Increasing the Signal-to-Noise Ratio: COVID-19 Clinical Synopsis for Outpatient Providers

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Abstract

The novel coronavirus (SARS-CoV-2), which is the cause of coronavirus disease (COVID-19 formally 2019-nCoV), has received widespread attention from the medical community. Despite the rapid publication of research on the virus and the disease it causes, there is a lack of concise and relevant material to help busy medical providers navigate recognition and management of the disease in the ambulatory setting. This review article aims to bridge this gap by briefly reviewing the key points of the evaluation and treatment of patients with COVID-19 in the ambulatory clinic environment.

Keywords

COVID-19, severe acute respiratory syndrome coronavirus 2, outpatients

Introduction

The novel coronavirus (SARS-CoV-2) was first detected in Wuhan, China, and began circulating in the global population in late 2019. The virus is a member of the *betacoronavirus* family and likely originated in bats, with the pangolin as a suspected intermediate responsible for transmission to humans.[1,2] The virus enters the respiratory epithelial cells at the angiotensin-converting enzyme II (ACE-II) receptor site and leads to a lower respiratory tract infection called coronavirus disease (COVID-19).

There have been over 1 million documented SARS-CoV-2 infections worldwide and close to 60 000 deaths.[3] The situation is rapidly evolving. New articles in both medical and popular media are published daily. This deluge of information can be overwhelming for busy primary care physicians. Therefore, there is a need for a concise primer that provides a discerning and high-yield review of current relevant information for these providers. This article fulfills that need by discussing transmission of the virus, clinical features and complications of COVID-19, diagnosis, recommendations for disposition of patients, public health interventions, pharmacotherapy, and practice management changes. Additionally, included is a brief review of current available information for the pediatric and peripartum patient populations and a final word on what questions remain.

Transmission

Primary Modes of Transmission and Infectivity

Transmission of the virus occurs primarily through respiratory droplets, however, airborne transmission (especially with aerosolizing procedures such as bronchoscopy or noninvasive ventilation) and fomite transmission have been shown to contribute to transmissibility in a nonclinical, controlled environment. The extent to which this actually occurs in the clinical setting is unknown at this time.[4] Therefore, all health care workers are encouraged by the Centers for Disease Control and Prevention (CDC) to wear full personal protective equipment (PPE), including an N95 respirator during all clinical encounters with patients who have confirmed or suspected infection with SARS-CoV-2.

The median incubation period for the virus is on average 4 to 5 days; however, the range of incubation has been observed to be as early as 2 days and as long as 27 days after exposure.[5,6] The virus is considered more infectious than

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Table 1. Frequency of Reported Symptoms With COVID-19.

Symptom	Observed in Patients With COVID-19 (%)
Fever	89-99
Cough	60-79
Fatigue	23-70
Sputum production	23-34
Dyspnea	19-31
Myalgia	15-35
Headache	8-14
Sore throat	14
Chills	12
Congestion	5
Diarrhea	3-10

seasonal influenzae, with a reproductive number (R_0) estimated at 2.2 to 2.4.[6-8]

Asymptomatic Transmission

Additionally, there is some evidence to suggest that certain individuals may be asymptomatic carriers and therefore contribute to community transmission.[9] One example comes from the Diamond Princess cruise ship where 18% of individuals with a positive result were asymptomatic.[10] Another study examining the rates of asymptomatic individuals repatriated from Wuhan to Japan were much higher at 41%.[11]

Despite this case series–level evidence, the prevalence of asymptomatic transmission in a typical community setting and its relevance to epidemiologic modeling remains unknown. This is an area of growing interest and is theorized to contribute to epidemiologic modeling of sustained community transmission in a significant way.

Clinical Presentation of COVID-19

Common Clinical Signs and Symptoms

The primary symptoms of COVID-19 (the disease caused by SARS-CoV-2) involve the lower respiratory tract (see Table 1).[5,12-14] A large majority of cases involve fever and cough. The cough is primarily reported to be nonproductive or "dry," but sputum production can be observed in up to a third of patients. Dyspnea may be reported or observed and correlates with disease severity.[15] Other symptoms include fatigue and myalgias, congestion, and pharyngitis. A small percentage of patients may have gastrointestinal symptoms, including diarrhea.

The constellation of COVID-19 symptoms may be difficult to distinguish from other viral processes. Given the extent of community transmission of SARS-CoV-2, providers must have a high degree of clinical suspicion and rely on the most common features of the disease in order to make a diagnosis. Clinical diagnosis may in fact become the norm, depending on regional variations in testing ability.

Natural History

The incubation period, as mentioned above, is 4 to 5 days on average. After this time, patients will usually begin to develop symptoms. COVID-19 is reported to follow a 2-week course: a viral replicative phase during the first week followed by a possible worsening in the second week due to development of a robust immune response.[14] Patients therefore should be monitored closely for worsening of symptoms well into the second week of illness.

Complications, Morbidity, and Mortality

Most cases of COVID-19 will be mild; however, some cases may be severe and can result in prolonged hospital stays and death. The true case fatality ratio is not known given the lack of population level epidemiologic data—driven by lack of widespread testing—and inconsistent reporting; however, estimates range from 2% to 8%.[16,17] Death from COVID-19 occurs from a number of complications, which include respiratory failure and acute respiratory distress syndrome (ARDS), acute renal failure, coagulopathy, sepsis, secondary bacterial infections, and cardiac injury (including fulminant myocarditis and cardiomyopathy).[5,13-15]

Worse outcomes have been noted in patients with certain comorbid conditions such as cardiovascular disease, diabetes, immune compromise (from medications or underlying conditions), lung disease (either restrictive or obstructive), and in the elderly—especially those older than 60 years.[14] Therefore, patients with these conditions should be preferentially tested based on local capability, and those who are positive should be monitored frequently with telephone calls or telehealth appointments in case their condition worsens (more on this below).

Diagnostic Evaluation

SARS-CoV-2 Testing

The Food and Drug Administration (FDA) now can provide Emergency Use Authorization (EUA) for testing modalities, which has increased capacity for testing development and availability. However, data on diagnostic performance is lacking on sensitivity, specificity, and appropriate use of these testing modalities.

The real-time reverse transcriptase polymerase chain reaction testing (rRT-PCR) is the recommended first-line diagnostic test. Several biomedical companies now offer point-of-care testing in addition to commercial laboratory testing accommodations. Nasopharyngeal sampling has

become the preferential standard in the United States,[18] but oropharyngeal and sputum sampling have demonstrated effectiveness as well.[19] The best available estimate of sensitivity is ~70% (range of 60% to 80%) with high specificity. Clearly, the negative predictive value of the test is lacking, so a single negative test result does not rule out COVID-19.[20-22] In the future, when community transmission is ubiquitous and pretest probability increases, a negative test result will become more useful—similar to increased negative predictive value of rapid flu testing during peak flu season. During periods of low levels of community transmission—our current state—negative testing should not exclude the possible diagnosis of COVID-19.

Other testing modalities include IgM (immunoglobulin M) and IgG (immunoglobulin G) detection at the point of care. Specimens are provided by venous or fingerstick draw, and best evidence shows that the results correlate relatively well with rRT-PCR testing.[23] At this time, the antibody response to SARS-CoV-2 is not well established, thus these tests are recommended for postexposure surveillance, not diagnosis.[19]

Who Needs Laboratory Testing for SARS-CoV-2?

The decision to initiate testing should be guided by the CDC interim guidelines which have remained in flux during the course of the pandemic.[24] These recommendations are a function of both testing capacity and risk stratification, with the goal of identifying and prioritizing testing of individuals at highest risk for severe disease. Current recommendations are that patients with characteristic symptoms who have one additional risk factor—hospitalization, a high risk medical condition such as diabetes, cardiovascular disease, chronic lung disease, immune compromise from medications or conditions otherwise, healthcare providers, residents of long term care facilities, and those with travel history to areas with outbreaks—should be tested for SARS-CoV-2. These recommendations will change in the future, so providers should monitor the CDC website and their local public health departments for the most up-to-date information.

Radiographic Studies

Computed tomography (CT) of the lungs has been proposed as a highly sensitive tool for detection of COVID-19, with estimates of 97% to 98% sensitivity.[20,22] Findings on CT consist of bilateral infiltrates and ground-glass opacities that correlate with disease severity.[14,25] Although superior diagnostically, the utility of this testing modality—availability, cost, radiation exposure, and so on—limits its use in the ambulatory setting and should continue to be used adjunctively until further guidance or recommendations are established.

Other Laboratory Testing

Additional laboratory testing, including a complete blood count and chemistry studies, may be useful for risk stratification of patients. COVID-19 is associated with lymphocytopenia, and more severe disease is associated with absolute lymphocyte counts <1000.[5,13,14] Additional chemistry studies, including D-dimer, C-reactive protein, ferritin, and lactate dehydrogenase (LDH), may serve a prognostic purpose, with elevation in these indices associated with increased mortality.[14] Use of these tests in the ambulatory setting is likely to be of little value and should only be considered as adjunctive and prognostic rather than diagnostic.

Patient Management Considerations

Symptomatic Patients With Confirmed COVID-19

A patient tested for the SARS-CoV-2 virus should be presumed to have the virus until results are available. The first step in management of these patients is clinical disposition. Patients with respiratory compromise should be directed to emergency departments for further evaluation and care. This includes patients with tachypnea, altered mentation, or hypoxia. Additionally, patients with COVID-19 should be hospitalized for standard indications, including volume status or an inability to perform normal activities of daily living.

A majority of patients with confirmed or suspected COVID-19 will be able to return home, and the focus on self-care at home involves minimizing risk of transmission to others, supportive therapy— fluids, rest, antipyretic, and analgesic medications—and precautions for return to clinic or the emergency department.

The major goal of home care is 2-fold. First, patients need salient counseling on supportive care measures and return precautions in the case of worsening disease. Second, patients need to stay isolated to help contain the spread of the virus in the community. Moreover, if other individuals, such as caregivers, need to interact with patients, measures including use of facemasks by all parties and scrupulous hand hygiene should be strictly observed to reduce the likelihood of further transmission.

Table 2 summarizes key points from the World Health Organization's and the CDC's recommendations on home care.[26,27]

In addition to self-care measures, patients should be followed up by telephone or telehealth appointments over the following days at appropriate intervals based on clinical disease severity and risk factors for complications given that worsening can occur, especially during the second week of illness. As stated previously, these individuals should remain in self-isolation in order to limit community spread of the virus. Patients should remain at home until

Table 2. Recommendations for Home Care for Patients With COVID-19.

Minimize shared space in the house by staying at least 6 feet from infected persons or isolating infected persons separately from well persons

Limit the number of caregivers to one (ideally someone without any risk factors for COVID-19 complications and otherwise healthy)

No nonessential visitors

Observe good hand hygiene at all times by washing and/or sanitizing

The patient should wear a mask as much if possible if they interact with other household members including care givers. Caregivers should also wear a mask during interactions with infected persons.

Contact surfaces should be cleaned frequently to minimize transmission

Contacts including caregivers should self-quarantine for 14 days after the last known close contact with an infected person(s). They should monitor themselves for symptoms and call their primary care provider if any symptoms develop.

The infected person or their caregiver should contact the patient's primary care provider if any symptoms worsen. Infected persons should go to the emergency department if respiratory distress or disease worsening develops or for life threating emergencies for which they would otherwise go.

they are fever free for 72 hours with improvement in cough and shortness of breath *and* at least 7 days have passed since symptoms first started.[27]

Symptomatic Patients Without Confirmed COVID-19

Given the limited testing capacity in some areas, patients who do not meet criteria to be tested may be discharged home or referred to local emergency departments based on standard indications. Patients discharged home who are not tested could in fact have SARS-CoV-2. Patients should be informed explicitly they may still contribute to transmission in the community and to their close contacts given the possibility of viral carriage which cannot be ruled out. These patients should be counseled in a similar manner to those patients who meet testing criteria and follow the same self-isolation discontinuation criteria described above as those with confirmed COVID-19.

Asymptomatic Patients With Close Contact to SARS-CoV-2

These individuals, while asymptomatic, still have the potential to transmit the virus given asymptomatic transmission rates. These individuals should be given self-quarantine precautions, which include 14 days of isolation from the time of the last known contact with the infected person in addition to standard infection control measures.[27]

Public and Community Health Interventions to Reduce Community Transmission

Social Distancing and Quarantine Measures

Large-scale public health interventions, including nonessential business closures, school closures, and social distancing practices should continue at this time. Providers should counsel all patients with whom they interact, via telephone, video visits, secure messaging, or in person, to continue adherence to these practices since they are crucial in decreasing community transmission. Additionally, the CDC is now recommending all persons wear cloth masks in public to help decrease rates of community transmission.[28]

Community health providers should reinforce these measures at every possible opportunity given demonstrated efficacy. Data from Wuhan have shown that strict quarantine measures lead to a direct and substantial reduction in R_0 to 1.05.[8] Preliminary reporting from Washington state, for example, also show a similar reduction in the R_0 from a level greater than 2.0 down to ~1.5, which means these interventions have directly decreased infectivity.[29,30]

Large-Scale Testing Programs

Large-scale testing programs have been lacking in the United States, which is well documented in scientific and popular media alike. If such testing programs were available, large numbers of people with the virus could be identified and quarantined thereby reducing community transmission.[31] This model has proven effective in places like South Korea.[32] Therefore, use of large-scale testing should be approached on a case-by-case basis in communities with margin to provide such services. Lessons learned in large-scale programs will need to be remembered and incorporated into pandemic response plans for future use.

Considerations for Practice Management

Rationale for Modifications to Routine Practice

There are 2 primary reasons to modify practice in response to the pandemic. First, social distancing and quarantine measures apply to physician offices as well. Therefore, minimizing patients' risk for exposure by offering alternative services is paramount. Second, in preparation for possible surges of patients infected with the virus, alternative strategies for provision of services will ensure sustainable

health care delivery. Two foundational strategies exist for accomplishing this goal: implementation of telehealth services and surge or alternative care site designation and preparation.

Telehealth Services

In order to increase access to care in an area of community wide quarantine, the US government has expanded its definition of reimbursable services, among other measures, to include telehealth.[33] Providers with the capacity should consider offering telemedicine services to keep patients with chronic conditions—those most at risk of complications from COVID-19—at home in an attempt to keep well patients at home. The American Medical Association provides resources for providers who are looking to institute these services.[34] Additionally, some low-risk patients with suspected COVID-19 may be treated via telehealth services effectively. It is important to note that not all patients are candidates for telehealth and may still require an in-person visit. This decision involves both the provider's clinical judgment and the patient's comfort with, and access to, telehealth service modalities.

Surge or Alternative Care Sites

Various resources for implementation of "surge procedures"—including parking lot or tent clinics, outdoor triage, and universal screening and masking—are available online to help practices stay flexible, protect healthcare providers, and maintain patient access.[35] These practices are becoming ubiquitous across the country. At our institution, for example, we have several "tent clinics," which have been constructed just for patients with suspected or confirmed coronavirus. These alternative care sites minimize viral exposure for healthy individuals and those at highest risk and allow for implementation of cohort models for medical staff, a practice that not only minimizes exposure but preserves personal protective equipment.

Additionally, all patients should be encouraged to call ahead prior to coming to clinic. Patients should be asked about symptoms and possible exposure to coronavirus and directed to these alternative care sites if appropriate. Doing so will eliminate both unnecessary office appointments and divert appointments that might be provided via telehealth services. This practice could direct patients to alternative care sites and, thus, prevent infected persons from coming into clinic.

Pharmacotherapy

Overview

The primary treatment pathways for COVID-19 involve identification of patients with the disease, monitoring for worsening, provision of supportive care measures, and reinforcement of interventions to reduce community transmission. However, additional pharmacotherapy considerations warrant discussion.

Anti-infectives

Chloroquine and hydroxychloroquine have received high levels of interest as therapeutic treatment options. The proposed mechanism involves disruption of cellular receptor mechanisms.[36] In vitro studies of hydroxychloroquine against SARS-CoV-2 have been proven at doses of 400 mg twice daily on day 1 followed by 200 mg twice daily for another 4 days.[37,38] Additionally, 2 studies, one a preliminary report from China, shows efficacy in vivo[39] and one from France shows decreased in vivo viral carriage, especially when combined with azithromycin.[40] Although possibly a therapeutic option in the future, no guidance exists at this time on which to base a recommendation for prescribing this regimen to patients in the ambulatory setting. Currently, these agents are only approved for use in the hospital setting.

Beside chloroquine products, there are few tangible options with an evidentiary foundation. Remdesivir is a novel therapeutic agent shown to inhibit RNA synthesis in viruses, including Ebola, for which it was originally developed.[41] Although there is proven in vitro efficacy,[38] there are no clinical trials on which to base recommendation for use of this medication. The protease inhibitor combination lopinavir-ritonavir has been under investigation as well based on past literature showing efficacy of the agents during the SARS epidemic.[42] A recent clinical trial, however, failed to demonstrate efficacy.[43]

Supportive Pharmacotherapy

Given lack of evidence for use of anti-infectives, supportive pharmacotherapy is the mainstay of treatment in the ambulatory setting. There has been a great deal of information in the popular media on the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Expert opinion based mostly on anecdotal evidence suggests possible worsened morbidity and mortality with NSAID use.[44] The mechanism for such an outcome is poorly understood but thought to relate to blunting of immune response by these medications and time to resolution of illness. Some experts worry that chronic pain patients may stop using NSAIDs, which could trigger an increase in opioid prescribing.[45] Given the—albeit low-level—evidence to suggest NSAIDs may worsen outcomes, providers should advise patients with COVID-19 on the use of acetaminophen prior to NSAIDs for symptomatic relief. The decision to continue NSAIDs for symptomatic and asymptomatic patients should be made with patients via shared decision making.

Similarly, corticosteroids may lead to worse outcomes. Data available from the SARS-CoV-1 and MERS-CoV epidemics show possible harm and decreased clearance of the virus from the respiratory tract.[46,47] Therefore, avoidance of steroids is currently recommended for now unless another indication for use is present.[48]

Use of ACE Inhibitors and Angiotensin Receptor Blockers

Another question prevalent in popular and scientific media alike concerns the use and continuation of angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) in patients with hypertension, diabetes, and kidney disease. SARS-CoV-2 enters cells via the angiotensin-converting enzyme II (ACE-II) as described above. ACE-II receptors are found in lungs, heart, intestine, and kidneys. ACE-II presence is upregulated in patients on ACE-I and ARB therapy and in diabetics.[49] Therefore, it has been postulated that these medications may predispose to increased infectivity. There has also been a question of whether ARBs in particular may even be protective from SARS-CoV-2.[50] The pathology of the virus and the role ACE-I and ARB medications play in pathogenesis is not fully understood at this time. Therefore, it is recommended that patients, both those who are ill and those who are healthy who use these medications should be continued on them unless there is a reason to discontinue them (hypotension, acute kidney injury, abnormal electrolytes, etc). Stopping them could in fact lead to more harm in high-risk patients.[51,52]

Bottom Line

There is no evidence-based therapeutic options for treatment in the outpatient setting at this time. Providers should counsel patients on appropriate use of acetaminophen and NSAIDs and continue ACE-Is and ARBs in patients with suspected or proven COVID-19.

Considerations for the Pediatric Population

There is much less data on the effects of SARS-CoV-2 in children. Best available evidence—derived from case series—demonstrates the less severe nature of the disease in children.[53-55] However, similar to adults, children with high-risk medical conditions may still be susceptible to worse outcomes.[56] There may also be a higher incidence of co-infection with bacterial pathogens in children with high risk medical conditions, based on case-level data looking at procalcitonin and imaging findings.[57] Supportive care should be the mainstay of treatment. Antibiotics should be used for

standard indications, and the use of antivirals and steroids should be avoided. Viral shedding may be prolonged in children—even those who are asymptomatic—which may contribute to sustained community transmission, although the evidence for this is purely conjectural at this time.[56]

Considerations for the Pregnant and Peripartum Population

Like knowledge of COVID-19 in children, there is a paucity of data regarding the disease in pregnant patients. At this time, the limited evidence suggests there is no vertical transmission of the virus.[58,59] One case study demonstrated the presence of IgM in a neonate born to a patient with confirmed SARS-CoV-2 infection, but the neonate tested negative on multiple rRT-PCR tests, and there was no placental or amniotic fluid collected for analysis.[60] The World Health Organization recommends that mothers continue to breastfeed, given the available data suggesting lack of viral transmission.[48] Additionally, pregnant patients using 17-hydroxyprogesterone for prevention of preterm birth should continue this therapy.[48]

What Remains Unknown

There is more we do not know about transmission dynamics and treatment of SARS-CoV-2 and COVID-19 than we do know. However, every passing day brings new information to the forefront of the medical literature and popular media. For example, recent reports show an increase in disease burden in African American communities.[61] Why this may be so remains undetermined, and big data analysis, which will come in the future, will ultimately provide the best insights. Moreover, the efficacy of interventions such as universal masking on disease transmission (which seems intuitive) has yet to be scrutinized with evidentiary rigor. The evidence for best uses of pharmacotherapy remain elusive. As time passes, knowledge gaps will be increasingly filled in, and public and community health officials will need to provide ongoing synthesis of the most important information.

Conclusions

There is much we do not know about the SARS-CoV-2 virus and COVID-19. However, providers in the ambulatory setting should be ready to recognize the disease based on the most common clinical symptoms, to understand the utility of testing modalities, and to provide best practice advice to patients with the disease, both on an individual level and on a public and community health level.

Declaration of Conflicting Interests

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