Pulmonary Procedures in the COVID-19 Era

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Abstract

Purpose of Review The purpose of this review is to discuss the impact of the COVID-19 pandemic on pulmonary procedures, including new guidelines, restrictions, techniques, and overall effect on patient care.

Recent Findings SARS-CoV-2 predominately impacts the pulmonary system and can result in a severe lower respiratory tract infection. Early guidelines based largely on data from the SARS epidemic recommended significant restrictions on procedure volume out of concern for healthcare worker safety. Newer data suggests relative safety in performing airway and pleural procedures as long as appropriate precautions are followed and new techniques are utilized. The introduction of effective vaccines and more reliable testing has led to a re-expansion of elective procedures.

Summary Many guidelines and expert statements exist for the management and practice of pulmonary procedures during the COVID-19 pandemic. A flexible and individualized approach may be necessary as our understanding of COVID-19 continues to evolve.

Keywords SARS-CoV-2 · COVID-19 · Aerosol-generating procedures · AGPs · Tracheostomy · Bronchoscopy

Introduction

In December 2019, a cluster of cases of viral pneumonia was reported to the World Health Organization (WHO) by the Wuhan Municipal Health Commission. The etiology would be identified the following month as the SARS-CoV-2 virus [1]. By March 2020, only 3 months after the initial case reports out of China, the WHO would officially declare the rapidly escalating global crisis a pandemic [2]. Since that time, over 170 million cases have been confirmed worldwide, with over 3.8 million deaths [3].

The novel coronavirus disease (COVID-19) manifests primarily as a lower respiratory tract infection, placing pulmonary and critical care physicians at the forefront of its management. While the majority of confirmed cases are mild, up to 20% may require intensive care support and 5–15% mechanical ventilation [4, 5]. Person-to-person spread is predominately by droplet dispersion, though airborne transmission is possible with certain aerosol-generating procedures (AGPs), such as bronchoscopy or tracheostomy [6]. Given the higher risk of transmission to pulmonary and critical care providers, particularly those performing invasive, and potentially AGPs, many guidelines and expert statements have emerged detailing changes in procedure technique and patient selection to better optimize patient care, while also minimizing risk to healthcare workers (HCWs).

While data and recommendations are constantly evolving, this review seeks to highlight the changes in pulmonary procedures that have occurred as a result of the COVID-19 pandemic.

Learning from SARS-COV-1

Initial understanding and recommendations for the management of COVID-19 were shaped by prior experiences with other viral epidemics, including the severe acute respiratory syndrome (SARS). The SARS outbreak, which occurred between 2002 and 2003, was the result of another novel coronavirus, SARS-CoV-1, which also spread largely by respiratory droplets. At the time of its containment in 2003, SARS had spread across 27 countries, resulting in over 8000 confirmed cases and 774 deaths [4]. Several aspects of the SARS outbreak are important to highlight:
1. A high proportion of cases were infections of HCWs. In Singapore, for example, 42% of the initial cluster of infections were among HCWs. Similar results were seen in other outbreaks around the globe, with 51%, 62%, and 33% of initial infections in Toronto, Hong Kong, and Taiwan being the result of transmission to and between HCWs, respectively [7]. At the time of containment in 2003, HCWs accounted for 21% of all confirmed cases of SARS [8].

2. Compared to the rapid response to COVID-19, 3 months elapsed between the first known case of SARS and reporting to the WHO. By the time of the WHO’s global alert, SARS had already spread outside of China [4].

3. The high degree of transmission to HCWs was, in part, the result of slow implementation of hospital precautions and use of personal protective equipment (PPE). This, in itself, was a result of the delayed global response. Following the universal implementation of contact and droplet precautions, further transmission within hospitals rapidly declined [7, 9, 10].

4. SARS is predominately transmitted by respiratory droplets. Aerosol transmission of SARS remains controversial [11]. Several studies, however, suggested aerosolization of the virus during certain AGPs or even nebulizer therapies [12]. Fowler et al. [13•] for instance, reported a significantly higher risk of developing SARS for nurses or physicians participating in AGPs as compared to HCWs not participating in AGPs, despite PPE adherence. Tran et al. [14•] described similar findings, showing a 6.6, 4.2, and 1.9 fold increased risk of contracting SARS for HCWs participating in tracheal intubation, bronchoscopy, and tracheostomy, respectively.

These findings strongly impacted the initial global response to the COVID-19 pandemic and served as the backbone for many of the WHO recommendations, including implementation of universal PPE and social distancing. Early society guidelines and expert panel recommendations for AGPs, including intubation, bronchoscopy, and tracheostomy were also born out of the prior experience with SARS.

**Transmission Risk, Aerosols, and Aerosol-Generating Procedures**

Like SARS, COVID-19 is spread from person-to-person through close contact with infected individuals and their respiratory secretions. Secretions are often grouped into two main categories: large respiratory secretions, or droplets, and smaller respiratory secretions, or aerosols. However, the distinction between these two is often blurred [15].

COVID-19 is spread predominately by respiratory droplets [16]. Droplets are > 5–10 μm in diameter and able to house active virus. Due to their larger size, as compared to aerosols, droplets are typically capable of traveling only 1–2 m from their source before falling to a surface [17]. A systematic review funded by the WHO demonstrated a significant reduction in viral transmission at distances > 1 m compared with distances less than 1 m (2.6% versus 12.8%, respectively) [18], findings which serve as the basis for the social distancing recommendation of six feet. Droplet contamination of surfaces in the form of fomites has also been shown, with viable virus detected for up to 72 h, depending on environmental conditions and surface type [19].

In contrast to droplets, aerosols are typically much smaller (< 5 μm in diameter) and capable of spreading over larger distances [20]. SARS-CoV-2 has been shown to be capable of spreading via this airborne transmission [19]; however, the additional risk of aerosolization by AGPs remains unclear.

One study looking at aerosol generation during controlled pig intubations and bronchoscopies showed no significant change in aerosol generation during any intubation and only small increases during less than half of the bronchoscopies [21]. A counter argument suggested a likely reduced aerosol burden due to the use of heavy sedation and paralysis, treatments which would have negated any cough reflex [22]. A second study also showed minimal change in particle production during intubation or extubation; however, a large production of fine particles (< 1 μm) were seen during both procedure-induced and volitional coughing [23]. The latter is consistent with other studies demonstrating a significantly higher aerosol production during coughing as compared to previously defined AGPs [24, 25].

These findings have led some to suggest abandoning the term “AGP” altogether, given the inaccurate implication that aerosolization occurs only during specifically defined procedures and that these procedures result in greater aerosol dispersion than those induced by a patient cough episode [25]. Such inaccuracies may provide a false sense of security to providers taking care of symptomatic patients outside of the intensive care setting, where risk of infectivity may be equally high or, in some situations, higher depending on the care with which PPE is applied [26].

While SARS-CoV-2 is capable of being aerosolized, the true risk of viral transmission to HCWs during AGPs also remains unknown. In one case report from Singapore, 41 HCWs were exposed to a COVID-positive patient during multiple AGPs. Despite the majority wearing only surgical masks at the time of the exposures, none ultimately tested positive [27]. More recently, Gao et al. [28•] showed a very low risk of viral transmission during bronchoscopies performed on COVID-positive patients in the ICU when utilizing a strict protocol involving paralysis, enhanced PPE, and endotracheal tube clamping prior to ventilator disconnection. Despite 14/45 providers not following the protocol
during at least one bronchoscopy, none tested positive by nasopharyngeal swab and only one had asymptomatic serologic conversion. Similarly, despite earlier concerns, Kwak et al. [29] demonstrated relative healthcare worker safety during the performance of early tracheostomy (average of 6.5 days from intubation to tracheostomy) in COVID-positive patients using a modified procedure technique and strict PPE adherence.

Initial concerns regarding viral transmission to HCWs, particularly during AGPs, were rooted in the high incidence of infectivity seen during the SARS epidemic [14•]. Newer data, however, has demonstrated important differences between the two viruses (Table 1). Viral dynamic studies have shown a peak viral load for SARS at 10–14 days after symptom onset [30, 31•]. This would suggest that most critically ill patients would be at peak infectivity while in the hospital and potentially while undergoing AGPs. Conversely, viral loads for SARS-CoV-2 appear to peak at the time of, or soon after, symptom onset, after which they decline progressively [32]. For most patients undergoing intubation, bronchoscopy, or tracheostomy, these procedures will occur after peak infectivity. Importantly, severity of illness does appear to contribute to viral load persistence, with patients with severe COVID-19 having higher viral loads up to 25 days after symptom onset [33]. Despite this, no studies to date have been able to isolate live virus from respiratory samples taken beyond 9 days of symptom onset, regardless of persistently elevated viral counts [30]. This discrepancy between viral load and infectivity may represent PCR amplification of inert virus.

Given the severity of infection and the potential for increased risk of transmission, appropriate precautions and strict PPE protocols remain critical when caring for patients with COVID-19, particularly when performing AGPs. These new findings, however, coupled with the introduction of effective vaccines, a rising population of fully vaccinated patients and a decreasing new case burden, have allowed for a re-expansion of pulmonary procedures and an overall lightening of certain restrictions, as detailed in the following sections.

Impact of COVID-19 on Pulmonary Procedures

Bronchoscopy

After only a few months into the pandemic, many national and international societies had released guidelines or expert statements on the use of bronchoscopy during the COVID-19 pandemic [34–37]. These recommendations were largely consistent across publications with the main goal of minimizing risk to providers while still providing necessary services to patients in both a safe and timely manner. Since no COVID-specific data existed for bronchoscopy at this stage in the pandemic, these guidelines were based largely on expert opinion and experiences with prior viral epidemics [38].

As the COVID-19 pandemic has evolved, new developments have necessitated flexibility and adaptation when considering protocols for bronchoscopic procedures. More and more patients now fit into a category of previously infected, for which consideration of timing of intervention—and whether or when to retest—has become important. The introduction of effective vaccines, too, has changed the landscape of the pandemic. For the first time, we are now seeing a growing population of fully vaccinated patients, for which long-term data is not yet available [39]. Finally, more data is emerging that demonstrates the relative safety of performing bronchoscopy in COVID-positive patients, as long as strict PPE precautions are utilized [28, 40, 41].

Our current protocol for bronchoscopy (Fig. 1) synthesizes prior guideline-based recommendations with more

| Table 1 | Data demonstrating the important differences between SARS-CoV-1 (SARS) and SARS-CoV-2 (COVID-19) |
|-----------------|--------------------------------------------------|
| Symptoms        | Fever, dyspnea, pulmonary infiltrates, myalgias, respiratory failure |
| Transmission pathways | Droplet, contact, fomite, aerosol |
| Symptom onset (days) | 2–10 |
| Symptom onset to peak viral load (days) | 6–14 |
| HCWs (%infected worldwide) | 21% |
| Total cases | 8,098 |
| Case fatality rate (%) | 9.7% |
| SARS-CoV-2 (COVID-19) | Fever, dyspnea, pulmonary infiltrates, myalgias, respiratory failure |
| Transmission pathways | Droplet, contact, fomite, aerosol |
| Symptom onset (days) | 4–14 |
| Symptom onset to peak viral load (days) | 0–2 |
| HCWs (%infected worldwide) | 3.9%* |
| Total cases | 188,000,000** |
| Case fatality rate (%) | 0.7–9.3%*** |

*These are imperfect numbers and reflect limited data up to May 2020 [72]; **As of July 14, 2021, by the WHO running calculations; ***Most countries fall between a case fatality rate (CFR) of 0.7 and 4.3%. There are a few countries, however, including Peru and Mexico, where CFR is as high as 9.3%.

Note. Adapted from "Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics," by E. Peterson, M. Koopmans, U. Go, et al, 2020, Lancet Infectious Disease, 20(9): e238–e244. Copyright 2020 by Elsevier Ltd. Adapted with permission from the COVID-19 resource centre.
recent evidence and new pandemic-related developments and is described in detail here.

Bronchoscopy was, and still remains, relatively contraindicated in COVID-positive patients. In these cases, focus has shifted to procedure prioritization. Procedural prioritization can be grouped into the following categories: emergent, urgent, time-sensitive, and elective (Table 2). In emergent situations, in which immediate care necessitates performing procedures in a patient with either confirmed or suspected COVID-19 infection, enhanced PPE precautions are recommended, including the use of gowns, gloves, hairnets, full-face shields/eye protection, and either an N95 mask or

![Algorithm for performing outpatient and inpatient bronchoscopies during the COVID-19 pandemic at our institution](image)

**Fig. 1** Algorithm for performing outpatient and inpatient bronchoscopies during the COVID-19 pandemic at our institution

### Table 2 Procedural prioritization grouped into the following categories: emergent, urgent, time-sensitive, and elective

| Emergent procedures** | Urgent procedures | Time-sensitive procedures | Elective procedures |
|-----------------------|-------------------|--------------------------|---------------------|
| Severe central airway obstruction | Diagnosis and staging of lung cancer | Whole lung lavage | Tracheostomy exchange |
| Massive hemoptysis | Evaluation of suspicious lung nodule or mass | Endobronchial valves for persistent air leak | Bronchial thermoplasty |
| Tracheostomy dislodgement or loss of airway | Fever and lung infiltrates in immunocompromised patient | Airway stent surveillance bronchoscopy | Endobronchial valves for emphysema |
| Stent migration or dislodgement | Mild-to-moderate central airway obstruction | Bronchoscopy for suspected sarcoidosis | Chronic cough evaluation |
| | Foreign body aspiration | | Tracheobronchomalacia evaluation |

**Emergent: needs to be completed immediately due to threatening of loss of life**

Urgent: needs to be completed within 24 h

Time-sensitive: needs to be completed within 4 weeks

Elective: can be postponed longer than 4 weeks

Note. Adapted from “American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients With Suspected or Confirmed COVID-19 Infection,” M. Wahidi, C. Lamb, S. Murgu et al, 2020, Journal of Bronchology Interventional Pulmonology, 27:e52-4. Copyright 2020 by Wolters Kluwer Health, Inc. Adapted with permission from the Wolters Kluwer Public Health Emergency Collection.
powered air purifying respirator (PAPR) [18, 42]. All providers should have experience with appropriate donning and doffing technique and specific stations pre-arranged for this purpose. During the procedure, the minimum number of staff necessary is recommended to avoid potential exposures. When possible, general anesthesia is encouraged, with a preference for an endotracheal tube over laryngeal mask airway (LMA) given a superior airway seal. Paralytic should be considered, as its use can negate cough and further minimize aerosolization [34, 38, 43].

If rigid bronchoscopy is performed in a COVID-positive or COVID-unknown patient, a closed-circuit ventilation strategy is preferred over an open system with manual or high frequency jet ventilation, and silicone caps can be used to seal equipment and minimize air leak [41]. Negative pressure rooms with at least 12 air exchanges per hour are recommended or, if not available, a non-negative pressure room with at least 12 air exchanges per hour while allowing for 20 min of room decontamination following each procedure [44].

For patients with urgent indications for bronchoscopy, including the diagnosis and staging of lung cancer, initial guideline-based recommendations were to proceed in a timely manner to avoid significant delays in patient care. All elective and non-urgent cases, however, including those for chronic cough, routine bronchoscopy-guided tracheostomy tube exchanges, tracheobronchomalacia evaluation, bronchoscopic lung volume reduction, and bronchial thermoplasty, were recommended to be postponed [34]. Now, as our understanding of COVID-19 has improved and testing has become both more reliable and ubiquitous, procedure restrictions have lightened.

In our practice, we no longer distinguish between urgent and elective outpatient cases. Instead, all patients being considered for bronchoscopy are screened using the following three criteria:

1. Symptom-based screening at the time of scheduling and within 48 h of the procedure
2. Confirmation of vaccination status
3. Determination of previous positive COVID testing

For patients who have documented administration of all required injections of either the Pfizer, Moderna, or Johnson and Johnson vaccines and are otherwise asymptomatic, bronchoscopy can proceed as scheduled without pre-procedure COVID testing. This change to our practice is based off the strong data supporting the effectiveness of the COVID vaccines [45–47], studies demonstrating a lower risk of transmission for asymptomatic patients [48] and increasing evidence demonstrating low risk of transmission during AGPs when appropriate PPE is utilized.

In patients who are not vaccinated, but have previously been infected and tested positive, timing is important. For those who have tested positive within the last 90 days, are at least 14 days from their initial positive result, and currently asymptomatic, no further testing is required. Based on viral dynamics data for SARS-CoV-2 [30] and studies demonstrating perceived neutralizing effect of acquired antibodies, these patients are felt to be at low risk for viral transmission [49]. If patients fall outside of this window or are otherwise symptomatic, repeat testing is required prior to bronchoscopic intervention.

For all other patients, COVID-19 testing is required prior to proceeding with bronchoscopy, with decisions on timing of the procedure dependent on test results, severity of symptoms, and procedural urgency. Regardless of vaccination status, prior positive testing, or current negative testing, all bronchoscopies continue to be performed using enhanced PPE precautions, given the possibility of asymptomatic carriers and false negative testing [50].

**Tracheostomy**

Tracheostomy is a frequently performed procedure in the critical care setting with the goal of facilitating weaning from mechanical ventilation, minimizing complications of long-term translaryngeal intubation, and improving patient comfort [51]. The procedure can be performed either in a surgical (open) or percutaneous approach and can occur at the bedside in the intensive care unit or in the operating room. With the rapid spread of COVID-19 and the rising case numbers, a growing population of patients with respiratory failure requiring prolonged mechanical ventilation led to questions regarding the feasibility, timing, and safety of performing tracheostomy in these patients.

Prior experience with the SARS epidemic suggested a high risk to providers when performing AGPs, including tracheostomy [14•]. As tracheostomy requires not only opening a patient’s airway, but also typically utilizes bronchoscopic guidance, it is largely considered the procedure with the highest risk of aerosol generation and, subsequently, the highest risk for viral transmission to HCWs. While tracheostomy does provide significant benefits to patients, it is, in nearly all cases, an elective procedure. Furthermore, initial data from the USA also demonstrated an exceedingly high mortality rate for patients with severe COVID-19 infection requiring mechanical ventilation, suggesting tracheostomy was unlikely to impact overall outcome in these patients [5]. For these reasons, early society guidelines for performing tracheostomy in COVID-19-positive patients recommended either late tracheostomy at 14–21 days or beyond [32•, 52, 53], or deferring tracheostomy entirely in favor of attempted extubation [54].

As the COVID-19 pandemic progressed and healthcare institutions experienced a rising number of mechanically ventilated patients, increasing stress on hospital resources and infrastructure necessitated consideration of earlier...
Despite surgical tracheostomy being the preferred approach during the SARS epidemic, percutaneous technique had evolved significantly since the early 2000s [32•]. Given the shortened procedural times, lack of tissue plane dissection, or need for electrocautery, as well as the wider availability of negative pressure rooms in the intensive care setting as compared to the operating room, the percutaneous approach was preferred over the open at many institutions [56]. Several strategies were then developed to modify the percutaneous dilatational tracheostomy (PDT) technique to minimize the risk of aerosolization.

The New York University (NYU) protocol utilizes a side-by-side approach, wherein the bronchoscope is inserted transcordally alongside the endotracheal tube, the latter of which is advanced into the distal trachea. This approach allows for incision, dissection, dilation, and tracheostomy placement to be performed without endotracheal cuff deflation or ventilator circuit disconnection [57•]. An alternative protocol from Emory University involves performing the incision and dissection, followed by the use of pausing mechanical ventilation (apnea) during the final key portions of the procedure, with average apnea times of approximately 3.9 min [58•].

Early data from NYU showed the feasibility and safety of performing PDT using their modified approach. Of the 98 patients in the study, 33% were able to be weaned off mechanical ventilation following tracheostomy, and overall mortality was only 7% in this population. Additionally, none of the 8 providers ultimately tested positive or developed symptoms, despite the procedures being performed on average 10 days after intubation [57•]. Similar results were demonstrated at the University of Pennsylvania, where 56.6% of patients were liberated from mechanical ventilation following tracheostomy and overall mortality was 11.3% in this group. Of the 29 PDT cases, 19 were performed using an apnea protocol, while 10 utilized the modified NYU protocol. No viral transmission to HCWs occurred [59].

These studies suggest a subset of patients with COVID-19 and respiratory failure who will benefit from tracheostomy placement and showed overall improved outcomes in this population compared to reports from earlier in the pandemic. These studies additionally demonstrate relative safety when performing tracheostomy in COVID-positive patients, as long as strict protocols and enhanced PPE precautions are followed, findings similar to the more recent results from bronchoscopy in this population.

At our institution, our preference is to perform PDT utilizing our previously described apnea protocol [58•]. If it is tolerated, all cases are performed using this approach regardless of COVID status, given the risks of false-negative testing and asymptomatic carriers. In patients with borderline oxygenation or those at higher risk for desaturation, an apnea test is performed prior to the procedure, in which the ventilator is turned off for 60 s and clinical status is monitored. We otherwise follow national guideline-based recommendations to utilize enhanced PPE precautions and disposable equipment when possible. We perform our cases with the minimum number of staff in the room to avoid over-exposure, and PDT is performed by the most experienced provider to reduce overall time in room. To further minimize risk of viral transmission, we typically perform PDT in our COVID-positive patients between days 10 and 14, which often translates to >14 days after their positive test result and even longer since symptom onset.

**Pleural Procedures**

Directly, SARS-CoV-2 appears to have modest impact on the pleural space. The virus has been shown to cause pleural effusions in up to 7.3% of patients [60], though imaging studies can detect pleural thickening in up to 32% of cases [61]. COVID-related pleural effusions are exudative, can be either lymphocyte or neutrophil-predominant, and typically demonstrate markedly elevated lactate dehydrogenase levels [60]. It remains unclear, however, how many of these effusions are related to patient comorbidities or superinfections, as opposed to a direct consequence of SARS-CoV-2 infection, particularly given that COVID-related effusions are found more frequently in patients over the age of 50 [62]. Regardless, SARS-CoV-2 has been detected in pleural fluid by PCR testing, suggesting that at least some cases are the result of direct COVID-19 infection [63].

In addition to effusions, limited data also points to a higher incidence of pneumomediastinum and spontaneous pneumothoraces in COVID-positive patients, both of which are more prevalent in patients requiring mechanical ventilation [64]. In our personal experience, we have found COVID-related pneumothoraces to be more difficult to manage, occasionally requiring multiple chest tubes to achieve complete re-expansion [pers. communication]. For patients with a persistent air leak, a viral filter should be attached to the chest drainage system, given the risk of viral aerosolization [65, 66].

Indirectly, the COVID-19 pandemic has largely affected the timing and management of outpatients with new-onset or recurrent effusions. Limited guideline recommendations exist, which focus on minimizing patient hospital visits and the associated potential viral exposure, as well as recommendations for continued appropriate PPE precautions [67]. For patients with new onset effusions, particularly those with suspicion for malignancy, diagnostic and therapeutic thoracentesis should be expedited to avoid delays in diagnosis and, potentially, treatment. In patients with recurrent effusions known to be malignant in etiology, early indwelling pleural catheter placement should be considered, and this
strategy should be favored over surgical decortication or talc instillation, given the associated longer hospital stays with the latter [68].

Since SARS-CoV-2 can be detected in pleural fluid analysis from infected patients, the possibility of viral transmission during pleural procedures should be considered. Arnold et al. [69] recently demonstrated that accessing the pleural space alone does not result in increased aerosol generation; however, the British Thoracic Guidelines do recommend enhanced PPE precautions when performing pleural procedures that may result in pleural fluid splash, including indwelling pleural catheter placement, in patients who are COVID-unknown or COVID-positive. In addition, we should also remember that pleural procedures have the tendency to induce cough, raising the question of whether all cases should be considered potentially aerosol-generating [70, 71]. It is currently our practice to wear standard precautions; however, the British Thoracic Guidelines do recommend enhanced PPE precautions when performing pleural procedures when performing all airway procedures, both out of space alone does not result in increased aerosol generation during pleural interventions, unless patients are known or suspected to be COVID-positive. To minimize aerosolization from patient cough episodes, all patients wear surgical masks during the procedure.

Conclusions

Our understanding of COVID-19 and the effects of the pandemic on healthcare worldwide are constantly evolving. Initial recommendations for performing aerosol-generating procedures were largely created based on expert opinion and prior experience with the SARS epidemic. As new data demonstrates, minimal risk of viral transmission to healthcare workers is possible if appropriate precautions are maintained and when implementing modified procedural techniques. Despite safety data and the rising population of fully vaccinated patients, we continue to apply full personal precautions when performing all airway procedures, both out of an abundance of caution and due to the continued risk of asymptomatic carriers. As pulmonary and critical care providers, it is likely that downstream effects of the COVID-19 pandemic will stay with us for a long time into the future.

Declarations

Conflict of Interest Matthew Schimmel declares no conflict of interest. David Berkowitz declares no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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