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Inflammation-mediated Polymicrobial Emergence and Dysbiotic Exacerbation (IMPEDE) hypothesis

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Abstract

Introduction: The nexus between periodontal inflammation and the polymicrobial biofilm in the gingival sulcus is critical to understanding the pathobiology of periodontitis. Both play a major role in the etiology and pathogenesis of periodontal diseases and each reinforces the other. However, this nexus is also at the center of a significant conundrum for Periodontology. For all mucosal polymicrobial biofilms, the most confounding issue is the paradoxical relationship between inflammation, infection, and disease. Despite significant advances made in both periodontal microbiology and periodontal pathobiology, the issue of which comes first, the inflammatory response or the change to a dysbiotic subgingival microbiota, is still debated. **Objective:** In this paper, the model for the pathogenesis of periodontitis based on the central role of inflammation and how this modulates the polymicrobial biofilm within the context of the continuum of health, gingivitis, and periodontitis, termed "Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation" (IMPEDE) is reviewed and how it integrates into and complements the 2017 World Workshop Classification of Periodontitis is presented.

Keywords: *Periodontitis. Biofilms. Inflammation.*

Introduction

In 2020, a new model for the pathogenesis of periodontitis termed "Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic Exacerbation" (IMPEDE") was proposed by Van Dyke, Bartold and Reynolds[1]. This was intended to assimilate with the 2017 World Workshop Classification of Periodontitis[2].

As early as 1981, Irwin Mandel observed that the specific flora of the deep pocket may be of significance only at a late stage of periodontal disease[3]. This elegantly surmises the basis of the IMPEDE model in that inflammation is probably a key event and the specific dysbiosis is a later "significant event". Indeed, periodontitis is now considered an inflammatory disease in which opportunistic and commensal bacteria, part of the normal oral microbiota, cause disease when the host is immunosuppressed. Thus, a concept of controlling periodontal inflammation to control periodontal infection has been proposed[4].

In 2018 a revised classification of the plaque-associated periodontal diseases was published based on the findings of the 2017 World Workshop Classification of Periodontitis[2]. The plaque-associated periodontal diseases varied in severity that ranged from periodontal health through to advanced dentition-threatening disease. Accordingly, the periodontal diseases were classified by a sequential process of stage and grade allocation. Despite this new approach to disease classification, a number of questions remain unanswered:

- What is the process that leads to progression from the well-contained inflammatory response seen in gingivitis to the more widespread destruction seen in periodontitis?
- What drives the subgingival microbiome to become dysbiotic?
- Does dysbiosis arise spontaneously or is it a result of the ever-changing local milieu of the periodontal pockets?
- How does the dysbiotic microbiota interact with host innate and acquired immune responses?
- Is infiltration of periodontal tissues by bacteria causative, or a result of disease?

In this paper the interrelationship between periodontal inflammation and microbial dysbiosis is considered. This is crucial to understanding the initiating events associated with the development of periodontitis and how it is currently staged.

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The paradox of periodontitis and effectiveness of oral hygiene

A long-time dilemma in Periodontology has been the so-called "Paradox of Periodontitis". Our clinics are full of patients who appear to have minor plaque deposits yet manifest with very significant periodontal destruction, while others have significant deposits of plaque yet show little overt disease. These observations highlight the fact that bacteria are necessary but not sufficient for development of periodontitis[5]. Accordingly, it seems appropriate to re-evaluate the role of oral hygiene & specific bacteria in the development of periodontitis.

Over 23 years ago it was noted that, notwithstanding the awareness by patients for appropriate oral hygiene, sustained encouragement by the dental profession for better oral hygiene, and the resultant overall improvement in population oral hygiene habits, the prevalence of advanced periodontitis had remained largely unchanged[6]. The situation today is no different: 90% of all humans have gingivitis; mild, moderate and severe periodontitis affect up to 62% of all adults; and approximately 20% of humans have severe periodontitis[7]. Indeed, there is insufficient evidence to conclude that the prevalence of periodontitis has changed over time[8].

This raises several questions. Why has our focus on oral hygiene not always been successful? Is it that we forgot the patient as a whole, with both the mouth and body connected? Several authors over the years have made similar observations. Improved oral hygiene, practices, devices and products have been shown to have a positive effect, as manifested by a reduction in plaque scores and in the prevalence of gingivitis, but they have had little effect on periodontitis[9]. Interestingly, the prevalence of severe forms of periodontitis has remained stable, thus factors other than plaque alone must be involved[10]. This raises the question: have we misunderstood, plaque/specific bacteria and host in the continuum of disease prevention and manifestation?

Plaque and periodontal risk

It is interesting to note that in one important periodontal risk assessment tool[11], dental plaque and specific periodontal pathogens do not form part of the assessment algorithm. This does not diminish the role of plaque/bacteria in the pathogenesis of periodontitis. It is evident that full-mouth assessment of the bacterial load must have a pivotal impact in the determination of the risk for disease recurrence. However, studies to date have been unable to identify what level of plaque accumulation is compatible with maintaining periodontal health. For example, many patients can tolerate plaque accumulations of 20-40%. Nonetheless, plaque control remains central to viable preventive and treatment strategies. Therefore, it is important that the full-mouth plaque score must be related to the host response (inflammatory parameters) of the patient[11].

Plaque has been noted to account for only 20% of the risk for periodontitis[12]. Therefore, one must question what role does the remaining 80% of risk factors play in this equation. Clearly, periodontitis is a multifactorial disease. Accordingly, predisposing and modifying factors must be accounted for in pretreatment assessment, and the contributions of all risk factors to disease pathogenesis must be recognized and taken into account when trying to unravel the pathobiology of periodontitis.

Pathology of periodontitis

The critical biological events to understand any pathological process and its management are: (1) initiation of disease, (2) exacerbation of disease and (3) resolution of the disease.

» *Initiation of periodontitis:* In most people (but not all), if dental plaque adjacent to the gingival margin is not disrupted regularly, gingivitis will ensue[13]. Gingivitis has been considered the precursor of periodontitis. However, of particular interest is that not all individuals who develop gingivitis proceed to develop periodontitis. Identification of the factors responsible for the conversion of chronic gingivitis to periodontitis remains unclear[14]. This observation was again highlighted in a review revisiting the Page and Schroeder model[15]. Here, the authors observed that there is a dichotomy between the homeostatic protective and destructive host responses, and that this issue still has not been adequately resolved.

» *Exacerbation of periodontitis:* This is when gingivitis progresses to periodontitis. The development and advancement of periodontitis occur with developing microbial dysbiosis. However, this appears to be an association rather than a causal event. Investigations into the exacerbation of periodontitis have been limited to associations with various events, but solid evidence for cause and effect has been difficult to substantiate. With increasing inflammation, there is a significant change in the subgingival environment, and this appears to coincide with alterations in the constituents and amount of subgingival biofilm and an associated microbial dysbiosis. Interestingly the influence of inflammation on the development of dysbiosis has been noted in other polymicrobial/inflammatory diseases[4,16-19]. Nonetheless, neither the host response nor the microbial biofilm are the sole drivers of disease initiation and progression. Indeed, the timing and sequence of how these components of periodontitis have not been well defined.

» *Resolution of periodontitis:* Resolution of periodontal inflammation is defined as restitution of tissue homeostasis and a return of a commensal plaque microbiome in equilibrium with the host. In periodontitis, spontaneous resolution of inflammation does not occur due to the

increased bacterial diversity and mass associated with the ongoing tissue inflammation and changing pocket milieu. Importantly, the evolving dysbiosis of the subgingival microbiome contributes to ongoing inflammation that further exacerbates the periodontitis condition. This ongoing vicious cycle seemingly can only be reversed by reducing the bacterial load, leading to a reduction in inflammation, prevention of further tissue destruction and modification of the dysbiotic biofilm. However, several animal studies of experimental periodontitis have shown that by targeting resolution of inflammation, periodontal bone resorption improves, bacterial mass decreases and dysbiosis is reversed[20,21]. Recently, in a human clinical trial, it was shown that topical application of the pro-resolving lipid mediator, Lipoxin A_4 (LXA_4), reduced gingival inflammation and increased the systemic levels of pro-resolution molecules systemically[22]. Thus, this therapy has the potential to modulate the progression and damage caused by periodontitis.

A paradigm shift in thinking

The proposal by Socransky *et al.*[23] in 1998 that complexes of bacteria were associated with the shift from periodontal health to disease was a seminal moment in Periodontology. However, it was always recognized that these groupings were "associations", and not "causative" for disease. While most microbes that colonize the human body are compatible with health, some can transform from a commensal to a pathogenic relationship with the host through mechanisms that are not well understood[24,25]. Indeed, a significant issue is the temporal relationship between inflammation and disease, because it is not clear which comes first, the immune response or the alteration in composition of the biofilm[26]. Nonetheless, it has been noted that periodontitis arises from an exuberant inflammatory response to the resident microbiota, and this is aggravated by the overgrowth of some disease-associated bacteria[27].

Hypotheses for periodontitis

Many hypotheses have been proposed to try to explain the pathogenesis of periodontitis. One of the earlier proposals was the Specific Plaque Hypothesis[28], which highlighted the importance of a small number of specific "pathogenic" species. Subsequently the Non-specific Plaque Hypothesis was proposed[29], which focused more on the overall mass of microbiota. A more plausible and interesting was the Ecological Plaque Hypothesis[30], in which it was proposed that "periodontal pathogens" appear as a result of the disease rather than cause it. Two recent proposals called the Keystone Pathogen Hypothesis[31] and the Polymicrobial Synergy & Dysbiosis model[32] suggest that certain microbes modulate the host response to impair immune surveillance and tip the balance from homeostasis to dysbiosis.

Most of the more recent proposals have focused on the so-called "keystone" bacteria as being the principal drivers of periodontitis. Although this seems reasonable, the evidence to support it is not so clear-cut because, in health, although the periodontal microbiome exists in a symbiotic relationship the host, putative periodontal pathogens are present, but not pathogenic.

Overall, periodontitis is an interaction between the inflammatory response, dysbiotic subgingival plaque biofilm and associated tissue damage, modified by factors such as smoking, systemic diseases and genetics. Importantly, inflammation always precedes the presence of dysbiotic microbes. Thus, it seems reasonable to focus our attention towards controlling the inflammation, to control the infection.

Evolving concepts

The one pathogen/one disease paradigm of the 1970's was replaced with a concept embracing the emergence of specific periodontopathic profiles that are associated with a number of ecologic determinants and host factors[33]. An alternative paradigm supporting the central role of inflammation, rather than specific microbiota, in the early pathogenesis of periodontitis has also been proposed[34]. Thus, while the predominant concept in Periodontology today is that dental biofilm/plaque is the etiologic factor of periodontitis, this could be questioned. We know that bacteria are essential but insufficient to cause disease. To successfully treat the disease, the pathogenesis (inflammatory/immune responses) must be interrupted. Therefore, the biofilm should not be the sole treatment focus, since the pathogenesis is inflammation. For decades we have been attacking the problem from the wrong aspect and perhaps targeting the inflammation to control the infection may be an answer[4].

Inflammation & dysbiosis in periodontitis – key facts

The relationship between the periodontal microbiome and the development of periodontitis is multifaceted and complicated. The tenet that specific periodontal pathogens initiate dysbiosis and disease can be questioned because there is scant evidence to support a causative role for any putative keystone pathogen with initiation of periodontitis in humans[34]. Furthermore, the "putative pathogens" or "pathobionts" that are associated with periodontitis are very minor components of the early-stage biofilm[35]. The later transformation to a dysbiotic microbiota appears to be a response to the altered pocket environment and associated inflammation[20,36]. A dysbiotic periodontal microbiome is linked to the development of periodontitis; however, whether disease is initiated by dysbiosis or is a result of inflammation has not been specifically proven[31,32].

Thus, understanding the nexus between inflammation and dysbiosis is critical[1]. The timing and sequence of microbial changes to periodontal inflammation is central to the pathogenesis of periodontitis. Understanding the inter-relationships between bacteria and inflammation is emerging[21,37]. Inflammation forecasts disease progression, and increased presence of periodontal pathogens in periodontitis occurs after onset of periodontitis[38]. Dysbiotic changes induced by inflammation are more complicated than mere overgrowth of particular bacteria. Changes in the local pocket milieu induce alterations in the physiology, pathogenicity, and expression of virulence factors by the dysbiotic microbiota[39]. Commensals can become pathobionts when specific genetic or environmental conditions are altered in the host[40]. In progressive disease, release of disease modifying products is upregulated by both commensals and pathogens[41]. These observations confirm that the microbiome and related inflammatory response are connected through bi-directional balance in health and disease.

A unifying hypothesis - Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation (IMPEDE) model

This model is designed to accommodate the current Classification of Periodontal Diseases. In this classification, periodontitis is viewed within a continuum from health to disease through four stages of severity and complexity, as well as extent and distribution (Fig. 1).

Four different stages of bacterial transitions have been identified during the transition from health to late-stage periodontitis. These are driven by inflammation, pocket formation, and bacterial composition (Fig. 2). The Inflammation-Mediated Polymicrobial Emergence and Dysbiotic Exacerbation (IMPEDE) model is further illustrated in Figure 3.

Stage 0 - Periodontal health. Presence of neutrophils in the gingival connective tissue, but there are no clinical signs of inflammation. This is considered to be a homeostatic state.

Stage I - Gingivitis. With accumulating commensal plaque bacteria, clinical signs of inflammation (redness, bleeding) become apparent.

Stage II - Initial/early periodontitis. Polymicrobial diversity is invoked due to the ongoing inflammation, and dysbiosis within the microbial community is triggered.

Stage III - Dysregulated inflammatory response and deeper pocket formation. The dysbiosis is exacerbated by inflammation-mediated changes to the local environment, and this results in a self-sustained feedforward loop

Stage IV – Late-stage periodontitis There is further inflammation-mediated dysbiosis of microbiota, and this results in further opportunistic infection and unregulated tissue damage.

This model can be used as a template for integration of treatment strategies into each of the periodontal disease classification stages (Fig. 4). The IMPEDE model demonstrates how inflammation drives each periodontitis classification stage and, accordingly, the clinical condition. Inflammation-mediated polymicrobial dysbiosis and tissue damage can be exacerbated and progressive if no treatment is provided. By focusing on this inflammation-driven problem treatment should be aimed at focusing on resolution of inflammation and tissue repair/regeneration.

Figure 1. Plaque-associated Periodontal Disease Stages. Four different stages of periodontal disease have been identified during the transition from health to late-stage periodontitis

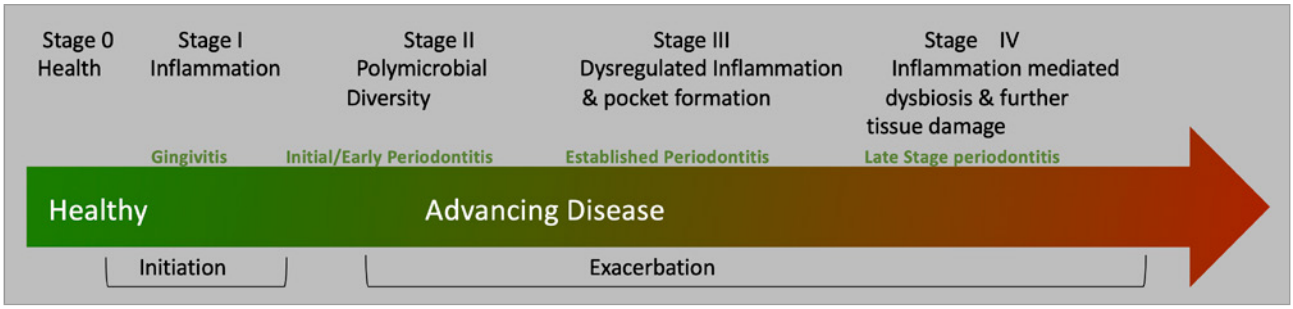

Figure 2. IMPEDE & Plaque-associated Periodontal Disease Stages.
Inflammation manifests within each classification stage as a principal driver of the clinical condition. (Source: adapted from Van Dyke TE, Bartold PM, Reynolds EC. The Nexus Between Periodontal Inflammation and Dysbiosis. Front Immunol 2020;11:9).

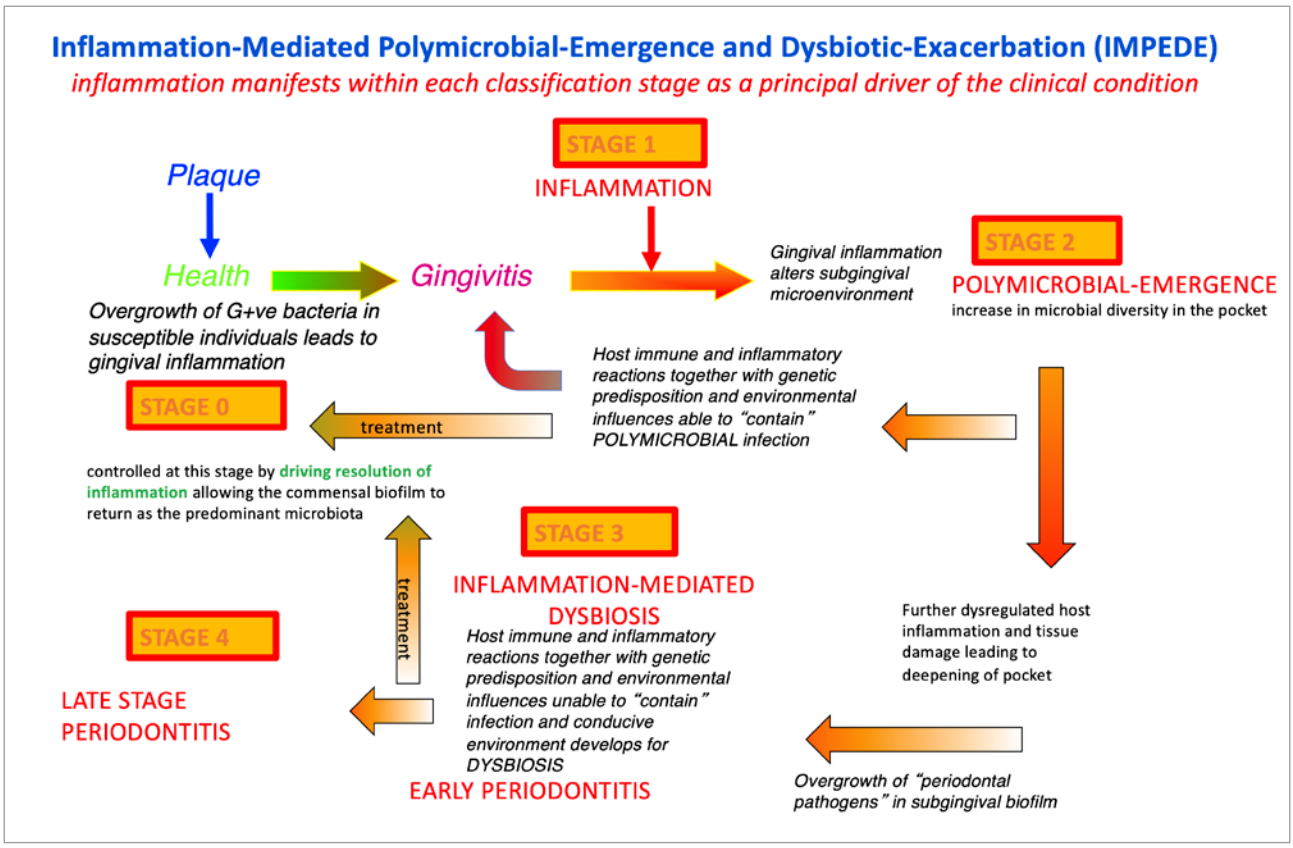

Figure 3. Inflammation-Mediated Polymicrobial Emergence and Dysbiotic Exacerbation (IMPEDE) model. Inflammation is considered to be the main driver of plaque-associated periodontitis. This model demonstrates how periodontal health, gingivitis, and periodontitis may develop, be contained or progress through five stages (0-IV). Stage 0: periodontal health; Stage I: Gingivitis (inflammation); Stage II: Initiation/early periodontitis (Polymicrobial diversity emerges); Stage III: Early-stage periodontitis: Inflammation-mediated dysbiosis and opportunistic infection; Stage IV: Late stage periodontitis. (Source: adapted from: Van Dyke TE, Bartold PM, Reynolds EC. The Nexus Between Periodontal Inflammation and Dysbiosis. Front Immunol 2020;11:9).

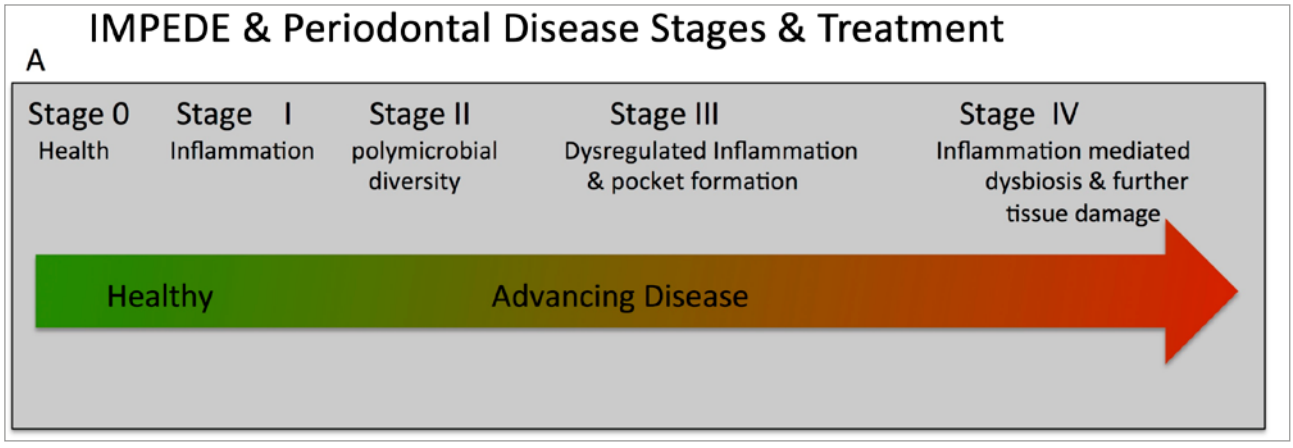

Figure 4. Inflammation-mediated polymicrobial dysbiosis and tissue damage can be exacerbated if no treatment is provided, or can be driven toward resolution of inflammation and tissue repair/regeneration if treatment is provided. (Source: adapted from Van Dyke TE, Bartold PM, Reynolds EC. The Nexus Between Periodontal Inflammation and Dysbiosis. Front Immunol 2020;11:9).

Conclusion

Contemporary Periodontology is witnessing a merging of opposing concepts, with the recognition of the crucial interplay between inflammation and microbiology in the pathogenesis of periodontitis. Emerging information indicates that the key driving force in the destructive features of periodontitis is ongoing and poorly controlled inflammatory host response. Only during the later stages of periodontitis does it become evident that specific microbial (dysbiotic) changes evolve and assume a role of considerable importance. It is important to note that this is not a novel proposal – just reworked to fit current findings and allow a logical fit with the 2017 classification.

Metagenomic, transcriptomic, proteomic, and metabolomics studies are providing key evidence to underpin earlier theories into believable working models. For example, changes in chemokine responses and microbial composition observed during experimental gingivitis demonstrate the variable host responses to a disruption in gingival homeostasis[42]. Consideration of such human variation in gingival inflammation may be useful to identify those individuals at high risk of developing periodontitis. Studies such as this underscore the plethora of host responses associated with differences in host immune outcomes and microbial biofilm evolution that may affect clinical manifestation of destructive inflammation.

The IMPEDE model is consistent with, and complementary to, the 2017 Classification of Periodontal Diseases. This model allows one to see how resolution of inflammation has the potential to the microbial profile and restoration of microbiological and host homeostasis. Thus, the inter-relationship between periodontal inflammation and microbial dysbiosis can be utilized.

Authors' contributions

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Conception or design of the study: PMB, TEVD.

Data acquisition, analysis or interpretation: PMB, TEVD.

Writing the article: PMB, TEVD.

Critical revision of the article: PMB, TEVD.

Final approval of the article: PMB, TEVD.

Overall responsibility: PMB.

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