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Ana Fabiola Plata
Master of Sciences Student, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, CP 64460, Mexico

Rosa Isela Sanchez Najera
Professor, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Josue Urian Lanas Ortiz
Professor, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Sung Soon Chang
Professor, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Juan Manuel Sifuentes Casas
Professor, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Hilda Lourdes Muñuzuri Arana
Professor, Facultad de Odontología, Universidad Autónoma de Guerrero, Acapulco de Juárez de Guerrero, México

Jose Francisco Giles Lopez
Professor, Facultad de Odontología, Universidad Autónoma de Guerrero, Acapulco de Juárez de Guerrero, México

Yuliana Moreno Alvarado
Dentistry Student, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Dr. Juan Manuel Solis Soto
Professor, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Corresponding Author:
Dr. Juan Manuel Solis Soto
Professor, Facultad de Odontologia, Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Fusobacterium nucleatum: Update on epidemiology, clinical manifestations, diagnosis and treatment

Ana Fabiola Plata, Rosa Isela Sanchez Najera, Josue Urian Lanas Ortiz, Sung Soon Chang, Juan Manuel Sifuentes Casas, Hilda Lourdes Muñuzuri Arana, Jose Francisco Giles Lopez, Yuliana Moreno Alvarado and Juan Manuel Solis Soto

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Abstract
Introduction: The oral pathogen *Fusobacterium nucleatum* is linked to several types of cancer. Understanding how this microbe promotes tumor growth could revolutionize cancer detection and treatment.
Objective: To analyze the literature on relevant aspects of *Fusobacterium nucleatum*, particularly its epidemiology, diagnosis, treatment, systemic and oral manifestations.
Methodology: A search strategy was carried out in PubMed, Scopus and Google Scholar databases, using a combination of keywords including: *F. nucleatum*, epidemiology, diagnostic, treatment and oral manifestations.
Results: Prevalence is shown in patients with colorectal cancer in Asia, especially in China, Japan and Iran, where they suggest its role as a potential biomarker for the diagnosis of the disease through its DNA in affected tissues using techniques such as PCR that has shown high effectiveness in cancer studies along with laboratory tests such as next generation sequencing (NGS) and bronchoscopy. Its treatment is based on a combination of surgical interventions and the use of specific antibiotics in which they also recommend the use of probiotics to boost the immune response. Its manifestations contribute to a variety of periodontal diseases and it is associated with adverse symptoms in dental treatments.
Conclusion: *Fusobacterium nucleatum* is crucial in colorectal and oral cancer, acting as a biomarker for its detection and migrating from the mouth to the colon, highlighting the need for targeted treatments and innovative strategies such as probiotics and nanotechnologies to counteract its pathogenic effects and prevent related diseases.

Keywords: *Fusobacterium nucleatum*, diagnosis, epidemiology, treatment, oral manifestations

1. Introduction
Evidence shows how the oral pathogen *Fusobacterium nucleatum* is implicated in various types of cancer, leading to the development of new detection and treatment strategies [1]. This Gram-negative anaerobic bacterium, initially isolated from dental plaque, is closely associated with periodontal disease and other oral conditions [2]. In addition, it has been linked to the progression of gynecological cancers such as breast, ovarian, endometrial and cervical cancers, due to its ability to influence the immune system and activate critical signaling pathways, as well as being associated with pregnancy complications and other health problems [3]. *F. nucleatum* also acts as an important agent in coaggregation within the oral cavity, facilitating adhesion between early and late plaque colonizers [4], and its ability to adhere and invade cells and enhance inflammation underscores its role in periodontitis and tissue destruction [5]. Furthermore, this bacterium is implicated in the progression of colorectal and oral cancer, adapting to hypoxic tumor environments and manipulating the immune system [6]. Its virulence factors and mechanisms to form biofilms not only promote its survival in the hostile oral cavity but also affect the oral microbiota and the host immune response [2].
A recent review has revealed a significant lack of organized data on the epidemiology, diagnosis, treatment and both systemic and oral manifestations of *Fusobacterium nucleatum*.

A thorough understanding of these aspects is crucial to improve the management of its oral and systemic health impacts. This will not only facilitate the development of more effective therapeutic strategies but will also allow the implementation of preventive measures that optimize health outcomes worldwide.

In this work we analyzed the literature on *Fusobacterium nucleatum* from an odontological point of view, particularly its epidemiology, diagnosis, treatment, systemic and oral manifestations.

2. Methodology

An electronic search was carried out through PubMed, Google Scholar and Scopus, using the terms: "*Fusobacterium nucleatum*", "epidemiology", "diagnosis", "treatment", "systemic manifestations", using Boolean operators "AND" and "OR". The quality of the articles was evaluated using guidelines tool. As inclusion criteria, only articles from high impact journals were collected, including systematic reviews, literature reviews or clinical studies that treated in behavior management techniques. Likewise, the search was delimited in terms of publication date, taking only recent articles, published mainly within the last 5 years. The selection of articles was made according to the relevance of the title and/or abstract to the topic to be analyzed. After the selection of relevant studies, their references were searched for possible additional relevant studies that met the inclusion criteria.

3. Results

3. Epidemiology

3.1 Regional

The prevalence of *Fusobacterium nucleatum* in Asia, particularly in China, Japan and Iran, has been evaluated in relation to colorectal cancer and other diseases. Studies use case-control methods and tissue sample analysis, suggesting a potential role of this bacterium in disease pathogenesis [7]. A meta-analysis in the same region highlighted a higher prevalence of *F. nucleatum* in patients with colorectal cancer compared to healthy controls, highlighting its relevance as a biomarker for the diagnosis and follow-up of this disease [8]. In addition, an investigation in Brazil found a high concentration of potentially oncogenic bacteria in colorectal cancer, with Fusobacterium being the most abundant genus in tumor tissues, indicating significant clinical and molecular characteristics in a Brazilian cohort of colorectal cancer patients [9].

3.1.1 Systemic

Research reveals that the presence of *Fusobacterium nucleatum* DNA in tissues affected by colorectal cancer is associated with decreased survival, highlighting its usefulness as a biomarker for predicting disease progression [10]. Furthermore, *F. nucleatum* has been observed to migrate from the oral cavity to the colon, although the specific mechanism in the bloodstream remains unclear. The abundance of this bacterium in colorectal cancer tissue is inversely related to overall survival, underscoring its impact on cancer progression [4]. In another study, *F. nucleatum* was found to promote the proliferation of oral squamous cell carcinoma cells through the CDH1/β-catenin pathway, providing new insights into its role in oral cancer progression and its potential as a target for treatments [11].

3.1.2 Oral

Studies highlight that the oral cavity harbors multiple subspecies of *Fusobacterium nucleatum*, with a more notable diversity in dental plaque compared to abscesses [12]. In particular, the subspecies *F. nucleatum* subsp. animalis is prevalent in inflamed areas and its impact on diseases such as colorectal cancer underscores the need for further research on how this oral bacterium affects such disease [13]. Furthermore, *F. nucleatum* subsp. polymorphum is the most commonly found subspecies in both healthy mucosa and oral potentially malignant lesions (OLK), suggesting that local host factors, such as glycosylation patterns and the local microbiome, may influence the selection of adhesins that facilitate oral colonization [14].

Studies highlight that *F. nucleatum* is crucial in the development of colorectal cancer, acting as a potential biomarker for disease detection and monitoring. Furthermore, its presence in the oral cavity and its migration to the colon suggest a significant impact on both oral and systemic pathology, underlining the importance of future research to develop specific treatments against its pathogenic effects.

3.2 Diagnosis

3.2.1 Systemic Diagnosis

Fusobacterium nucleatum DNA was found in the tumor tissue of 109 cases, representing 13%. There is an inverse correlation between CD274 expression in the tumor and the presence of *F. nucleatum* in colorectal cancer, showing that the higher the bacterial presence, the lower the CD274 expression, according to multivariate probability adjustments [15]. Additionally, it was observed that the presence of *F. nucleatum* is negatively associated with peritumoral lymphocytic reaction, with an increased lymphocytic response in the absence of the bacterium [16]. It was also linked to a reduction in the density of memory helper T cells in the stroma, suggesting pathogenic interactions between the microbiota and the immune system [17]. *F. nucleatum* was reported to be found in 86.7% of colorectal cancer cases and in 73.1% of precancerous colon disease cases. IgA and IgG levels of *F. nucleatum* were significantly higher in patients with colorectal cancer compared to healthy individuals [18]. An analysis of 1,198 individuals revealed the effectiveness of *F. nucleatum* as a biomarker of colorectal cancer, with high diagnostic accuracy [19]. Finally, *F. nucleatum* is considered a significant risk factor for colorectal cancer, highlighting its potential as a target for colorectal cancer prevention and treatment [20]. A case of a patient with squamous cell cancer and empyema caused by *Fusobacterium nucleatum* was reported, where NGS and bronchoscopy were crucial for rapid identification of pathogens and pathology [21].

3.2.2 Oral Diagnostics

The ability of Porphyromonas gingivalis and *Fusobacterium nucleatum* to induce oral cancer has been robustly verified through both *in vitro* and *in vivo* studies, pointing to their potential as biomarkers for the detection of oral cancer. Virulence factors such as FimA and FadA of these bacteria are also presented as potential therapeutic targets to prevent this disease [22]. In another study, *F. nucleatum* was detected in root canals, showing significant differences in its presence between primary and secondary infections using culture and nested PCR methods [23]. In addition, it was observed that E. faecalis can adhere to *F. nucleatum* under biofilm conditions, which impacts the survival of *F. nucleatum* by generating an acidic environment and producing hydrogen peroxide [24]. In inflammation-related research, *F. nucleatum* has been shown to induce an inflammatory state in RAW264.7 cells,

increasing cytokine production and various types of cell death, a phenomenon significantly reduced by inhibition of ZBP1 protein [25]. Early identification of biomarkers is crucial for the effective management of oral cancer [26].

F. nucleatum is significantly relevant in the progression of colorectal and oral cancer, impacting both survival and immune response of patients. Its high prevalence in cancer underscores its potential as a biomarker for diagnosis and monitoring, and opens possibilities for its use in preventive and therapeutic treatments. In addition, their interactions in biofilm environments and their ability to modify the immune response highlight the need for strategies that address their influence in both oral and gastrointestinal cavities.

3.3 Treatment

3.3.1 Systemic Treatment

The most effective strategies to manage *Fusobacterium nucleatum* infections include the combination of surgical interventions and antibiotic treatments such as penicillins and metronidazole, specifically for head, neck and other soft tissue problems [27]. On the other hand, Boreak *et al*. explore the use of the antibiotics Lomefloxacin and Enoxacin, which act on the lipopolysaccharide biosynthesis of *Fusobacterium nucleatum*, as a treatment for endodontic infections. This in silico approach suggests a potential for the development of new therapeutics [28]. Furthermore, nanosystems combined with chemotherapeutics are emerging as promising, improving the efficacy of chemotherapy against tumors and counteracting *Fusobacterium nucleatum*-induced resistance and immunosuppression [29]. In the oral cancer setting, vaccines employing phage-like particles, in addition to presenting tumor antigens and being used in targeted therapies, show promise in preventing oral infections [30].

3.3.2 Oral Treatment

Modern strategies for oral treatment of *Fusobacterium nucleatum* include inhibition of virulence factors and biofilms to minimize antibiotic resistance and adverse immune reactions, as well as the use of microbiota replacement therapies, such as probiotics, to preserve oral health without relying exclusively on antibiotics [31]. In addition, the incorporation of specific probiotics such as Lactobacillus rhamnosus and Bifidobacterium breve is recommended to counteract *F. nucleatum* and boost immune responses against cancer [32]. For systemic implications, such as bacteremia, the use of antibiotics such as metronidazole and amoxicillin has been shown to be effective against *F. nucleatum* infections [33]. In the context of the interaction between *F. nucleatum* and Porphyromonas gingivalis, neutralization of FomA significantly reduces bacterial co-aggregation, biofilm formation and the production of volatile sulfur compounds, and vaccination targeting FomA has been observed to protect against gingival inflammation caused by co-infection [34]. Finally, periodontal treatment has been shown to reduce the presence of *F. nucleatum* in the stool of patients with colorectal tumors, although whether this reduction can prevent the development and progression of colorectal cancer remains to be determined [35]. Strategies to treat *F. nucleatum* infections include combinations of surgeries and antibiotics such as penicillins and metronidazole for systemic cases, as well as innovative approaches such as biofilm inhibition and the use of probiotics for oral treatments; the aim is to improve the efficacy of therapy against tumors and reduce bacterial resistance, highlighting the potential of new therapies such as nanosystems and specific vaccines to combat infection and prevent associated diseases such as colorectal cancer.

3.4 Manifestations

3.4.1 Systemic Manifestations

A recent study highlighted that *Fusobacterium nucleatum* may contribute to systemic inflammation during treatments such as chemotherapy and hematopoietic stem cell transplantation, influencing the development of conditions such as febrile neutropenia [36]. Another study suggests that changes in the oral microbiome, combined with genetic and lifestyle factors, could cause Fusobacterium, commonly present in the mouth, to occasionally become carcinogenic [5]. In addition, it was observed that *F. nucleatum* can move from the oral cavity to other parts of the body, potentially causing various diseases, including cancers, and was found to produce significant amounts of butyric acid, crucial for colonocytes, which have an anti-inflammatory role [37].

3.4.2 Oral Manifestations

It has been observed that the presence of *F. nucleatum* is associated with various symptoms in endodontic patients, such as spontaneous pain, sensitivity, swelling and problems in dental restorations [23]. In relation to periodontal diseases, bacterial populations vary according to the severity of the clinical manifestation, with *F. nucleatum* being one of the frequent pathogens in acute conditions such as abscesses, in addition to its presence in chronic periodontitis [38]. Furthermore, it has been documented that *Fusobacterium nucleatum* is not only a major agent in periodontitis and other oral diseases, but is also considered a factor in the promotion of colorectal cancer [26]. The oral diseases most commonly associated with this pathogen range from gingivitis to more severe periodontitis, highlighting its significant role in the pathogenesis of these conditions [39, 40].

F. nucleatum is instrumental in triggering systemic inflammation during medical treatments such as chemotherapy, potentially contributing to the development of cancers due to its migration from the oral cavity to other organs. It is also prevalent in severe oral manifestations such as periodontitis and endodontic diseases. Its influence on various systemic and oral conditions underscores the need for effective management and treatment strategies.

4. Conclusion

F. nucleatum plays a critical role in colorectal and oral cancer progression, serving as a promising biomarker for diagnosis and monitoring. Its migration from the oral cavity to systemic sites underscores its impact on both local and systemic diseases, necessitating targeted therapeutic strategies. Current treatments, including antibiotics and biofilm inhibitors, require enhancement to combat resistance and improve efficacy. Innovative approaches like probiotics, nanosystems, and vaccines hold potential for managing *F. nucleatum* infections and preventing associated cancers. Further research is essential to develop effective interventions against its pathogenic effects in oral and systemic health.

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6. Author's Contribution

Not available.

7. Conflict of Interest

Not available.

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Not available.

9. References

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