Management of Low to Medium Severity COVID-19 in the Ambulatory Setting

Information contained herein is believed accurate as of 08/14/2020 and is not a substitute for clinical judgment. Implementation of the guidance contained herein is in the sole discretion of the provider and the provider's medical practice.

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Prevention

Routes of transmission

SARS-CoV-2 can be transmitted via direct contact (virus deposited on persons), indirect contact (virus deposited on objects), and airborne routes (virus transmitted from droplets and aerosols). Contact tracing study and R naught data collected to date suggest droplet-mediated airborne transmission to represent the dominant mode of infection, with aerosol transmission occurring occasionally. Handwashing, social distancing, and wearing face covers are all important for preventing infection, as is controlling contact duration and time, with face masks being perhaps the most important practical mechanism for source control. As we know from other infection control data, doffing personal protective equipment (PPE) is generally considered the time of greatest risk when working with infected patients. The following table outlines criteria defining a significant contact, based on current CDC and WHO standards.

Figure 1: Contact and index case interaction: Significant contact definitions

Evaluation of exposure significance Exposure characteristics: Index case actively infected (see below)						
		Any duration of exposure	Exposure duration of more than 15 minutes and less than 6 feet separation from infectious index case			Less than 15 minutes duration or more than 6 feet separation
Protection worn by contact ↓	Exposure details →	Aerosol exposure from COVID-19 patient	Index case wearing surgical mask	Index case wearing cloth mask**	Index case without mask	Index case with or without mask (exception for aerosol exposures; see column to left)
Gown, gloves, N95*, eye protection						
Gown, gloves, surgical mask, eye protection						
Surgical mask and eye protection						
Surgical mask						
Cloth mask						
No mask						

Significant contact

No significant contact

* N95 = N95 rated mask or equivalent

** Surgical masks are more effective at source control than cloth masks.

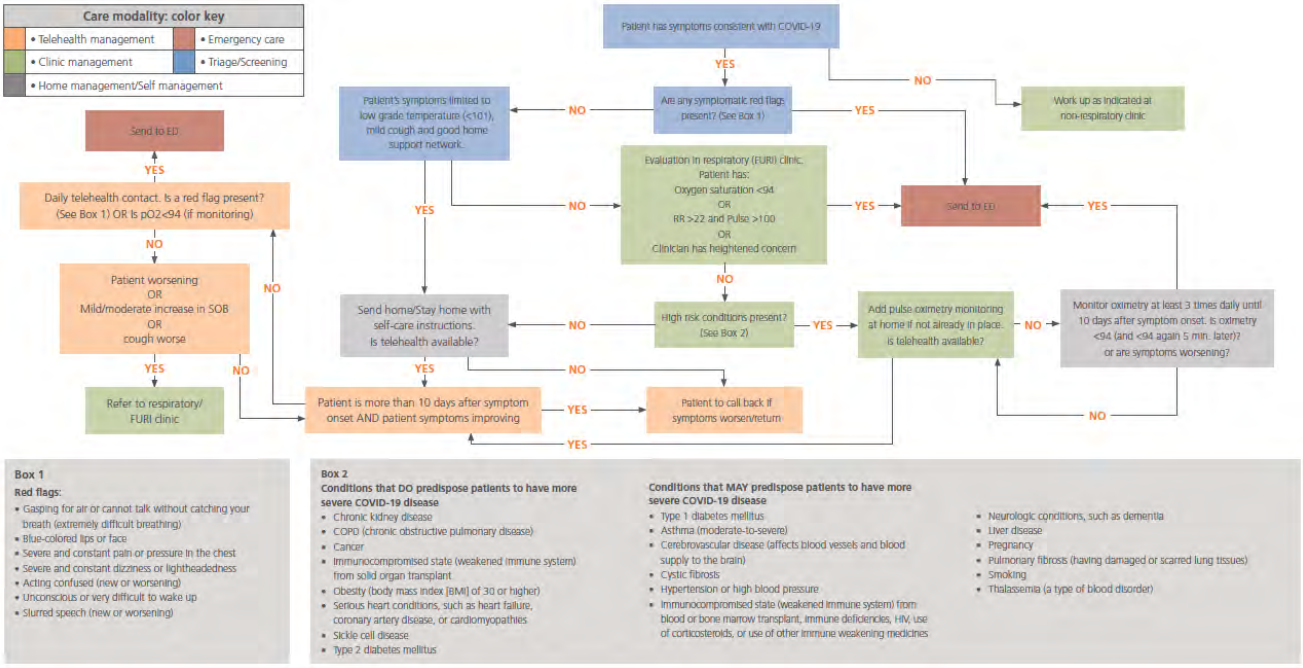
Infectious definition: Persons with COVID-19 are infectious with the following characteristics:

1. An index case with confirmed or suspected COVID in the 48 hours prior to through 10 days after symptom onset.
2. An asymptomatic index case with a positive PCR test beginning 48 hours prior to continuing to 10 days after test acquisition or until isolation begins.

Ambulatory management should focus on early detection of serious or worsening COVID-19. Clinical factors should drive decisions about who is evaluated in person. The flexible set of care settings OptumCare clinical teams have developed (including in-home care services, telehealth, F/URI clinics, and drive through evaluations) should be leveraged to achieve these objectives. Affiliated physicians should become fully acquainted with the options available to OptumCare patients in their local market. Only when there is little question about a patient's respiratory status should a remote evaluation of COVID-19 symptoms be considered.

The following decision tree summarizes our latest guidance for managing COVID-19 in the ambulatory setting and decision criteria for care advancement e.g. hospital admission, all of which is discussed in further detail in the sections that follow.

Figure 2: Ambulatory management of COVID-19 patients



Diagnosis

Clinical suspicion for COVID-19 should be driven by exposure risk factors that suggest a significant contact with an infected person, and symptoms. It should be recognized that patients with non-specific symptoms have a non-COVID etiology most of the time, unless they live in a high prevalence region or have high risk of exposure.

The most common symptoms of COVID-19 cannot distinguish the disease from common viral infections and include fever, cough, and shortness of breath. Other non-specific symptoms include myalgias, headache, non-specific gastrointestinal symptoms, and upper respiratory tract symptoms. However, anosmia (loss of taste or smell) is reasonably specific and has been reported in up to 55% of patients with COVID-19, with higher incidence in women[1]. Clinically apparent dyspnea a few days following upper respiratory symptom onset is also suggestive of COVID-19[2]. It should be noted that asymptomatic hypoxia is relatively common, so evaluators should have high index of suspicion for respiratory distress. While major and minor symptom criteria have been developed, decisions to test must be made on an individual basis using an approach that weighs exposure risk heavily.

Clinical impression alone cannot rule out COVID-19 without testing. It is appropriate to diagnose COVID-19 presumptively when testing is not available, or results are indeterminate. Importantly, in the setting of a high-risk exposure and/or high clinical suspicion **a negative COVID-19 test (RT-PCR or point of care) does not exclude infection**. It is clinically responsible to make a presumptive diagnosis of COVID-19 and make follow-up and quarantine recommendations on this basis given the inadequate sensitivity of commercially available tests. Conversely, a positive test should be considered positive and accurate.

RNA testing of symptomatic individuals

When test availability allows, all patients with the symptoms described below should receive viral antigen or molecular testing if within the appropriate clinical timeframe.

Antigen or molecular viral COVID-19 tests only enjoy satisfactory sensitivity between two days prior and five to seven days after symptom onset[3]. If a patient presents between day five and seven of symptom onset, a molecular test could be considered but sensitivity will be even more limited (see Table 1 for details). These tests have little value beyond seven days of symptom onset due to declining viral load. In a low prevalence region antibody testing is also not yet reliable (high false positive rate) and often does not change management because the duration and completeness of protection of antibodies is not fully understood.

Antibody testing may be warranted 15 days after onset of symptoms and to identify post-COVID-19 complications.

Patients who receive a negative RNA test within the window period for whom there is high pre-test probability of disease should be considered positive for purposes of clinical follow-up and self-quarantine but may benefit from a second test 24-72 hours after the initial negative. Figure 3 provides more detail on re-testing criteria.

The practice of limiting COVID-19 tests to those who have first tested negative for influenza is no longer recommended given coinfection has been described[4] – influenza tests should be used in patients who

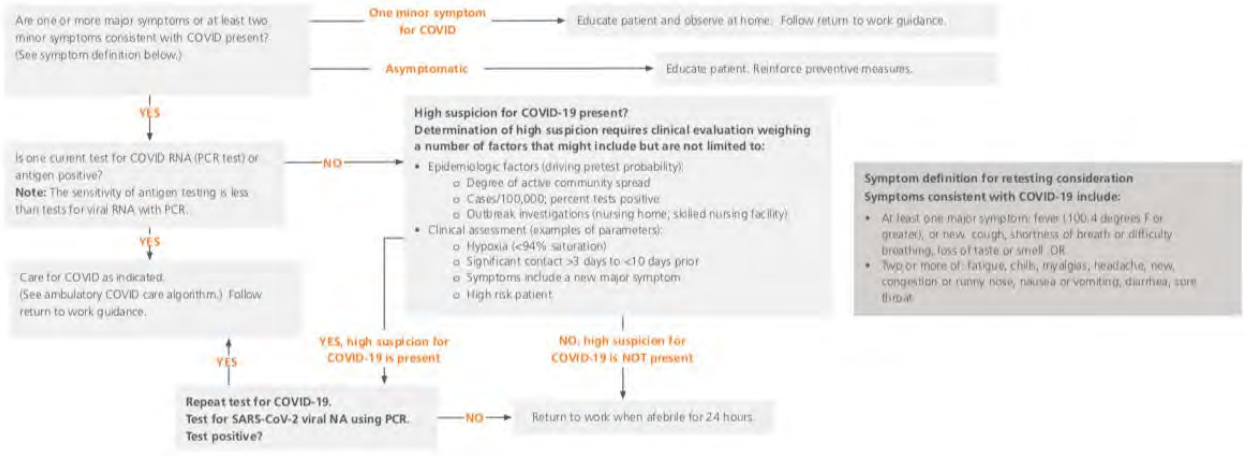
present within 48 hours of symptom onset and in whom antiviral treatment would be initiated if influenza is the causal agent, and then only when influenza is actively circulating in the community.

Table 1: Testing for symptomatic patients (outpatients, not immunosuppressed)

	Time from symptom onset			
Test recommended[2,3]	< 48 hours[4]	≤ 5 days	5-7 days[5]	> 7 days[5]
COVID-19 antigen test	Indicated	Indicated	Not recommended	Not recommended
COVID-19 molecular test	Indicated	Indicated	Uncertain value	Not recommended
Influenza rapid antigen test	Indicated in select patients[4]	Not recommended	Not recommended	Not recommended

1. All patients with influenza-like symptoms should self-isolate, test for COVID-19 and follow return-to-work[2] guidance.
2. Testing recommendations should be based on the test sensitivity and specificity in given clinical situation.
3. Serologic testing does not have a role in the assessment of persons suspected to have acute COVID-19 disease. Serologic testing (IgG antibody) does not become reliably positive until 15-30 days after symptoms onset.
4. Antivirals directed against the influenza virus are only effective when initiated within 48 hours of symptom onset.
5. SARS-CoV-2 viral RNA rapidly decreases in patients after five to seven days after symptom onset, and viral RNA may not be consistently detectable.

Figure 3: Testing for COVID-19: Retesting for high suspicion for COVID-19



Asymptomatic RNA testing and work-based screening

RNA testing in asymptomatic individuals should be reserved for selected circumstances. Baseline testing of all patients or residents in long-term care facilities should be undertaken. In addition, re-testing should be considered following positivity in another resident or staff member. Other clinical circumstances that may indicate a need for asymptomatic testing include in anticipation of aerosol-generating procedures (AGPs), administration of immunosuppressive therapy, prior to surgery, patients in high risk congregate setting (e.g. Department of Corrections custody), women in pregnancy near-term, and in hospitalized patients when community prevalence is very high (e.g. > 10%).

Transmission of COVID-19 appears to occur during an asymptomatic or presymptomatic period about 40-80% of the time. This has prompted some workplaces to institute testing in asymptomatic individuals to prevent workplace outbreaks. Falsely reassuring negative tests or persistent viral shedding beyond the typical 10 days following infection when patients are no longer contagious may complicate such strategies. False positives can be common in low prevalence environments and could contribute to confusion as well. In settings with available testing resources it is appropriate to test asymptomatic individuals who have had a high-risk exposure (e.g. close contact with an infected person, household contact), with an optimal interval period of 5-7 days following the exposure. **The CDC no longer recommends a test-based strategy to "clear" or discontinue transmission-based precautions (TBP) for the vast majority of patients who previously tested positive. A time-based strategy is strongly recommended due to the persistence of non-infectious genetic material that may be detected after normal recovery has already occurred.** Exceptions may include severely immunosuppressed patients.

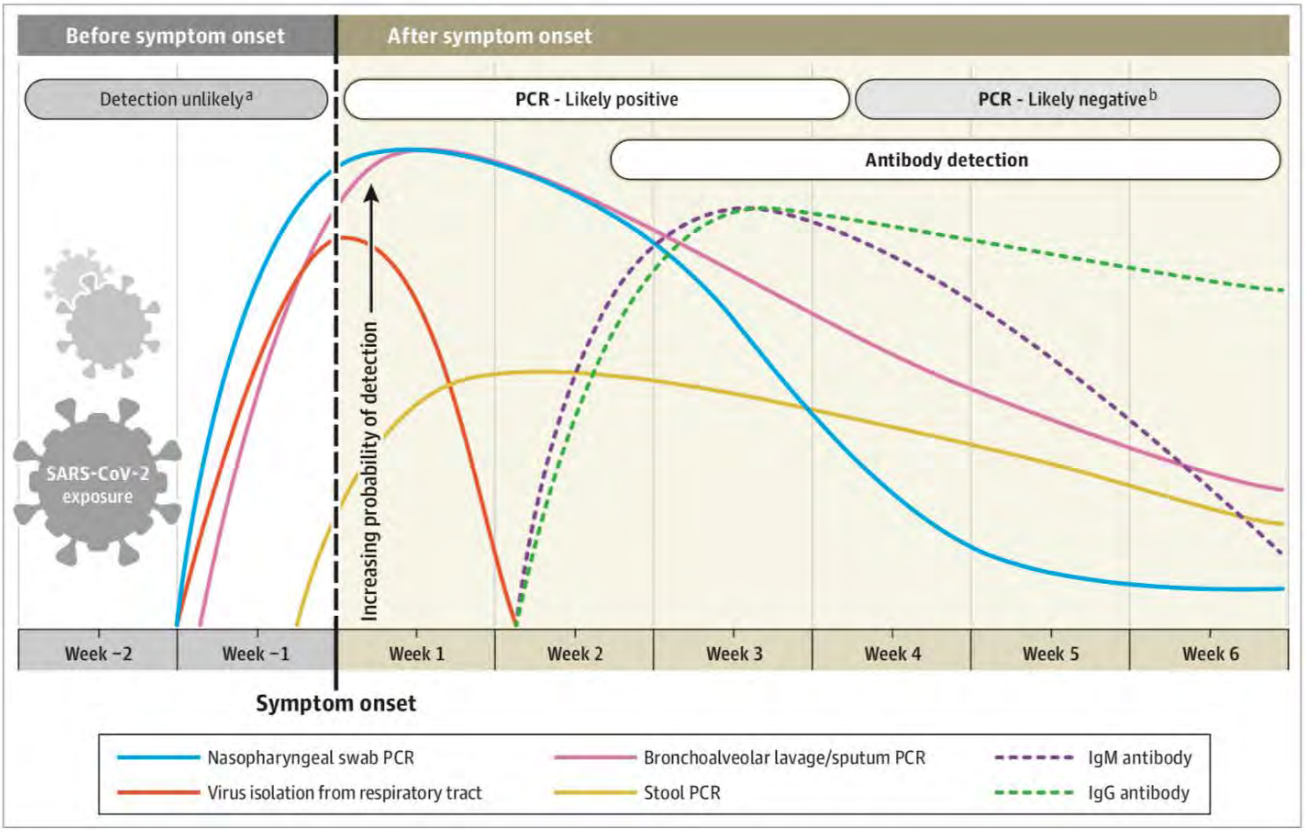
Antibody testing

Serologic antibody testing should not be used to diagnose acute COVID-19 infection, as antibodies are not typically detectable until more than 15 days following symptom onset. Antibody testing can be clinically useful to assess patients presenting late in their disease course and still require medical support (such as hospitalized patients) and in individuals with suspected post-infectious syndromes.

Because the false positive rate of antibody tests is much higher than that for viral RNA tests, the positive predictive value of antibody tests tends to be mediocre (i.e. 60-70%) unless baseline disease prevalence or pre-test probability is very high. Community prevalence levels would need to be much higher than is found in the vast majority of the United States to yield reliable information in most circumstances.

Antibody test sensitivity generally increases with time, with 20-30% of patients testing positive at one week post infection, 58-66% at two weeks, and 75-88% at three weeks[5]. In settings where a false-positive result would alter management, it may be reasonable to perform a second, different antibody test. Figure 4 provides a helpful visual overview of test type and appropriate window for use.

Figure 4: Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Adapted from: Sethuraman N, Jeremiah SS, et al. Interpreting diagnostic tests for SARS-CoV-2. JAMA. June 9, 2020. Vol 323, 22:2249-2251.

Ambulatory management

Most patients (80%) with COVID-19 can recover at home. The ambulatory management strategy should aim to maximize patient safety by early detection of clinical deterioration warranting hospital admission while minimizing the risk of virus transmission from unnecessary in-person patient visits.

Patients should be instructed to rest, drink plenty of fluids, and take precautions to avoid infecting others in their household or outside the home, including wearing a mask whenever in the same room or within 6 feet of another person and asking all in the same household to do the same. Self-monitoring should include checking their temperature several times a day and, if feasible, twice-daily monitoring of SpO2 with a pulse oximeter.

The ambulatory evaluation should assess the time course and severity of dyspnea, oxygenation, overall disease acuity (e.g. presence of dizziness, orthostasis, confusion, fever), and outside support available to the patient should they deteriorate and require the assistance of a caregiver.

Determining the need for inpatient care

There is clear evidence that delayed presentation for hospital care can lead to inferior outcomes, particularly increased rates of respiratory and renal failure. Special attention should be given to patients at higher risk of bad outcomes if hospitalized – these patients should receive preferential access to home SpO2 monitors and be followed proactively. All patients should monitor symptoms and immediately contact a healthcare provider if those symptoms progress, with close attention to worsening dyspnea (especially at rest) or chest tightness or discomfort.

Some patients delay presentation because they do not feel subjectively short of breath, even though their respiratory efficiency is deteriorating critically. When dyspnea develops it tends to happen four to eight days into the disease course, but it may happen later. In patients who ultimately developed acute respiratory distress syndrome (ARDS), deterioration began 2.5 days following the first appearance of dyspnea[6]. Table 2 lists signs and symptoms warranting immediate emergency medical care.

Table 2: COVID-19 symptoms signaling need for emergency care

Criteria for going to the emergency room or calling 911
Gasping for air or cannot talk without catching your breath (extreme breathing difficulty)
Blue-colored face or lips
Severe and constant pain or pressure in the chest
Severe and constant dizziness or lightheadedness
Acting confused (new or worsening)
Unconscious or very difficult to wake up
Slurred speech (new or worsening)

Assessment of hypoxia should focus on both subjective impression and objective signs. When evaluating a patient over the phone, the clinician should ask the patient to describe any breathing problem in their own words and determine whether normal speech or activity are disrupted, or if the patient has shortness of breath at rest. Signs of deterioration should also be deliberately assessed.

Patients with mild symptoms do not need to be seen in-person and can often self-manage. Criteria to guide a decision to bring the patient to a fever / upper respiratory infection (F/URI) clinic should focus on those with temperature >101, significant cough, or lack of a good home support network. In addition, patients should be instructed to call their primary care office for further instructions if any of the below criteria in Table 3 are met.

Table 3: Criteria for patients to contact their primary care provider

Criteria for contacting your primary care provider
Trouble breathing or inability to count backwards from 8 to 1 on single breath
SpO2 values consistently at or below 94%, even in the absence of subjective trouble breathing (two readings 10 minutes apart)
Fever >101
Significant cough or ongoing pain or pressure in the chest
Respiratory rate >22 AND pulse >100
Symptoms worsening (but not to the extent of emergency criteria box above)

Patients at high risk for severe disease due to age $\geq$ 65 or comorbidities should have access to a home pulse oximeter and be instructed to take a reading twice a day for at least ten days, or longer if symptoms have not improved by that point. Objective evaluation of SpO2 is important, as hypoxia is commonly proportionally worse than clinical signs suggest. It is also reasonable to put in place telehealth follow up calls for all patients with dyspnea, aged 65+, or who have one or more risk factors on the list in Figure 2. Supervised recovery shelters should also be considered for at-risk patients without sufficient social support, if available locally. It should be noted that patients with mild hypoxia who have been evaluated and considered stable can expect some improvement in respiratory function by resting in a prone position.

Adverse hospital outcomes can be minimized by ensuring early admission for patients showing deterioration. There are a number of scores under evaluation for structured detection of COVID-19 deterioration, including the NEWS2 score and a recently published model from the Cleveland Clinic[7]; however, at this time evidence on effectiveness of these models is still being accumulated.

Medications in the ambulatory setting

Currently there is no treatment appropriate for patients being managed in the ambulatory setting beyond supportive management with fluids, rest, and anti-inflammatories. A brief review of commonly discussed therapies follows.

Treatments

Hydroxychloroquine

Numerous trials have evaluated the effectiveness of hydroxychloroquine in both the inpatient and ambulatory settings and failed to show any benefit [8], [9], [10],[11] . It should not be used for treatment or prevention of COVID-19.

Dexamethasone

The RECOVERY trial showed improved mortality in hospitalized patients receiving dexamethasone (33% reduction in ventilated patients, 20% reduction in those on oxygen alone). There is no evidence for benefit in patients with mild to moderate illness not requiring oxygen or other respiratory support.

Tricor / Fenofibrate

An in-vitro study has suggested that lipid metabolism activation properties of fenofibrate could reverse SARS-CoV-2's tendency to create lipid deposits in lung tissue and prevent more serious lung complications. No in-human observational data has yet been shown to support this theory, although researchers at Optum and UHG (and other researchers elsewhere) are actively evaluating observational data for any evidence of effect. At this time treatment with fenofibrate is not recommended for this purpose.

Colchicine

Colchicine is a powerful anti-inflammatory agent and has been used with some success to treat recurrent pericarditis[12] and to reduce the frequency of major adverse events after acute MI[13]. A single open-label randomized control trial of colchicine versus usual care in 105 patients showed significant reduction in clinical deterioration in the colchicine group and lower D-dimer levels, suggesting a possible anti-thrombotic effect[14]. Several larger trials investigating the role of colchicine in treatment of COVID-19 are ongoing – at this time we do not recommend its use for preventing complications of COVID-19.

Famotidine

It has been hypothesized that the antihistamine action of famotidine could help mitigate the effects of cytokine storm and potentially have a direct inhibitory effect on viral replication. An observational study comparing COVID-19 inpatient who did and did not receive IV famotidine during their hospitalization observed lower rates of intubation and death in patients receiving famotidine[15]. There are several prospective trials underway to further investigate the impact of famotidine – at this time we do not recommend its use in the treatment of COVID-19.

Prevention

Measles-mumps-rubella (MMR) and BCG-tuberculosis Vaccines

Live-attenuated vaccines have long been known to produce transient non-specific immune stimulation that can protect against infection by agents not covered by the specific vaccine. The MMR and BCG vaccines have been previously observed to produce this effect and there is observational evidence suggesting that individuals living in regions with routine MMR vaccination have lower COVID-19 mortality rates. Several randomized clinical trials are currently underway to test effectiveness of these vaccines in COVID-19. Unless new evidence emerges, we do not recommend these vaccines for treatment or prevention of COVID-19.

Vitamin D and C supplementation

A significant meta-analysis has shown Vitamin D supplementation to be protective against acute respiratory tract infection, with particular benefit for those who were deficient prior to treatment[16]. It is unclear whether this effect extends to COVID-19. Observations have correlated worse COVID-19 mortality to countries with more widespread Vitamin D deficiency[17] and while provocative, are not sufficient to recommend Vitamin D supplementation at this time. However, it is appropriate to consider treatment of patients who are deficient per usual protocols.

At this time the data in support for vitamin C as prevention or treatment for COVID-19 is sparse.

Zinc

Zinc gluconate has been shown to meaningfully reduce common cold symptom duration through a mechanism that may involve interference with various stages of the viral life cycle[18]. To date only one favorable very small case series (4 patients) reporting on the use of zinc to treat outpatients has been published[19], but further research is ongoing. It should be noted that therapeutic levels of zinc (e.g. 75mg/day or higher) can impair taste and smell, an important factor to consider given this mimics an important distinctive symptom of COVID-19.

Complications of COVID-19

Most complications of COVID-19 infection occur in patients with severe enough disease to require hospitalization. The following briefly reviews some more common complications.

Hypercoagulability

Most studies describing hypercoagulability in COVID-19 patients have focused on those in hospital or ICU settings. The typical laboratory findings include elevated D-dimer, high fibrinogen and high factor VIII activity. The typical clinical manifestation is thrombosis and the prevalence appear to correlate highly with COVID-19 disease severity. Venous thromboembolism has been noted in 20-69% of ICU patients[20], in 3-21% of non-ICU inpatients[21] and in outpatients as well, although no studies are yet available to estimate prevalence in ambulatory patients. Stroke and myocardial infarction have also been noted, with an overall incidence (including both ambulatory and inpatient) of 1.6% and 8.9%, respectively[22].

We do not recommend routine coagulation testing or prophylactic anticoagulation for outpatients because there is not yet good evidence that the preventive benefit outweighs the bleeding risks. This recommendation extends to antiplatelet therapy.

It may be appropriate to offer prophylactic anticoagulation to select COVID-19 positive outpatients with known thrombotic risk factors, for example in patients with a prior VTE or those recovering from prior surgery. In all patients there should be high index of suspicion for clinical manifestations of clotting including DVT, PE, MI, and stroke and relevant clinical findings should be worked up in the usual manner. Treatment of documented findings in ambulatory COVID-19 patients should be carried out in the usual manner.

Cardiac inflammation and arrhythmia

Accumulated epidemiological data suggests a low rate of new onset arrhythmia or conduction disorder due to COVID-19, with most occurring in patients admitted to the hospital[23], [24]. Patients with COVID-19 can have sustained evidence of myocardial inflammation, including raised native T1

and T2 signals on cardiac MRI up to several months following apparent resolution of other symptoms[25]. The clinical significance of these findings is not yet known.

It is reasonable to perform an ECG during a clinic visit for COVID-19 to establish a baseline to help evaluate future myocardial infarction or other cardiac injury. Continuous ECG monitoring in the ambulatory setting is not recommended.

Neurologic

Significant neurologic complications of COVID-19 include anosmia and dysgeusia (40-80% of patients)[26], encephalopathy (uncommon in ambulatory patients, but present in up to 2/3rds of patients with ARDS)[27], stroke (<1% to 6%, depending on disease severity)[28], and Guillian-Barre Syndrome (GBS) (<0.5% in hospitalized patients)[29].

Dysfunction of taste and smell is transitory and usually resolves spontaneously within a few weeks. Confusion and other alterations of mental status are indications for admission and evaluation in the inpatient setting. Reported cases of GBS developed simultaneously with other symptoms and were characterized by rapid, progressive limb weakness and a high rate of respiratory failure. Patients with suspected GBS should be promptly admitted for evaluation and supportive management.

Patients with cancer

Evidence is accumulating that COVID-19 prevalence is higher in patients with cancer[30], and that these patients are at higher likelihood for severe disease, particularly those with hematologic and lung cancers[31], [32]. Data from two large cancer and COVID-19 registries suggests active anti-cancer treatment does not worsen COVID-19 disease course[33], [34].

In addition to the usual indications, it is reasonable to administer an RNA COVID-19 test to cancer patients who have had confirmed COVID-19 contact (5-7 days after that contact), those being admitted for elective procedures, and prior to immunosuppressive therapy[35]. Decisions about continuing, discontinuing or delaying anti-cancer therapy in cancer patients with COVID-19 should be handled by the oncologist following local protocols which vary by institution. Otherwise the ambulatory management strategy for those with COVID-19 infection should not differ from the approach used in patients without cancer.

End of life planning

Because so many hospitalized elderly patients do poorly, end-of-life discussions and advanced directives should be addressed early in the disease course, if not already in place. If possible, elderly or other high-risk patients diagnosed with COVID-19 should be prioritized by existing palliative care programming to help address these questions before patients become hospitalized.

Resolution

Patients with mild disease usually recover completely within two weeks. However, patients with moderate to severe disease can see symptoms like headache, fatigue, and dyspnea linger for months, not unlike the prolonged recovery course seen for ambulatory pneumonias.

Post discharge management

Quarantine requirements

Discharged patients should be considered infectious and continue to isolate for at least ten days following symptom onset AND 24 hours since last fever without antipyretics AND improvement of symptoms. Patients with more severe illness (hospitalization) or those that are immunosuppressed should continue to isolate for at least twenty days following symptom onset AND 24 hours since last fever without antipyretics AND significant improvement of symptoms.

Follow up requirements

Management post-discharge should focus on ensuring the patient maintains a stable recovery and vigilantly watching for sequelae such as venous thromboembolism (VTE), myocardial infarction, and decompensation of pre-existing chronic illness. All discharged COVID-19 patients should receive face-to-face or telehealth follow-up, ideally within 24-48 hours of discharge. Patients sent home on supplemental oxygen should be monitored particularly closely.

Medical, surgical and obstetrical COVID-19 patients typically receive VTE prophylaxis with LMW heparin upon admission. All patients discharged with documented VTE should receive three months of anticoagulation, typically with a factor Xa inhibitor like rivaroxaban. It is also reasonable to extend prophylaxis for patients at continued high risk of coagulation issues because of age, prolonged immobility during recovery, and those who underwent surgery during hospitalization.

Long-term sequelae

Reliable information about long-term issues with COVID-19 are largely lacking given our current time-course in this pandemic. Patients with COVID-19 precipitated ICU stays may experience post-intensive care syndrome, which is characterized by global decline in physical, cognitive, and psychiatric function. They may also suffer from critical care neuromyopathy due to the long intubation times typical of COVID-19 ICU trajectories. In addition, long-term lung restriction and reduction in diffusion capacity has been noted in patients experiencing both mild and severe pneumonias[36].

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