

***Trabajo de fin de grado***

***Grado en Odontología***

***Manifestaciones orales  
producidas por SARS-COV-2.***

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## ***Abstract***

*An outbreak of pneumonia caused by a new coronavirus, dubbed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in January 2020 in Wuhan, China. Since then, the infection has spread rapidly causing a pandemic that affects more than 2 million people worldwide. Italy was the first country in Europe to register a high incidence of disease associated with the coronavirus (COVID-19)*

*In relation to the current global situation due to Sars Cov-2 infection, data from PCR-positive patients have been related. The most typical presentation of COVID-19 is an acute respiratory syndrome whose most common symptoms include fever, cough, and dyspnea. Most oral lesions are closely related to the patient's immune status, the oral environment also carries side effects associated with salivary gland disorders, activations of inflammatory processes*

*In addition, data about dental care during the period of the pandemic have been deepened, analyzing what have been the reasons for consultation and what the most frequent treatments. Taste and swallowing disorders often identified as first / early signs of infection. The presence of ulcerated lesions, frequent in consultations during the pandemic, has been a consequence of the aggravated situation of the mouth. In addition, the stress of the period contributed to the appearance of discomfort, dental attrition and injurious processes that have led the patient to a susceptibility to trauma / fractures in the confinement period.*

*In the most recent publications, SARS-COV2 has been related to periodontal disease, having an explanation, the possibility of oral microorganisms to take advantage of the decrease in the pH of the habitat and end up with gingival and periodontal problems. Oral hygiene also has a fundamental relevance in the degree and severity of the appearance of oral manifestations.*

# Resumen

Un brote de neumonía causado por un nuevo coronavirus, denominado coronavirus 2 del síndrome respiratorio agudo severo (SARS-COV2), comenzó en enero de 2020 en Wuhan, China. Desde entonces, la infección se ha propagado rápidamente provocando una pandemia que afecta a más de 2 millones de personas en todo el mundo. Italia ha sido el primer país de Europa en registrar una alta incidencia de enfermedad asociada al coronavirus.

Con relación a la actual situación global debido a la infección por Sars-COV-2, se han relacionado datos de los pacientes positivos a PCR. La presentación más típica de Sars-COV-2 es un síndrome respiratorio agudo cuyos síntomas más comunes incluyen fiebre, tos y disnea. Las mayorías de las lesiones orales están muy relacionadas con el estado inmunitario del paciente; también el entorno bucal conlleva efectos secundarios asociados a trastornos de glándulas salivales, activaciones de procesos inflamatorios.

Además, se han profundizado datos acerca de la atención dental durante el periodo de la pandemia, analizando cuales han sido los motivos de consulta y cuales los tratamientos mas frecuentes.

Trastornos gustativos y deglutorios, muchas veces identificados como primeros/temprano signos de infección. La presencia de lesiones ulceradas, frecuentes en las consultas durante la pandemia, ha sido consecuencia de la situación agravada de la boca. Además, el estrés del periodo contribuye a la aparición de molestias, atriciones dentales y procesos lesivos que han conllevado el paciente a una susceptibilidad a traumatismos/fracturas en el periodo de confinamiento.

En las publicaciones más recientes se ha relacionado SARS-COV-2 con la enfermedad periodontal, teniendo explicación, la posibilidad de los microorganismos orales de aprovechar

de la bajada del PH del hábitat de este modo, los pacientes acaban con problemas gingivales y periodontales. También la higiene oral tiene una relevancia fundamental en el grado y severidad de aparición de las manifestaciones orales.

# Introducción

Las infecciones producidas por Sars-COV-2, han tenido una extensión mundial desde los primeros meses del 2020, llegando desde China, Wuhan, como primer sitio de infección y de casos graves; que en breve tiempo se manifestó en Europa y en todo el mundo.

Desde el principio los estados han intentado contener la pandemia, poniendo el mundo en *lock-down*. Los pacientes, infectados y ingresados en el hospital, han presentado síntomas y signos de la enfermedad, debido a la susceptibilidad individual del paciente varía la gravedad de la afectación.

El primer contacto con los coronavirus fue en el 1960, con el descubrimiento de los primeros tipos (E229 and OC43) seguidos por (NL63 and HKU1). El OC43 y el HKU1 provienen de ratones mientras que E229 y NL63 provienen de murciélago. Los coronavirus pertenecen a una particular familia del virus capaz de corregir el material genético, evitar mutaciones y seguir envolviéndose, intercambiándose fragmentos de RNA desde otros CV. El Sars-COV-2 está muy relacionado con Sars-Cov, teniendo como ventajas de difusión tener diferentes sitios de glicosilación que pueden tener un impacto mayor en la difusión pandémica. (1)

La mayoría utiliza la enzima presente en la conversión de Angiotensina 2 (ACE), proteínas presentes en adultos en gran cantidad y difusión en sitios como glándulas salivales, tracto digestivo (colon, intestino), tejido muscular cardíaco y en los pulmones conduce a la infiltración de leucocitos, aumento de la permeabilidad de los vasos sanguíneos y paredes alveolares, y disminución de surfactante en el pulmón, causando síntomas respiratorios. El agravamiento de la inflamación local causa una tormenta de citocinas, lo que resulta en un síndrome de respuesta inflamatoria sistémica.



Los niños tienen menor posibilidad o vulnerabilidad por la cantidad inferior de receptores ACE2 en respecto a un adulto. Su presencia está enfocada esencialmente en los tractos oro faríngeos y en los alveolos pulmonares. (2)

Siendo los síntomas mas comunes en pacientes enfermos por Sars-COV-2, pulmonares y gastrointestinales, llevando a estadios mas graves. Las personas más susceptibles han sido los mayores, por tener un cierto grado de avance de los sistemas vitales, los enfermos sistémicos (Hipertensión, diabetes, problemas vasculares y obesos). Aunque la edad desde el principio ha sido el principal factor de riesgo, los jóvenes con graves/ moderados problemas, respiratorios o cardiacos han dejado bajar la edad media de complicaciones más graves llegando a veces a la muerte. (3)

El uso de la mascarilla, gel hidroalcolico y distanciamiento social ha permitido, al menos de recuperar la vida de cada día en una forma diferente de la normalidad pre-confinamiento.

Con las debidas precauciones, el mundo se puso otra vez en marcha luchando contra del Sars-COV-2, protocolizando normas de higiene para cualquier sector, de menos a mayor riesgo según el ámbito.

Unos de los sectores de mas riesgo de contacto es la odontología, con el estrecho contacto con la boca. La producción de aerosoles durante los tratamientos ha puesto en marcha una serie de protocolos para prevenir y evitar los contagios.

El mismo odontólogo o auxiliar/higienista , durante la pandemia sufre cierto grados de estrés, debidos a los confinamientos, a los riesgo que implica atender a un paciente en la consulta y a la incertidumbre que desde el principio de la infección nos sigue acompañando hacia un destino hasta ahora todavía no claro.(4)

La atención dental desde el principio de la pandemia ha sido muy estricta y relacionada con las necesidades de emergencias/urgencia, pocos enfocados en citas de rutina y otros cerraron las

clínicas. Se intento volver a la normalidad, clasificando los tratamientos según riesgo de generar aerosoles, utilización de doble mascara FFP2/FFP3 en situaciones de generación de aerosoles, utilizando dique de goma, desinfección y ventilación natural del aire. Además, se disminuyo el numero de aforo de la sala de espera y se intento minimizar el numero de citas por pacientes, es decir citas mas largas, pero menos veces. Desde el principio de la pandemia y durante los periodos mas intensos de la atención hospitalaria, la atención dental en los hospitales ha sido de tratamientos de urgencias, por eso se explica la falta de recogida de datos desde el repentino empiezo de los síntomas. (5)

La mayoría de las lesiones orales han sido muy relacionadas al estado inmunitario del paciente , por esa razón se tomaron datos de pacientes con PCR positiva , para poder agrupar las lesiones bajo un mismo denominador(6), dependiendo de eso otro factor que afectó los pacientes y toda la población en *lock down* fue el grado de estreses que comportaba el confinamiento, así que se realizaron búsquedas acerca los tratamientos y los motivos mas frecuentes de atención dental desde el principio de la pandemia. (7)

Los motivos de urgencia/emergencia han sido muy relacionado a dolores de muelas en la mayoría de los casos, restauraciones rotas, traumatismo dental y aparatología de ortodoncia y protésicas.

Siendo la boca muchas veces espejo de la situación sistémica del paciente, se han buscados manifestaciones comunes a pacientes infectados, comparando asociaciones de edades y sexo. (2)

Entre todos los datos se encontró una prevalencia de síntomas y alteraciones de la mucosa oral como ageusia y lesiones ulcerosas.

La ageusia es una afección poco común que se caracteriza por una pérdida completa de la función gustativa de la lengua. Entre los trastornos del gusto se distinguieron también los

diferentes grados de afectación: Hipogeusia, que comporta una disminución de sentido del gusto; Disgeusia que comporta una alteración de la sensación del gusto. (8)

Los datos encontrados desde el principio de la pandemia han sido observados hasta las últimas publicaciones para poder asociar el estado higiénico bucal, estado sistémico del paciente y sus propias necesidades/ urgencia de tratamiento a infección por Sars-COV-2.

## **Objetivos**

### Principal

Evaluar las diferentes manifestaciones orales del SARS-COV2

### Secundarios

Evaluar cuales han sido las más frecuentes en pacientes positivos

Estudiar cuales tratamientos han sido los más frecuentes durante la pandemia;

# Metodologías

## **-Análisis de búsqueda de estudio:**

Se han buscado artículos desde PubMed, utilizando palabras claves como “*Oral manifestation Sars cov-2*”, “*Oral disease during Covid-19 pandemic*”, “SARS COV2 “, “Oral diseases” , “*Gingivitis in covid patients*” . Se han elegido artículos entre fechas de febrero 2020 hasta abril 2021. Se han incluido en la búsqueda artículos acerca las manifestaciones orales, sobre la naturaleza y la biología del virus.

Se ha realizado una búsqueda sobre las manifestaciones orales del Sars COV-2, 28 artículos entre los cuales se han elegido estudios poblacionales / casos control de clínicas privadas, otros sobre los métodos de entrada del virus en la cavidad oral y su consecuente manifestación en la cavidad oral.

. Se ha hecho una búsqueda más específica sobre estas manifestaciones para describirlas y clasificarla.

Luego se han buscado artículos acerca del tema de la atención odontológica y se han clasificado los tratamientos más recurrentes, que tipo de atención profesional hemos tenido durante la pandemia y como evaluar dichas manifestaciones en periodos de infecciones de Sars-COV-2.

Los criterios de exclusión de los artículos han sido relacionados al tipo de estudio, muchos fueron relacionados a la descripción del coronavirus en ratones para lo que está relacionado a la interacción huésped-virus, solo se tomaron estudios en humanos. Por el tiempo y los pocos conocimientos acerca del Sars-COV-2 se eligieron solo publicaciones recientes.

Se descartaron artículos, que no han utilizado el método PCR a la hora de diagnosticar la positividad y considerarlos en los estudios.

## Resultados

Los resultados encontrados en el artículo J. **Amorim dos Santos etc**, proponen el deterioro gustativo como manifestación más común en su estudio, que por la mayoría de los casos se demostró como primera y teniendo en cuenta un cierto grado de afectación del sentido del gusto. **Salzano, Giovanni Maglito etc**, también de acuerdo con el artículo anterior que la alteración química sensitiva se nota en el principio de la infección, en este estudio en los primeros 4 días, indicando como la posible causa de las manifestaciones orales está con relación a la cantidad de Ace2 presentes en los conductos de las glándulas salivales. En el artículo de **Chen, Lili Zhao, JiajiaPeng** y de **Daniele Corbi, Stefano Mammucari**, se encontraron datos similares acerca de la pérdida y alteración química sensitiva, pero haciendo diferencia en el sexo. La prevalencia de xerostomía y ageusia, que fueron las manifestaciones más identificadas en pacientes positivos, fueron en mayor proporción más afectadas las mujeres. Ambos sexos, teniendo estas alteraciones, llegaron a padecer inflamación bucal.

En relacionar una buena/mala higiene oral con la gravedad de manifestación oral por Sars-Cov-2, se han encontrado que las alteraciones producidas por deterioro gustativo y alteración de las glándulas salivales llegando a ser xerostomía. El ambiente bucal, seco y sin posibilidad de defensa va a ser hábitat ideal para la proliferación de Gram -, que son los patógenos más dañinos, como en el artículo de **Nathalie Botros**, el *Chlamydia neumonia* (C.N), lleva a casos de padecer neumonía adquirida, además de las lesiones periodontales y gingivales.

**Esam HALBOUB et cols** , destacando en el estudio prevalencias de lesiones orales tipo ulcerativas, vesciculobullosa, lesiones macula eritematosas y paperas; siendo el sitio mas frecuente para la manifestación de estas alteración el paladar duro, seguido del dorso de la lengua y de la mucosa labial.

Muchas de las lesiones encontradas en las publicaciones han tenido muchas veces relación con sobreinfección por hongos y/o bacterias. En el artículo de Jairo **Corchuelo**’ **Francisco Chavier Ulloa**, además de identificar las manifestaciones relacionadas con el Sars-COV-2, ha destacado como el tratamiento de las lesiones orales con antibióticos o antifúngicos, llevan el microbioma oral a ser mas fuerte y agresivo frente a lesione presentes en la cavidad oral.

Resultados similares acerca de las infecciones oportunistas relacionadas con las lesiones orales se han encontrados en el artículo de **Juliana Amorim dos Santosa y cols**, donde, además los signos más característicos del Sars-COV-2 como disgeusia, xerostomía asociada a disminución del flujo salival, ulceraciones y gingivitis, se identificaron lesiones oportunistas como candidiasis, petequias, úlceras traumáticas, infecciones por Herpes simple, lengua geográfica.

La relevancia del grado psicológico

En el artículo de **Abanoub RIAD y cols**, destaca, entre las lesiones de la queilitis angular, con una prevalencia en el estudio clínico ha encontrado presencia de placas rojizas predominantes las unilaterales izquierdas (64,7%), derecha de (23,5%) y bilateralmente (11,8%).

En los artículos analizados se han destacado, en la mayoría de los casos, presencia de trastornos sensitivos de diferentes grados de intensidad (hipogeusia, disgeusia y augesia). Trastornos en la salivación, como la xerostomía, mientras en el entorno bucal se han encontrados datos de

lesiones rojizas y ulcerosas, frutos de un trastorno primario o secundario de un daño vascular-hematológico.

Se destacó una importancia relevante de una buena higiene oral a la hora de prevenir complicaciones sistémicas por el coronavirus.

En el estudio de **Daniele Corbi y cols** el 45,9% de los pacientes refirieron una intensidad de xerostomía de 5 (intermedia), el 19,6% reportaron que la xerostomía se presentó como primer síntoma con un tiempo de aparición desde la positividad de 3-7 días. Además de xerostomía, se encontraron también disfunciones al deglutir por el 39,2%, necesitando de fluidos para completar la acción.

La manifestación más común fue la disgeusia por el 59,5%, reportado con una intensidad de 8; el 78,8% cuantificó la duración de la manifestación en 6 días (4-7).

El estado sistémico inmunitario, los factores de riesgos como la obesidad, la diabetes, HT y patologías cardíacas, escasa higiene bucal, todos han tenido mucha relevancia en los estudios descriptos. Además de las manifestaciones más frecuentes encontradas en pacientes Sars-COV-2 positivos como las alteraciones de los sentidos y percepción de olores y sabores, el resto fueron todas manifestaciones/ lesiones relacionadas con las manifestaciones ya en infección del coronavirus, en sus primeras etapas. El descenso del PH y de la salivación, además de ser un trastorno incómodo y molesto para el paciente tiene repercusión en la flora biológica oral, que regula la coexistencia de microorganismos-huésped.

En el artículo de la doctora **Carmen Martín Carreras-Presas y cols**, han encontrado inflamación gingival hasta llegar a gingivitis úlcero necrotizante, lesiones ulcerosas, ageusia, hiposmia, adenopatías, lesiones herpéticas.

En la mayoría de los datos relacionados a las manifestaciones mas tempranas del Sars-COV-2 es la disgeusia y la xerostomía, como marca el artículo de **Ameen Biadsee y cols**, ambas manifestaciones van a crear un ambiente desfavorable para la salud oral, relacionado con una escasa o ausente higiene oral, el paciente va a padecer distintos grados de severidad de las manifestaciones orales.

Desde esta base, el estudio de **Christopher J. Coke y cols**, intentaron observar tramite su estudio

la relación entre la gravedad de afectación oral del Sars-COV-2 y la higiene bucal, destacando una prevalencia de manifestaciones de intensidades mayores en los paciente con una mala higiene bucal.

Estudios como el de **Almudena Nuño González y cols**, han identificado en sus publicaciones los signos característicos de la “lengua COV2”, marcando a través de sus estudios las variaciones y alteraciones que sufre la lengua en situación de infección. Los autores describen una lengua engrosada, con posibles lesiones en los bordes como evidencia de la expansión y contacto entre las caras oclusales de los dientes, alteraciones en el dorso también son predecibles con presencias de zonas depapiladas. Todo este cuadro acompañado de disgeusia y sensación de boca ardiente.

Los datos obtenidos gracias a artículos acerca la atención dental durante la pandemia, una atención diferente del normal, enfocada en urgencias. En el artículo de **Faccini, Melissa Ferruzzi y cols**, se han destacado mas el dolor, fracturas de restauraciones/ prótesis, traumatismo dental, rupturas de aparatos ortodonticos y trastornos temporomandibulares (TMD).



Para las atenciones rutinarias, los dentistas han encontrado un aumento en las demandas en campos de prevención, tratamientos como profilaxis, extracción de dientes, blanqueamiento de dientes.

# Discusión

Desde el descubrimiento de los coronavirus, con lo cuales el ser humano tuvo contacto en el pasado, el NL63-COV, SARS COV-1, se relacionaron con el nuevo Sars-COV-2. Desde un inicio tan repentino se desconocían, su origen y su método de infección/ ingreso en la célula humana. Los tres utilizan la enzima para la conversión de la Angiotensina 2 (ACE2) como primer contacto con la célula del huésped mediante una glicoproteína (*spike* o S) presente en la superficie del virus que permite el reconocimiento del receptor y permite la fusión de la membrana. Desde ese momento la proteína S se divide en dos, S1 y S2 mediante unas proteasas transmembrana serina 2 (TMPRSS2).

La S1 contiene el RBD que liga directamente con el dominio péptidas de la molécula ACE2 mientras que S2 permite la fusión de membrana.

Una vez ligada S1 a ACE2, S2 se divide ulteriormente mediante proteasas presentes en el huésped. El mediador lo hace una proteasa abundante en el tracto respiratorio y en muchos tejidos humanos, codificada por el gen Furin, llamada furina, para ingresar en las células. Una vez entrado en la célula, toma el control de las proteínas quinasas (activadores y inhibidores de enzimas mediante procesos de fosforilación), entre estas hay una red p38/MAPK muy activa en las células infectadas por Sars-COV-2, conocida por modular los procesos inflamatorios.

Las cantidades de ACE2 presentes en el huésped varía según las edades, parece que los niños tienen menor posibilidad de tener infección por tener una densidad baja de receptores ACE2 en el epitelio nasal. (2)

Además de la presencia de ACE2 en el tracto respiratorio, se encontraron densidades variables de la misma molécula en la membrana celular de los conductos salivales de la glándula salivales. (9)

Entre los resultados obtenido desde los estudios de **J. Amorim dos Santos<sup>1</sup>, A.G.C. Normando, R.L.Carvalho da Silva, A.C. Acevedo<sup>1</sup>, G. De Luca Canto, N. Sugaya, A.R. Santos-Silva, and E.N.S. Guerra**, se han encontrado como manifestación oral mas común, sobre una muestra de 10,228 pacientes (4,288 hombres ,5770 mujeres y 170 desconocidos), el deterioro gustativo como la mas frecuente con una prevalencia del 45%. Entre los distintos trastornos del gusto, 38% disgeusia y 35% hipogeusia, mientras que augesia tuvo una prevalencia del 24%. (8)

En el estudio realizados por **Abanoub RIAD,<sup>1</sup> islam KASSEM,<sup>2</sup> Julien ISSA,<sup>3</sup> Mai BADRAH,<sup>4</sup> and Miloslav KLUGAR<sup>1</sup>** se ha intentado asociar la presencia de queilitis angular en paciente positivos a Sars-COV-2, de edad entre 20-64 anos, 13 hombres y 12 mujeres.

De los síntomas comunes y característicos del coronavirus, 4 tenían fiebre persistente, 3 con faringitis, 2 con augesia y el resto con atrición dentaria y todos se han quejado por salivación excesiva en los días anteriores. El examen clínico ha encontrado presencia de placas rojizas unilaterales izquierda de las comisuras bucales (11 pacientes 64,7%), derecha de (4 pacientes 23,5%) y bilateralmente (2 pacientes 11,8%). (10)

Se podrían encontrar explicaciones entre la asociación del queilitis angular con afectación de las glándulas salivales ya que el artículo anterior necesita de mas búsquedas sobre el tema de la enzima ACE2 y las afectaciones salivales.

**Thais Bianca Brandao, DDS, PhD,a,b Luiz Alcino Gueiros, DDS, PhD,c Thayanara Silva Melo, DDS, MSc,c Ana Carolina Prado-Ribeiro, DDS, PhD,b,d Ana Cristina Froelich Alo Nesrallah, DDS,a Gladys Villas Boas Prado, MD, PhD,e Alan Roger Santos-Silva, DDS, PhD,d and Cesar Augusto Migliorati, DDS, PhDf**

### **Several**

Reporta una serie de casos clínico de lesiones órale encontradas en la cavidad oral. En los casos propuestos se han encontrado lesiones tipo ulceroso aftoso en los lugares notos por la expresión de los receptores ACE 2 , como el epitelio de la lengua y el tejido de las glándulas salivales.(11)

**Ameen Biadsee , Ameer Biadsee , Firas Kassem , Or Dagan Shchada Masarwa 3, Zeev Ormianer**

En artículo se han encontrado en una serie de casos con test de evaluación a distancia por 140 paciente en cuarentena, enfocando el cuestionario en los síntomas que han tenido como la xerostomía, dolor oro facial, funciones olfativas y gustativas. De los 140, se hace una diferencia entre todos los síntomas destacando una prevalencia de la secreción nasal en las mujeres con un índice (0,018p), dolor facial y anosmia ( $p=0,1$  y  $p<0,001$ ). EL 38% señalo como síntoma inicial la disfunción olfativa y el 56% de los pacientes refirió xerostomía.(12)

**Alberto Jose Peraza Labrador, Luciano Hermios Matos Valdez, Roberto Onner Cruz Tapia, Douglas Magno Guimaraes,**

En este estudio, se han encontrado en cuatro pacientes positivos a PCR, lesiones como vasculitis, estomatitis inespecíficas y lesiones ulcerosas. Se recogen datos también de diferentes países con la tabla 1.

TABLA 1

TABLE 1 Characteristics of the COVID-19 reported cases that presented oral mucosal lesions

Author	Age and gender	Clinical presentation and location	Symptoms	Clinical presumptive diagnosis	SARS-CoV-2PCR performed test
Chaux-Bodard et al	45 F	Ulcer Tongue	Asymptomatic	Oral ulcer associated with COVID-19	Performed
Martín Carreras-Presas et al	56 M	Ulcer Palate	Pain	Herpetic infection	Not performed
Martín Carreras-Presas et al	58 M	Small ulcers Palate	Pain	Herpetic infection	Not performed
Martín Carreras-Presas et al	65 F	Vesicles Lips	Pain	Erithema multiforme	Performed
		Erythema gingiva	Pain	Desquamative gingivitis	
Dantes Soares et al	42 M	Ulcer Buccal mucosa	Pain	NR	Performed
		Macules Hard palate, tongue, lips	Pain	NR	
Amorim Dos Santos et al	67 M	Plaque Tongue	NR	Oral candidiasis	Performed
		Pinpoint ulcers Tongue	NR	Herpetic recurrent oral lesions	
Present cases	41 F	Bulla Hard palate	Asymptomatic	Angina bullosa hemorrhagic-like lesion	Performed
	51 F	Macule Hard palate (left side)	Asymptomatic	Vascular disorder	Performed
		Papule-plaque Hard palate (right side)	Asymptomatic	Vascular disorder	
	55 F	Bulla Tongue	Asymptomatic	Angina bullosa hemorrhagica-like lesion	Performed
	41 M	Small macules Hard palate	Burning sensation	Nonspecific mucositis	Performed

Abbreviations: F, female; M, male; NR, not registered; PCR, polymerase chain reaction.

(13)

Chaux-Bodard et al describieron la primera asociación oral con COVID-19. La úlcera oral informada fue precedida por eritema macular y dolor (probablemente asociada con vasculitis) en una paciente adulta, que también desarrolló una lesión cutánea. En este caso, la úlcera sanó.

Martín Carreras-Presas et al informaron diferentes tipos de Lesión de la mucosa oral (úlceras, vesícula, ampolla y descamativa gingivitis) que sería clínicamente similar a otros virus infecciones mucocutáneas, incluido el herpes simple, herpes zoster o trastornos

inmunológicos. Las lesiones orales fueron auto limitantes y la resolución se vio entre 3 y 10 días después del examen con tratamiento sintomático. Publicaciones recientes de lesiones de la mucosa oral relacionadas con COVID-19 apoyan la asociación con daño orgánico y / o complicaciones por trombocitopenia, anticoagulantes terapia, coagulación intravascular diseminada.

En este contexto, la presentación clínica y los hallazgos histológicos sugieren la posibilidad de que la cavidad bucal presente alteraciones primarias o secundarias a un daño vascular-hematológico relacionado Sars-COV-2.(13)

**Salzano, Giovanni**

**Maglitter, Fabio, Vaira, Luigi Angelo, Salzano, Francesco Antonio, De Riu,**

realizaron un estudio de cohorte en 4 hospitales en Italia: el Hospital Bellaria-Maggiore en Bologna, Hospital universitario de Sassari, Hospital universitario de Salerno y Hospital San Paolo en Milán entre un periodo de tiempo desde 16 de abril 2020 hasta del 2 de mayo. Los criterios de inclusión fueron: Sars-COV-2 positivos, adultos mayores de los 18 años. Se excluyeron los pacientes que no quisieron participar a el estudio, se relacionan casos acerca de la pérdida química sensitiva del gusto, definiéndola una de las manifestaciones tempranas del Sars-COV-2 , en una muestra de 300 pacientes en los primeros 4 días de infección detecto un 60,4% de casos.(14) En otro estudio reportado se considera la pérdida de gusto en el 29,2% como primer síntoma. (15) (16)

Aunque en 7,2% de los casos, una severa ageusia o hipogeusia pueden persistir por mas de 60 días.(17)

Describiendo la causa de todo eso, la infección de las células del epitelio olfatorio y gustativo, muy ricos de convertidores de angiotensina 2 (Ace2). En la mayoría de los casos la recuperación ocurrió a las 3 semanas. (18)

**Chen, Lili Zhao, JiajiaPeng, JinfengLi, XiaoshuangDeng, XuliangGeng, ZhiShen,ZhenyuGuo,FengyuanZhang, QianwenJin, YangWang, LinWang, Songlin**

En este artículo se observó la presencia de Ace 2 en las glándulas salivales; Además, se encontraron en una muestra de 31 paciente de los cuales, 15 hombres y 16 mujeres, síntomas de ageusia 47,2% (36,5% hombres y 46,4% mujeres), Xerostomía 46,3% (46,2% en hombres y 46,4 en mujeres) y el 11,1% (13,5% en hombres y 8,9 en mujeres) presentaron signos de inflamación en la cavidad oral. La saliva, confirmando presencia de proteínas Ace2, pueden ser medio de diagnóstico complementario a la prueba nasofaríngea. (19)

Resultados acerca xerostomia y disminucion de sentido gustativo fueron concordantes con los anteriores, en el artículo de **Daniele Corbi, Stefano Mammucari, Federica Alessi, Riccardo Pampena, Giuliano Bertazzoni, Paolo J. Fantozzi, Emanuele Pampena, Domenico Di Vanna, Eugenia Pellegrino, Salvatore Minisola, Claudio Maria Mastroianni, Antonella Polimeni, Umberto Romeo, Alessandro Villa**

Mediante un estudio de corte retrospectivo, realizados mediante los datos del ED (*Emergency department*) del policlínico Umberto I en Roma, en un periodo desde 6 de marzo hasta el 30 de abril 2020, se tomaron datos de 326 pacientes positivos a PCR por Sars COV-2.

Los datos acerca la xerostomía se clasificaron mediante una escala de 0 (ausencia), 1-2 (muy bajo), 3-4 (bajo), 5-6 (intermedio), 7-8 (alto), 9 y 10 (intensidad máxima), analizando los síntomas por intensidad de xerostomía, pérdida de la función gustativa y olfatoria.

Los pacientes encontrados fueron clasificados por hábitos de fumar (34,2%), beber (44,1%) y por signo y síntomas presentados en el departamento de emergencias como: Fiebre (90,9%), HT (26,1%), problemas crónicos pulmonares (9,9%) y tos (46,8%).

El 45,9% de los pacientes refirieron una intensidad de xerostomía de 5 (intermedia), el 19,6% reportaron que la xerostomía se presentó como primer síntoma con un tiempo de aparición desde la positividad de 3-7 días. Además de xerostomía, se encontraron también disfunciones al deglutir por el 39,2%, necesitando de fluidos para completar la acción.

La manifestación más común fue la disgeusia por el 59,5%, reportado con una intensidad de 8; el 78,8% cuantificó la duración de la manifestación en 6 días (4-7).

Los síntomas reportados en concomitancia o como sola manifestación de infección SARS-COV2 han sido Xerostomía, y disfunciones olfatorias y gustativas. (20)

Siendo considerada la infección por coronavirus una afectación inflamatoria a nivel sistémico, en el artículo de los autores **Nadya Marouf, BDS, MSc<sup>1</sup>, Wenji Cai BDS, MSc<sup>2</sup>, Khalid N. Said, BDS<sup>1</sup>, Hanin Daas, MSc<sup>3</sup>, Hanan Diab, BDS, MSc<sup>1</sup>, Venkateswara Rao Chinta<sup>4</sup>, Ali Ait Hssain, MD<sup>4</sup>, Belinda Nicolau, DDS, PhD<sup>2</sup>, Mariano Sanz, MD, PhD<sup>5</sup>, Faleh Tamimi, BDS, PhD<sup>3</sup>**

Se relacionó la infección por Sars-COV-2 con la enfermedad periodontal, teniendo ambos la misma característica común, la inflamación. Además, se investigó acerca la posibilidad de padecer menores grados de afectaciones bucales teniendo una buena higiene oral.

A través de un estudio de caso-control sobre el COVID-19, se realizaron a los pacientes positivos a PCR, RX para controlar la evolución y el estado periodontal. Entrando en la



definición de Periodontitis, se refiere a la pérdida ósea de 2 o más zonas de dientes no adyacentes.

Las asociaciones que confirman un impacto de la periodontitis en el desarrollo del COVID-19, han sido por complicaciones COVID-19 (OR=3.67, 95%CI 1.46-9.27), muerte (OR=8.81, 95% CI 1.00-77.7), necesidad de ventilación asistida (OR=4.57, 95% CI 1.19-17.4). De los 568 pacientes seleccionados por el estudio, 258 tenían periodontitis. Los resultados obtenidos desde este estudio han demostrado que el riesgo de padecer complicaciones por la infección al coronavirus además de tener una situación periodontal desfavorable ha sido: OR de 6.34 (95%CI 2.79-14.61) para cualquier complicación, OR 5.57 (95% 2.40-12.9) curas intensivas "ICU", OR 7.31(95% 2.21-26.3) con ventilación asistida. (21) (4)

Otros estudios también como el anterior, intentaron buscar relaciones si el estado de salud bucal puede influenciar la aparición y el grado de manifestaciones orales en pacientes positivos a COVID-19. En el artículo de **Nathalie Botros** , **Parvati Iyer** , **David M. Ojcius** , los datos obtenidos han relacionado pacientes con diferentes situaciones sistémicas en acto ( Hipertensión, diabetes, inmunosupresión) o, condiciones de salud bucal y infecciones por Sars-COV-2. Además de identificar que los pacientes más susceptibles de padecer manifestaciones medio/graves por Sars-COV-2 son mayores con una o más afectaciones crónicas. Al mismo tiempo una pobre salud oral puede perjudicar la aparición de síntomas de infección del coronavirus a nivel no solo en campo oral. Siendo la cavidad oral reservorio de patógenos y la enfermedad periodontal una situación favorable para los microorganismos GRAM – para ambiente y reservorio para su proliferación, como el *Chlamydia neumonia*; los pacientes estudiados y reportados en este artículo, con enfermedad periodontal activa, han mostrado mayor probabilidad de padecer neumonía adquirida.

Por esa razón la rehabilitación y el mantenimiento de la salud oral esta aconsejada a cualquier edad para poder evitar complicaciones non orales y disminuir la morbilidad del Sars-COV-2.(22)

**Esam HALBOUB,Sadeq Ali AL-MAWERI,Rawan Hejji ALANAZI, Nashwan Mohammed QAID,Saleem ABDULRAB**

En esta publicación, se observaron los datos recogidos de 16 estudios, con 25 pacientes confirmados por PCR Sars-COV-2.

De las manifestaciones orales, las más comunes han sido: lesiones ulcerativas, vesiculobullosa, lesiones maculo-eritematosas y paperas. Mientras que, por sitio de afectación intraoral, el que mas presentó fue el paladar duro, seguido del dorso de la lengua y de la mucosa labial.

Para las lesiones ulcerativas, manifestación mas común, se encontró en el dorso de la lengua, paladar duro y mucosa bucal; siendo en algunos casos primer signo de Sars-COV-2.

Para las lesiones vesiculobullosa, se encontraron lesiones en rasgos desde vesículas, lesiones erythroematosa, y petequias. La mayoría de las lesiones orales han tenido una correlación con maculas cutáneas.

En los que presentaron paperas, se encontró dolor a nivel de la glándula parótida sin supuración.  
(23)

En el artículo de **Jairo Corchuelo** , **Francisco Chavier Ulloa** , se han reportado datos recogidos en pacientes asintomáticos e identificados positivos a Sars-COV-2 mediante tele consulta entre las ciudades de Nueva York y Cali. Las manifestaciones encontradas, además de alteraciones de la salivación y de la función gustativa fueron, lesiones orales con sobreinfección de infecciones oportunistas, como resultado de exceso de uso de antibióticos, alteraciones del

sistema inmunitario o procesos inflamatorios activos. Además, el microbioma oral esta compuesto y regulado por PH de la saliva, una vez alterado el equilibrio de convivencia entre el huésped y el patógeno, muchas de las lesiones presentes o recién salidas pueden ser causa de manifestaciones dolorosas y desagradables para los pacientes.

Muchos de los casos confirmados Sars-COV-2 presentando lesiones orales, han sido tratados con antifúngicos como la Nistatina, que en la mayoría de los casos fue el tratamiento definitivo de la lesión ora, confirmando lesiones sobreinfectadas/producidas por *Cándida albicans* (C.A). Se encontraron linfadenopatias a nivel cervical , candidiasis oral , xerostomía y petequias, han sido reportados en otros estudio en paciente asociados a *virus de inmunodeficiencia humana* (HIV) ; proponiendo un visión desde los avances científicos del HIV aplicables al nuevo virus.(24) Resultados similares se encontraron en el estudio de **Juliana Amorim dos Santosa Ana Gabriela Costa Normandoa,b Rainier Luiz Carvalho da Silvaa,c Renata Monteiro De Paulac Allan Christian Cembranelc Alan Roger Santos-Silvab Eliete Neves Silva Guerraa**. Preguntaron y analizaron los datos de pacientes Sars-COV-2 positivos tramite PCR y las manifestaciones orales encontrados en los casos reportados han sido varias infecciones oportunistas, disgeusia, xerostomía asociada a disminución del flujo salival, ulceraciones y gingivitis por causa de un sistema inmunitario comprometido. En este estudio se recomienda el seguimiento odontológico por necesidad de control del dolor y calidad de vida en pacientes ingresados en hospital por el coronavirus, tras su dimisión por la posibilidad de padecer: candidiasis, petequias, disgeusia, úlceras traumáticas, infecciones por *Herpes simple* (H.S), lengua geográfica. (25)

Nuevas publicaciones señalan manifestaciones orales con mismos sitios de afectación, pero con diferente forma. En el artículo de **Almudena Nuño González Pedro Herranz Pinto Kyrylo Magaletsky, Ander Mayor y Marta Feito**, publicado en *el british journal dermatology*, los autores han identificados como muy característicos, el edema lingual en forma de U o la glositis con depapilacion en parche, acompañado con sensación de ardor de la cavidad oral. Identificando, la llamada “lengua COVID “, las manifestaciones que afectan la lengua aumentando su tamaño, presentando perdidas de papilas en parche y teniendo escasa o nula función gustativa.(26)

En el artículo de los autores **Faccini, Melissa Ferruzzi, Fernanda Mori, Aline Akemi Santin, Gabriela Cristina Oliveira, Renata Cristina De Oliveira, Ricardo Cesar Gobbi Queiroz, Polyane Mazucatto Salmeron, Samira Pini, Nubia Inocencya Pavesi Sundfeld, Daniel Freitas, Karina Maria Salvatore**, se reportaron datos acerca la atención dental durante el principio y el curso de la pandemia. Recogiendo datos y informaciones de 537 profesionales en Brasil, analizaron que tipo de atención han podido ofrecer durante el confinamiento, cuales han sido los motivos de consulta y cuales los mas frecuentes. Considerando que los pacientes atendidos a consulta odontológica han sido sometidos a protocolos ante la exposición al coronavirus. El 64% atendieron pacientes solo por motivo de emergencia/urgencia dental, 26% mantuvieron las citas rutinarias y el 9,3% cerraron la clínica dental. Los que han seguido con las citas rutinarias han sido jóvenes profesionales.

El 44,1% de citas por urgencias ha sido detectada en aumento muchas veces por el estado de ansiedad y estrés del paciente. Entre los varios motivos de urgencia, se han destacado el dolor

(71,4%), fracturas de restauraciones/ prótesis (40,4%), traumatismo dental (37,3%), rupturas de aparatos ortodonticos (25,2%) y trastornos temporomandibulares (TMD) por el (9.5%).

Para las atenciones rutinarias, los dentistas ha encontrado un aumento en las demandas en capos de prevención, tratamientos como profilaxis (49,1%), extracción de dientes (26,9%) , blanqueamiento de dientes(14,7%).(27)

**Carmen Martín Carreras-Presas, Juan Amaro Sánchez , Antonio Francisco López-Sánchez, Enric Jané-Salas, Maria Luisa Somacarrera Pérez**

Los autores, reportan casos de pacientes sospechosos positivos, en Madrid, por tele consulta por el principio de mayo. Las limitaciones de este estudio ha sido la falta de prueba serológicos disponibles para los pacientes y el personal sanitario.

Los datos relacionados a las manifestaciones dermatológicas de piernas, manos han sido relacionados a lesiones como vasculitis, urticaria y lesiones similares a la varicela. Por lo que pertenece el campo oral, se han encontrado inflamación gingival hasta llegar a gingivitis ulcero necrotizante, lesiones ulcerosas, ageusia, hiposmia, adenopatías, lesiones herpéticas, lesiones vesiculoso ampulosos, lesiones erosivas. (28)

## **Responsabilidad social**

Identificando la patología oral asociada a la infección por Sars-COV-2, podemos influir en la mejora de la calidad de vida del paciente, ya que gracias a la investigación y evolución en odontología se pueden mantener dientes que en otras ocasiones se habrían quitado. Además, podemos contribuir, tratando estas patologías, al bienestar de pacientes, que en muchas ocasiones tiene multitud de dolencias asociadas.

# Conclusiones

**. Las manifestaciones orales encontradas** en los pacientes confirmados positivos a PCR fueron diferentes de paciente a paciente, dependiendo del estado sistémico inmunitario, el estado psicológico, el estado de limpieza bucal y sus relacionados hábitos como el humo, alcohol, consumo de drogas.

Los síntomas mas tempraneros y mas frecuentes ha sido la disgeusia o alteración del gusto, manifestándose por la mayoría de los casos como primera manifestación con una durabilidad de 7 a 10 días desde el principio de la infección, aunque hay pacientes en los que persiste mas tiempo. Alteraciones de la salivación también influyeron en la percepción de los sabores, la consistencia de la saliva se ha confirmado alterada por alteraciones a nivel de la secreción llegando a xerostomía. Además, se encontró presencia de lo que se ha identificado receptor de entrada y fusión a membrana celular humana, el enzima de la conversión de la angiotensina 2 (ACE2), en los conductos salivales.

**. Las lesiones orales encontradas** han sido varias, localizadas en el paladar, encía, lengua y comisuras labiales, como, lesiones herpéticas, úlceras, aftas, petequias, lesiones vasculares similares a las mismas manifestaciones de la mononucleosis, queilitis angular, enantemas.

El estado periodontal y el estado inmunitario y sistémico en situación de infección por SARS COV-2 fue relevante a la hora de tener manifestaciones mas acentuadas, tanto da ser percipidas como manifestaciones sistémicas.

Con la disminución de la atención dental al principio de la pandemia y el ambiente bucal afectado por síntomas salivales, ha dado la posibilidad a los microorganismos presentes en la cavidad oral de afectar directamente o sobre infectar lesiones ya presentes.

**La atención dental fue enfocada** en citas de urgencias por dolor o rupturas de aparatos/ prótesis/ obturaciones, muchas de las demandas de urgencia odontológicas han sido producidos por un cierto grado de estrés que ha llevado el SARS-COV-2 desde el principio.



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ANEXOS

Review

## Comprehensive Structural and Molecular Comparison of Spike Proteins of SARS-CoV-2, SARS-CoV and MERS-CoV, and Their Interactions with ACE2

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**Abstract:** The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has recently emerged in China and caused a disease called coronavirus disease 2019 (COVID-19). The virus quickly spread around the world, causing a sustained global outbreak. Although SARS-CoV-2, and other coronaviruses, SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) are highly similar genetically and at the protein production level, there are significant differences between them. Research has shown that the structural spike (S) protein plays an important role in the evolution and transmission of SARS-CoV-2. So far, studies have shown that various genes encoding primarily for elements of S protein undergo frequent mutation. We have performed an in-depth review of the literature covering the structural and mutational aspects of S protein in the context of SARS-CoV-2, and compared them with those of SARS-CoV and MERS-CoV. Our analytical approach consisted in an initial genome and transcriptome analysis, followed by primary, secondary and tertiary protein structure analysis. Additionally, we investigated the potential effects of these differences on the S protein binding and interactions to angiotensin-converting enzyme 2 (ACE2), and we established, after extensive analysis of previous research articles, that SARS-CoV-2 and SARS-CoV use different ends/regions in S protein receptor-binding motif (RBM) and different types of interactions for their chief binding with ACE2. These differences may have significant implications on pathogenesis, entry and ability to infect intermediate hosts for these coronaviruses. This review comprehensively addresses in detail the variations in S protein, its receptor-binding characteristics and detailed structural interactions, the process of cleavage involved in priming, as well as other differences between coronaviruses.



## Review Article

## On the genetics and immunopathogenesis of COVID-19

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## ABSTRACT

Most severe cases with COVID-19, especially those with pulmonary failure, are not a consequence of viral burden and/or failure of the 'adaptive' immune response to subdue the pathogen by utilizing an adequate 'adaptive' immune defense. Rather it is a consequence of immunopathology, resulting from imbalanced innate immune response, which may not be linked to pathogen burden at all. In fact, it might be described as an auto-inflammatory disease. The Kawasaki-like disease seen in children with SARS-CoV-2 exposure might be another example of similar mechanism.

## 1. Introduction

As of now, the spread of the COVID-19 pandemic has not been matched by an effective immune response to curtail the viral infection. Nevertheless, the outbreak has been matched by an outpour of publications in both server and peer-reviewed journals. While it will take quite some time to find a cure for the disease, the time is right now to curate the unprecedented flow of scientific data. In a cursory PubMed search, I came up with 27,746 results for COVID-19 and 14,064 publications that include the nomenclature SARS-CoV-2, which was only coined in February and first published in the beginning of March [1]. Under these circumstances an exhaustive review of the literature would be impractical, or worse, confusing. Rather, I offer a selective analysis of the literature, in the hope of generating some insight—or at least some relevant hypotheses.

## 2. What is new about the new virus?

Not much—the coronaviruses (CoV), identified in the 1960's, is a family of enveloped positive-strand RNA viruses infecting vertebrates [2] that have the largest genomes among all RNA viruses (~30,000 bases) [3]. Their genomes are more than three times as big as those of HIV and hepatitis C, and more than twice influenza's. The E229 and OC43 coronaviruses discovered in 1966, were the first pathogenic CoV that crossed the species barrier and infected humans [4,5] followed by NL63 [6] and HKU1 [7]. As of now, these four endemic human CoV are

responsible for up to 35% of seasonal common colds. Two of them (OC43 and HKU1) came from rodents, and the other two (E229 and NL63) from bats [8]. In 2002, an outbreak of severe acute respiratory syndrome caused by a CoV [9] originated from bats, was retrospectively named SARS-CoV-1. The epidemic ended in July 2003, after intense public health mitigation measures leaving behind a total of 8096 subjects infected and 774 (9.6%) fatalities in over thirty countries. The second major spillover in 2012, Middle East Respiratory Syndrome (MERS) reproduced the severe clinical phenotype of SARS [10]. According to WHO data as of the end of January 2020 there were 2519 confirmed MERS-CoV infections and 866 deaths, a fatality rate of just over 35%. The present outbreak is the third documented spillover of an animal CoV to humans that has resulted in severe disease, to emerge in two decades [11]. However, the current coronavirus-associated acute respiratory disease discovered in December 2019 in Wuhan, China, and named coronavirus disease 19 (COVID-19) became a major global pandemic. As of August 23, there are 23.4 million confirmed cases of SARS-CoV-2 infections globally with 807,134 fatalities due to COVID-19, according to Johns Hopkins University's count.

The three CoV that cause severe disease – SARS-CoV-1 (the cause of SARS), MERS-CoV, and SARS-CoV-2 –all came from bats [12–14]. But experts think there is usually an intermediary, an animal infected by the bats that carries the virus into humans. With SARS, the intermediary is thought to be civet cats, which are sold in live-animal markets in China [13]. The origin of SARS-CoV-2 is still unclear. The virus shares 96% of its genetic material with a CoV found in a bat in a cave in Yunnan,

# Clinical Characteristics of COVID-19 Patients With Gastrointestinal Symptoms in Northern Italy: A Single-Center Cohort Study

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**INTRODUCTION:** The most typical presentation of COVID-19 is an acute respiratory syndrome whose most common symptoms include fever, cough, and dyspnea. However, gastrointestinal symptoms, such as diarrhea and nausea/vomiting, are increasingly reported in patients affected by COVID-19. This study aimed to describe the prevalence and time of onset of gastrointestinal symptoms in patients affected by COVID-19 and to find potential associations between gastrointestinal symptoms and clinical outcomes.

**METHODS:** We performed a prospective single-center cohort study, enrolling patients who received diagnosis of COVID-19 at our institution between March 23, 2020, and April 5, 2020. We collected patient demographics and medical history, laboratory data, and clinical outcomes. Furthermore, we used a specifically designed questionnaire, administered to patients at time of diagnosis, to obtain data on the presence and time of onset of fever, typical respiratory symptoms, gastrointestinal symptoms, and other symptoms (fatigue, headache, myalgia/arthralgia, anosmia, ageusia/dysgeusia, sore throat, and ocular symptoms).

**RESULTS:** In our cohort, 138 (69%) of 190 patients showed at least 1 gastrointestinal symptom at diagnosis; if excluding hyporexia/anorexia, 93 patients (48.9%) showed at least 1 gastrointestinal symptom. Gastrointestinal symptoms, in particular diarrhea, were associated with a lower mortality. At multivariate analysis, diarrhea was confirmed as independent predictive factor of lower mortality.

**DISCUSSION:** Gastrointestinal symptoms are very frequent in patients with COVID-19 and may be associated with a better prognosis. These data suggest that, in some patients, the gastrointestinal tract may be more involved than the respiratory system in severe acute respiratory syndrome coronavirus 2 infection, and this could account for the less severe course of disease.

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## INTRODUCTION

An outbreak of pneumonia caused by a novel coronavirus, named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in January 2020 in Wuhan, China (1). Since then, the infection has rapidly spread causing a pandemic, affecting more than 2 million people across the world. Italy has been the first country in Europe to register a high incidence of coronavirus-associated disease (COVID-19), with most cases in Lombardy, a region in northern Italy. On April 28, 2020, the Italian National Institute of Health reported 74,346 infected and 13,581 deaths in Lombardy (2).

The most typical presentation of COVID-19 is an acute respiratory syndrome whose most common symptoms include

fever, cough, and dyspnea. However, as the pandemic progresses, gastrointestinal (GI) symptoms, such as diarrhea and nausea/vomiting, are increasingly reported in patients affected by COVID-19 (3–5).

The first Chinese studies describing digestive manifestations in patients infected with SARS-CoV-2 reported variables percentages of GI symptoms (40%–50%) (3,6). A recent meta-analysis of 47 studies has reported a prevalence of GI symptoms (diarrhea, nausea, vomiting, and abdominal pain) of less than 10% in 10,890 patients with COVID-19 (7).

Diarrhea is one of the most commonly reported GI symptoms. It has been proven that SARS-CoV-2 entry into cells is mediated by the interaction between the envelope-anchored viral spike

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Review

# SARS-CoV-2 Infection and Oral Health: Therapeutic Opportunities and Challenges

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**Abstract:** The novel corona virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the disease it causes, COVID-19 (Coronavirus Disease-2019) have had multi-faceted effects on a number of lives on a global scale both directly and indirectly. A growing body of evidence suggest that COVID-19 patients experience several oral health problems such as dry mouth, mucosal blistering, mouth rash, lip necrosis, and loss of taste and smell. Periodontal disease (PD), a severe inflammatory gum disease, may worsen the symptoms associated with COVID-19. Routine dental and periodontal treatment may help decrease the symptoms of COVID-19. PD is more prevalent among patients experiencing metabolic diseases such as obesity, diabetes mellitus and cardiovascular risk. Studies have shown that these patients are highly susceptible for SARS-CoV-2 infection. Pro-inflammatory cytokines and oxidative stress known to contribute to the development of PD and other metabolic diseases are highly elevated among COVID-19 patients. Periodontal health may help to determine the severity of COVID-19 infection. Accumulating evidence shows that African-Americans (AAs) and vulnerable populations are disproportionately susceptible to PD, metabolic diseases and COVID-19 compared to other ethnicities in the United States. Dentistry and dental healthcare professionals are particularly susceptible to this virus due to the transferability via the oral cavity and the use of aerosol creating instruments that are ubiquitous in this field. In this review, we attempt to provide a comprehensive and updated source of information about SARS-CoV-2/COVID-19 and the various effects it has had on the dental profession and patients visits to dental clinics. Finally, this review is a valuable resource for the management of oral hygiene and reduction of the severity of infection.

**Keywords:** COVID-19; periodontitis; Angiotensin Converting Enzyme 2 (ACE-2); saliva; inflammation; oxidative stress; dental practice

## 1. Introduction

Corona viruses are a diversified class of viruses with zoonotic origin, highly transmitted in humans, causing mild to severe respiratory infections. In 2002 and 2012, respectively, two highly pathogenic coronaviruses emerging in humans were (a) severe acute respiratory syndrome coronavirus (SARS-CoV) and (b) Middle East respiratory syndrome coronavirus (MERS-CoV), causing deadly respiratory illness. At the end of 2019, a novel coronavirus designated as SARS-CoV-2 emerged as a pneumonia of the lower respiratory tract in a patient in Wuhan, China on December 29, 2019 [1,2]. The World Health Organization (WHO) classified COVID-19, the disease associated with the virus SARS-CoV-2, as a global pandemic. Several patients with pneumonia were then reported to have contracted the novel

## Dental care during COVID-19 pandemic: Survey of experts' opinion

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### Abstract

**Objectives:** The current COVID-19 outbreak in conjunction with the need to provide safe dental treatments and the limited knowledge on the efficacy of protective measures has posed dentists into a challenging situation. Therefore, the present article aimed at collecting experiences and recommendations of frontline clinical experts on critical aspects of dental treatment provision during pandemic.

**Material & Methods:** From a total of 32 European countries, one leading academic expert in Oral and Maxillofacial Surgery or Oral Surgery per country was asked to participate in an anonymous online 10-item survey on COVID-19 covering the topics of safety of dental settings, personal protective equipment (PPE), and patient-related measures to reduce transmission risk. Data collection took place from April 12th to May 22nd, 2020.

**Results:** A total of 27 experts from different European countries completed the survey. The transmission risk of SARS-CoV-2 in dental settings for aerosol-generating procedures was considered high by all experts except two. For aerosol-free and aerosol-generating procedures, more than 80% of the experts recommended face protection and caps for every single treatment. For aerosol-generating procedures, additional measures (FFP2/FFP3 masks and gowns) were suggested by the vast majority of the experts. To reduce transmission risk, all experts recommended limiting aerosol-generating procedures and reducing the number of patients in waiting areas as well as hand hygiene for the patients.

**Conclusion:** The limitation of aerosol-generating procedures along with the usage of adequate personal protection equipment was considered to be crucial to protect dental healthcare providers and patients, thus reducing the transmission risk of COVID-19.

Kathrin Becker, Giulia Brunello, Katarzyna Gurzawska-Comis contributed equally to this work.

Stefano Sivoletta, Frank Schwarz, and Björn Klinge contributed equally to this work.

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# Recognizing the Relationship Between Disorders in the Oral Cavity and Systemic Disease



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## KEYWORDS

• Oral cavity • Oral disorder • Systemic disease • Trauma • Pediatric dentistry

## KEY POINTS

- Systemic disease may present with signs in the oral cavity. Its recognition contributes to the diagnosis of that illness during clinical examination.
- Medical and dental providers collaborate in the care and management of children with systemic illness that involves the oral cavity.
- When acute-onset oral cavity symptoms that families do not attribute to primarily dental conditions occur, children may present at their pediatrician office, an urgent care facility, or an emergency department. These providers then need to provide first-line interventions for dental conditions.

## INTRODUCTION

The mouth as the portal to the rest of the body has long justified the link between oral and systemic health. Today, the expansion of interdisciplinary care as a means to provider better care has reemphasized the need to have once-siloed disciplines, at a minimum, be aware of key health indicators traditionally outside their realm. More focused to this article, provision of simpler services, in the past restricted to peculiar providers, are now shared among providers. Examples include blood pressure monitoring by dental providers and the application of fluoride varnish by pediatric providers. This emerging crossover of service provision demands better understanding of how oral and systemic health relate to one another; can be synergistic in patient health; or, if ignored, can lead to potential problems.

Oral conditions can affect or be a manifestation of systemic health. For example, children with multiple decayed teeth (caries) can have difficulty with learning, have

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# Genetic and developmental disorders of the oral mucosa: Epidemiology; molecular mechanisms; diagnostic criteria; management

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## 1 | INTRODUCTION

Oral mucosal lesions may appear as ulcers, color changes and alterations in size and configuration of oral anatomy. This review presents a broad overview of genetic and developmental disorders of the oral mucosa that might be recognized in children, adults and the elderly.<sup>1-3</sup> A number of genetic disorders (Table 1) have specific manifestations of the oral mucosa caused by a derangement of one or several of the components of the tissue. Many of them follow the skin or systemic signs of the underlying genetic disease, but in a few cases, oral signs represent the first manifestation of the disorder. Disorders during embryonic development (Table 2) might lead to a wide range of abnormalities in the oral cavity; some of them are quite common but of negligible concern, whereas others are rare but serious, affecting not only the oral mucosa, but also other structures of the oral cavity (ie palate, tongue and gingiva).

## 2 | GENETIC DISORDERS

### 2.1 | Genodermatoses

#### 2.1.1 | Chondro-ectodermal dysplasia

Chondro-ectodermal dysplasia, also termed Ellis-van Creveld syndrome, is a rare disease first described in 1940 by Ellis & van Creveld.<sup>4</sup> Approximately 150 cases have been reported worldwide to date.<sup>5</sup> The

exact prevalence is unknown, but the syndrome seems more common among the Amish community. This rare condition is inherited as an autosomal recessive trait with a variable expression. Mutations of the Ellis van Creveld protein 1 and 2 genes, located in a head-to-head configuration on chromosome 4p16, have been identified as causative.<sup>6,7</sup> The mutations of Ellis van Creveld belong to the short rib-polydactyly group and especially type III (Verma-Naumoff syndrome).



Chondro-ectodermal dysplasia is characterized by the presence of short ribs, polydactyly, growth retardation and ectodermal and cardiac defects. The most constant oral findings are fusion of the upper or lower lip to the gingiva and hypertrophy of the labiogingival fraenum, resulting in the disappearance of the mucolabial fold, or the presence of multiple fibrous bands. Oligodontia and small conical teeth with enamel hypoplasia are also present.<sup>8</sup> The differential diagnosis from similar chondrodystrophies, such as Jeune dystrophy, McKusick-Kaufman syndrome, includes oro-facial-digital syndrome, and Weyers acro-dental dysostosis.<sup>9-11</sup> The oral dental management is quite complex and often requires a multidisciplinary approach to correct the dental defects. Orthodontics and maxillofacial oral surgery are often involved in the treatment; moreover, comprehensive restorative treatment is fundamental to manage enamel hypoplasia and to replace missing teeth.<sup>10</sup>

#### 2.1.2 | Dyskeratosis congenita

Dyskeratosis congenita or Zinsser-Engman-Cole syndrome is a multi-system disorder,<sup>12</sup> first described by Zinsser in 1906 and recognized

# Oral Manifestations in Patients with COVID-19: A Living Systematic Review

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## Abstract

This living systematic review aims to summarize evidence on the prevalence of oral signs and symptoms in patients with COVID-19. The review was reported per the PRISMA checklist, and the literature search was conducted in 6 databases and in gray literature. Studies published in any language mentioning oral symptoms and signs in patients with COVID-19 were included. The risk of bias was assessed by the Joanna Briggs Institute appraisal tools. The certainty of evidence was evaluated through GRADE assessment. After a 2-step selection, 40 studies were included: 33 cross-sectional and 7 case reports. Overall, 10,228 patients (4,288 males, 5,770 females, and 170 unknown) from 19 countries were assessed. Gustatory impairment was the most common oral manifestation, with a prevalence of 45% (95% CI, 34% to 55%;  $I^2 = 99%$ ). The pooled eligible data for different taste disorders were 38% for dysgeusia and 35% for hypogeusia, while ageusia had a prevalence of 24%. Taste disorders were associated with COVID-19 (odds ratio [OR], 12.68; 95% CI, 6.41 to 25.10;  $I^2 = 63%$ ;  $P < 0.00001$ ), mild/moderate severity (OR, 2.09; 95% CI, 1.25 to 3.49;  $I^2 = 66%$ ;  $P = 0.005$ ), and female patients (OR, 1.64; 95% CI, 1.23 to 2.17;  $I^2 = 70%$ ;  $P = 0.0007$ ). Oral mucosal lesions presented multiple clinical aspects, including white and erythematous plaques, irregular ulcers, small blisters, petechiae, and desquamative gingivitis. Tongue, palate, lips, gingiva, and buccal mucosa were affected. In mild cases, oral mucosal lesions developed before or at the same time as the initial respiratory symptoms; however, in those who required medication and hospitalization, the lesions developed approximately 7 to 24 d after onset symptoms. Therefore, taste disorders may be common symptoms in patients with COVID-19 and should be considered in the scope of the disease's onset and progression. Oral mucosal lesions are more likely to present as coinfections and secondary manifestations with multiple clinical aspects (PROSPERO CRD42020184468).

**Keywords:** gustatory dysfunction, coronavirus infections, meta-analysis, oral-systemic disease(s), systematic reviews, evidence-based medicine

## Introduction

Recently, a global pandemic burden has emerged by the human-to-human transmission of a novel coronavirus disease (COVID-19). Since the outbreak in December 2019, COVID-19 has affected >11,301,800 people (World Health Organization 2020b; Zhou, Yang, et al. 2020). The most common symptoms are fever and dry cough and in some cases shortness of breath, dysosmia, and dysgeusia (Guan et al. 2020; Lechien et al. 2020 [see Appendix References 1]). Most human cases of COVID-19 are mild (80%), while 20% of infected patients may develop severe disease, and 5% may become critically ill and develop pneumonia or acute respiratory distress syndrome, which requires mechanical ventilation and intensive care unit hospitalization (Epidemiology Working Group and Chinese Center 2020).

Current research shows that coronavirus invades human cells via the receptor angiotensin-converting enzyme 2 (ACE2) through scRNA-seq data analyses. The study identified the organs that are at risk and are vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (e.g.,

lung; Zou et al. 2020). Therefore, cells with ACE2 receptor distribution may become host cells for the virus and cause inflammatory response in related organs and tissues, such as the tongue mucosa and salivary glands (Wang et al. 2020; Xu, Li, et al. 2020; Xu, Zhong, et al. 2020). SARS-CoV-2 interaction with ACE2 receptors may also impair taste bud sensitivity, which could induce dysfunctional gustatory responses (Mariz

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A supplemental appendix to this article is available online.

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## Brief communication: Immunohistochemical detection of ACE2 in human salivary gland

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### Abstract

The novel, severe acute respiratory syndrome coronavirus (SARS-CoV-2) was firstly reported in late December of 2019 and subsequently caused a global outbreak. It has been shown that SARS-CoV-2 uses ACE2 (Angiotensin Converting Enzyme 2) as a cellular receptor for host cell entry through the surface unit of SARS-CoV spike glycoprotein. In this brief report, we analyze ACE2 protein expression and localization in human salivary gland, and propose a possible role of saliva in the pathogenesis of Coronavirus disease 2019 (COVID-19).

### KEYWORDS

aspiration pneumonia, COVID-19, salivary gland, SARS-CoV-2

## 1 | INTRODUCTION

Coronaviruses are enveloped RNA virions, which belong to the family of Coronaviridae, and cause mild respiratory disease in humans; however, the SARS-CoV (Severe acute respiratory syndrome coronavirus) and the MERS-CoV (Middle East respiratory syndrome coronavirus) explored in 2002-2003 and in 2012, respectively, caused fatal severe respiratory diseases. The novel coronavirus SARS-CoV-2, the causative agent of coronavirus disease 19 (COVID-19), was firstly reported late in December 2019 and subsequently caused a global outbreak. SARS-CoV-2 shares ~80% amino acid identity with SARS-CoV, and it has been shown in the involvement of ACE2 (angiotensin converting enzyme 2) as a cellular receptor of a surface unit of SARS-CoV spike glycoprotein.<sup>1</sup>

Several transmission routes of SARS-CoV-2 have been proposed including both direct and contact transmission.<sup>2</sup> Importantly, recent studies have proposed saliva as a potential reservoir for COVID-19 asymptomatic infection.<sup>3,4</sup> Some studies have shown ACE2 expression in human salivary gland by analyzing the mRNA expression,<sup>1,3</sup> however, evidence of immunohistochemical ACE2 expression and its localization in human salivary gland is still unknown. Herein, we evaluate

ACE2 protein expression and localization in human salivary gland, and propose a possible role of saliva in the pathogenesis of COVID-19.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethics Statement

This study was approved by the Institutional Ethical Review Board of Osaka University Graduate School of Dentistry (no. R1 E-46) and performed in accordance with the Committee guidelines and regulations.

### 2.2 | Tissue materials

Four salivary gland tissues, two tongue tissues (Table 1) and C57BL/6 mouse tissues (for positive control) were fixed with 10% neutral-buffered formalin and embedded in paraffin wax. All the tissues were confirmed to be normal by two pathologists. The 4 µm-thick sections were used for further studies.

## Angular cheilitis of COVID-19 patients: A case-series and literature review

Dear Editor,

We have read with great interest the correspondence of Rodríguez et al. (2020) which demonstrated angular cheilitis (AC) in two patients of coronavirus disease (COVID-19) (Díaz Rodríguez et al., 2020). Therefore, we aim to report according to the CARE guidelines, a series of 17 laboratory-confirmed COVID-19 patients with AC (Gagnier et al., 2013).

The referenced patients sought care at our department from April to June 2020 due to pain related to either one or both oral commissures. All included patients had previously undergone a polymerase chain reaction (PCR) testing for SARS-COV-2, which confirmed their infection with a mean cycle threshold (Ct) value of  $28.71 \pm 5.22$  (17–34). Their mean age was  $39.94 \pm 13$  (20–64) years old, and twelve (70.6%) of them were females. In regard to the characteristic symptoms of COVID-19, four patients (23.5%) had persistent fever, three patients (17.6%) had pharyngitis, and two patients (11.8%) had ageusia. While one patient (5.9%) had lost the mandibular first molar, one patient (5.9%) had reported bruxism previously, and two patients (11.8%) had presented signs of dental attrition. All patients complained of excessive salivation during the preceding days of their examination.

Clinical examination has revealed reddish swollen patches corresponding to AC found unilaterally on the left commissure of 11 patients (64.7%), the right commissure of four patients (23.5%), and bilaterally in two patients (11.8%). The day of PCR testing was set as a reference time point for estimating the onset of AC. The mean onset of AC was  $1.82 \pm 0.95$  (0–3) days, and the mean duration was  $3.35 \pm 1.77$  (2–8) days. Five patients (29.4%) had generalized cheilitis in addition to AC. The pain severity was subjectively assessed by the patients using an 11-item numerical rating scale (NRS) when with "0" denoting "no pain" and "10" denoting "pain as bad as you can imagine" (Williamson & Hoggart, 2005). The mean pain severity was  $5.06 \pm 1.89$  (2–9), and the mean pain duration was  $2.41 \pm 0.87$  (2–5) days. The patients received symptomatic treatment, including mouthwash of Chlorhexidine Gluconate 0.3% and antifungal ointment of Nystatin to ease their pain.

The statistical analysis revealed that age and gender did not have a significant association with any of the clinical or laboratory variables. The duration of pain was strongly correlated with pain severity and the duration of AC until its complete recovery (Pearson Correlation = .526, and .625;  $p = .030$ , and  $.007$ , respectively). All the investigated patients agreed to use their clinical and laboratory results for academic purposes while concealing their identifying personal data.

Our findings rule out the possibility of decreased vertical dimension as a local factor for developing AC; because the majority of our patients had their first molars in occlusion and did not present signs of bruxism or dental attrition. The increased expression of angiotensin-converting enzyme II (ACE2) in salivary glands underpinned by the high positivity of salivary samples for SARS-COV-2 can cause salivary glands disorders such as acute parotitis which may affect the salivary consistency in terms of increased serous secretion and enzyme content (Riad et al., 2020). However, there is a lack of evidence on salivary consistency and flow of COVID-19 patients, the increased salivation reported by our patients might cause AC as the salivary enzymes can irritate the skin of the mouth corners leading to maceration and digestion. (Park et al., 2011).

On reviewing the emerging evidence of cheilitis in relation to COVID-19, twenty-six patients were reported to have various types of cheilitis. In Moscow, Khabadze et al. (2020) demonstrated that out of 90 hospitalized COVID-19 patients with oral mucocutaneous manifestations, there were 21 patients (23.3%) presented with AC associated in some of them with facial xeroderma and petechiae of buccal mucosa (Khabadze et al., 2020). In the case-series of Rodríguez et al. (2020), a 53-year-old male patient reported burning sensation with unilateral AC complicated by persistent anosmia and dysgeusia that lasted even after the relief of AC. There was also a 78-year-old hospitalized female with AC associated with pseudomembranous candidiasis lesions on the tongue and palate (Díaz Rodríguez et al., 2020). The youngest case was reported in Italy, for a 9-year-old Down's syndrome male patient who complained of symptomatic glossitis adjacent to mild cheilitis while being SARS-COV-2 positive (Mazzotta et al., 2020). Alsibai et al. (2020) described pustular, erythematous rash on the upper trunk in association with cheilitis in a 66-year-old recently recovered female patient (Drak Alsibai et al., 2020). A rare adult patient with Kawasaki-like multisystem inflammatory syndrome had cheilitis associated with left neck swelling, periorbital edema, and targetoid erythematous while being SARS-COV-2 positive (Shaigany et al., 2020).

Cheilitis and strawberry tongue were frequently observed in the pediatric patients diagnosed of Kawasaki-like multisystem inflammatory syndrome; therefore, dentists and pediatric dentists are supposed to pay attention to these alarming manifestations as they may help in early diagnosis of these patients (Riad et al., 2020). Moreover, COVID-19 can cause cheilitis indirectly; a cross-sectional study for frontline healthcare workers revealed that due to the excessive use

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# Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ?



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Several viruses transmitted through saliva, such as herpes simplex virus, cytomegalovirus, and Zika virus, are capable of infecting and replicating in the oral mucosa, leading to painful oral ulcers. Few studies have described the oral manifestations of coronavirus disease 2019 (COVID-19). There is growing evidence that angiotensin-converting enzyme 2 (ACE2), the main host cell receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is highly expressed on the epithelial cells of the tongue and of the salivary glands, which may explain the development of dysgeusia in patients with COVID-19. Hence, it is important to understand if SARS-CoV-2 can infect and replicate in oral keratinocytes and fibroblasts, causing oral ulcerations and superficial necrosis. Here, we report a series of 8 cases of COVID-19 infection, with oral necrotic ulcers and aphthous-like ulcerations which developed early in the course of disease after the development of dysgeusia and affected the tongue, lips, palate, and oropharynx. A short review of the literature regarding the important role of ACE2 in SARS-CoV-2 cellular entry is also provided, bringing new insights into oral keratinocytes and minor salivary glands as potential targets. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e45–e51)

Coronavirus disease 2019 (COVID-19) has had a massive impact worldwide as a result of the mode of infection spread, the resulting severe acute respiratory syndrome, and the global death toll. Since the identification of this new airborne infectious microorganism (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) in Wuhan, China, millions of cases have been diagnosed worldwide, with mortality rates ranging from 3% to 12%.<sup>1</sup>

In addition to fever, fatigue, dry cough, myalgias, sore throat, breathing difficulties, and respiratory complications that often deteriorate to severe acute respiratory syndrome, patients infected by SARS-CoV-2 may develop a myriad of other local and systemic complications, such as acute cardiac damage, acute renal failure, gastrointestinal complications, dysgeusia, anosmia, and neurologic symptoms, including Guillain-Barré syndrome.<sup>2-4</sup>

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is detected in the cell membrane of numerous human organs and tissues,

including the lungs, kidneys, liver, epithelial cells of the tongue and salivary glands, upper respiratory tract, nervous system, and skeletal muscle, among others.<sup>5-8</sup>

Although SARS-CoV-2 can be detected in saliva and oropharyngeal secretions,<sup>9-12</sup> the routes of infection remain elusive, and little is known about the routes of transmission through the oral mucosa. Thus, more clinical evidence and research are needed to confirm the ability of SARS-CoV-2 to infect the oral tissues and its pathogenic mechanisms in the oral and oropharyngeal mucosae. This report on a case series presents 2 patterns of oral ulcerations—aphthous-like and superficial necrosis—affecting multiple oral sites in patients diagnosed with COVID-19. These lesions develop in oral sites known to express ACE2 receptors, as recently described in the tongue epithelium and the salivary glands tissue,<sup>6,7</sup> after the manifestation of dysgeusia.

## CASE 1

An 81-year-old man with cough and progressive chest tightness present for 10 days was admitted to the Emergency Department of the Hospital Sírio-Libanês, São Paulo, Brazil, on March 26, 2020. The patient had a history of well-controlled hypertension and chronic obstructive pulmonary disease. Fifteen days earlier, on March 11, 2020, he had come in contact with a family member who had traveled to Israel and had been recently diagnosed with SARS-CoV-2 pneumonia. In our patient, dysgeusia appeared on March 16, 2020. Five days later, the patient developed chills and fever, and a maximum body temperature of 37.7°C. On March 25, 2020, the patient developed a dry cough and mild dyspnea. Physical examination revealed normal body temperature (36°C); blood pressure 108/67 mm Hg; heart rate 83 beats per minute;

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# Olfactory and Oral Manifestations of COVID-19: Sex-Related Symptoms—A Potential Pathway to Early Diagnosis

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## Abstract

**Objective.** The coronavirus disease 2019 (COVID-19) pandemic poses a threat to global health. Early diagnosis is an essential key to limit the outbreak of the virus.

**Study Design.** Case series, study conducted between March 25, 2020, and April 15, 2020.

**Setting.** Ambulatory, nonhospitalized patients who were quarantined in a designated hotel for COVID-19 patients and were recruited by an advertisement at the hotel.

**Subjects and Methods.** In total, 140 patients participated in a web-based questionnaire assessing initial symptoms of common viral diseases, olfactory and taste functions, xerostomia, and orofacial pain.

**Results.** A total of 58 men and 70 women participated. Initial symptoms were cough (59.4%), weakness (47.7%), myalgia (46.9%), fever (42.2%), headache (40.6%), impaired sense of smell (38.3%), impaired sense of taste (32.8%), sore throat (26.6%), runny nose (26.6%), and nasal congestion (22.7%). All symptoms were more frequent among women; however, only runny nose was statistically significant ( $P = .018$ ). The most common combination of symptoms was cough and weakness (37.5%). A total of 25.8% reported olfactory and taste dysfunctions in the absence of other symptoms. In a comparison between the sexes, cough and runny nose were the most common combination in women ( $P = .018$ ). A total of 38.3% of patients reported olfactory dysfunction as an initial symptom. Anosmia and facial pain were more common among women ( $P < .001$  and  $P = .01$ , respectively), and 56% of patients reported xerostomia.

**Conclusion.** A considerable number of patients presented with olfactory and oral disorders. Interestingly, women presented with a different cluster of symptoms than men, which may suggest a new clinical approach to diagnosing COVID-19 disease.

## Keywords

coronavirus, COVID-19, anosmia, xerostomia, dysgeusia

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered coronavirus. The causative pathogen was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the seventh type of the coronavirus family to affect humans.<sup>1,2</sup> On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic.

The virus is transmitted from human to human via droplet transmission and direct contact with oral, nasal, and eye mucous membranes.<sup>3</sup> Studies suggest that COVID-19 may become airborne through aerosols generated during clinical procedures.<sup>4</sup>

COVID-19 has an incubation period of 1 to 14 days, with most ranging from 3 to 7 days.<sup>5</sup> Other studies suggest an incubation period of 5.2 days.<sup>6</sup> According to the WHO, an acute respiratory infection, fever, and cough are the most valid diagnostic clinical features.<sup>7</sup>

Social isolation has proven effective in avoiding contamination among the population.<sup>8</sup> Early detection of symptoms is essential. Some common orofacial manifestations of viral infection may contribute to early diagnosis of COVID-19 infection. Recent reports demonstrated that loss of taste and smell can be the first and only manifestations of infection.<sup>9,10</sup>

This study assessed early manifestations of COVID-19, with an emphasis on olfactory and oral disorders.

## Materials and Methods

The study was conducted in the Department of Oral Rehabilitation, School of Dental Medicine of Tel Aviv University, in

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# Oral mucosal lesions in patients with SARS-CoV-2 infection. Report of four cases. Are they a true sign of COVID-19 disease?

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## Abstract

**Background:** Vesiculobullous and macular lesions in the oral mucosa have been reported in patients positive for SARS-CoV-2 infection. Nonetheless, the significance and physiopathology of oral manifestations have not been clearly established in the clinical progression or outcome of the infection.

**Aim:** To describe the clinico-pathological oral mucosal lesions in four patients with confirmed SARS-CoV-2 infection.

**Methods and Results:** Four patients with COVID-19 disease and confirmed by polymerase chain reaction (PCR) presented angina bullosa hemorrhagica-like lesion, vascular disorder, and nonspecific stomatitis, one patient with histological analysis demonstrated perivascular reactive lymphocytic infiltrate, focal capillary thrombosis, and hemorrhage. According to the discrimination of other local and systemic conditions and the synchronous onset of oral and systemic symptoms, the diagnosis of oral lesions probably associated with COVID-19 was established.

**Conclusion:** Infection with SARS-CoV-2 may result in oral manifestations with various clinical presentations, which presumably support the hypothesis of thrombi formation and vasculitis; nevertheless, these findings need more evidence and a long-term follow up of patients to accurately establish the significance of the oral mucosa affection in the COVID-19 disease.

## KEYWORDS

case reports, COVID-19, oral manifestations, SARS-CoV-2

## 1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), etiology for the new Coronavirus disease 2019 (COVID-19), has reached a high infectivity rate with approximately worldwide projections of 23 000 000 million cases and 900 000 deaths by September 2020.<sup>1</sup> Elderly

patients (> 70 years) and vulnerable patients with comorbidities, such as hypertension, diabetes, cardiovascular disease, lung disease, chronic kidney disease, and immunosuppressed conditions, predispose to develop severe acute respiratory, heart, and kidney failure and poor prognosis.<sup>2</sup> The clinical course of COVID-19 depends on the host immune response, and frequent symptoms include fever,

## Remote psychophysical evaluation of olfactory and gustatory functions in early-stage coronavirus disease 2019 patients: the Bologna experience of 300 cases

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### Main Article

Dr L A Vaira takes responsibility for the integrity of the content of the paper

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#### Key words:

COVID-19; Taste; Smell; Anosmia; Ageusia; SARS-CoV-2 Infection; Coronavirus

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### Abstract

**Background.** An objective evaluation of coronavirus disease 2019 in the first days of infection is almost impossible, as affected individuals are generally in home quarantine, and there is limited accessibility for the operator who should perform the test. To overcome this limitation, a recently validated psychophysical self-administered test was used, which can be performed remotely in the assessment of early-stage coronavirus disease 2019 patients.

**Methods.** Olfactory and gustatory functions were objectively assessed in 300 patients in the first 7 days from coronavirus disease 2019 symptom onset.

**Results.** Seventy per cent of the patients presented olfactory and/or gustatory disorders. The dysfunctions detected were mainly complete anosmia (47 per cent) or ageusia (38 per cent). A significant correlation was found between taste dysfunction and female gender (odds ratio = 1.936,  $p = 0.014$ ) and fever (odds ratio = 2.132,  $p = 0.003$ ).

**Conclusion.** The psychophysical evaluation protocol proposed is an effective tool for the fast and objective evaluation of patients in the early stages of coronavirus disease 2019. Chemosensitive disorders have been confirmed to be frequent and early symptoms of the coronavirus infection, and, in a significant number of cases, they are the first or only manifestation of coronavirus disease 2019.

### Introduction

The high frequency of chemosensitive disorders in patients with coronavirus disease 2019 (Covid-19) is a clinical finding reported by several authors in Europe and America.<sup>1–10</sup> These symptoms are typical of the early stages of the disease,<sup>11,12</sup> and, considering their specificity, they may be useful as a screening marker.<sup>13,14</sup>

Psychophysical tests are crucial to determine the exact frequency, extent and clinical characteristics of these chemosensitive disorders, and to monitor their recovery over time. However, most of the studies currently present in the literature are based on anamnestic or observational evidence. As of 25 May 2020, only four objective studies had been published.<sup>15–18</sup> These few studies mainly include patients with advanced stages of Covid-19 at the time of worst impairment, preventing the evaluation of chemosensitive functions. An objective evaluation in the first days of the disease is almost impossible, as these patients are generally in home quarantine, and there is limited accessibility for the operator who should perform the test.

A few weeks ago, Vaira *et al.*<sup>19</sup> proposed and validated a new self-administered psychophysical test that can be performed remotely for the evaluation of olfactory and gustatory functions in patients in home quarantine. Using this test, we have objectively evaluated the chemosensitive functions of 300 Covid-19 patients, belonging to the healthcare staff of the Bellaria-Maggiore Hospital in Bologna, within the first 7 days of Covid-19 clinical onset.

### Materials and methods

This cohort study was conducted on severe acute respiratory syndrome 2 (SARS-CoV-2) positive patients monitored by the Surveillance and Prevention Department of Bellaria-Maggiore Hospital in Bologna, between 16 April and 2 May 2020. All the subjects were healthcare staff at the hospital.

In order to be eligible for enrolment in this study, patients had to meet the following inclusion criteria: adult over 18 years of age; SARS-CoV-2 infection confirmed by

## Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study

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### Abstract

**Background:** Objective data on chemosensitive disorders during COVID-19 are lacking in the Literature.

**Methods:** Multicenter cohort study that involved four Italian hospitals. Three hundred and forty-five COVID-19 patients underwent objective chemosensitive evaluation.

**Results:** Chemosensitive disorders self-reported by 256 patients (74.2%) but the 30.1% of the 89 patients who did not report dysfunctions proved objectively



Case report

# Hypogeusia as the initial presenting symptom of COVID-19

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## SUMMARY

COVID-19 is the disease caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first arose in Wuhan, China, in December 2019 and has since been declared a pandemic. The clinical sequelae vary from mild, self-limiting upper respiratory infection symptoms to severe respiratory distress, acute cardiopulmonary arrest and death. Otolaryngologists around the globe have reported a significant number of mild or otherwise asymptomatic patients with COVID-19 presenting with olfactory dysfunction. We present a case of COVID-19 resulting in intensive care unit (ICU) admission, presenting with the initial symptom of disrupted taste and flavour perception prior to respiratory involvement. After 4 days in the ICU and 6 days on the general medicine floor, our patient regained a majority of her sense of smell and was discharged with only lingering dysgeusia. In this paper, we review existing literature and the clinical course of SARS-CoV-2 in relation to the reported symptoms of hyposmia, hypogeusia and dysgeusia.

## BACKGROUND

For many sick people with viral upper respiratory infections (URIs), the experience of eating food and perceiving flavour is often blunted either secondarily from rhinitis and resulting nasal obstruction or from direct viral injury to olfactory neuroepithelium. Retronasal olfaction, a combination of orthonasal smell and taste, is a sensory process that allows humans to perceive flavour, which is defined as the perception of anything beyond the five taste dimensions of food: sweet, salty, bitter, sour and umami.<sup>1</sup> This process is temporarily impaired during URIs due to mucosal inflammation and congestion of the nasal passages, thus physically blocking the entry of odour and flavour molecules to the olfactory cleft.<sup>2</sup> In contrast, post-URI olfactory loss is a neural process that occurs due to viral insult<sup>2</sup> and most commonly results in hyposmia late in the course of viral infection.<sup>3</sup> This type of viral insult can result in either temporary loss of olfaction or, in some cases, permanent loss of smell.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of many pandemic coronaviruses that have been identified. The current outbreak of COVID-19 that began in Wuhan, China, has constituted a public health emergency of international concern, now creating a global impact with over 2.4 million cases to date.<sup>4</sup> The clinical sequelae vary from mild and self-limiting URI symptoms to

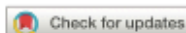
severe respiratory distress, acute cardiopulmonary arrest and death.<sup>5</sup> Coronaviruses have previously been identified as a family of viruses associated with anosmia.<sup>6</sup> Anecdotal evidence from otolaryngologists worldwide has suggested that otherwise mild cases of COVID-19 caused by the novel betacoronavirus, SARS-CoV-2, may be significantly associated with olfactory dysfunction.

We present a case of COVID-19 resulting in ICU admission, presenting with the initial symptom of disrupted taste and flavour perception prior to respiratory involvement. The purpose of this paper was to review the clinical course of SARS-CoV-2 in relation to the reported symptom of hyposmia and hypogeusia.

## CASE PRESENTATION

A 59-year-old African-American female presented to our institution by ambulance on 29 March 2020, secondary to several days of shortness of breath, fatigue and loss of appetite. Medical history was significant for hypertension, hyperlipidaemia and asthma, requiring infrequent use of albuterol reported less than one time per month. Social history was notable only for a remote history of tobacco abuse, but she denied any current tobacco, drug or alcohol use. Of note, the patient did endorse that her husband, whom she lives with at home, was complaining of shortness of breath and a non-productive cough several days prior to her arrival. Her husband's symptoms lasted only 3–4 days and had resolved completely. She reported no past otolaryngological surgeries or use of any nasal sprays, or homeopathic or herbal medications.

Roughly a week prior to admission, the patient began to experience a subtle decrease in appetite and disinterest in food. These symptoms were isolated and preceded any indication that she was ill. Over the week prior to her presentation, the foods she normally enjoys tasted 'bland and metallic'. The patient described her diet as 'varied and including many spices and strong flavours, particularly using herbs in Jamaican and Caribbean cuisines'. When questioned further, she also admitted to a slowly diminishing ability to smell that progressed to complete anosmia in the absence of congestion or any other nasal symptoms. However, she did not make the connection to this early symptom and the subsequent respiratory distress until specifically questioned. She noted in particular that when preparing her normal meals, she could no longer appreciate any of the typical culinary aromas.



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## Main Article

Dr L A Vaira takes responsibility for the integrity of the content of the paper

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COVID-19; Ageusia; Anosmia; Gustatory Dysfunction; SARS-CoV-2; Coronavirus; Hypogeusia; Smell; Taste

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# Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study

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## Abstract

**Background.** The long-term recovery rate of chemosensitive functions in coronavirus disease 2019 patients has not yet been determined.

**Method.** A multicentre prospective study on 138 coronavirus disease 2019 patients was conducted. Olfactory and gustatory functions were prospectively evaluated for 60 days.

**Results.** Within the first 4 days of coronavirus disease 2019, 84.8 per cent of patients had chemosensitive dysfunction that gradually improved over the observation period. The most significant increase in chemosensitive scores occurred in the first 10 days for taste and between 10 and 20 days for smell. At the end of the observation period (60 days after symptom onset), 7.2 per cent of the patients still had severe dysfunctions. The risk of developing a long-lasting disorder becomes significant at 10 days for taste (odds ratio = 40.2, 95 per cent confidence interval = 2.204–733.2,  $p = 0.013$ ) and 20 days for smell (odds ratio = 58.5, 95 per cent confidence interval = 3.278–1043.5,  $p = 0.005$ ).

**Conclusion.** Chemosensitive disturbances persisted in 7.2 per cent of patients 60 days after clinical onset. Specific therapies should be initiated in patients with severe olfactory and gustatory disturbances 20 days after disease onset.

## Introduction

Chemosensitive dysfunction is now considered one of the most frequent symptoms in the early stages of coronavirus disease 2019 (Covid-19).<sup>1–11</sup> Objective psychophysical evaluation is challenging because of logistical and safety problems. Consequently, as of 1 July 2020, only six retrospective psychophysical studies have been published,<sup>12–17</sup> and only three of them investigate both olfactory and gustatory functions.<sup>12–14</sup>

In the absence of prospective studies, the long-term recovery rate of chemosensitive function has not yet been determined. Although many authors have reported complete recovery in most patients within a few weeks,<sup>4,5,7,8,10</sup> psychophysical studies have found that around 25 per cent of patients evaluated 30 days after the clinical onset of Covid-19 have severe chemosensitive disorders (i.e. anosmia, ageusia, severe hyposmia or severe hypogeusia).<sup>12,13</sup> Clearly, there is still potential for delayed recovery, but the consequence of such a frequent, persistent severe chemosensitive dysfunction, given the high incidence of infection, means that there will be a significant number of patients with potentially long-term morbidity.

In order to understand the longer-term recovery rate of chemosensitive functions, so as to aid the counselling of patients and guide if and when it is appropriate to start a specific therapy, we prospectively evaluated 138 Covid-19 patients with psychophysical tests in 3 Italian hospitals for a period of 60 days from clinical onset of the disease.

## Materials and methods

This multicentre prospective study involved three Italian Covid-19 hospitals: University Hospital of Sassari, San Paolo Hospital in Milan, and Bellaria-Maggiore Hospital in

## Commentary

# Ageusia, A Highly Specific Symptom of COVID-19, for Which an Unaware Patient May Seek Dental Assistance



The rapid worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has profoundly changed dental practice with the initial suspension of all clinical activities except emergent situations. In Europe, many countries are moving toward the so-called 'phase 2', coexistence with the virus. Of course, the resumption of activities will cause a rise in the contagion curve. To slow this rise in cases, it will be essential to be able to identify suspicious cases and to ensure that such patients undergo a nasopharyngeal swab. A knowledge of the most frequent symptoms in the early stages of coronavirus disease 2019 (COVID-19) is mandatory to achieve this goal and dentists, through the anamnestic information collected during the triage procedures, will have a fundamental role in this process.

Taste and smell disturbances were reported as rare findings in these patients, in the Chinese case series, affecting only 5% of patients.<sup>1</sup> At the end of March, we first realised that in Italian COVID-19 patients the incidence of these conditions was much higher, and, in particular, these symptoms were very frequent in the early stages of the disease.<sup>2,3</sup> Subsequently, similar findings have been reported by several authors in Europe and America,<sup>4-6</sup> with incidences of around 70% of these patients. Chemosensitive disorders represent early symptoms of COVID-19, commonly occurring within 2-3 days after the clinical onset.<sup>7-9</sup> The latest data reported by Petrocelli et al.,<sup>4</sup> evaluating the gustatory function in 300 patients in the first 4 days from the clinical onset, detected a taste dysfunction in 60.4% of the cases. Interestingly, in a large multicentre Italian study recently published by our group, chemosensitive symptoms proved to be the first symptom of COVID-19 in 29.2% of patients and the only one in 9.5% of cases.<sup>9</sup> In most patients, the recovery of gustatory function generally occurs within 3 weeks. However, in 7.2% of cases, severe ageusia or hypogeusia can persist for more than 60 days.<sup>10</sup>

The pathogenesis of these disorders is probably related to the infection of the support cells to the olfactory and gustatory receptors, rich in angiotensin converting enzyme 2 (ACE2) receptors.<sup>11</sup> In fact, ageusia is a well-known side effect of ACE2-inhibitors.

Ageusia is a rare condition that is characterised by a complete loss of taste function of the tongue. This condition is one of the typical symptoms of COVID-19 has important implications in dental practice. At the beginning of the epidemic in Italy, an abnormal number of patients attended our dental, neurological and surgical clinics on account of the detection of sudden onset ageusia, not associated with any other symptoms. Subsequently, SARS-CoV-2 infection was

soon diagnosed in these patients following the further onset of fever and cough. This strange coincidence was the reason that prompted us to start investigating the role of chemosensitive disorders in COVID-19.

Based on the growing number of reports that place these COVID-19 symptoms as the second most frequent after fever, several countries are including chemosensitive disorders in their guidelines for the diagnosis of SARS-CoV-2 infection.

Dentists should be warned that in respect of patients seeking assistance for the sudden onset of ageusia, a suspicion of ongoing coronavirus infection should be considered in a differential diagnosis. In the same way, chemosensitive disorders should be investigated in the anamnestic data collection during pretriage procedures. If present or recently experienced, the patient should be referred to a COVID-19 hospital for a nasal swab for identification of the virus.

Based on the frequency of these symptoms, which can often be the reason why the patient attends for a dental appointment, we think it is essential that they are included in the dental association national guidelines that will be the issued for the resumption of clinical activity during the post-epidemic era.

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## Conflict of interests

None declared.

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## Detection of SARS-CoV-2 in saliva and characterization of oral symptoms in COVID-19 patients

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### Abstract

**Objectives:** In order to provide a more comprehensive understanding of the effects of SARS-CoV-2 on oral health and possible saliva transmission, we performed RNA-seq profiles analysis from public databases and also a questionnaire survey on oral-related symptoms of COVID-19 patients.

**Materials and methods:** To analyse ACE2 expression in salivary glands, bulk RNA-seq profiles from four public datasets including 31 COVID-19 patients were recruited. Saliva and oropharyngeal swabs were collected. SARS-CoV-2 nucleic acids in saliva were detected by real-time polymerase chain reaction (RT-PCR). Additionally, a questionnaire survey on various oral symptoms such as dry mouth and amblygeusia was also carried out on COVID-19 patients.

**Results:** ACE2 expression was present at detectable levels in the salivary glands. In addition, of four cases with positive detection of salivary SARS-CoV-2 nucleic acids, three (75%) were critically ill on ventilator support. Furthermore, we observed the two major oral-related symptoms, dry mouth (46.3%) and amblygeusia (47.2%), were manifested by a relatively high proportion of 108 COVID-19 patients who accepted the questionnaire survey.

**Conclusions:** This study confirms the expression of ACE2 in the salivary glands and demonstrates the possibility of SARS-CoV-2 infection of salivary glands. Saliva may

Lili Chen, Jiajia Zhao, Jinfeng Peng are co-first authors of the manuscript.

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## Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19<sup>☆,☆☆</sup>



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### ABSTRACT

**Background:** The novel Coronavirus Disease-19 (COVID-19) continues to have profound effect on global health. Our aim was to evaluate the prevalence and characterize specific symptoms associated with COVID-19.

**Methods:** This retrospective study included 326 patients with confirmed SARS-CoV-2 infection evaluated at the Emergency Department of the Umberto I Polyclinic Hospital, Rome, Italy between March 6th and April 30th, 2020. In order to assess xerostomia, olfactory and gustatory dysfunctions secondary to COVID-19, a telephone-based a modified survey obtained from the National Health and Nutrition Examination Survey (NHANES) 2013–2014 for taste and smell disorders and the Fox Questionnaire for dry mouth were administered to 111 patients (34%) after discharge between June 4th and June 12th.

**Results:** Taste dysfunction was the most common reported symptom (59.5%;  $n = 66$ ), followed by xerostomia (45.9%;  $n = 51$ ) and olfactory dysfunctions (41.4%;  $n = 46$ ). The most severe symptom was olfactory dysfunction with a median severity score of 8.5 (range: 5–10). Overall 74.5% ( $n = 38$ ) of patients with xerostomia, 78.8% ( $n = 52$ ) of patients with gustatory dysfunctions and 71.1% ( $n = 33$ ) of patients with olfactory dysfunctions reported that all symptoms appeared before COVID-19 diagnosis. Overall, the majority of patients reported one symptom only (45.9%,  $n = 51$ ), 37 (33.3%) reported the association of two symptoms, and 23 (20.7%) patients reported the association of three symptoms at the same time.

**Conclusion:** Xerostomia, gustatory and olfactory dysfunctions may present as a prodromal or as the sole manifestation of COVID-19. Awareness is fundamental to identify COVID-19 patients at an early stage of the disease and limit the spread of the virus.

### 1. Background

The recent Coronavirus Disease-19 (COVID-19) pandemic continues to have profound social and economic effects, with more than twelve millions infections and more than half a million deaths reported globally by July 1st, 2020 [1,2]. Patients affected by COVID-19 may present

with a variety of conditions that usually start from two to 14 days after exposure, and range from a mild flu-like condition to a life-threatening multi-organ failure with mortality being significantly higher among those having co-morbidities, older individuals and among those who require hospital admission and ventilation support in intensive care units [3].

<sup>☆</sup> We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

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# Association between periodontitis and severity of COVID-19 infection: A case-control study

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## Abstract

**Aim:** COVID-19 is associated with an exacerbated inflammatory response that can result in fatal outcomes. Systemic inflammation is also a main characteristic of periodontitis. Therefore, we investigated the association of periodontitis with COVID-19 complications. **Materials and Methods:** A case-control study was performed using the national electronic health records of the State of Qatar between February and July 2020. Cases were defined as patients who suffered COVID-19 complications (death, ICU admissions or assisted ventilation), and controls were COVID-19 patients discharged without major complications. Periodontal conditions were assessed using dental radiographs from the same database. Associations between periodontitis and COVID-19 complications were analysed using logistic regression models adjusted for demographic, medical and behaviour factors.

**Results:** In total, 568 patients were included. After adjusting for potential confounders, periodontitis was associated with COVID-19 complication including death (OR = 8.81, 95% CI 1.00–77.7), ICU admission (OR = 3.54, 95% CI 1.39–9.05) and need for assisted ventilation (OR = 4.57, 95% CI 1.19–17.4). Similarly, blood levels of white blood cells, D-dimer and C Reactive Protein were significantly higher in COVID-19 patients with periodontitis.

**Conclusion:** Periodontitis was associated with higher risk of ICU admission, need for assisted ventilation and death of COVID-19 patients, and with increased blood levels of biomarkers linked to worse disease outcomes.

## KEYWORDS

Covid-19, death, ICU admissions, periodontitis, ventilation

## 1 | INTRODUCTION

Coronavirus SARS-CoV-2 is a strain of the severe acute respiratory syndrome-related coronavirus (SARr-CoV), member of the Coronaviridae family and the responsible agent of the disease referred as 2019 coronavirus disease (COVID-2019). This emerging

respiratory tract infection has resulted in over 75 million confirmed cases and almost 1.6 million deaths as of Dec 22<sup>th</sup>, 2020 (WHO, 2020b).

While most patients with COVID-19 present mild symptoms (Huang et al., 2020), nearly 14% of confirmed cases develop severe conditions requiring hospitalization and oxygen support, 5% need

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## News and Perspectives

**Is there an association between oral health and severity of COVID-19 complications?**Nathalie Botros <sup>a</sup>, Parvati Iyer <sup>b</sup>, David M. Ojcius <sup>c,\*</sup><sup>a</sup> University of the Pacific, Arthur Dugoni School of Dentistry, San Francisco, CA, USA<sup>b</sup> Department of Diagnostic Sciences, University of the Pacific, Arthur Dugoni School of Dentistry, San Francisco, CA, USA<sup>c</sup> Department of Biomedical Sciences, University of the Pacific, Arthur Dugoni School of Dentistry, San Francisco, CA, USA

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## ABSTRACT

Most patients with severe complications from COVID-19 have underlying conditions such as obesity, diabetes, and hypertension. In parallel, there is growing evidence for a link between periodontitis and non-oral systemic diseases. The oral cavity is also a reservoir for respiratory pathogens, and patients with periodontal disease are more likely to develop hospital-acquired pneumonia than healthy individuals. We therefore hypothesize that improving oral health could decrease the severity of COVID-19 symptoms and reduce the associated morbidity.

The new coronavirus SARS-CoV-2 was first detected in late 2019 and has quickly developed into a global pandemic [1]. Age is one of the highest risk factors for developing severe symptoms of COVID-19, the disease caused by infection with SARS-CoV-2 [2]. Thus, individuals over the age of 65 and those living in long-term care facilities are especially vulnerable to morbidity and mortality due to infection with SARS-CoV-2. However, persons with chronic lung disease, moderate to

severe asthma, severe obesity, diabetes, chronic kidney disease, and liver disease are also at high risk for severe COVID-19 symptoms. A recent study lists hypertension, obesity, and diabetes as the three major underlying conditions with the most unfavorable outcomes in COVID-19 patients requiring hospitalization [3].

While COVID-19 can affect multiple organs in the body, including the kidneys and liver [4,5], the main cause of

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## Orofacial manifestations of COVID-19: a brief review of the published literature

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**Abstract:** Coronavirus disease 2019 (COVID-19) has spread exponentially across the world. The typical manifestations of COVID-19 include fever, dry cough, headache and fatigue. However, atypical presentations of COVID-19 are being increasingly reported. Recently, a number of studies have recognized various mucocutaneous manifestations associated with COVID-19. This study sought to summarize the available literature and provide an overview of the potential orofacial manifestations of COVID-19. An online literature search in the PubMed and Scopus databases was conducted to retrieve the relevant studies published up to July 2020. Original studies published in English that reported orofacial manifestations in patients with laboratory-confirmed COVID-19 were included; this yielded 16 articles involving 25 COVID-19-positive patients. The results showed a marked heterogeneity in COVID-19-associated orofacial manifestations. The most common orofacial manifestations were ulcerative lesions, vesiculobullous/macular lesions, and acute sialadenitis of the parotid gland (parotitis). In four cases, oral manifestations were the first signs of COVID-19. In summary, COVID-19 may cause orofacial manifestations that might be the initial features in several cases. However, the occurrence of orofacial manifestations in COVID-19 seems to be underreported, mainly due to the lack of oral examination of patients with suspected and/or confirmed COVID-19. Oral examination of all suspected and confirmed COVID-19 cases is crucial for better understanding and documenting COVID-19-associated orofacial manifestations.

**Keywords:** COVID-19; Coronavirus; Oral manifestations, Review.

### Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus 2019 disease (COVID-19) has caused an unprecedented global healthcare crisis. By the time of this writing, over 19 million people have been infected, and approximately 728,013 have lost their lives worldwide.<sup>1</sup> While most cases are either asymptomatic or affected with mild symptoms, a considerable fraction of cases develop severe respiratory symptoms, leading to acute severe respiratory distress (ASRD) and sometimes multiple organ failure.<sup>2</sup>



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Full Length Article

## Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID)



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## ARTICLE INFO

**Keywords:**  
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## ABSTRACT

**Introduction:** Coronavirus disease 2019 (COVID-19) causes a hypercoagulable state. Several autopsy studies have found microthrombi in pulmonary circulation.

**Methods:** In this randomized, open-label, phase II study, we randomized COVID-19 patients requiring mechanical ventilation to receive either therapeutic enoxaparin or the standard anticoagulant thromboprophylaxis. We evaluated the gas exchange over time through the ratio of partial pressure of arterial oxygen (PaO<sub>2</sub>) to the fraction of inspired oxygen (FiO<sub>2</sub>) at baseline, 7, and 14 days after randomization, the time until successful liberation from mechanical ventilation, and the ventilator-free days.

**Results:** Ten patients were assigned to the therapeutic enoxaparin and ten patients to prophylactic anticoagulation. There was a statistically significant increase in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio over time in the therapeutic group (163 [95% confidence interval - CI 133–193] at baseline, 209 [95% CI 171–247] after 7 days, and 261 [95% CI 230–293] after 14 days),  $p = 0.0004$ . In contrast, we did not observe this improvement over time in the prophylactic group (184 [95% CI 146–222] at baseline, 168 [95% CI 142–195] after 7 days, and 195 [95% CI 128–262] after 14 days),  $p = 0.487$ . Patients of the therapeutic group had a higher ratio of successful liberation from mechanical ventilation (hazard ratio: 4.0 [95% CI 1.035–15.053]),  $p = 0.031$  and more ventilator-free days (15 days [interquartile range IQR 6–16] versus 0 days [IQR 0–11]),  $p = 0.028$  when compared to the prophylactic group.

**Conclusion:** Therapeutic enoxaparin improves gas exchange and decreases the need for mechanical ventilation in severe COVID-19.

**Trial registration:** REBEC RBR-949z6v.

## 1. Introduction

The primary clinical presentation of severe coronavirus disease 2019 (COVID-19) is an acute respiratory failure with extreme hypoxemia, which ultimately requires mechanical ventilation [1]. Recent clinical investigations found a high incidence of thrombotic complications in these patients, even with the standard anticoagulant thromboprophylaxis [2,3]. In addition to diffuse alveolar damage, several autopsy studies have demonstrated microthrombi in pulmonary

circulation [4–6]. This microvascular thrombosis may contribute to impaired gas exchange in these patients.

Some observational studies have shown anticoagulation benefits with reduced mortality, mainly in patients requiring mechanical ventilation [9,10]. However, considerable levels of uncertainty remain about this therapy.

Our objective was to evaluate whether therapeutic anticoagulation could improve gas exchange compared to the standard anticoagulant thromboprophylaxis, reducing the need to maintain mechanical

**Abbreviations:** aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; CrCl, creatinine clearance; COVID-19, Coronavirus disease 2019; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DIC, disseminated intravascular coagulation; FiO<sub>2</sub>, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; LMWH, low molecular weight heparin; PaO<sub>2</sub>, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; RT-PCR, reverse transcriptase-polymerase chain reaction; SAPS3, simplified acute physiology score 3; SIC, sepsis-induced coagulopathy score; SOFA, sequential organ failure assessment score; UFH, unfractionated heparin; ULN, upper limit of normal

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Article type : Research Letter

**Prevalence of mucocutaneous manifestations, oral and palmoplantar findings in 666 patients with COVID-19 in a field hospital in Spain**

Dear Editor:

Coronavirus disease 2019 (Covid-2019) has been associated with several cutaneous manifestations(1–3). A temporary field hospital was implemented during the pandemic peak in Madrid, Spain, to attend COVID-19 patients with mild to moderate pneumonia.

A team of dermatologists working as medical volunteers performed a cross-sectional study between April 10 and April 25, 2020 to evaluate cutaneous findings of such patients.

A total of 666 COVID-19 patients fulfilled the inclusion criteria (either positive RT-PCR testing for SARS-CoV-2 or bilateral pneumonia). The mean age was 55.67 years; with a slight female predominance (58%). Remarkably, 47.1% were from-Latin America.

Globally, 304 (45.65%) of our patients presented one or more mucocutaneous manifestations. Oral cavity findings were seen in 78 (25.65%) cases, including transient lingual papillitis (11.5%), glossitis with lateral indentations (6.6%)(Figure 1A), aphthous stomatitis (6.9%), glossitis with patchy depapillation (3.9%) (Figure 1B) and mucositis (3.9%). Burning sensation was reported in 5.3% of patients and taste disturbances (dysgeusia) was commonly associated.

Palmoplantar involvement was observed in 121 patients (39.8%) and included diffuse desquamation in 77 patients (25.3%), often favouring the weight bearing areas and reddish-to-brown acral macules on palms and soles in 46 (15.1%)(Figure 1C and 1D). Mild pruritus was occasionally reported. Fungal cultures of plantar desquamation performed in 9 patients ruled out superficial mycoses. Histological study from the acral macules was performed in 4 patients, showing a mild to moderate lymphocytic infiltrate surrounding the blood vessels and the eccrine

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# Dental Care during COVID-19 Outbreak: A Web-Based Survey

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## Abstract

**Objective** This survey aimed to assess the effects of coronavirus disease 2019 (COVID-19) on elective and urgency/emergency dental care and dentists concerned.

**Materials and Methods** A web-based survey was performed using Google forms questionnaire sent to dentists in Brazil. Questions included: personal information, type of dental care provided during quarantine, if emergencies increased, the dental office biosafety routine, among others. The levels of concern about the impact of quarantine on dental care and patient oral health conditions and the economic impact on dental practices were evaluated using a 0- to 10-point scale. Statistical analysis included descriptive, percentages, one-way ANOVA, Tukey, and chi-square tests.

**Results** During quarantine, 64.6% of the dentists attended only urgency/emergency treatments, while 26.1% maintained routine appointments, and 9.3% closed the dental offices. A higher percentage of dentists from the least affected states continued routine dental treatment; dentists were younger and presented a significantly lower level of concern about dental treatments and oral health conditions of their patients. An increase in urgency/emergency procedures was reported by 44.1% of the dentists, mostly due to the unavailability of routine/elective dental care and increased patient anxiety and stress. The main causes of urgency/emergency appointments were toothache, dental trauma, and broken restorations, besides the breakage of orthodontic appliances and temporomandibular disorders. Dentists reported a high level of concern about the economic impact caused by quarantine.

**Conclusions** The pandemic/quarantine has negatively affected the clinical routine. Personal protection/hygiene care must be adopted and reinforced by dental professionals/staff to make dental procedures safer.

## Keywords

- COVID-19
- pandemic
- dental care
- emergencies
- dentistry

## Introduction

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) is the virus responsible for the infection called coronavirus disease 2019 (COVID-19)

(coronavirus disease).<sup>1</sup> The manifestation of COVID-19 started in Wuhan (China) and has spread to practically all countries, with the World Health Organization (WHO) declaring it a high-risk pandemic. On June 10, 2020, there were 12,102,328 cases contaminated and 551,046 deaths due

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## Oral vesiculobullous lesions associated with SARS-CoV-2 infection

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### 1 | INTRODUCTION

Humans infected with SARS-CoV-2 are at risk of developing serious and life-threatening conditions, such as severe acute respiratory syndrome.

Recent data suggest the more common signs and symptoms of SARS-CoV-2 infection to be headache, sore throat, hyposmia, hyposgeusia, diarrhea, dyspnea, and in severe cases pneumonia. (Wang et al., 2020).

Some authors in Italy reported cases of dermatologic implication in patients affected by SARS-CoV-2 infection (Recalcati, 2020). Since then, we have seen more reports describing dermatologic involvement, including lesions that range from affectation of hands and feet in teenagers to vasculitis, rash, urticaria, and varicella-like lesions. (Estebanez et al., 2020).

Spain has been severely affected by the COVID-19 outbreak (Bonanad et al., 2020). The majority of dental clinics and university clinics are closed, only treating emergencies if the entity has the protective measures necessary. There is a nationwide lack of serological tests available, both for patients and for healthcare providers.

We here present three cases associated with this virus: two where there is a suspicion of COVID-19 and one case of confirmed infection. All cases presented ulcers or blisters in the oral cavity, appearing and developing during the isolation period between the last week of March and the first week of April 2020. We were not able to examine them in our clinic due to the state of alarm declared from the 14th of March, but offered the possibility of video consultations.

### 2 | PATIENT 1

A 56-year-old healthy male patient without any relevant medical history was isolated with suspected infection of SARS-CoV-2. He presented asthenia and fever for 2 days, reporting hyposmia, dysgeusia, and enlargement of lymph nodes in the neck. Testing for COVID-19 was not performed in the hospital due to the non-severity of his case. He was sent home by his general practitioner. He complained of pain in his palate and sore throat. We asked him to send us a photograph (Figure 1). The lesions resembled a herpetic recurrent



**FIGURE 1** Multiple orange-colored ulcers with an erythematous halo and symmetric distribution on the right hard palate of the patient