



# Herpesvirus Periodontitis: Infection Beyond Biofilm

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**ABSTRACT** Herpesviruses, including Epstein-Barr virus and cytomegalovirus, occur at high copy counts in aggressive periodontitis, and may interact synergistically with periodontopathic bacteria in the etiology of the disease. Herpesvirus active periodontal infections may impair local host defenses and thus increase the aggressiveness of resident periodontopathic bacteria. The bacteria, in turn, may augment the virulence of the herpesviruses. The abundance of herpesviruses in periodontitis redefines the pathogenic paradigm of the disease and may have significant clinical implications.

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**P**eriodontitis is a complex infectious disease that is associated with specific bacterial species.<sup>1</sup> Healthy gingival sites are predominated by facultative gram-positive bacteria, whereas periodontitis lesions mainly harbor anaerobic and proteolytic gram-negative species.<sup>2</sup> Microbiological culture and culture-independent molecular studies have identified more than 1,200 bacterial species and 19,000 phylotypes in the oral cavity, and at least 400 bacterial species in subgingival sites, but despite the long list of different bacteria in periodontitis, less than 20 species are designated major periodontal pathogens.<sup>3-6</sup>

It is becoming increasingly clear that major clinical characteristics of periodontitis are difficult to explain solely on the basis of a bacterial infection.<sup>7</sup> It remains an enigma why most patients

show periodontitis in relatively few teeth despite an omnipresence of periodontopathic bacteria in saliva. Also, many periodontitis lesions are self-limiting with short-duration morbidity despite a persistent presence of periodontopathic bacteria in the periodontal pocket. Moreover, as clearly evidenced in localized aggressive (juvenile) periodontitis, periodontal tissue destruction tends to occur in a bilateral symmetrical pattern around the midline of the mouth, and may almost reach the apex in one tooth while barely affecting a neighboring tooth sharing the same interproximal space.

The conventional explanation is that periodontitis-prone teeth exhibit anatomies predisposing to enhanced plaque accumulation, but studies have failed to identify a close relationship between supragingival plaque amount and destructive periodontal disease.<sup>8</sup> Case in point is

the lingual surface of mandibular molars, which frequently shows massive biofilm build-up but little or no attachment loss, and localized aggressive (juvenile) periodontitis that reveals little plaque formation at sites with rapidly advancing disease. As periodontal pockets of all morphologic types amass high microbial densities, the mere anatomy of the subgingival area is also unlikely to be a key determinant of periodontitis disease severity. Because of the many puzzling clinical features of periodontitis, and as mostly indirect evidence exists for a bacterial etiology of the disease, it is our contention that a pure bacterial cause of periodontitis has been overemphasized.

A Swedish epidemiologic study of 30 years duration may provide indirect evidence for that argument.<sup>9</sup> The study found the percentage of periodontally healthy individuals increased from 8 percent to 44 percent with a parallel decrease in the proportions of subjects with gingivitis and moderate periodontitis, but the prevalence of advanced periodontitis patients remained unchanged at 6-8 percent during the 30-year study period.<sup>9</sup> Apparently, several cases of advanced periodontitis have an etiology that is unresponsive to conventional mechanical therapy.

Recent studies showing the presence of herpesviruses in severe periodontitis sites may provide new important insights into the causation of the disease.<sup>10</sup> Individual periodontitis lesions can harbor millions of genomic copies of herpesviruses as well as papillomaviruses, human immunodeficiency virus (HIV), human T-lymphotropic virus type 1, torquetenovirus, and hepatitis B and C viruses.<sup>11,12</sup> Viruses reside in high levels within gingival tissue. Saliva can contain several additional viruses of medical importance, but their relationship to periodontitis has still to be determined.<sup>13</sup> New gene sequencing

TABLE 1

### Herpesviruses in Gingival Biopsies From Periodontitis Lesions and Clinically Healthy Sites\*

Herpesvirus	Periodontitis (14 subjects)	Healthy periodontium (11 subjects)	P ( $\chi^2$ test)
Herpes simplex virus type 1	8 (57) <sup>***</sup>	1 (9)	0.04
Epstein-Barr virus	11 (79)	3 (27)	0.03
Human cytomegalovirus	12 (86)	2 (18)	0.003
Human herpes virus-6	3 (21)	0 (0)	0.31
Human herpes virus-7	6 (43)	0 (0)	0.04
Human herpes virus-8	4 (29) <sup>***</sup>	0 (0)	0.17
Presence of herpesviruses	14 (100 %)	5 (45 %)	0.007

\* Contreras et al.<sup>16</sup>

\*\* No. (%) virus-positive samples.

\*\*\* Three patients were confirmed HIV-positive.

technologies will undoubtedly expand the list of viruses in the periodontal virome.<sup>14</sup> Taken together, periodontitis sites can harbor viral copy counts that approach the total bacterial count. The abundance and the variety of pathogenic viruses in periodontitis lesions suggest that viruses are not merely an epiphenomenon of gingival inflammation but are causally related to disease development.

The present article discusses the relationship between herpesviruses and periodontitis, and proposes that a coinfection of active herpesviruses and periodontopathic bacteria constitutes a major cause of periodontitis. Herpes simplex virus type 1, Epstein-Barr virus, and cytomegalovirus are the most studied herpesviruses in periodontology, and they are the main focus of this review. The concept of a herpesviral-bacterial combined etiology of periodontitis may explain a number of the clinical characteristics of the disease and provide new tools for the management of the disease.

#### Herpesvirus Characteristics

The biological characteristics of the herpesvirus family and of other oral viruses were outlined in a recent review and will here only be summarized briefly.<sup>15</sup> Herpesvirus virions vary in size from 120

to 250 nm and consist of a double-stranded linear DNA molecule surrounded by an icosahedral capsid, a proteinaceous tegument, and a host-derived lipid-containing envelope with embedded viral glycoproteins. Eight herpesvirus species with distinct biological and clinical characteristics infect humans: herpes simplex virus type 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6, 7 and 8. Herpesviruses establish a lifelong infection and occur in a latent and in an active stage. Herpesviral persistence as a latent infection requires subversion or evasion of the host's innate and adaptive immune systems, and of the intrinsic antiviral defense that operates at the intracellular level. Reactivation from latency may happen spontaneously or be triggered by a concurrent infection, fever, drugs, tissue trauma, emotional stress, exposure to ultraviolet light, or other factors that impair the host immune defense. Herpesvirus reactivation in turn induces additional immunosuppression, possibly leading to bacterial or viral superinfections, which may not be resolved until the herpesvirus active infection is subdued by the immune system or by pharmacotherapeutics.

Herpesvirus infections show a distinct tendency to cellular and tissue tropism.

TABLE 2

## The Prevalence of Subgingival Herpesviruses\*

Herpesvirus	Aggressive periodontitis	Chronic periodontitis	Healthy periodontium
Herpes simplex virus type 1	78 % <sup>††</sup>	26 %	0 %
Epstein-Barr virus	58 %	46 %	8 %
Cytomegalovirus	42 %	52 %	8 %

\*Adapted from Slots.<sup>10</sup>

††Median percentage value obtained from more than 20 worldwide studies.

Herpesviruses target various cells of the immune system and subvert host immune functions to their own advantage. Herpes simplex virus type 1 is usually associated with primary infections of the orofacial area and with latent infection of the trigeminal and spinal ganglia. Epstein-Barr virus infects B-lymphocytes, where it establishes latency. Cytomegalovirus infects several cell types and establishes latency in macrophage-granulocyte progenitor cells and in peripheral blood mononuclear cells.

Herpesvirus infections induce strong antiviral innate and adaptive immune responses, which, although incapable of eradicating the infection, are generally effective in controlling viral replication and preventing clinical disease.<sup>14,45</sup> The cellular immune response plays a key role in controlling herpesvirus infections by means of major histocompatibility complex class I-restricted cytotoxic CD8+ T-lymphocytes that recognize viral peptides on the surface of infected cells. Individuals having an Epstein-Barr virus-cytomegalovirus dual infection tend to show markedly stronger T-lymphocyte responses and more severe disease than subjects who are monoinfected by either of the viruses. To evade antiviral immune responses herpesviruses encode genes that interfere with the activation of major histocompatibility complex-restricted T-lymphocytes and of natural killer cells, modify the function of cytokines and their receptors, interact with complement factors, modulate signal transduction and transcription factor activities, suppress apoptosis, and alter various other cellular functional-

ities. Herpesviruses may participate in disease development by manipulating the regulation of these cellular processes.

Most individuals become infected with herpesviruses early in life, and 60-100 percent of adults are carriers of herpes simplex virus type 1, Epstein-Barr virus, and cytomegalovirus. Herpesvirus infections are a major cause of morbidity in patients with deficits in innate and adaptive immunity, and may also cause clinical disease in immunocompetent persons. The clinical outcome of herpesvirus infections ranges from subclinical or mild disease to encephalitis, pneumonia, and even to cancer, including lymphoma, sarcoma, and carcinoma.<sup>22</sup> Herpes simplex virus type 1 produces herpetic gingivostomatitis and cold sores, and herpes simplex virus type 2 causes genital ulcerous disease and occasionally oral disease. The Epstein-Barr virus is the causative agent of infectious mononucleosis and oral hairy leukoplakia, and is implicated in the etiology of nasopharyngeal carcinoma and various lymphomas. Cytomegalovirus infection is of major clinical significance in pregnant women, newborn infants with congenital infection, immunosuppressed transplant patients, and HIV-infected individuals.

### Herpesviruses in Periodontal Disease

The occurrence of herpesviruses in various types of periodontal disease has been studied by qualitative and quantitative polymerase chain reaction identification techniques. TABLE 1 shows a significantly higher occurrence of herpesviruses in biopsies from periodontitis lesions than from healthy periodontal sites.

TABLE 2 summarizes findings from more than 20 studies worldwide on the prevalence of herpes simplex virus, Epstein-Barr virus, and cytomegalovirus in subgingival sites. Aggressive periodontitis lesions tend to show herpesviruses in a reactivated state, and individual lesions may yield subgingival copy counts as high as  $8.3 \times 10^8$ /ml for Epstein-Barr virus and  $4.6 \times 10^3$ /ml for cytomegalovirus, and the gingival tissue of periodontitis lesions may house even higher viral loads.<sup>16,17</sup> A recent study associated the Epstein-Barr virus and cytomegalovirus with peri-implantitis.<sup>18</sup> In contrast, infected healthy periodontal sites and gingivitis lesions typically harbor herpesviruses in a nontranscriptional phase and in copy counts of only 1,000 to 20,000/ml.<sup>19</sup> Other viruses of the herpesvirus family and various nonherpesviruses can also inhabit advanced periodontitis lesions.<sup>20</sup> The remarkably high copy counts of pathogenic viruses in aggressive periodontitis lesions makes it unlikely that these infectious agents are acting merely as harmless bystanders present in proportion to the severity of the underlying periodontal pathosis.

### Herpesvirus Periodontopathic Potential

It is assumed that periodontitis debuts in genetically or environmentally predisposed individuals who are infected with virulent infectious agents and reveal persistent gingival inflammation and distinct immune responses.<sup>11,19</sup> Fitting that concept, herpesviruses are implicated in the development of periodontitis. The

pathogenicity of herpesviruses is executed through direct virus infection and replication, and via a virally induced alteration of the host immune defense. The early phases of periodontitis in immunologically naïve hosts may predominantly involve cytopathogenic events, whereas most clinical manifestations in immunocompetent individuals are secondary to cellular or humoral immune responses. A periodontal herpesvirus infection may induce a significant portion of the immune reactions in periodontitis.<sup>10</sup>

The Epstein-Barr virus and cytomegalovirus can infect and alter functions of periodontal monocytes, macrophages and lymphocytes, and may exert direct cytopathic effects on periodontal fibroblasts, keratinocytes, endothelial cells, bone cells, and polymorphonuclear leukocytes. A periodontal herpesvirus infection may increase the pathogenicity of the periodontal microbiota by expressing herpesvirus proteins on eukaryotic cell membranes that may serve as new bacterial binding sites, or by inducing abnormalities in the adherence, chemotaxis, phagocytic and oxidative, secretory, and bactericidal activities of polymorphonuclear leukocytes.<sup>11</sup> However, the interaction between herpesviruses and bacteria is most likely bidirectional, with bacterial enzymes or other inflammation-inducing factors having the potential to activate periodontal herpesviruses.<sup>11</sup> Experimental mice infected with murine cytomegalovirus-*Porphyromonas gingivalis* exhibited a significantly higher mortality rate than mice infected with murine cytomegalovirus-*Escherichia coli*.<sup>20</sup> The potential of *P. gingivalis* to suppress interferon-gamma antiviral host response, probably by means of proteolytic enzymes, may partly explain the observed increase in cytomegalovirus pathogenicity.<sup>21</sup>

A statistical relationship has been

found between various herpesviral-bacterial consortia and periodontal disease severity, indicating a periodontopathogenic synergy between the infectious agents. Numerous studies of medical diseases and experimental infections have revealed that a viral-bacterial coinfection produces more severe illness than a single infection by either of the two types of infectious agents.<sup>11</sup> Periodontal herpes simplex virus type 1, the Epstein-Barr virus, and cytomegalovirus have been linked to an elevated occurrence

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of the putative periodontal pathogens *P. gingivalis*, *Tannerella forsythia*, *Dialister pneumosintes*, *Prevotella intermedia*, *Prevotella nigrescens*, *Treponema denticola*, *Campylobacter rectus* and *Aggregatibacter (Actinobacillus) actinomycetemcomitans*.<sup>7,11</sup> The Epstein-Barr virus and cytomegalovirus seem to be most closely associated with *P. gingivalis* and *T. forsythia*, two bacterial species with high periodontopathogenic potential, and the linkage between cytomegalovirus and *P. gingivalis* appears to be particularly strong.<sup>7,22-24</sup>

Herpesvirus infections induce an expression of pro-inflammatory cytokines and chemokines as part of the host defense against the viral infection.<sup>25</sup> The Epstein-Barr virus and cytomegalovirus

infections can up-regulate interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  gene expression of monocytes and macrophages.<sup>26</sup> In turn, interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  may upregulate matrix metalloproteinase, downregulate tissue inhibitors of metalloproteinase, and activate osteoclasts.<sup>27</sup> Increased levels of pro-inflammatory cytokines in periodontal sites have been associated with an enhanced risk of periodontal tissue destruction.<sup>27,28</sup>

Even though pro-inflammatory cytokines have the potential to initiate collagen degradation and alveolar bone resorption, the periodontal cytokine response may actually be beneficial overall by preventing the activation and widespread dissemination of virulent viruses. Perhaps periodontitis can teleologically be viewed as the biological price paid by the host to control periodontal herpesviruses and avoid viral dissemination and serious systemic diseases.

### Herpesvirus-Bacterium-Host Response Model of Periodontitis

**FIGURE 1** depicts a model for the development of periodontitis, which as its core, has a sequential infectious process that proceeds from bacteria to herpesvirus to bacteria.<sup>11</sup> In the herpesviral-bacterial model of periodontitis, herpesvirus-related cytopathogenic effects, immune evasion, immunopathogenicity, latency, reactivation from latency, and tissue/site tropism comprise important aspects of periodontal pathosis. Initially, bacteria in the dental biofilm induce gingivitis, which permits latent herpesviruses embedded in macrophages, T-lymphocytes and B-lymphocytes to enter the periodontium.<sup>29</sup> Cytomegalovirus can replicate in gingival tissue, which may help to sustain the periodontal infection. Reactivation of the latent herpesviruses may occur spontane-

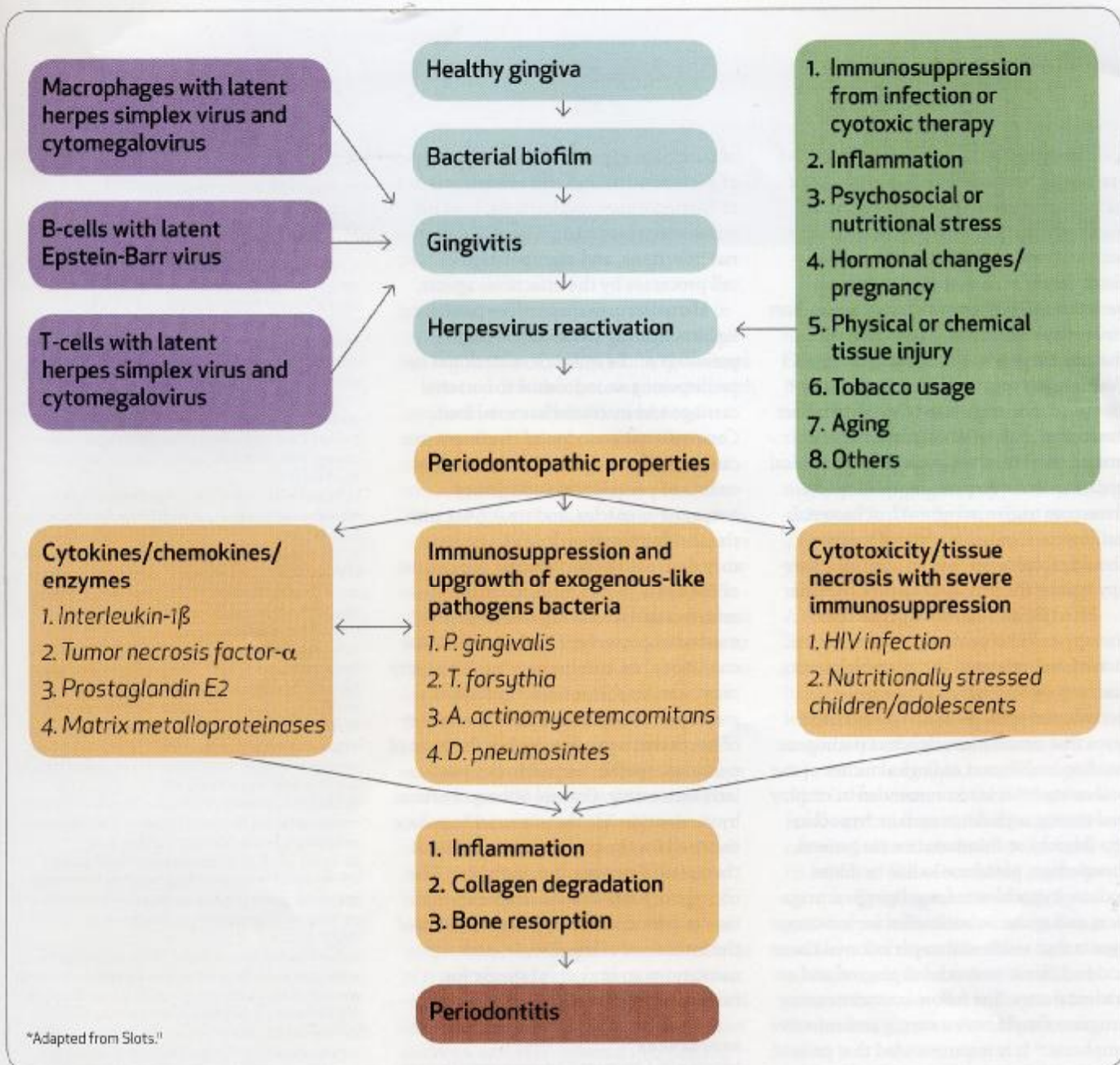


FIGURE 1. Herpesvirus model of periodontitis.\*

ously or during periods of decreased host defense, resulting from drug-induced immunosuppression, concurrent infection, unusual and prolonged emotional stress, hormonal changes, physical trauma, etc. Perhaps not coincidentally, most herpesvirus activating factors are

also suspected risk factors/indicators for periodontitis.<sup>30</sup> As described above, the pro-inflammatory cytokines released during the herpesvirus infection can potentially activate matrix metalloproteinases and osteoclasts and impair the immune defense against periodontopathic bacteria.

### Therapeutic Concepts

Periodontal scaling and root planing, or other means of instrumental removal of dental biofilms, can lower herpesvirus counts in the periodontal pocket and in saliva. Topical antiseptics that are active against both herpesviruses and bacteria (e.g.,

sodium hypochlorite and povidone-iodine) can further reduce the periodontal load of pathogenic agents.<sup>37-46</sup> Selective patients may also benefit from systemic treatment with antiviral and antibacterial medications. Sunde et al. described a refractory periodontitis patient with high Epstein-Barr virus copy counts who was treated with the anti-herpesvirus drug valacyclovir-HCl (Valtrex, 500 mg twice a day for 10 days).<sup>37</sup> The treatment suppressed the Epstein-Barr virus to an undetectable level for at least one year and resulted in a "dramatic" clinical improvement.<sup>37</sup> As periodontal herpesviruses may trigger overgrowth of bacterial pathogens, a systemic antiviral therapy should probably precede an antibiotic therapy against the periodontopathic bacteria.

Effective anti-infective periodontal therapy includes professional administration of well-tolerated antimicrobial agents, each exhibiting high activity against periodontal pathogens, and delivered in ways that simultaneously affect pathogens residing in different ecological niches of the oral cavity.<sup>38,39</sup> It is recommended to employ oral rinsing with dilute sodium hypochlorite (bleach) or chlorhexidine for general disinfection, povidone-iodine or dilute sodium hypochlorite for subgingival irrigation, and systemic antibiotics for infectious agents that reside within periodontal tissue and in difficult-to-reach subgingival and extradental sites. The follow-up maintenance program should have a strong anti-infective emphasis.<sup>40</sup> It is recommended that patient self-care includes subgingival irrigation with dilute sodium hypochlorite and oral rinsing with dilute sodium hypochlorite or chlorhexidine two to three times per week.

### Summary and Perspectives

Periodontal research has long been a significant strength of the University of Southern California School of Dentistry, and periodontal viral infection is an area

of particular expertise. The etiopathogeny of periodontitis includes virulence factors of herpesviruses and bacteria, host immune responses against viral and bacterial infections, and manipulation of host cell processes by the infectious agents.

Herpesviruses may induce periodontitis by activating tissue-destroying pathways of the immune system and by predisposing an individual to bacterial carriage and increased bacterial load. Conventional periodontal treatment can cause a multiple-fold reduction in copy counts of periodontal and salivary herpesvirus species, and treatment with the anti-herpesvirus drug valacyclovir may decrease the periodontal copy count of the Epstein-Barr virus to virtually undetectable level and give rise to a marked improvement in the periodontal conditions. As anti-herpesvirus immunity may be an important determinant of a stable periodontium, a future availability of herpesvirus vaccines makes the topic of periodontopathic herpesviruses particularly interesting. Control of herpesviruses by vaccination has the potential to reduce the need for the traditional periodontal therapies of surgery and antibiotics. The concept of herpesviral-bacterial co-infection in periodontitis may unlock many of the intricacies of the disease, and constitutes an important theme for further research. ■■■■

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