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EDITORIAL

Viral pandemics and oral health: Lessons learned from HIV to SARS-CoV-2

Not since the human immunodeficiency virus (HIV) and the acquired immune deficiency syndrome (AIDS) pandemic began have we had a transformative experience in dentistry that has made us deeply reexamine our practices and come to terms with a new reality of how dentists care for their patients' health. What is different now compared with 1985 is the more rapid pace of research and broad global public emphasis on conquering the severe acute respiratory coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) and limiting its spread, which has resulted in damage to both our health and finances. Both are pandemics to be reckoned with. HIV introduced the enduring era of blood-borne pathogens and now SARS-CoV-2 has brought us into the era of respiratory pathogens. Though HIV targets lymphocytes and immune function and SARS-CoV-2 targets the angiotensin-converting enzyme 2 (ACE2) widely expressed receptor cells and the renin-angiotensin system, lessons from our experience with HIV can inform aspects of our response to the highly infectious SARS-CoV-2.

ENHANCED INFECTION CONTROL

Dentists, who at the start of the AIDS pandemic were described as working in a confined, dark, contaminated space with sharp instruments, have of necessity established themselves as experts in infection control practices, which have continued to evolve over time. I began dental school training at the University of North Carolina at Chapel Hill in 1982 at the nascency of the AIDS pandemic, when the hepatitis B virus (HBV) was the main infectious disease of concern at the time. My infection control training was from James J. Crawford, PhD, and I was memorably impacted by his *If Saliva Were Red* video.[1] Originally developed in the 1970s, this video graphically illustrated the widespread dissemination of the otherwise invisible saliva around the dental operatory during routine practice. From this dramatic demonstration, it became clear that there was a need for improved cross-infection control practices to prevent infection with blood-borne pathogens. Until the discovery of HIV in 1985, dentists typically wore gloves only for surgical and some endodontic procedures, long-sleeved gowns were nonexistent in restorative dental practice, handpieces were not routinely autoclave sterilized, and masks and protective eyewear were rarely used in general dental settings. And yes, as we somewhat painfully adapt today to the extra gear, particularly the N95 respirator and full-face shields, in the 1980s we mourned the loss of fine tactile sensations with routine use of gloves. In the early days of the AIDS pandemic, enhanced sterilization and engineering designs helped keep us safer from sharps injuries, dental unit waterline contamination and suction equipment backflow, and handpiece cross-contamination, as today enhanced air handling systems, face shields, and new office designs help to keep us safer in our aerosol-generating environment. We have now added plexiglass barriers as social distancing/sneeze-guard shields to protect our main office staff, as lessons from our early use of disposable plastic cover barriers on operatory light handles, dental chairs, and operatory trays/handpiece setups taught us how to simplify maintaining clean surfaces prone to contamination with potentially infectious agents. We now are challenged with quickly introducing more safety measures for our work in an environment of droplets and aerosols from the mouth in this age of a respiratory pandemic. An early survey in May and June 2020 of practicing dentists in private practice and public health settings in the United States, a short 2 months after the first COVID-19 wave and national shortages of personal protective equipment caused offices to move to emergency only dental care, showed that 99.7% of offices had implemented enhanced infection control procedures.[2] These were most often more frequent disinfection and COVID-19 screening procedures including temperature checks, social distancing, and providing face masks to staff and patients.[2]

Meeting the challenges of producing a safer office practice environment and educating the public and our dental team members on our risk mitigation strategies are helping overcome public fear of COVID-19 spread in the dental office. The early days of the AIDS pandemic were filled with fear of spread of AIDS in the dental office. A common practice in the early days of the AIDS pandemic among practices that would accept patients with AIDS was providing care only at the end of the day so the invisible virus would dry and die on surfaces overnight. Uncertainty over many aspects of the new airborne COVID-19 disease and the dramatically increased demand on a limited supply of personal protective equipment caused a shutdown of dental practices to only emergency dental services and limitations on use of aerosol-generating dental equipment. Today, with practices reopened, a main concern is

SARS-CoV-2 viral particles lingering in the air in the operatories, suggesting the need to allow time between patients for the room air to settle and/or introduction of high-efficiency particulate air filtration systems. Fortunately, with today's widespread influence of the Internet, transition to electronic health records, and patient engagement in health, many patients have the capacity for audio/video visits with their health care providers. These technological advances helped to transform the nascent telehealth system into one that is a robust alternative for triage and dental visits not requiring hands-on examination and procedural-based care, helping to solve health care access challenges.

A RACE FOR VACCINES FOR PREVENTION

As soon as vaccines became available against HBV, health care workers were immunized, and over a short time period vaccine technology moved from plasma-derived to recombinant DNA technology.[3] Despite globally widespread infant HBV vaccination programs implemented in the ensuing years, HBV has not been eradicated. Whereas HIV has eluded the efforts to develop a preventive vaccine largely due to its global genetic diversity,[4] SARS-CoV-2 appears to be relatively genetically stable, thus creating hope for success in efforts toward creation of a SARS-CoV-2 vaccine. What would be most useful for prevention of future pandemics would be development of a vaccine that is widely effective against many alpha and beta human coronavirus strains. Though hope for a COVID-19 vaccine to quell transmission is widespread, we must not lose sight of the fact that diverse vaccine development technologies and novel drug discovery efforts made today will benefit our response to the next pandemic. Given the length of time for drug and vaccine development and approval, we now need to commit to getting ahead of the curve with well-organized and well-funded collaborative efforts to add to the pipeline.

SALIVARY DIAGNOSTICS

Molecular evidence of both viruses can be found in whole saliva fluids, although in lower concentration than in blood. Evidence supports that SARS-CoV-2 is community spread via saliva droplets and aerosols through coughing, sneezing, speaking, singing, and breathing.[5] One of the key reasons for HIV testing advocacy was the observation that HIV-infected individuals who were unaware of their infection were the most likely to spread HIV; this is also true for SARS-CoV-2, where 80% of transmission may be due to undocumented asymptomatic infection.[6]

Saliva-based SARS-CoV-2 diagnosis of this enveloped, positive-sense, single-strand RNA virus by reverse transcription polymerase chain reaction or immunoglobulin/antigen detection has emerged as a promising testing option to the traditional nasopharyngeal swab test.[5] It is likely that the work that went into developing the more recent generation antibody/antigen tests for HIV helped accelerate the pace of development of testing modes for SARS-CoV-2. OraSure Technologies Inc (Bethlehem, PA) delved into saliva or oral fluid−based HIV antibody testing. Their efforts, which moved from lab to rapid point-of-care to at-home testing over the course of several years, have likely paved the way for more rapid progress and acceptance of saliva-based rapid SARS-CoV-2 testing. To date, one study analyzing multiple immunoglobulin response to SARS-CoV-2 in various biological fluids, including self-collected saliva for rapid SARS-CoV-2 diagnosis, has been published as a protocol without results,[7] so additional results of this study and others are needed to support antibody testing for SARS-CoV-2 in saliva. The real hope is for saliva-based point-of-care rapid tests, as was created in OraQuick Advance HIV-1/2 (OraSure Technologies, Inc) for diagnosis of HIV infection.

THERAPEUTICS

There has been limited progress in developing a specific treatment for COVID-19 at present despite advances in repurposing the nucleotide analogue antiviral Remdesivir and exploiting passive immunity approaches with production of convalescent plasma from recovered patient therapies or multiple neutralizing monoclonal antibody cocktails (Regeneron and Eli Lilly). It took considerable research investments and 6 years for approval of azidothymidine, the first antiretroviral drug in the fight against HIV, originally synthetized for use as a cancer treatment agent, and even longer until highly effective antiretroviral therapies were available.[8] We are just at the beginning of our human interaction with coronavirus diseases, and since cross-species transmission of viral pathogens has emerged as a threat to humans,[9] a sustained investment in antiviral research can better prepare us for the future. Our repurposing of today's antiviral drug discoveries fuels hope of more rapid solutions to future viral pandemics that are inevitable.

HEAD AND NECK FINDINGS

Dysgeusia and anosmia have resulted from this new viral infection's destruction of target nerves in the gustatory and olfactory sensory systems. Evidence now supports glial and neuronal stem cell invasion of ACE2, which is the main host cell receptor of the SARS-CoV-2 virus, and a secondary receptor, transmembrane protease, serine 2, explaining the development of dysgeusia and anosmia.[10]

Head and neck involvement of COVID-19 extends beyond the changes in taste and smell. ACE2 and transmembrane protease, serine 2 receptor expression, enabling viral entry into the host and clinical expression of disease, has been found in human major and minor salivary glands and oral epithelium, including epithelial cells, fibroblasts, T cells, and B cells.[10] A recent living systematic review of literature published through June 6, 2020, of the prevalence of oral signs and symptoms in patients with COVID-19, involving 10,228 patients in 19 countries, showed that the most common finding was gustatory impairments (45% of patients), suggesting that this condition should be considered important in the clinical picture of COVID-19's initial presentation and disease progression.[11] Of the different taste disorders, the most common was dysgeusia (38%), followed by hypogeusia (35%) and ageusia (24%).[11] The authors of this review reported that the diversity of oral mucosal lesion presentations including irregular and aphthous-like ulcers, white and erythematous plaques, blisters, petechiae, and desquamative gingivitis, found on the lips, tongue, palate, buccal mucosa, and gingiva, suggests coinfections and secondary manifestations of COVID-19.

Nearly every month, new reports are revealing oral lesions possibly or probably associated with COVID-19 infection, with a predominance of attention increasingly placed on hemorrhagic and aphthous-like ulcerations with necrosis[12] and vesiculobullous and macular lesions.[13] Cruz Tapia et al.[13] suggested that their 4 cases of angina bullosa hemorrhagica–like lesions, vascular disorder, and nonspecific stomatitis support thrombi formation and vasculitis in the oral mucosa of patients with COVID-19. Interestingly, the dermatology literature is also demonstrating that vesicular rashes appear early and may help diagnosis, and vascular rashes may be useful in predicting severe disease.[14] To determine co-occurrence of skin lesions (exanthems) and oral cavity lesions (enanthems) in patients with COVID-19, oral cavities were examined in 21 patients with skin rashes and 6 had oral lesions (29%), all on the palate, described as macular and/or petechial, with no association with drug intake, and laboratory studies suggested that they were a stronger indicator of viral etiology than a drug reaction.[15]

When the diversity of oral mucosal and salivary gland disorders was observed in patients with HIV/AIDS, international collaborative groups such as the European Community-Clearinghouse on Oral Problems Related to HIV Infection and World Health Organization (WHO) Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus gathered to reach consensus on presumptive and definitive diagnostic criteria of multiple lesions and to classify them according to levels of association with HIV from strongly associated, less commonly associated, to those seen in HIV infection.[16] As more becomes known about oral manifestations of SARS-CoV-2, vaccination efforts continue slowly, and future coronavirus infections/pandemics are likely, the need may arise for an international collaborative consensus to be reached for defining and classifying oral lesions and the dysgeusia/anosmia that is emerging as a clinical feature of COVID-19. Will global teleconferencing be used to develop this data-driven expert consensus? Similar to patients who have HIV infection, the host immune response to SARS-CoV-2 likely affects COVID-19 disease expression and clinical course of disease in the oral cavity.

COVID-19 DISEASE SEQUELAE ARE NOT FULLY UNDERSTOOD

SARS-CoV-2 is not known to result in chronic infection, yet many post-COVID-19 symptoms including myocardial and neurologic consequences are suggested. Medium- and long-term consequences of infection, particularly if severe disease manifests, are yet unexplored. Are there persistent autoimmune sequelae? What is the trajectory of recovery of smell and taste? Are relapses or reinfections possible? Will there be other delayed neurologic or neurovascular symptoms or diseases? Is there potential for SARS-CoV-2 virus to hone to cranial nerves such as in the case of varicella zoster virus contracted as varicella (chicken pox) and lying dormant in the dorsal root ganglia of the trigeminal nerve that reactivates a lifetime later as shingles (herpes zoster)? Will there be common or rare long-term sequelae? Can we determine who is at greatest risk? Are underlying mechanisms of SARS-CoV-2 infection expressed as immunologic disease manifestations that may become more apparent with aging of recovered patients? Are there preventive approaches that can be developed to alleviate subsequent clinical disease expression?

We learned from HIV disease management that the antiretroviral drugs can have acute and long-term toxicities, including ulcers, xerostomia/parotid lipomatosis, taste disturbances, perioral paresthesia, erythema multiforme, and facial fat wasting.[17] Will there be oral toxicities or benefits of COVID-19 treatments particularly as treatments target the cytokine storm, a procoagulant state, and local and systemic activation of inflammation?

WE ARE BETTER TOGETHER

In this new global pandemic, we need to learn from early disease hotspots and continually reassess successes and failures of varied prevention, diagnosis, and treatment approaches. In the United States, both HIV and SARS-CoV-2 infection rates and deaths tend to be higher among people of color, those living in poverty, and other vulnerable populations. As with HIV, many more SARS-CoV-2-infected individuals are asymptomatic in disease expression. Fortunately, we believe that SARS-CoV-2 is cleared from the body with time and in most people an antibody response to the virus may provide protection from further infection and disease progression.

To give a global perspective of relative disease burden, the WHO reported that an estimated 38 million (31.6-44.5) globally were living with HIV at the end of 2019, 1.7 million (1.2-2.2) were newly infected with HIV in 2019, and there were 690,000 (500,000-970,000) HIV-related deaths in 2019.[18] Although likely underestimates, the WHO similarly reported that COVID-19 cases for the year 2020 already exceed 2019 HIV cases at 42.5 million, as we enter the second fall 2020 wave, with 1,147,301 confirmed COVID-19 deaths (for 2020, with the first case reported on January 4, 2020, through October 25, 2020).[19] This means that deaths from COVID-19 this year are approaching double the number of annual deaths last year from HIV.

THIS WILL HAPPEN AGAIN. WHO WILL TAKE THE LEAD?

With viruses constantly mutating and evolving and people living in closer proximity to animals, our future likely holds the possibility of new strains of coronavirus or other viruses that infect animals making the transition to humans and resulting in human-to-human spread, like SARS-CoV-2 did. Systems need to be developed for early recognition and containment. A broader understanding and mitigation of underlying conditions that support animal-to-human disease transmission are critical for prevention.

To understand our current enemy, the SARS-CoV-2 virus; manage COVID-19 disease; consequences; and prepare for and, it is hoped, prevent future zoonotic viral pandemics, we need international multidisciplinary teams leading research to determine which characteristics of COVID-19 are universal versus those mediated by local conditions of health, medical resource access, cultural customs, and other social determinants of health. We have seen this with our fight against HIV/AIDS through the collaborative efforts of the International AIDS Society, established in 1988 and representing 180 countries; activities of the WHO and the Joint United Nations Programme on HIV/AIDS; and many international nonprofit and nongovernmental organizations.

We have witnessed great strides in the early months of this pandemic when the US National Institutes of Health created supplemental funding for existing extramural grants to add components related to the clinical impact of SARS-CoV-2 on patients' health outcomes. Internationally, as was the case at my home academic institution, many researchers engaged in and supported for their HIV/AIDS work pivoted to work on COVID-19. Though many COVID-19 studies could be conducted in laboratory biosafety level 2 (BSL-2) laboratories using standard precautions, those studies involving virus isolation required BSL-3 laboratories and procedures.[20] Because this is similar to the biosafety categorization for work with HIV,[21] many already established BSL-3 laboratories engaged in HIV research became rapidly repurposed as COVID-19 research facilities. Almost overnight, our HIV clinical researchers became COVID-19 researchers, as critical new studies were designed. Without HIV/AIDS, this research infrastructure needed for COVID-19 work would likely not have existed. We now need better mobilization of scientific collaboration globally and continued support of federal and international agencies to sustain our work in prevention and treatment for COVID-19 to prepare us for future outbreaks and sustain our global population. This is a global health crisis, and it requires a global response.

WHERE DO WE GO FROM HERE?

The COVID-19 pandemic has further revealed the fundamental place of dentistry in the health system as an essential health care service whose role is to ensure eradication of disease and management of pain in the maxillofacial structures to preserve quantity and quality of life and to prevent decline in a person's systemic health. We have been effective at keeping patients with dental complaints out of our nation's hospital emergency departments during the early COVID-19 shutdowns. We have adapted and will continue to adapt to the challenges ahead. The question arises as to whether we can now mobilize our oral health team to participate in viral disease testing and vaccination efforts in the days ahead.

I am hoping that we have many "wins" in 2021 for our further integration into the health system.

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