic options were described to the patient and her parents. The first was surgical exposure and orthodontic repositioning in the 1.3 arches; the second was first extraction and replacement and implant-prosthetic replacement at 18 years. The third option was the extraction of the included canine and the closure of the space by mesialization of the posterior-posterior sectors with the disadvantage of creating a class 2 relationship on the right. The fourth option, to be listed albeit obsolete, was a treatment with surgical exposure and extraction of the canine with subsequent self-transplant. Lastly, no treatment is an option when discussing not vital therapies. Among all, the first recommended option was approved by the parents.

*Treatment progress*

As a first step, the previously fixed equipment was removed. In the same session were fixed self-ligating brackets type FACE prodigy from the second premolar to the second premolar and bands on the first molars with .014 NiTi archwires on both jaws and the addition of a closed stainless steel passive coil between 1.2 and 1.4 for the space maintenance of the canine region (Fig. 4).

The exposure of the canine was carried out with a full-thickness palatal flap, positioning of a button on the exposed surface and a metal wire .011 intertwined with eyelets (Fig. 5). The traction of the canine was carried out with a lever in TMA .017x.025 attached to the transpalatal arch with activation of 45° and distal and extrusive direction (Fig. 5).

Panoramic X-ray showed a lower inclination of the canine axis and a shorter distance from the occlusal plane, a shift also confirmed by clinical examination and palpation.

An orthodontic miniscrew was positioned in the lower arch between 4.4. and 4.5. (Aarhus System Miniscrews of American Orthodontics 8 mm x 1.5 mm in diameter) consequently, a slight loss of anchorage in the upper right arch, with an initial displacement of the occlusal was obtained (Fig. 6). The traction of the canine continued with the application of elastic between a hook tied to 1.3 and the head of the miniscrew.

The canine surface clinically appeared in the palate four months after the application of the miniscrew. Next, a lever with an Australian .020 thread was applied directly between the transpalatal arch and the button on the canine.

The following archwires sequencing was used: .016 nickel-titanium, .020x.020 Niti Bioforce, .019x.025 nickel-titanium, .019x.025 stainless steel. The retention phase included a Hawley retainer appliance in the upper arch and a cuspid-to-cuspid fixed retainer in the lower arch.

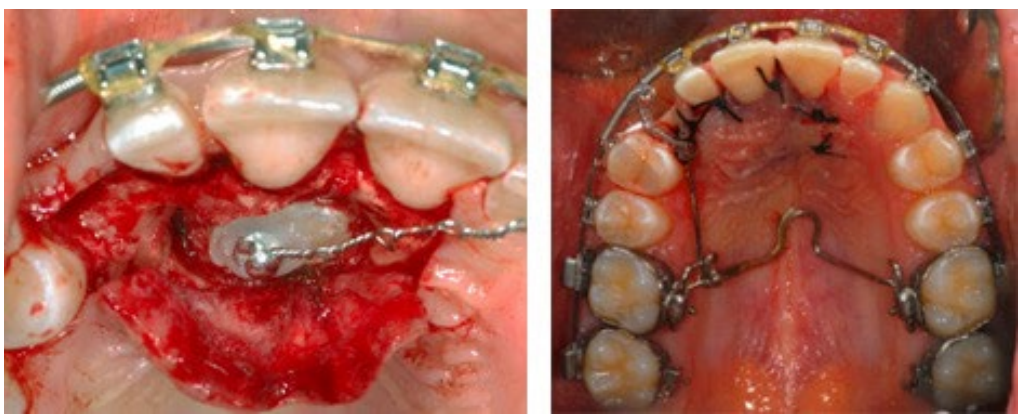

**Fig. 5.** *Impacted canine exposure and traction.*

## RESULTS

The treatment goals were achieved. The canine was repositioned on the arch, and the skeletal relationship was controlled with a nice facial profile. The occlusal, functional, and esthetic results were satisfactory; therefore, the patient and her family were happy with her smile. The patient presented class I molar and canine relationship and good intercuspation. The patient showed a full smile, maintenance of the class I molar and canine relationship, centered median lines, and a good upper arch. The end-treatment panoramic x-ray showed that all roots were in good parallelism (Fig. 7). The patient was also fully satisfied with the results. The cephalometric analysis and the overlaps showed skeletal class I and control of the mandibular protrusion, with a slight reduction in the ANB and Wits index and good control of the incisive proclination. The treatment lasted less than 3 years and comparing the initial and final check-ups highlighted the results achieved and the patient's satisfaction.

## DISCUSSION

Maxillary canine impaction usually needs multidisciplinary care, which involves oral surgery, periodontics, and orthodontic treatment. The clinicians working on the case must communicate well to provide optimal patient care (10). The management of impacted canines can be divided into two treatment categories: interceptive treatment and corrective treatment.

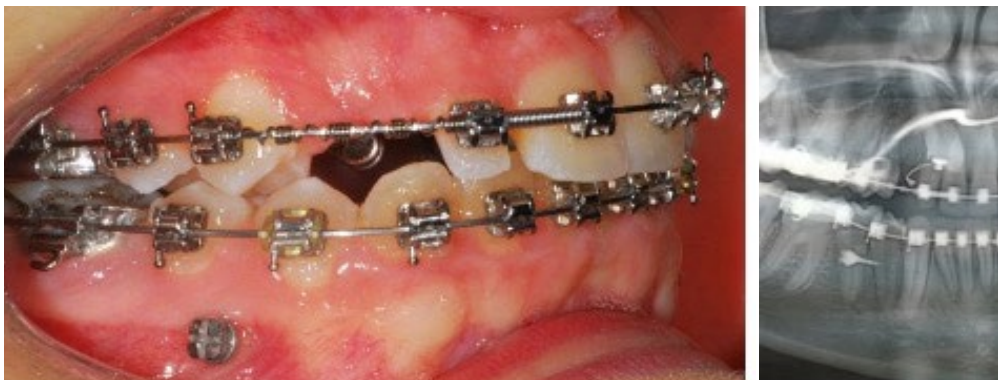

**Fig. 6.** *Miniscrew positioned between 4.4. and 4.5.*

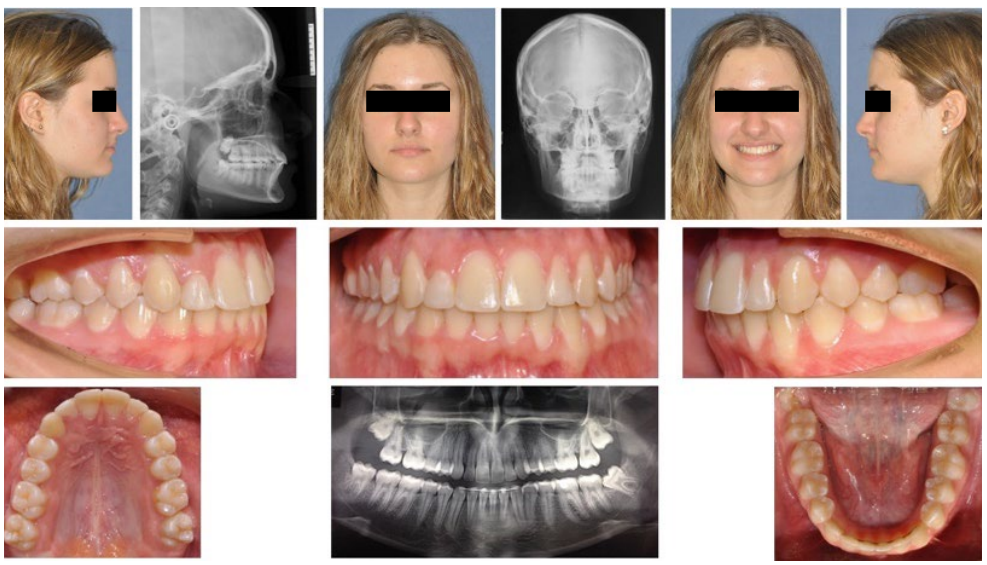

**Fig. 7.** *Post-treatment records.*

The impacted canine is always challenging for orthodontists, particularly when the patient is in permanent dentition after the pubertal growth peak (11, 12).

Preventing maxillary canine impaction is the ideal form of treatment and provides the best long-term results. Orthodontic management of impacted canines may offer considerable challenges.

Good tomographic images are fundamental to a successful therapy since they allow professionals to accurately identify and locate the position of the impacted tooth, evaluate possible injuries to adjacent roots, and quantify the bone around each tooth. It also helps detect possible ankylosis in the roots of such teeth (13), which could be interpreted as the most probable cause for them failing to reach the expected position during the eruptive movement. Visualizing these ankylosed zones may help professionals choose a different treatment protocol than conventional surgical exposure followed by orthodontic traction; this will assist in the right choice for either the impacted tooth extraction, auto-transplantation, or the execution of a deep alveolar corticotomy followed by immobilization, especially if the canine is more labially positioned. The success of early interceptive treatment for impacted maxillary canines is influenced by the degree of impaction and the patient's age at diagnosis (14).

The most desirable approach for managing impacted maxillary canines is early diagnosis and interception of potential impaction. The most common methods used to bring palatally impacted canines into occlusion are surgically exposing the teeth and allowing them to erupt naturally during early or late mixed dentition (15) and surgically exposing the teeth and placing a bonded attachment to and using orthodontic forces to move the tooth (10).

To prevent undesirable periodontal responses, clinicians should consider factors including impaction depth, the edentulous site's anatomy, and the orthodontic force's speed and direction (16). The results of several studies have shown that surgical exposure and orthodontic eruption of palatally impacted maxillary canines have minor effects on the periodontium (15, 17,18, 19).

In cases of surgical exposure aimed at triggering impacted canine displacement, good communication between the orthodontist and the surgeon is essential to adopt the most appropriate technique. In order to choose the type of surgical exposure (open or closed), elements like impaction depth, anatomy of the edentulous area, and the type of orthodontic force to be employed are some of the factors to be considered.

The treatment options and benefits of each therapeutic modality must be presented to the patient and parents. Also, the risks of the impacted canine surgical exposure may have iatrogenic consequences, including damage to the impacted canine and the neighboring teeth; damage to blood vessels and nerves adjacent to the impacted tooth and, in severe cases, bone fracture; these risks must also be presented to the patient. In the end, managing impacted canines are important in terms of esthetics and function (20).

Finally, regarding general risk, doctors have always to wear protection systems when treating the patient, as the recent pandemia has demonstrated (21-23).

In conclusion, the canines play an important functional and esthetic role, and altered eruption of these teeth is an important patient concern. Indeed, untreated impacted canines can result in various complications, so early diagnosis and intervention are extremely important.

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*Letter to the Editor*

# DOES A SECONDARY BURNING MOUTH SYNDROME EXIST?

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## ABSTRACT

Burning mouth syndrome is characterized by the absence of signs but by the chronic persistent "burning" symptom. According to some authors, a distinction should be made between primary and secondary forms of BMS, thus eliminating the unknown aetiology of burning. The diagnosis of BMS is still a diagnosis of exclusion, and this excludes the possibility that a secondary BMS may exist.

**KEYWORDS:** *burning, pain, discomfort, taste, sensation*

## INTRODUCTION

Burning Mouth Syndrome (BMS) is a pathological condition defined according to the International Classification of Orofacial Pain Committee as "an intraoral burning or dysaesthetic sensation, recurring daily for more than 2 hours per day for more than 3 months, without evident causative lesions on clinical examination and investigation" (1).

Recent metanalytic data show that its prevalence in the general population is 1.73%, with a higher prevalence in females (1.15%) than males (0.38%). The age of onset is usually 50 years, especially in the peri-postmenopausal age (2).

The burning that characterizes this condition is chronic, assimilated to the sensation of ingesting the chilli pepper. Some patients report a feeling of sourness, similar to the sensation caused by eating an unripe lotus. The burning sensation can be associated with xerostomia and dysgeusia (3). The triad characterizes the "full-blown BMS": burning, xerostomia, and dysgeusia, while in the oligosymptomatic BMS, the burning is associated with one symptom (xerostomia or dysgeusia). In the monosymptomatic form of BMS, burning is the only symptom, usually localized at the tip of the tongue (4).

The burning sensation affects, in most cases, the tip of the tongue, the palate in the retro-incisive region and the labial vestibule. In rare cases, the BMS is localized to the gingiva, the buccal mucosa, or the soft palate. The anterior portion of the oral cavity is the most involved in the symptoms, and the reasons for this characteristic are not still understood. Some authors report BMS and associated vulvodynia, fibromyalgia, TMJ, and cutaneous disorders (5-7).

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## DISCUSSION

The onset of burning symptoms differs in different patients. Some report an acute onset following dental treatments, ingesting particular foods or taking medications. Other patients, on the other hand, report a gradual, more nuanced beginning, not connected to events. Several authors have reported the importance of "life events" in initiating BMS. Bereavement, divorce and problems with children or elderly parents can trigger the burning sensation. Carcinophobia and/or previous cancer diagnosis are related to BMS (8).

Often defined as "enigmatic", the BMS still presents many aspects not clearly understood, such as the etiological origin. Psychological disorders such as depression and anxiety, neurological damages (alterations in the small-diameter nerve fibres -C fibres), reduction in estrogen and progesterone levels and salivary impairment are described as the "putative" cause of BMS, but a definitive and irrefutable etiological link has not yet been demonstrated (9-10).

*Primary and secondary BMS*

Scala et al. introduced the concept of "primary" (idiopathic) and "secondary" (resulting from identified precipitating factors) BMS since this allows for a more systematic approach to patient management (11).

In the secondary BMS, well-known pathologies or deficiencies cause the burning sensation: diabetes, B12 vitamin, allergy, iron, zinc and folate deficiencies are the most frequent cause of burning that represents a symptom and not the syndrome (12). In fact, in our opinion, in these cases is not possible to diagnose BMS because the symptom belongs to the underlying disease.

Improving the diabetic status or replacing vit. B12, folate or iron, the burning sensation disappeared, and this confirms that it was only an oral symptom (13). Therefore, the secondary forms of BMS describe burning symptomatology of the oral cavity but not exclusive to the latter.

On the contrary, the true, idiopathic BMS persists even after administering estrogen, vitamins or antidiabetic drugs (14).

Understanding the precipitating factors involved in secondary BMS would also be essential. Even stress or anxiety, trauma, parafunctions or subclinical candidiasis infection factors can be involved in the burning sensation (15).

Therefore, the "exclusion diagnosis" of BMS excludes any possibility that primary and secondary forms may exist. If all the potential causes determining oral burning have been excluded from the diagnostic process, it is possible to determine only "sine causa" BMS.

## CONCLUSION

BMS is considered an idiopathic and primary disease. Oral burning present in other known pathologies would not be included in the diagnosis of BMS but would represent a symptom of the underlying pathology.

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*Letter to the Editor*

# MOLECULAR MECHANISM OF SARCOLEMMA DISEASE: A SHORT REVIEW

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## ABSTRACT

Genetic mutations expressing components of the dystrophin-glycoprotein complex (that attaches cytoskeleton to cell membrane, the sarcolemma) can cause several muscular dystrophies. This short literature review has been conducted to assess the molecular basis of possible mechanisms and factors which affect sarcolemma and result in muscular dystrophies. A better knowledge of mechanisms that improve sarcolemma repair could lead to new therapeutic targets in treating muscular dystrophy.

**KEYWORDS:** *Sarcolemma, cell, muscle, disease, apparatus*

## INTRODUCTION

Skeletal muscle is a relatively well-organised organ system that develops mobility and energy metabolism in multicellular organisms. Genetic abnormalities are responsible for deteriorating muscle cell integrity resulting in gradual muscle waste with negative effects such as early mortality (1). Generally, mutations in different genes impact different muscle groups, and these disorders have been organised into many groups based on this. However, clinically diverse symptoms have been linked to mutations in various areas of the very same protein or perhaps even identical mutations (2). The underlying molecular biology processes disrupted in most of these disorders have been elucidated thanks to gene mapping investigations in families with affected members. Mutations of various proteins, and several structural proteins and enzymes that change several of these proteins post-translationally, have been linked to muscular dystrophy.

*Role of proteins*

Dystrophin is a large protein that anchors the sarcomere to the sarcolemma of the muscle to sustain synchronous stretching and contractions. "Duchene muscular dystrophy (DMD-d)" and "Becker muscular dystrophy" (BMD)

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are two main dystrophinopathies resulting from mutations that lead to abnormal dystrophin expression, producing asynchronous sarcomere lengthening and sarcolemma tearing (3, 4). Increased expression of utrophin, a protein comparable to dystrophin in function and structure, was found in dystrophic animal models with mutant dystrophin, likely as a key mediator for diminished dystrophin functionality (1).

The characterisation of the DMD locus product dystrophin and its localisation in the sarcolemma brought to comprehend the disease, with the identification and characterisation of the "dystrophin-associated protein complex" (4). Other muscle illnesses have been linked to a variety of novel sarcolemmal proteins. Autosomal recessive "limb-girdle muscular dystrophies (LGMD)" have been linked to mutations in any of the four "dystrophin-associated sarcoglycan subunits" (5). While "merosin-deficient congenital muscular dystrophy" has been linked to mutations in the laminin 2-chain gene (6).

The major constituents of the "skeletal muscle dystrophin-glycoprotein complex", alpha- and beta-dystroglycan, were discovered to connect dystrophin to proteins in the extracellular matrix (7). During strong muscle contractions, the dystrophin-associated complex can be considered a functional entity that reinforces the plasma membrane. Genetic mutations coding sarcolemmal proteins that aid in membrane re-sealing due to trauma, such as the dysferlin gene, trigger other muscular dystrophies. Although the caveolin-3 deficiency is sarcolemmal, it causes a change in vesicular trafficking that may have been linked to a different aetiology (8).

Dysferlin (DYSF) is also a sarcolemmal protein which might be lacking in some LGMDs patients (LGMD2B). In so many geographical locations, LGMD2B is reported to be the second most common type of dystrophy, but not everywhere (9). Massive immune cell infiltrates have been found in the muscle of dysferlinopathy patients, while dysferlin-negative monocytes have been demonstrated to be more aggressive, although macrophage adhesion and motility have been modulated. DYSF mutations are linked to various clinical manifestations, ranging from severe functional impairment to moderate late-onset forms (10). Approximately 25% of cases are clinically misinterpreted as polymyositis. The identical mutations induce "Miyoshi myopathy type 1", a distal myopathy (11). Separation of clinical phenotypes, on the other hand, is more likely to occur and is not warranted by pathological differences.

Just before initial symptoms, some individuals were quite athletic, which shows that intense strength training may alter the penetrance of DYSF mutations. As a result, regeneration appears to be slowed (12). Dysferlin plays an important role in muscle healing; hence techniques to aid membrane re-sealing in dysferlinopathy will be developed.

*Biochemical signaling and molecular processes*

The lack of functioning dystrophin is the biological aetiology of DMD. The other Dystrophin Glycoprotein Complex (DGC) components are reduced or absent from the muscular membrane, causing the shock-absorbing link at the sarcolemma to become disorganised. In mice, the deletion of the DGC-actin axis produces a threefold reduction in muscle elasticity (13); therefore, lateral force transfer is destabilised due to this. It increases the number and size of sarcolemmal microtears, primarily due to eccentric muscular contractions; this clarifies why big, non-hydrophobic muscle proteins can pass through the lipid bilayer, resulting in enhanced serum activity (14). Micro-tears are commonly related to inflammation and delayed onset muscle discomfort in healthy people (15). Any brief inflammatory reaction in healthy muscle regeneration is preceded by the activation and the proliferation of myoblasts, which differentiate into myocytes. They merge to generate myofibers, which have concentrated nuclei and heal the muscle. Generally, micro-tear creation and restoration of the lipid bilayer often proceed in DMD, but they gradually lead to muscle fibre loss. The inflammatory reaction becomes chronic and harmful in this instance (16).

Some investigations demonstrate the notion of Ca2+ ion passage into the cytoplasm via microtears and likely active calcium channels (17). High calcium concentrations or functional ischemia associated with loss of Nitric Oxide Synthetase (NOS) at the sarcolemma might have been the cause of nocturnal muscular cramps in DMD children following substantial day movements (14). Calcium entrance activates calpains, disrupting muscle protein homeostasis. Calpains are proteins belonging to the family of calcium-dependent, non-lysosomal cysteine proteases (proteolytic enzymes) expressed ubiquitously in mammals and many other organisms. Fibre degradation and death will result as a result of this.

Furthermore, upregulation of the calpain inhibitor calpastatin in mice model has been shown to attenuate the dystrophic process. It is simple to believe that calpain-mediated proteolysis is primarily involved in muscle atrophy.

Other processes have yet to be discovered. Excess calcium influx can cause fibre necrosis, which activates important damage pathways that eventually replace damaged muscle with connective and adipose tissue (18).

Nitric oxide (NO) is a signalling molecule that controls skeletal muscle processes such as blood circulation during contraction, force production, respiration, and glucose homeostasis. The breakdown of DGC stability delocalises NOS from the sarcolemma observed in DMD patients and dystrophic animal models. In the cytosol, it seems to be diffusely decreased (19). According to research, BMD (Becker muscular dystrophy) patients with losses of exons encoding R16/17 motifs inside the rod domain have the most severe form (20). As a result, NOS mislocalisation significantly contributes to the dystrophic phenotype by causing functional ischemia, exacerbating fatigue-mediated damage, decreasing satellite cell activation, and raising inflammatory responses (21).

A review suggests that porcine DMD models replicate human DMD disease in an accelerated phase. Immunofluorescence and Western blot analysis revealed dystrophin deficiency in DMD mutant pigs. The pigs showed a compensatory increase of utrophin, like DMD patients; mild at two days and severe at three months. The utrophin signal was limited to the vascular system in 2-day-old DMD piglets, but strong staining of the sarcolemma was detected in 3-month-old DMD pigs (22).

*Role of lipid metabolism*

Plasma or tissue lipid changes have been described in DMD patients (23). It was also suggested that plasma lipids play a substantial role in pathophysiology and that lipid-lowering and vascular-targeted therapy could help DMD patients (24). Statins have been described as pleiotropic medicines, meaning that in addition to decreasing cholesterol, they are known to be involved in processes linked to DMD progression, including autophagy and "NADPH oxidase 2-mediated oxidative stress". Phosphatidylcholine, sphingomyelin, cholesterol, triglycerides, and an increase in monounsaturated fatty acid species were found in the muscles of DMD patients, whereas no substantial changes in lipid metabolism were found in the muscles of BMD patients, save for lower carnitine levels (25).

Animal model of DMD with "congestive cardiomyopathy" has been widely used to explore cardiac participation in DMD (25). Only the heart, not the skeletal muscles, had a considerable reduction in total phospholipid concentration in these animals. Including both cardiac and skeletal muscles; nevertheless, the amount of phosphatidylcholine. Furthermore, DMD mice had lower activity as well as expression of "fatty acid synthase" and "stearoyl-CoA desaturase" in the liver, as well as lower insulin levels, as relative to control mice (26). Insulin insufficiency may contribute to fatty acid metabolism problems.

*Role of mitochondrial impairment/dysfunction*

Dystrophin deficiency causes a range of cellular stress factors by disrupting sarcolemmal stability, including cytoskeletal structure. In DMD patients and "dystrophin-deficient mouse model of DMD", increased oxidative stress, decreased handling of cellular Ca2+, and a substantial decrease in nitric oxide signalling due to defective activity of NOS have been described (27). Furthermore, cardiac remodelling switches energy expenditure from mitochondrial oxidation of long-chain fatty acids to extra-mitochondrial oxidation of carbohydrates in the early compensatory phase, which precedes clinical heart symptoms. All of these data suggest that mitochondrial metabolic changes exist in DMD hearts before the onset of cardiomyopathy (25).

## CONCLUSION

The focus of this brief review was on muscular dystrophies induced by mutations in sarcolemmal as well as sub-sarcolemmal proteins. The type of sickness, the hereditary cause, and the pathological pathways that could lead to future therapeutic approaches have been summarised. Mutations in genes expressing sarcolemmal proteins cause X-linked Duchenne and Becker muscular dystrophies, as well as "autosomal recessive limb-girdle muscular dystrophies". To better understand the condition, we attempt to present a critical synthesis of what we think to be the key components.

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