

Oral manifestations during dengue infection: a systematic review

Gustavo Canales Sermeño¹, Marisel R Valenzuela Ramos², Pedro M Dias Monteiro³,
Dario E Medina Castro⁴, Nicole K Medina Valera⁴

1. Universidad Nacional "San Luis Gonzaga". Ica, Perú.

2. Universidad Tecnológica de los Andes (UTEA). Abancay, Perú.

3. Universidad César Vallejo (UCV). Lima, Perú.

4. Universidad Nacional de Trujillo (UNT). Trujillo, Perú.

ABSTRACT

Dengue is a global public health problem, especially in countries with tropical and subtropical climates. **Aim:** To describe the oral manifestations, present during dengue infection. **Materials and method:** A qualitative systematic review was conducted in OSF Registries. The search was conducted in PubMed, Scielo and Scopus, from June 15 to July 18, 2023, using MeSH term equations with Boolean operators. A total 299 articles were analyzed in three stages, leaving 8 studies for review. RAYYAN was used for selection and tables for study analysis. Studies were assessed under two criteria: metadata, and intraoral and extraoral manifestations of dengue. **Results:** The review included 8 studies, published in 2012, 2013, 2014, 2019, 2020 and 2021. The studies reported hemorrhagic dengue and type 1 dengue as diagnoses. They recorded presence of hemorrhagic and edematous gums, maculopapular lesions in the mucosa of the lower lip with pain and dysphagia, Pseudomembranous candidiasis, and edematous and erythematous taste buds. **Conclusions:** Reports of oral manifestations of dengue are deficient, and further research is required to enable correct diagnosis and differentiation from other pathologies.

Keywords: dengue - oral manifestations - *Aedes aegypti*

Manifestaciones orales durante la infección por dengue: una revisión sistemática

RESUMEN

El dengue es un problema de salud pública mundial en especial cuando se trata de países con climas tropicales y subtropicales. **Objetivo:** Describir las manifestaciones orales presentes durante la infección por dengue. **Materiales y Método:** Se realizó una revisión sistemática cualitativa registrada en OSF Registries. La búsqueda se realizó en PubMed, Scielo y Scopus; desde el 15 de junio al 18 de julio del 2023, y se empleó ecuaciones de términos MeSH con operadores booleanos. Se obtuvieron 299 artículos analizados en tres etapas, quedando 8 investigaciones para su revisión. Se empleó RAYYAN para la selección y tablas para el análisis de los estudios. Se valoraron los estudios bajo dos criterios: metadatos y manifestaciones intraorales y extraorales por dengue. **Resultados:** Se revisaron 8 estudios publicados en el 2012, 2013, 2014, 2019, 2020 y 2021. Reportaron como diagnóstico dengue hemorrágico y dengue tipo 1, señalaron la presencia de encías hemorrágicas y edematosas, lesiones maculopapulares en mucosa de labio inferior con dolor y disfagia; asimismo, se registró candidiasis pseudomembranosa, papilas gustativas edematosas y eritematosas. **Conclusiones:** Los reportes de manifestaciones orales por dengue son deficientes, se requiere de más investigaciones para poder realizar un correcto diagnóstico y diferenciarlo de otras patologías.

Palabras clave: dengue - manifestaciones bucales - *Aedes aegypti*

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Corresponding Author:

Gustavo Canales Sermeño
20186827@unica.edu.pe

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INTRODUCTION

Dengue is a global public health problem, especially in countries with tropical and subtropical climates, where dengue is endemic. In the last 50 years, the incidence of dengue has multiplied by 30¹.

In Perú, as of week 20 in 2023, 98,760 cases of dengue and 121 deaths from dengue had been reported (93 confirmed and 28 under investigation). These figures have increased since 2017, when as of the same week, 49,031 cases had been reported; and 2022, with 38,887 cases².

The departments hardest hit by dengue as of week 20 were Piura, with 28,114; Lima, with 10,431; Ica, with 9,120, and Lambayeque, with 8,550. The departments Arequipa, Moquegua, Huancavelica and Apurimac had not reported dengue cases as of week 20. The most common clinical form of dengue is dengue without warning signs, followed by dengue with warning signs and severe dengue².

Dengue is caused by the dengue virus (DenV), which belongs to the family Flaviridae, and has four serotypes (DENV 1-4)³. The infection is transmitted by the *Aedes aegypti* mosquito⁴, considered to be the main vector⁵.

Dengue infection has various presentations, depending on the DenV. It can present as undifferentiated febrile illness or viral syndrome, febrile dengue (which is the classic presentation with fever), dengue hemorrhagic fever and dengue shock syndrome^{4,6}.

In febrile dengue, symptoms begin with a high fever that lasts 4 to 8 days, severe headache, retroorbital pain, loss of appetite, metallic taste, vomiting, diarrhea, and abdominal pain. There may be rashes on the face, limbs and trunk. Other features include bleeding gums, epistaxis, heavy menstrual periods and gastrointestinal bleeding. Hemorrhagic dengue is characterized by pyrexia, hemorrhagic phenomena, hepatomegaly and features of renal failure. Dengue shock is associated with a rapid pulse, cold and clammy skin, perioral cyanosis and high mortality⁴.

The literature reports that oral manifestations are not common in dengue. However, the oral mucosa is affected in 30% of patients with dengue viral infections and more frequently in patients with dengue hemorrhagic fever⁷. Clinically, crusting can be observed on the lips and tongue, and vesicles on the soft palate. Bleeding of the tongue and gums, hemorrhagic plaques, petechiae, purpura, and ecchymosis have also been reported⁸.

It is therefore essential for dentists to identify the manifestations of dengue in the oral cavity, as bleeding is often the only early manifestation of the disease. This could help to provide early diagnosis and rapid treatment, thereby avoiding significant complications.

The aim of the current study was to describe the oral manifestations present during dengue infection, based on a literature review.

MATERIALS AND METHOD

Eligibility criteria

This review was registered in OSF Registries⁹ and developed to answer the PICO question: What are the oral manifestations that occur during dengue infection?

Studies that were considered for review underwent a selection process according to the inclusion and exclusion criteria established by the authors.

The review included case reports or clinical cases published in any language and any year in the databases used, addressing oral manifestations of dengue, without restrictions due to patient age or systemic status. Any research articles without free access or that did not clearly address the issue were excluded.

Sources of information:

Three databases were used to collect the studies: PubMed, Scielo and Scopus. Articles were collected from June 15 to July 18, 2023.

Search strategy

The search strategy consisted of equations made up of Medical Subject Headings (MeSH NLM) terms and Boolean operators, with the intention of qualifying the information and finding relevant material. All the authors corroborated and approved the strategy and took part in the search. The following formulas were developed and adjusted according to the database: (oral manifestations OR oral implications oral OR clinical oral OR) AND (Dengue OR Breakbone Fever OR Fever, Breakbone OR Classical Dengue Fever OR Classical Dengue Fevers OR Dengue Fever, Classical OR Break-Bone Fever OR Break Bone Fever OR Fever, Break-Bone OR Dengue Fever OR Fever, Dengue OR Classical Dengue OR Classical Dengues OR Dengue, Classical).

The terms were specifically tailored to find studies related to the research objectives.

Study selection process

Three criteria were applied to collect the articles: analysis of the title, the abstract and the full text. The systematic review followed the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)^{10,11}.

A total 299 articles were collected from the four databases mentioned above. The articles were uploaded to the RAYYAN web application¹² and any duplicates were identified and deleted from the total

number of studies and proceed to the analysis. First, only the titles were analyzed to determine whether the articles fit the previously established inclusion and exclusion criteria. Any articles that did not provide free access were eliminated. Secondly, the abstracts of the selected articles were evaluated, and thirdly, the full texts were analyzed. The articles that passed all three stages were reviewed and analyzed. The entire study selection process is described in a flowchart provided by PRISMA 2020 (Fig. 1).

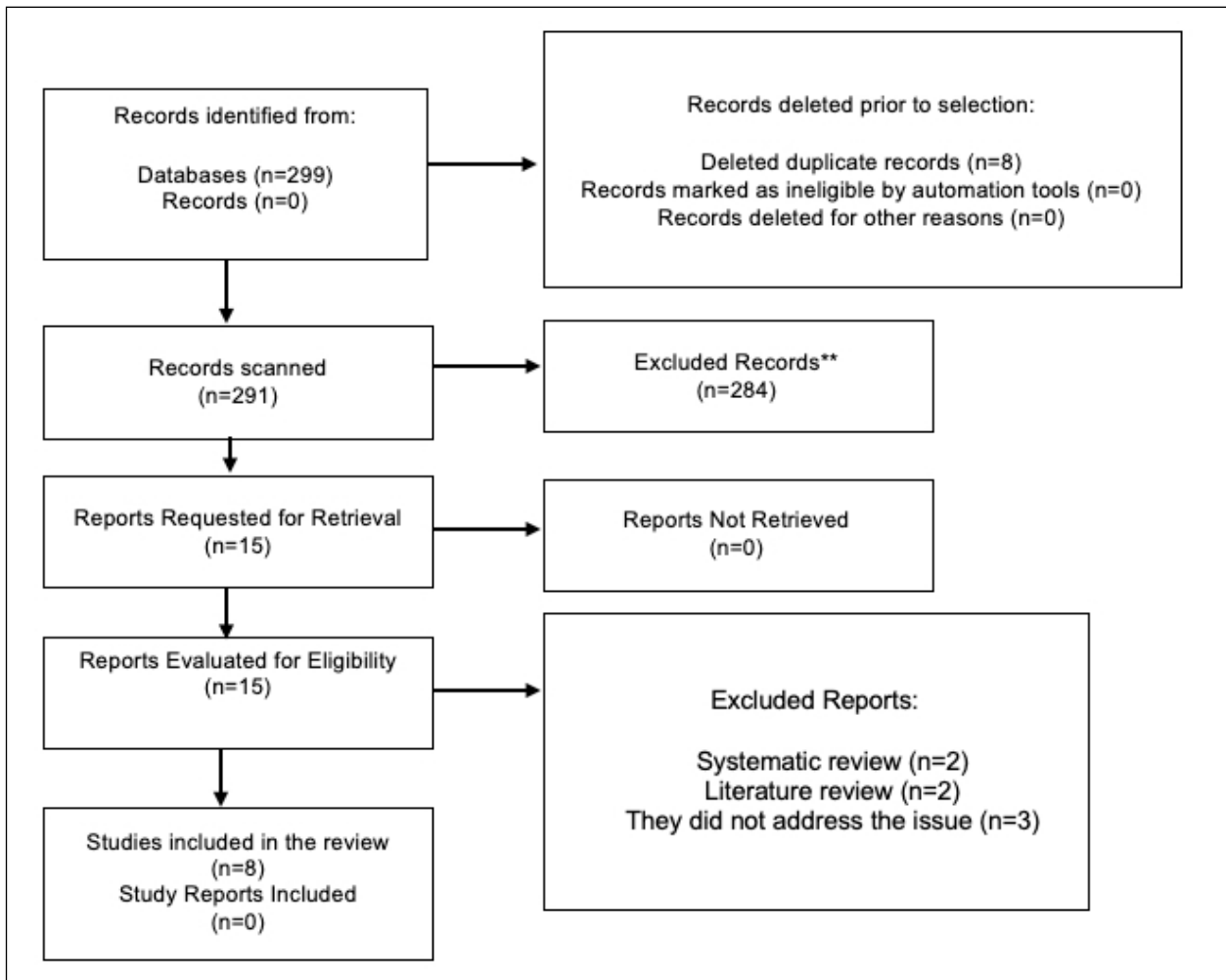


Fig 1: PRISMA-2020 flowchart of the study selection process

Data Extraction Process

The studies were exported from the databases according to the formats they contain, such as PubMed XML, CSV, BibTeX, and then uploaded to the RAYYAN web application¹². This process was carried out individually, uploading folder by folder. RAYYAN enabled the authors to identify any duplicates automatically.

List of data: The data extracted from the scientific articles were organized in two tables. Table 1 focused on determining the metadata of the studies, taking as indicators database, scientific journal, country, title, authors, type of study and year of publication. Table 2 focused on determining the oral manifestations of dengue, whose indicators were title of the study, population, sex, age, type of dengue, personal

pathological history, extraoral and systemic clinical examination, and intraoral clinical examination.

Bias and Quality Assessment

A limitation to this review was the difficulty in identifying the risk of bias and quality of the included studies, as there is no tool to evaluate case reports or clinical cases.

Meta-analysis

This systematic review was performed only up to the qualitative phase. The type of study of the articles reviewed did not enable the quantitative phase to be performed.

RESULTS

A total 299 scientific articles were collected and uploaded to the Rayyan application for discrimination. The application automatically detected 8 duplicates, which were eliminated from

the total collected, leaving 291 studies for analysis. During the first selection phase, studies were selected by reading the title, based on which 284 were eliminated and 15 were accepted, as they met the inclusion criteria. These remaining 15 studies were analyzed in the second phase, which consisted of reading the abstract. Before continuing with the selection phases, free access to these studies was verified, and they were downloaded in PDF format for the next stage. Eight studies qualified for the third and final phase of selection, which consisted of analyzing the full text^{6,7,13-18}.

Of the 7 articles excluded in the second and third phases, 2 were systematic reviews, 2 were literature reviews, and 3 did not address the topic of the current review. The entire study selection process was organized in a PRISMA 2020 diagram (Fig. 1). Metadata analysis:

Table 1 describes the main metadata of the articles reviewed. The selected studies were case report

Table 1. Metadata of reviewed articles

Database	Journal	Country	Title	Author(s)	Type of study	Year of publication
Scielo	The South African Dental Association	South Africa	Detrimental orofacial manifestations of dengue and dengue hemorrhagic fever-clinical case series, review of the causes, complications, and vaccine strategies	Dutta SR, Singh P	Case Report	2021
PubMed	Brazilian Journal of Otorhinolaryngology	Brazil	Uncommon oral manifestations of dengue viral infection	Fernandes CIR, et al	Case Report	2020
PubMed	The American journal of tropical medicine and hygiene	Japan	Oral Manifestation Like Forchheimer Spots of Dengue Fever	Yamamoto K	Case Report	2019
PubMed	Quintessence International	Brazil	Severe oral manifestation of dengue viral infection: a rare clinical description	FSC Bridges, et al	Case Report	2014
PubMed	Journal of natural science, biology, and medicine	India	Oral presentation in dengue hemorrhagic fever: A rare entity	Mithra R, et al	Case Report	2013
Scielo	Revista del Nacional (Itauguá)	Paraguay	Granulomatosis with polyangiitis (Wegener's) associated with dengue	Montiel - Jarolín D, et al	Case Report	2013
Scielo	Brazilian Journal of Oral Sciences	Brazil	Unusual yet isolated oral manifestations of persistent thrombocytopenia: a rare case report	Byatnal A, et al	Case Report	2013
PubMed	Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology	India	Postextraction bleeding following a fever: a case report	Dubey P, et al	Case Report	2012

studies, of which 5 were indexed to the PubMed database and 3 belonged to Scielo. These studies were published in the following high-impact scientific journals indexed to Scopus: The South African Dental Association¹³; Brazilian Journal of Otorhinolaryngology⁶; The American Journal of Tropical Medicine and Hygiene¹⁴; Quintessence International¹⁵; Journal of Natural Science, Biology, and Medicine⁷; Revista del Nacional (Itauguá)¹⁶; Brazilian Journal of Oral Sciences¹⁷; and Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology¹⁸. The countries where the research was conducted were Brazil^{6,15,17}, India^{7,18}, Japan¹⁴, South Africa¹³ and Paraguay¹⁶. The studies were published in several years: 1 article in 2012¹⁸, 3 articles in 2013^{7,16,17}, 1 article in 2014¹⁵, 1 article in 2019¹⁴, 1 article in 2020⁶ and 1 article in 2021¹³.

Intraoral and extraoral manifestations of dengue:

The studies reviewed reported diagnosed dengue hemorrhagic fever and dengue type 1. Reported oral characteristics or oral manifestations of dengue viral infection included presence of hemorrhagic and edematous gums of the type located in the anterior region of the dental arches, edematous and hemorrhagic labial vermilion, maculopapular lesions in the mucosa of the lower lip with pain and dysphagia. Spontaneous active gingival bleeding was also mentioned¹⁵. Pseudomembranous candidiasis, edematous and erythematous taste buds, and transient lingual papillitis were reported⁶. Defective post-extraction clot formation with the presence of exudate was described in a dengue patient undergoing dental surgery¹⁸.

Other reports mentioned hemorrhagic plaques surrounded by blue-green pigments, with an irregular surface, on the jugal mucosa and dorsal region of the tongue⁷. Patients also experienced xerostomia, tonsillitis, sacral tongue, pink macules on the hard palate¹⁴, ulcers on the adherent gingiva and jugal mucosa, and blue pigmentations on the posterior mucosa^{13,16}. On palpation, edematous, hemorrhagic lesions with rough surfaces bled¹⁷.

These signs and symptoms were present in both male and female patients, with no predilection for either sex. Patient age ranged from 6 to 62 years. Medical histories recorded presence of high fever for 5 days or longer, red spots on the lower appendages, joint pain, blepharodema, myalgia, cough, subconjunctival hemorrhage, headache, skin rash, bilateral submandibular

lymphadenopathy, and respiratory complications, as described in Table 2.

DISCUSSION

Dengue is a viral febrile disease transmitted by the *Aedes aegypti* mosquito, which is common in tropical Southeast Asia¹⁹. The development of the disease may go unnoticed or generate a severe clinical picture²⁰. The World Health Organization (WHO) classified this disease into two groups: severe and non-severe. In Perú, non-severe dengue is more prevalent²¹.

Dengue causes various alterations in the oral cavity. Regarding the intraoral and extraoral manifestations, the reviewed studies specified the presence of hemorrhagic and edematous gums, edematous and hemorrhagic labial vermilion, maculopapular lesions in the lip mucosa, cheilophagia and dysphagia. Pseudomembranous candidiasis, edematous and erythematous taste buds, and inflammatory lingual papillitis were also reported. Patients also experienced xerostomia, tonsillitis, sacral tongue, pink macules on the hard palate, ulcers on the adherent gum and jugal mucosa, blue pigmentations on the posterior mucosa. On palpation, the edematous, hemorrhagic lesions with rough surfaces bled. In patients who underwent extractions, the clot was observed to have an infectious process. These results are consistent with those reported by Joob B and Wiwanitkit V, which indicated that oral bleeding was the presentation of dengue hemorrhage¹⁹. Similarly, Mushtaque RS et al. reported the presence of mild lip swelling in a 32-year-old patient diagnosed with dengue²². Thomas EA et al. found small-diameter vesicles on the soft palate, and erythema and crusts on the vermilion and the dorsal part of the tongue²³. These studies are consistent with the results found in the case reports. However, there is little scientific evidence on dengue and its impact on the oral cavity, even though the disease is endemic in tropical countries.

In dengue case reports published from 2012 to 2021 in PubMed, the evidence collected was limited, as only 8 of the case reports reviewed reported oral manifestations. This number that is too low to increase knowledge in stomatology about this viral infection. Although dengue is endemic in Perú, little evidence of oral manifestations has been reported. The evidence reviewed shows that the oral manifestations of dengue infection are diverse and

Table 2. Intraoral and extraoral manifestations of dengue

Title	Population, sex and age	Type of dengue fever	Personal pathological history	Extraoral and systemic clinical examination	Intraoral clinical examination
Detrimental orofacial manifestations of dengue and dengue hemorrhagic fever-clinical case series, review of the causes, complications, and vaccine strategies	Male aged 55-65 years (age not specified)	Dengue hemorrhagic fever	Fever for several weeks and body temperature ranging from 110°F to 120°F.	Joint pain from the past few days with a history of fever. On clinical evaluation, petechiae were observed on the upper face and neck. He had an axillary temperature of around 125°F. The respective submandibular lymphadenopathies were obvious.	Raised hemorrhagic plaques on the right posterior buccal mucosa, as well as on the dorsum of the tongue and the floor of the mouth, xerostomia and the tongue were all covered with plaques.
	49-year-old female	Dengue hemorrhagic fever	High fever for more than a few weeks, stomach pain, and occasional bleeding from the nose and gums.	Petechiae all over the body, including the upper and lower appendages, except the palms of the hands and soles of the feet, the lower part of the face, and neck. Axillary temperature 103° F. On palpation, the respective submandibular lymphadenopathy was evident.	Common ulcerative and hemorrhagic ulcers on both sides of the lower jaw, starting from the canine region to the molar. Petechiae were also present on the extraoral inferior aspect and in the intraoral right lower posterior molar and premolar regions. At the intersection of the hard and soft palate and mainly on the hard palate, on both sides, small vessels filled with blood stood out. A blue hemorrhagic strip was observed in the right posterior buccal mucosa strip.
	25-year-old male	Dengue hemorrhagic fever	Headache, orbital pain, hematemesis, and hematochezia.	High fever, muscle pain, and rash.	Petechiae, bleeding gums, ulcer, dry mouth.
Uncommon oral manifestations of dengue viral infection	1 case: Female, 29 years old.	Not specified	Not reported.	High fever, headache, muscle pain, and rash.	Pseudomembranous candidiasis, fungiform papillae that had an edematous and erythematous appearance, characterizing transient lingual papillitis.
Oral Manifestation Like Forchheimer Spots of Dengue Fever	1 case: Male, 6 years old.	Dengue type 1	A 4-day history of fever, cough and blepharedema in 2014.	Bronchial asthma and attention deficit hyperactivity disorder treated with methylphenidate.	Submucosal hemorrhages on the hard palate and pink spots on the soft palate.
Severe oral manifestation of dengue viral infection: a rare clinical description	1 case: Male, 18 years old.	Dengue hemorrhagic fever	Dengue infection	Bilateral subconjunctival hemorrhage, epistaxis, leg skin rash, thrombocytopenic disorder.	Edematous hemorrhagic upper gum in the anterior region, edematous and hemorrhagic upper lip, small maculopapular lesions on the lower lip and mucosa of the left cheek that prevented adequate oral functions and hygiene. Active spontaneous gingival bleeding.

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Table 2. Intraoral and extraoral manifestations of dengue

Title	Population, sex and age	Type of dengue fever	Personal pathological history	Extraoral and systemic clinical examination	Intraoral clinical examination
Oral presentation in dengue hemorrhagic fever: A rare entity	1 case: Middle-aged female.	Dengue hemorrhagic fever	History of fever from 1 week ago and temperature ranged from 102° F to 104° F. The blisters initially began on the left buccal mucosa and then affected the right buccal mucosa, tongue, and the back of the palate. Patient had also complained of red spots on his lower limbs for 3 days. The history revealed that patient had joint pain from the time of the onset of the fever.	Petechiae on upper and lower limbs, face and neck. He had an axillary temperature of approximately 102° F. Bilateral submandibular lymphadenopathies were present.	Raised hemorrhagic plaques on both the right and left buccal mucosa, dorsum of the tongue near the tip. The hemorrhagic plaques were surrounded by blue-green mucosa and the surface of the hemorrhagic plaques was irregular. At the junction of the hard and soft palate, a diffuse area of erosion of 3 × 4 cm was present. The tonsils on the right and left sides were enlarged and swollen. The patient had xerostomia and the tongue appeared to be sore.
Granulomatosis with polyangiitis (Wegener's) associated with dengue	1 case. A 69-year-old male.	Dengue hemorrhagic fever	Bilateral otalgia and mastoiditis 20 days before admission was interpreted as otitis and treated with cephalosporins and imipenem, in addition to myringotomy. A chronic smoker of 10 cigarettes a day for 20 years, he quit 10 years ago.	Bipalpebral edema, pale conjunctivae, nasal passages with blood clots, bilateral free and patent external ear canal.	In the mouth there were ulcers on the lips, tongue and hard palate, some covered with scabs.
Unusual yet isolated oral manifestations of persistent thrombocytopenia: a rare case report	1 case. A 50-year-old female.	Dengue hemorrhagic fever	Patient had dengue six months earlier, for which she had undergone a blood transfusion, according to previous medical reports.	No significant findings.	Multiple hemorrhagic blisters on the left sublingual mucosa, as well as on the left lateral surface of the tongue and the floor of the mouth. The overlying surface was bluish-black and there was light profuse bleeding on palpation. The right side of the palate and the right posterior buccal mucosa revealed the presence of brown plaques with a rough surface. These lesions bled upon touching.

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Table 2. Intraoral and extraoral manifestations of dengue

Title	Population, sex and age	Type of dengue fever	Personal pathological history	Extraoral and systemic clinical examination	Intraoral clinical examination
Post-extraction bleeding following a fever: a case report	1 case. A 62-year-old male.	Dengue hemorrhagic fever	High fever for 5 days before having the extraction	Facie pale and weak, temperature rose to 100°F, pulse and blood pressure of 94 beats per minute and 130/80 mm Hg. On palpation, the abdomen was found to be tender.	Large clot attached to the exposed alveolus by extraction and a continuous exudation of blood around the periphery of the blood clot formed.

range from swelling in the mucous membranes to bleeding in the gum and lip. It is important to expand the scientific evidence to enable correct differential

and definitive diagnosis, since multiple pathologies have similar characteristics.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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