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Staphylococcus aureus, an orthodontic point of view

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Abstract
Introduction: Staphylococcus aureus is a pathogen present worldwide that produces a large number of toxic molecules, has a 47.5% mortality rate in patients infected with methicillin-resistant Staphylococcus aureus (MRSA), but its prevalence and its contribution to infections in the oral cavity and in the orthodontic area have not been thoroughly investigated.
Objective: To analyze the current literature on the presence of Staphylococcus aureus in relation to orthodontics, as well as its prevalence, virulence, biofilm and treatment.
Methodology: An electronic search was carried out in the databases PubMed, Google scholar and SCOPUS, compiling articles on Staphylococcus aureus published in the last 5 years; the following keywords were used for the search: "Staphylococcus aureus", "prevalence", "virulence", "biofilm", "treatment", "systemic", "oral", "dental", "orthodontics", among others.
Results: A prevalence of Staphylococcus aureus of 90.9% was found on the surface of removable orthodontic appliances. The common virulence factor presents in systemic, oral cavity and proposed orthodontic-related infections is enterotoxins. Adhesion and biofilm formation on the arch wires can be a source of Staphylococcus aureus colonization. The use of 0.2% chlorhexidine rinse is recommended before performing any treatment in oral cavity.
Conclusions: It is of utmost importance to inform patients undergoing orthodontic treatment of the risks that can occur if daily removal of the oral micro biota and cleaning of removable appliances before placing them in the mouth is not carried out.

Keywords: Staphylococcus aureus, epidemiology, virulence, biofilm, treatment

1. Introduction
The highest mortality in patients infected with methicillin-resistant Staphylococcus aureus (MRSA) was observed in 47.5% and was significantly associated with an increased risk of death [1].
Staphylococcus aureus is a worldwide pathogen that produces a large number of toxic molecules that can damage host immune cells [2]. Its virulence factors promote bacterial adhesion and invasion through damage to the tight junction barrier and keratinocytes; because of this they can inhibit the activation and transmigration of various immune cells [3]. With the evolution of bacteria and the abuse of antibiotics, drug resistance against Staphylococcus aureus has gradually increased and clinical anti-infective treatment for MRSA has become more difficult [4].
With the increase of micro biota and a lack of oral hygiene application, a higher incidence of periodontal diseases such as localized gingivitis/mild periodontitis [5], in which Staphylococcus aureus may be present [6], can be found. This can be related to some recent reports indicating high rates of MRSA carriage in the oral cavity [7]. Therefore, the oral cavity should be considered as a possible source of toxigenic Staphylococcus aureus strains, and thus a potential risk of cross-infection and dissemination to other sites in the body [8].
It is important to emphasize that some fixed components used in orthodontics (molar tubes, ceramic brackets, and elastomeric ligatures) were found to show high risks of causing periodontal disease [9], because orthodontic appliances seem to be associated with a qualitative increase in the subgingival microbiota [10] and also with a frequent increase in the amount of supragingival plaque in the vestibular region of the teeth [11].

In the literature there is no adequate review of the Staphylococcus aureus bacterium and its relationship with orthodontics; therefore, the objective is to analyze the current literature available on the presence of this bacterium in orthodontic treatment, as well as its prevalence, virulence, biofilm, and treatment.

2. Materials and Methods

The search for articles was performed and analyzed by a researcher within the PubMed, Google scholar and SCOPUS database, emphasizing articles published in the last 5 years. The quality of the articles was analyzed based on the PRISMA guidelines, i.e., identification, review, choice, and inclusion. The quality of the review was assessed using the measurement instrument for the assessment of systemic reviews (AMSTAR-2) [12]. The search was performed using the logical Boolean operators AND, OR and NOT, in conjunction with the following keywords "Staphylococcus aureus", "prevalence", "virulence", "biofilm", "treatment", "systemic", "oral" "dental", "orthodontics", among others.

3. Results and Discussion

3.1 Prevalence

Patients infected with MRSA showed a high mortality of 47.5% and was significantly associated with an increased risk of death. 1 This pathogen has been found with a prevalence of 62.4% in dairy herds in the United States [13]. In turn, this pathogen has been observed on environmental surfaces in playgrounds, where Staphylococcus aureus and MRSA were found to be 31.8% and 3.9%, respectively [14].

Staphylococcus aureus was the most common pathogen causing periprosthetic joint infections found in 26% of cases [15], and in patients with and without metabolic syndrome, bacterial counts of Staphylococcus aureus were found in 34% [16]. Among healthcare workers in a tertiary care center, 24.76% were found to have Staphylococcus aureus growth, and of these, 7.1% were methicillin-resistant [17].

The prevalence of oral cavity isolates of methicillin-sensitive Staphylococcus aureus and MRSA was 89.1% and 10.9%, respectively [18]. Staphylococcus aureus is considered the most common Staphylococcus species found in cleft lip and palate patients, accounting for 47.4% postoperatively [19]. High rates of Staphylococcus aureus resistance to penicillin, tetracycline and gentamicin were detected, respectively, 58.3%, 42.4% and 35.2% in analyzed samples of dental patients [20].

Based on the findings in relation to orthodontics, a significant increase in the prevalence and intensity of bacteremia was observed after spacer placement prior to orthodontic banding. One of the predominant bacteria isolated in the blood cultures were Staphylococcus species [21]. There is a direct relationship between the use of removable orthodontic appliances and an increase in pathogenic periodontal microorganisms. After 4 weeks wearing the removable orthodontic appliance, Staphylococcus aureus was found on the oral mucosa with a frequency of 89.09% and on the surface of the removable orthodontic appliance with a frequency of 90.9% [22]. There was a significant difference where Staphylococcus aureus was found in 7 patients without orthodontics with 36.8% and 2 patients with orthodontics with 10.5% ($p<0.05$) so the authors conclude that the use of chromium nickel brackets does not significantly alter the composition of the oral microflora [23].

Staphylococcus aureus is the most common species of Staphylococcus found in patients with cleft lip and palate, representing 47.4% postoperatively. Furthermore, a prevalence of Staphylococcus aureus of 90.9% was found on the surface of removable orthodontic appliances.

3.2 Virulence

A critical component defining the virulence of a purR mutant is the increased production of SarA, which limits protease production to an extent that promotes the accumulation of critical Staphylococcus aureus virulence factors [24]. They also define alpha-toxin as an essential virulence determinant during the interaction of Candida albicans with Staphylococcus aureus in intra-abdominal infection and describe a novel mechanism by which a human pathogenic fungus can increase the virulence of a highly pathogenic bacterium [25].

One of the most important virulence factors secreted by Staphylococcus aureus is α-hemolysin exotoxin, which can result in methicillin-resistant pneumonia that can present as a mild respiratory infection or severe respiratory failure and septic shock [26]. In addition, if this pathogen is persistent, it can cause mastitis, which produces several virulence factors, including enterotoxins [27]. Some data indicate that β-toxin is also an antiangiogenic virulence factor and highlight a mechanism in which β-toxin exacerbates invasive Staphylococcus aureus infections by interfering with tissue revascularization and vascular repair [28].

The oral cavity should be considered as a possible source of axigenic egc-positive Staphylococcus aureus strains, in terms of potential risk of cross-infection and dissemination to other body sites [8]. The enterotoxin gene cluster was the most frequently detected virulence factor in both SASM oral cavity isolates and MRSA, and in turn, genes encoding enterotoxins (sea, seb, sec, seh, sek), exfoliative toxin A and toxin-1 were present [20].

The pathogen Staphylococcus aureus has been considered as a transient member of the oral microbiota which in strains isolated from periodontal lesions presents a high-level expression of virulence genes such as: spa, coa, icaAB, clfB, ebps and sdrD; and also presents resistance to drugs such as methicillin, ampicillin, dicloxacillin, cefotaxime and penicillin [29]. The presence of periodontitis promotes the carriage of Staphylococcus aureus and may favor the spread of more pathogenic strains, because the strains possessed a distinct genotypic and phenotypic background, characterized by the presence of a greater number of enterotoxins encoding genes [30].

In HIV-positive patients, Staphylococcus aureus is one of the most common pathogens causing infection in these patients, and its pathogen-associated molecular patterns can effectively induce lytic reactivation of Kaposi's sarcoma from infected oral cells via Toll receptor reactive oxygen species and the cyclin D1-Dicer viral microRNA axis [31].

The ability to adhere to HeLa epithelial cells and strong biofilm production capabilities together, with high genotypic expression of icaA/icaD genes are an important equipment of Staphylococcus aureus to colonize orthodontic appliances [32].

There are several virulence factors of the Staphylococcus aureus pathogen which together provide the bacterium with the necessary elements that make it a very contagious pathogen. The common virulence factor presents in systemic, oral cavity and proposed orthodontic infections are enterotoxins. The above information has helped in understanding the pathogenesis of persistent infections caused by this microorganism.

3.3 Biofilm

The ClfB gene is an essential protein in biofilm formation in Staphylococcus aureus, which is increasingly expressed during biofilm formation and is involved in cell adhesion, pathogenicity, and infection by this bacterium [33].

It has been shown that 20% of all Candida albicans bloodstream infections are polymicrobial in nature, with Staphylococcus aureus being the third most common co-isolated organism which is well known for its ability to form persistent biofilms in the host and interactions within these biofilm communities can lead to increased virulence, drug tolerance and immune evasion [34].

Metabolic changes, during Staphylococcus aureus and Candida albicans infection, regulate virulence, enhance toxin production in Staphylococcus aureus or contribute to cell wall morphogenesis and remodeling in Candida albicans. Both bacteria form polymicrobial biofilms, which have higher biomass and reduced susceptibility to antimicrobials relative to monomicrobial biofilms [35]. In turn, in this interaction between bacteria, upregulated genes in biofilms correspond to multiple gene ontology terms, including those attributed to virulence, biofilm formation, and binding to proteins such as ACE2 and multiple heat shock protein genes [36].

Fusobacterium nucleatum-Staphylococcus aureus interaction revealed that RadD outer membrane adhesion is partially involved in aggregate formation and that RadD-mediated interaction leads to increased expression of the global staphylococcal regulatory gene sarA [37]. Staphylococcus aureus adhesion to oral epithelial cells and bacterial biofilm formation increased with e-cigarette exposure because it led to immunosuppression, determined by reduced secretion of IL8, IL6 and IL1β by oral epithelial cells during co-culture with Staphylococcus aureus [38].

Staphylococcus aureus strains have developed several resistance mechanisms, especially in patients with chronic antibiotic treatment, in which zirconia restorations are recommended because their surface has a weaker bacterial biofilm formation compared to other biomaterials with limited microorganism adhesion characteristics which can affect the occurrence and progression of oral cavity infections [39]. Adhesion and biofilm formation on orthodontic archwires can be a source of bacterial colonization of Staphylococcus aureus [40]. The results of biofilm-forming capacity indicated that Staphylococcus aureus showed more affinity for stainless steel materials so that control of the surface properties of materials is of crucial importance to prevent biofilm formation on dental materials [34]. Findings in a study using automated biochemical tests suggest that patients undergoing orthodontic treatment with fixed appliances have a more complex biofilm with a higher level of bacterial resistance [41].

Biofilm formation on rough orthodontic retainer surfaces by SASM is going to depend on cell adhesion enhanced by poly-N-acetylglucosamine production, whereas MRSA biofilm formation may be regulated by surface adhesions [42].

There is considerable controversy as to which genes are involved in Staphylococcus aureus biofilm due to its interactions with other pathogens and its resistance to various antibiotics, however, I consider it important to mention that the ClfB gene is essential in biofilm formation in Staphylococcus aureus. As for orthodontic patients, adhesion, and biofilm formation on the archwires can be a source of Staphylococcus aureus colonization.

3.4 Treatment

Surgical sutures based on zinc oxide nanoparticles have good antibacterial potential against Escherichia coli and MRSA, which was determined by an antibacterial wound assay in rats [43]. Antiseptic treatment has limited antimicrobial efficacy towards mature biofilms when applied during clinically relevant treatment periods [44].

Methanol extract of Salvadora persica has a significant antibacterial effect against Staphylococcus aureus and streptococcal isolates, and may be a good alternative method to control the oral pathogen [45]. In addition, the results of an *in vitro* antibacterial test study showed that hydrogels composed of hyaluronic acid and chitosan incorporated with the drug dexamethasone can inhibit MRSA in peri-implantitis [46].

The degradation of steel materials has shown problems related to localized corrosion and the formation of biofilms, in one of the studies found that in the processing by submerged friction agitation of steel materials almost no bacterial adhesion was found, which was evaluated with bacterial strains Staphylococcus aureus [47]. In turn, the combined use of titanium brush and citric acid can produce the reduction of Staphylococcus aureus on the surfaces of dental implants [48].

An alternative treatment alternative on titanium surfaces is the use of photothermal polydopamine nanoparticle coatings, which can kill Staphylococcus aureus adhering to the surface within an irradiation time interval of about 3 minutes [49].

Routine use of a 0.20% chlorhexidine mouth rinse prior to tooth extraction is recommended to reduce the risk of bacteremia after tooth extraction [50].

Within the orthodontic field, nickel-titanium wires coated with a zinc oxide nano-coating were found to exhibit significant antibacterial activity against Staphylococcus aureus [51]. Also, an enzymatic method on uncleaned orthodontic bands revealed that 5% of the sample showed bacterial growth, while manual scrubbing, use of enzymatic solution and a combination of both showed no bacterial growth [52]. The use of a 0.2% chlorhexidine mouth rinse is recommended prior to spacer placement in orthodontic patients due to the high risk of bacteremia [21].

The treatment of this bacterium is complicated, several authors mention that many strains of this bacterium have developed resistance to the effects of antibiotics, therefore its treatment with antibiotics should be very thorough. It is recommended to wash the instruments with enzymatic solutions with manual scrubbing, and as for the treatment in the oral cavity it is of great help the use of 0.2% chlorhexidine rinse before performing any treatment.

4. Conclusions

Here it should be considered that Staphylococcus aureus can be found in the oral cavity and that there is a direct relationship between the use of removable orthodontic appliances and the increase of pathogenic periodontal microorganisms. It is important to mention that one of the essential genes for the formation of Staphylococcus aureus biofilms is the ClfB gene and due to its diverse interactions with other pathogens and chronic antibiotic treatments, Staphylococcus aureus strains have developed several resistance mechanisms. There is little information about this bacterium in relation to orthodontics, but the information gathered in this article shows us that it is very important to inform our patients about the risks of contagion that exist from this and other pathogenic periodontal bacteria.

5. Conflict of Interest

Not available

6. Financial Support
Not available

7. References

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