Review Article

Severe acute respiratory syndrome-coronavirus-2 viral infection and orofacial clefts: A review on patient care during and after COVID-19 pandemic

ABSTRACT

To summarize the details on severe acute respiratory syndrome-coronavirus-2 (SARS-Cov-2) viral infection and the effects of this infection on care of patients with orofacial clefts and provision of guidelines for orofacial cleft surgeries during Corona virus disease 2019 (COVID-19) by using recent available literature. PubMed and Google Scholar and current reports from major health bodies such as the Centers of Disease Control and Prevention, World Health Organization, National Institutes of Health, and major national associations of cleft lip and palate were searched for information which is relevant from orthodontic care for orofacial cleft point of view. Major priority is given to recent articles and peer-reviewed articles. Narration is done due to limitations in the quality of evidence and rapidly evolving information on the nature of COVID-19. Major relevance to the dental field is human-to human transmission of SARS-CoV-2. People who are infected mostly show mild symptoms, but patients with advanced age or any underlying disease or comorbidity may show severe multiorgan complications. During the COVID-19 pandemic, it is important to maintain social distancing and minimize direct contact. Most clinics and hospitals have determined that multidisciplinary visits, feeding, and speech-language evaluations are largely nonessential and can tolerate a delay. A specific plan with good foundation should be followed for emergency orthodontic care with effective communication and triage.

Keywords: COVID-19, orofacial cleft, pandemic, severe acute respiratory syndrome-coronavirus-2, transmission

INTRODUCTION

Corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has been designated as a pandemic and Public Health Emergency of International Concern by World Health Organization (WHO). There is a huge amount of risk to the team that is performing the procedures as this infection is transmitted through droplets.

Furthermore, there is increased amount of risk in children and adolescents who are immunocompromised or having any underlying comorbidities and malnutrition.

The knowledge and understanding about this infection is constantly changing and updated through experiences and constant research. The aim of this article review was to provide a comprehensive summary of the implications of SARS-CoV-2 infection and COVID-19 on the care of patients

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with orofacial clefts and the provision of guidelines for orofacial cleft surgeries during COVID-19, using currently available data and literature.

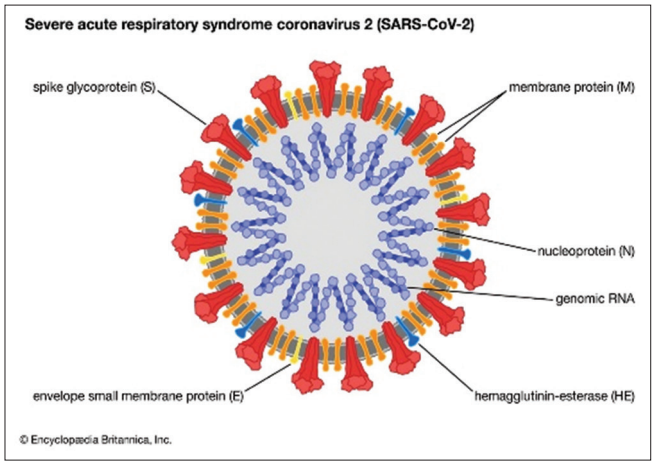

Figure 1: Structure of severe acute respiratory syndrome-coronavirus-2

MATERIALS AND METHODS

A wide selection of sources was searched and summarized to ensure that all relevant information regarding the rapidly evolving COVID-19 pandemic and any orthodontic implications for cleft patients were obtained. These sources included peer-reviewed literature publications from electronic databases such as PubMed and Google Scholar using the following search terms: "Coronavirus," or "COVID-19," or "SARS-CoV-2," or "2019-novel coronavirus," separately combined with "Orofacial cleft," "cleft lip," "cleft palate," "structure," "incubation," "latency," "transmission," "symptoms," "dentistry," "infection control," "treatment," and "protocol." Up-to-date reports and communications from major health bodies such as the Centers for Disease Control and Prevention (CDC), WHO, National Institutes of Health, and major national associations on cleft lip and palate and health professional regulatory bodies were also referenced.

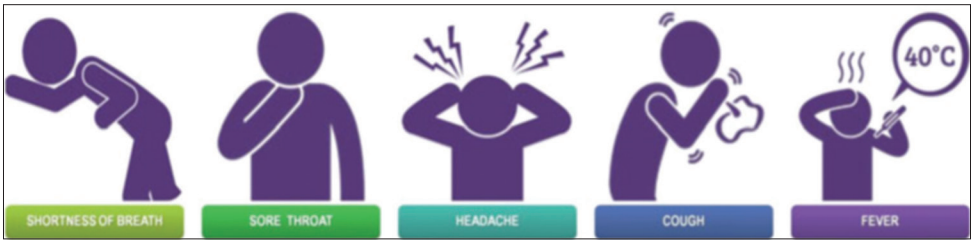

Figure 2: Typical symptoms of COVID-19

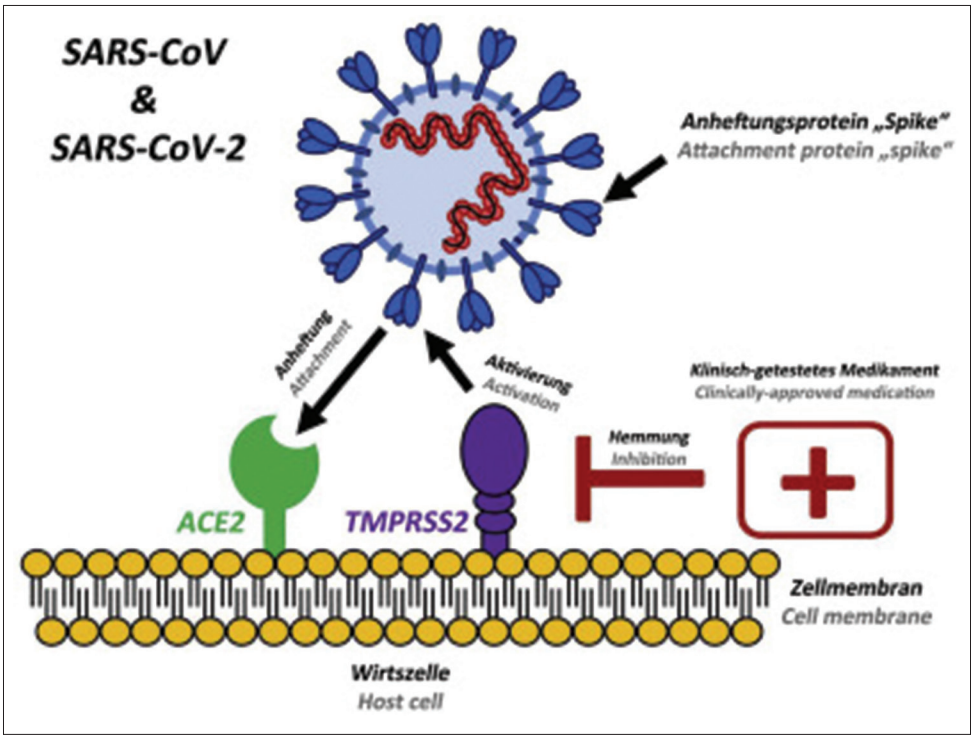

Figure 3: Binding of severe acute respiratory syndrome-coronavirus-2 to cell membrane

Table 1: Sources of information and literature included in this review article, with levels of evidence*

Author reference number	Country	Title/topic	Type of study	Level of evidence
Park *et al*.[1]	Korea	Virus isolation from the first patient with SARS-CoV-2 in Korea	Short communication	5
Kumar *et al*.[2]	India	Structural, glycosylation and antigenic variation between 2019-nCoV and SARS-CoV	Narrative review	5
Zhu *et al*. (2019)[3]	China	A novel coronavirus from patients with pneumonia in China, 2019	Case series	4
Yan *et al*.[4]	China	Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2	Narrative review	5
Zhang *et al*.[5]	China	Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors	Investigational, Mechanism-based reasoning	5
Yang *et al*.[6]	China	COVID-19, A growing threat to children?	Narrative review	5
Cruz and Zeichner[7]	United states	COVID-19 in children: Initial characterization of the pediatric disease	Narrative review	5
Dong *et al*.[8]	China	Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China	Case series	4
Chen *et al*.[9]	China	Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus	Narrative review	5
Xia *et al*.[10]	China	Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults	Case series	4
Kam *et al*.[11]	Singapore	A well infant with COVID-19 with high viral load	Case series	4
Gu *et al*.[12]	China	COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission	Short communication, investigational, mechanism- based reasoning	5
WHO (2020)[13]		How does COVID-19 spread?	Expert opinion	5
Zhao *et al*.[14]	China	Anesthetic management of patients with COVID-19 infections during emergency procedures	Case series	4
Belser *et al*.[15] Ocular tropism of respiratory viruses	United States	Ocular tropism of respiratory viruses	Narrative review	5
Lu *et al*.[16]	China	2019-nCoV transmission through the ocular surface must not be ignored		
Chen *et al*.[17]	China	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	Case series	4
Rothe *et al*.[18]	Germany	Transmission of 2019-nCoV infection from an asymptomatic contact in Germany	Correspondence, mechanism-based reasoning	5
To *et al*.[19]	China	Consistent Detection of 2019 Novel Coronavirus in Saliva	Case series	5
Lu *et al*.[20]	China	Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding	Case series	4
Chan *et al*.[21]	China	Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan	Case series	4
Guo *et al*.[22]	China, Singapore	The origin, transmission and clinical therapies on COVID-19 outbreak - an update on the status	Narrative review	5
Walls *et al*.[23]	United states	Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein	Review of reported data	5
Suri *et al*.[24]	Toronto	Clinical orthodontic management during the COVID-19 pandemic	Systemic review	5
Wang *et al*.[25]	China	Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak	Correspondence, mechanism-based reasoning	5
Li *et al*.[26]	China	Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2infection diagnosis	Correspondence, mechanism-based reasoning	5
Zhou *et al*.[27]	China	CT features of COVID-19 pneumonia in 62 patients in Wuhan, China	Case series	4
Chung *et al*.[28]	China	CT imaging features of 2019-nCoV	Case series	4
Lauer *et al*.[29]	United States, Germany	The incubation period of COVID-19 from publicly reported confirmed cases: estimation and application	Case series	4

Contd...

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Author reference number	Country	Title/topic	Type of study	Level of evidence
Lan *et al*.[30]	China	Positive RT-PCR test results in patients recovered from COVID-19	Correspondence, case series	4
Ling *et al*.[31]	China	Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients	Case series	4
Gostic *et al*.[32]	United states	Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19	Case series	4
U.S. National Library of Medicine (2020)[33]	United states	Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) to prevent SARS-CoV-2	Expert opinion	5
ACPA[34]	United states	Orthodontic treatment during the COVID-19 pandemic	Expert opinion	5
CLAPA[35]	United kingdom	Cleft and COVID-19	Expert opinion	5
van Doremalen *et al*.[36]	United States	Aerosol and surface stability of SARS-CoV2 as compared with SARS-CoV-1	Correspondence, investigational, mechanism-based reasoning	5
Zhou *et al*.[37]	China	A pneumonia outbreak associated with a new coronavirus of probable bat origin	Case series	4
Li *et al*.[38]	China	Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia	Case series	4
Wang *et al*.[39]	China	Oral health management of children during the epidemic period of COVID-19	Narrative review	5
Sabino-Silva *et al*. (2020)[40]	Canada, Brazil	Coronavirus COVID-19 impacts to dentistry and potential salivary diagnosis	Correspondence, mechanism-based reasoning	
American Association of Orthodontists (2020)[41]	United States	COVID-19 resources for orthodontists	Expert opinion	5
Centers for Disease Control and Prevention (2020)[42]	United States	What to do if you are sick	Expert opinion	5
Ti *et al*.[43]	Singapore	What we do when a COVID-19 patient needs an operation: Operating room preparation and guidance	Correspondence, expert opinion	5
Kim *et al*.[44]	Korea	Recommendations for anesthesia in patients suspected of coronavirus 2019 nCoV infection	Expert opinion	5

*Level of evidence rating scheme based on OCEBM Levels of Evidence Working Group. "The Oxford Levels of Evidence 2:" Oxford Centre for Evidence-Based Medicine. Available at: https://www.cebm.net/index.aspx?o¼5653. Accessed on 12 October, 2020. COVID-19: Coronavirus disease 2019, SARS: Severe acute respiratory syndrome, CoV-2: Coronavirus 2, ACE: Angiotensin-converting enzyme 2, nCoV: Novel coronavirus, ACPA: The American Cleft Palate-Craniofacial Association, CLAPA: Cleft lip and palate association, OCEBM: Oxford Centre for Evidence-based Medicine, mRNA: Messenger RNA, CT: Connective tissue

RESULTS

Due to the rapidly evolving nature of the disease and the need for scientific evidence to be available quickly, most of the studies were descriptive, small investigational studies, narrative reviews, and expert opinions [Table 1]. More recent studies and peer-reviewed studies were preferred when available. As the evidence is still new and limited in quality, a narrative synthesis was undertaken to provide a broad review of key aspects relevant to orthodontists during the current pandemic.

DISCUSSION

Structure of the virus

SARS-CoV-2 is a single-stranded RNA virus. Electron microscopy revealed the coronavirus-specific morphology of SARS-CoV-2 with virus particle sizes ranging from 70 nm to 90 nm.[1-3] A surface viral protein named spike glycoprotein is present on virus which interacts with cell surface having angiotensin-converting enzyme 2 (ACE2) receptor. The viral membrane glycoprotein (M) and envelope (E) of SARS-CoV-2 are embedded in host membrane-derived lipid bilayer encapsulating the helical nucleocapsid comprising viral RNA [Figure 1].[4,5]

Pathophysiology

The genome of SARS-CoV-2 is similar to other coronaviruses that comprise of ten open reading frames (ORFs). The first ORFs (ORF1a/b), about two-thirds of viral RNA, are translated into two large polyproteins pp1a and pp1ab, which processed into nonstructural proteins (nsp1nsp16).[20,21] The genome of SARS-CoV-2 encodes for four structural proteins similar to other coronaviruses. These proteins are

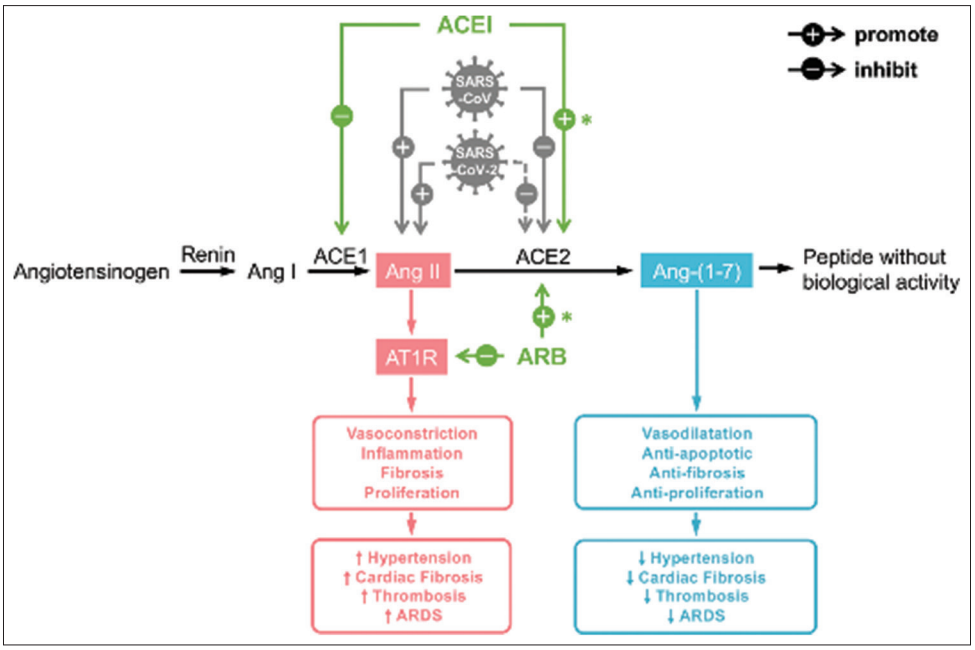

Figure 4: Severe acute respiratory syndrome-coronavirus-2 has been shown to exhibit novel glycosylation sites in the spike glycoprotein of 2019-novel coronavirus, suggesting that the virus may utilize different glycosylation sites to interact with its receptors. Studies have demonstrated that severe acute respiratory syndrome-coronavirus-2 spike protein has higher affinity to the angiotensin-converting enzyme 2 receptor as compared with severe acute respiratory syndrome[23]

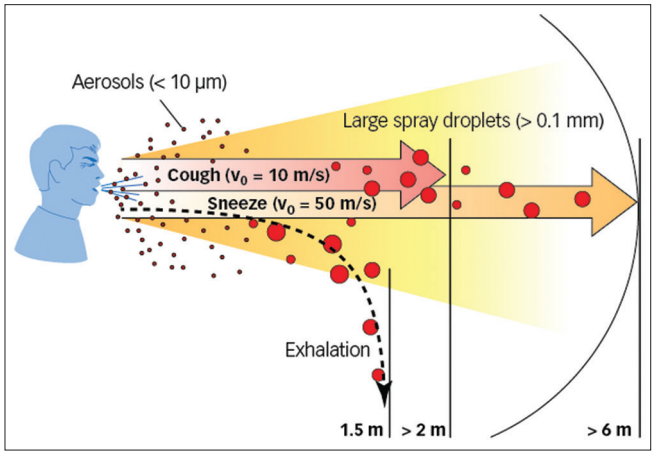

Figure 5: How aerosols transmitted in air[20]

S (spike), E (envelope), M (membrane), and N (nucleocapsid) protein which are required to make complete virus particles [Figure 2].

S protein is responsible for the attachment and entry of SARS-CoV-2 to the host target cell receptor, probably ACE2 mainly expressed on Alveolar epithelial cell type II (AECII) cells, including extrapulmonary tissues such as heart, kidney, endothelium, and intestine [Figure 3].[22]

Symptoms and progression of disease

As we have seen children and adolescents have lower death rates still they can be a potential transmitter of infection. Children infected with coronavirus often present with fever, cough, and breathing difficulties [Figure 4].

Many children also report vomiting, diarrhea and a fore mentioned symptom. Children born from infected mothers have higher risk of contracting the infection from the mother.[6] There is also very close resemblance of the symptoms with coronavirus and viral pneumonia. It has been reported that children often have milder symptoms than adults and the elderly.[7-10]

Transmission

A report mentions that even an apparently healthy infant had heavy viral load which indicates that children can even transmit infection without manifesting the illness [Figure 5].[11-19]

Phases of severe acute respiratory syndrome-coronavirus-2 infections

Based on current epidemiological investigation, the incubation period is 1–14 days, mostly 4–7 days. And the COVID-19 is contagious during the latency period [Figure 6].[23,24]

COVID-19 and orofacial cleft

Many syndromes have cleft as a part of it which could increase the risk of infection. However, an unrepaired cleft without syndrome doesn't make someone more likely to catch the virus. The two most common syndromes where a cleft (usually cleft palate) is a symptom are pierre robin sequence and sticklers syndrome.

Table 2: Recommended protocol for Cleft lip and palate patient care during and after COVID-19 pandemic

Age group of patients	Surgical procedures	Recommendations
0-3 months	PSIO	Due to the short and critical timeframe to initiate PSIO therapy after birth for effective outcome, the use of NAM or other PSIO methods could be considered for each case in discussion with the surgeon and the caregiver Because this practice requires frequent instrumentation of the mouth and nose, appropriate PPE and hand hygiene should be utilized Alternative home practices like "Lip taping," nasal stents, or other forms should be considered Monitoring should be done with telehealth visits
3 months	Primary cleft lip surgery	Surgeons should delay primary cleft lip repair There are no studies that demonstrate a relationship between delaying primary lip repair and a negative impact on speech or feeding If the surgery can be performed as outpatient procedure, then the surgery could be considered
9-12 months	Primary palate surgery	Patients with a cleft palate often have difficulty with nutrition and ultimately with speech production There are many alternate clinical treatments available to address nutrition and hydration for infants with unrepaired cleft palate Telehealth or phone conversations between health-care providers and parents may be sufficient to address feeding difficulties The physiology of PRS can also impact breathing functions. Local protocol to be follow for neonatal airway management associated with PRS Tracheostomy does lead to increased aerosolization-mandibular distraction for airway management could be discussed and encouraged The association between age of palatal surgery and speech is a critically important consideration under normal operations During the present COVID-19 pandemic, the child's well-being and safety, and that of the health care providers, should always be the primary consideration The increased risk of future VPI does not supersede the risk of COVID infections and sequelae on the patient and provider to justify urgent palate repair at this time Cleft palate repair may be delayed Once the ban is lifted prioritization is important starting with the oldest children first Teams should lead the discussion of this re-entry plan Where available, preoperative COVID testing could be employed This may become more feasible as more supplies become available and turnaround times for results shorten
2-4 years	Speech evaluation/ revision	Surgery procedures in the region of nasal-oral mucosa are at high risk due to the aerosolization of the virus Consideration can be given to perceptual evaluations via telemedicine or in office visits where unique patient circumstances apply Instrumentation of the nose with barium for video speech evaluation or via nasoendoscopy is considered non-essential and could be delayed VPI surgery is an elective surgery that may be safely deferred for several months, and in many cases longer, without conferring significant negative impact on speech outcomes When the ban on elective surgical procedures is lifted, sites may choose to prioritize palate repair surgery cases before VPI surgeries in coordination with the resources of the local environment
9-11 years (adolescence)	Cleft lip and nose surgery	Revision surgery is elective Surgeons should consider delaying these procedures to preserve hospital resources and limit potential exposure to the health care team
	Phase 1 orthodontics and alveolar bone grafting preparation	Given the time-sensitive nature of alveolar bone grafting and risk of permanent periodontal damage to teeth erupting in the unrepaired alveolar cleft, care could be prioritized on a case-by-case basis in consultation between the surgeon, orthodontist, and patient caregiver Alveolar bone grafting could be classified as Tier 2A in the American College of surgeons' classification scheme for cases (time-sensitive care, https://www.facs.org/covid-19/clinicalguidance/triage) and fulfill the AAO's statement on the justification of emergency orthodontic care as "being critically necessary to prevent harm to the patient" Preoperative testing could be considered according to applicable guideline and local resources
15-18 years (late adolescence)	Orthognathic surgery	Orthognathic surgery may be suggested to manage occlusion, sleep apnea, or appearance Nonsurgical management of sleep apnea should be done The AO-CMF group is suggesting closed techniques for the management of facial fractures at this time Orthognathic surgery in patients with cleft lip and palate, other than in patients with severe sleep apnea not controlled with conservative measures, is nonessential and should be delayed

PSIO: Presurgical infant orthopedics, PRS: Pierre Robin Sequence, NAM: Nasoalveolar moulding, PPE: Personal protective equipment, VPI: Velopharyngeal Insufficiency, AAO's: American Association Of Orthodontics, AO-CMF: American orthodontics-craniomaxillofacial surgery

Delaying cleft lip and/or palate repair surgery

Careful priority should be given to the backlog surgeries of cleft which was scheduled [Table 2].

Speech is mainly affected by cleft palate repair which makes it more time-sensitive. However, research is ongoing to work out when the best time to operate is, as there's no clear evidence that 6 months is better than 12 months.

For alveolar bone graft surgery, there is a reasonably long "window of opportunity" during which this can be performed,

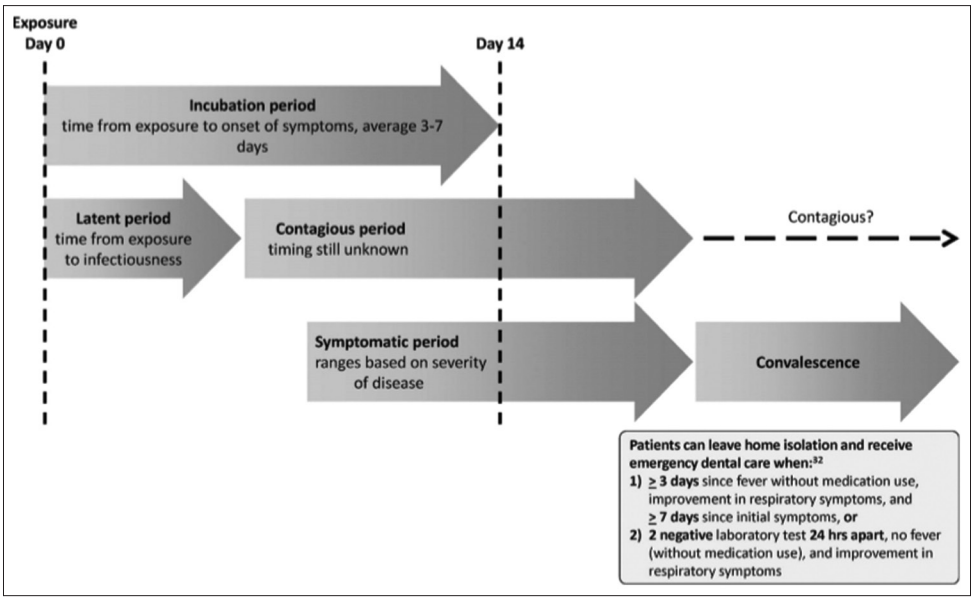

Figure 6: Six phases of severe acute respiratory syndrome-coronavirus-2 infections[24]

so the most important thing at this time is keeping up the care of any orthodontic appliances.

Most orthodontic appliances can be left as they are for some months without issues as long as the usual aftercare instructions are followed.

1. Maintaining excellent oral hygiene: Brush three times a day with a standard toothbrush, followed by an interdental brush. Use a fluoride mouthwash once a day
2. Low sugar diet: Where possible, avoid all snacking on sugars and drinks with added sugar. Avoid fizzy drinks in particular
3. Avoid hard or sticky food: that could break the brace wire or brackets off a tooth.

CONCLUSIONS

- Despite low mortality and low infection rate among children and adolescents, they play a crucial role in the spread of infection in this ongoing pandemic of coronavirus disease
- Adequate prevention measures, early identification, and isolation will be helpful in altering the course of this pandemic
- Telehealth or phone conversations with parents may be sufficient
- It is also imperative that care teams proactively establish a re-entry plan and prioritize patients for future evaluation and treatment
- Guidelines and practice advisories issued by federal, state/provincial, and local health and regulatory authorities should be followed.

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Conflicts of interest

There are no conflicts of interest.

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