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INTRODUCTION

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in a global pandemic. The disease is designated COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV.

This topic will discuss the management of COVID-19 in hospitalized adults. Our approach to hospital management is based on limited data and evolves rapidly as clinical data emerge. Clinicians should consult their own local protocols for management, which may differ from our approach. Interim guidance has been issued by the World Health Organization and, in the United States, by the Centers for Disease Control and Prevention [2,3] and the National Institutes of Health COVID-19 Treatment Guidelines Panel [4]. Links to these and other related society guidelines are found elsewhere. (See 'Society guideline links' below.)

The management of patients with COVID-19 in the home and outpatient setting is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults".)

The epidemiology, clinical features, diagnosis, and prevention of COVID-19 are discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features,

diagnosis, and prevention" and "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings".)

Issues related to COVID-19 in specific populations are discussed elsewhere:

- (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues".)
- (See "Coronavirus disease 2019 (COVID-19): Pregnancy issues".)
- (See "Coronavirus disease 2019 (COVID-19): Considerations in children".)
- (See "Coronavirus disease 2019 (COVID-19): Cancer care during the pandemic".)
- (See "Coronavirus disease 2019 (COVID-19): Issues related to kidney disease and hypertension".)

Community-acquired coronaviruses, severe acute respiratory syndrome (SARS) coronavirus, and Middle East respiratory syndrome (MERS) coronavirus are discussed separately. (See "Coronaviruses" and "Severe acute respiratory syndrome (SARS)" and "Middle East respiratory syndrome coronavirus: Virology, pathogenesis, and epidemiology".)

EVALUATION

Our objective in the evaluation of hospitalized patients with documented or suspected COVID-19 is to evaluate for features associated with severe illness (table 1) and identify organ dysfunction or other comorbidities that could complicate potential therapy. The diagnosis of COVID-19 is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Diagnosis'.)

Although we check several laboratory tests to evaluate patients with documented or suspected COVID-19, the prognostic value of many of them remains uncertain, and other institutions may not include all these tests.

At least initially, we check the following laboratory studies daily:

- Complete blood count (CBC) with differential, with a focus on the total lymphocyte count trend
- Complete metabolic panel
- Creatine kinase (CK)
- C-reactive protein (CRP)
- Ferritin

Initially, we check the following studies every other day (or daily if elevated or in the intensive care unit):

- Prothrombin time (PT)/partial prothrombin time (PTT)/fibrinogen
- D-dimer

We check the following studies at baseline and repeat them if abnormal or with clinical worsening:

- Lactate dehydrogenase, repeated daily if elevated
- Troponin, repeated every two to three days if elevated
- Electrocardiogram (ECG), with at least one repeat test after starting any QTc-prolonging agent (see "Coronavirus disease 2019 (COVID-19): Arrhythmias and conduction system disease", section on 'Monitoring for QT prolongation')

We also check hepatitis B virus serologies, hepatitis C virus antibody, and HIV antigen/antibody testing if these have not been previously performed. Chronic viral hepatitis could affect interpretation of transaminase elevations and exacerbate hepatotoxicity of certain therapies; underlying HIV infection may change the assessment of the patient's risk for deterioration and would warrant initiation of antiretroviral therapy.

We check a portable chest radiograph in hospitalized patients with COVID-19; for most patients, this is sufficient for initial evaluation of pulmonary complications and extent of lung involvement. Although chest computed tomography (CT) was frequently used in China for evaluation of patients with COVID-19, we reserve chest CT for circumstances that might change clinical management, in part to minimize infection control issues related to transport. This is consistent with recommendations from the American College of Radiology [5]. Although certain characteristic chest CT findings may be seen in COVID-19, they cannot reliably distinguish COVID-19 from other causes of viral pneumonia. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Imaging findings'.)

We do not routinely obtain echocardiograms on patients with COVID-19; developments that might warrant an echocardiogram include increasing troponin levels with hemodynamic compromise or other cardiovascular findings suggestive of cardiomyopathy. Acute myocardial injury has been a described complication of COVID-19. (See "Coronavirus disease 2019 (COVID-19): Myocardial injury", section on 'When to suspect myocardial injury and key considerations'.)

Secondary bacterial infection has not been a frequently reported feature of COVID-19; if this is suspected (eg, based on chest imaging or sudden deterioration), we check two sets of blood cultures and sputum Gram stain and culture. Procalcitonin can be checked to assess the risk of secondary bacterial infection; however, since elevated procalcitonin levels have been reported as COVID-19 progresses, they may be less specific for bacterial infection later in the disease course [6-9].

As above, the prognostic value of the results of some of the tests we use to evaluate patients with COVID-19 is uncertain, and the optimal use of these markers remains unknown. As an example, although some clinicians also note the potential utility of troponin levels to inform the risk of severe COVID-19 and provide a baseline for comparison in patients who develop manifestations of myocardial injury [10], others reserve troponin level testing for patients who have specific clinical suspicion for acute coronary syndrome [11]. One concern is that the results could lead to unnecessary use of medical resources (eg, serial troponins, electrocardiograms and cardiology consults for elevated troponin). If troponin is checked in a patient with COVID-19, clinicians should be aware that an elevated level does not necessarily indicate acute coronary syndrome. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Myocardial injury", section on 'Troponin'.)

GENERAL MANAGEMENT ISSUES

Empiric treatment for bacterial pneumonia in select patients — For patients with documented COVID-19, we do not routinely administer empiric therapy for bacterial pneumonia. Data are limited, but bacterial superinfection does not appear to be a prominent feature of COVID-19.

However, since the clinical features of COVID-19 may be difficult to distinguish from bacterial pneumonia, empiric treatment for community-acquired pneumonia is reasonable when the diagnosis is uncertain. Empiric treatment for bacterial pneumonia may also be reasonable in patients with documented COVID-19 if there is clinical suspicion for it (eg, new fever after defervescence with new consolidation on chest imaging). If empiric antibiotic therapy is initiated, we attempt to make a microbial diagnosis (eg, through sputum Gram stain and culture, urinary antigen testing) and reevaluate the need to continue antibiotic therapy daily. In such settings, a low procalcitonin may be helpful to suggest against a bacterial pneumonia; however, elevated procalcitonin has been described in COVID-19, particularly late in the course of illness, and does not necessarily indicate bacterial infection [6-9]. (See "Procalcitonin use in lower respiratory tract infections", section on 'Guiding antibiotic therapy'.)

The diagnosis of and empiric antibiotic regimens for community-acquired and health care-associated pneumonia are discussed elsewhere. (See "Overview of community-acquired pneumonia in adults" and "Epidemiology, pathogenesis, microbiology, and diagnosis of hospital-acquired and ventilator-associated pneumonia in adults" and "Treatment of hospital-acquired and ventilator-associated pneumonia in adults".)

Prevention of and evaluation for venous thromboembolism — We favor pharmacologic prophylaxis of venous thromboembolism for all hospitalized patients with COVID-19, consistent with

recommendations from several expert societies [12-14]. Dosing and selection of pharmacologic agents to prevent venous thromboembolism in hospitalized patients with COVID-19 are discussed in detail elsewhere (algorithm 1). (See "Coronavirus disease 2019 (COVID-19): Hypercoagulability", section on 'Inpatient VTE prophylaxis'.)

Several studies suggest a high rate of thromboembolic complications among hospitalized patients with COVID-19, particularly those who are critically ill. The thromboembolic risk with COVID-19 as well as the evaluation for and management of these complications are discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Hypercoagulability", section on 'VTE' and "Coronavirus disease 2019 (COVID-19): Hypercoagulability", section on 'Indications for full-dose anticoagulation'.)

Uncertainty about NSAID use — There are minimal data informing the risks of non-steroidal anti-inflammatory drugs (NSAIDs) in the setting of COVID-19. We use acetaminophen as the preferred antipyretic agent, if possible, and if NSAIDs are needed, we use the lowest effective dose; this is consistent with the general approach to fever reduction in adults (see "Pathophysiology and treatment of fever in adults", section on 'Treating fever'). We do not discontinue NSAIDs in patients who are on them chronically for other conditions, unless there are other reasons to stop them (eg, renal injury, gastrointestinal bleeding).

Concern about possible negative effects of NSAIDs was raised by anecdotal reports of a few young patients who received NSAIDs early in the course of infection and experienced severe disease [15,16].

However, there have been no clinical or population-based data that directly address the risk of NSAIDs. Given the absence of data, the European Medicines Agency (EMA), WHO, and the United States National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel do not recommend NSAIDs be avoided when clinically indicated [4,17,18].

Avoiding nebulized medications — Inhaled medications should be administered by metered dose inhaler, whenever possible, rather than through a nebulizer, to avoid the risk of aerosolization of SARS-CoV-2 through nebulization.

If a nebulizer must be used, appropriate infection control precautions should be taken. These are discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues", section on 'Nebulized medications (spontaneously breathing patients)'.)

Limited role of glucocorticoids — We agree with recommendations by the WHO and CDC that systemic glucocorticoids **not** be used in patients with COVID-19, unless there are other indications

(eg, exacerbation of chronic obstructive pulmonary disease) [19,20].

For those without pre-existing pulmonary disease, we also avoid inhaled glucocorticoids. The use of inhaled glucocorticoids in patients with asthma or chronic obstructive pulmonary disease in the setting of COVID-19 is discussed in detail elsewhere. (See "Acute exacerbations of asthma in adults: Emergency department and inpatient management", section on 'Advice related to covid-19 pandemic' and "Stable COPD: Overview of management", section on 'Advice related to COVID-19'.)

Glucocorticoids have been associated with an increased risk for mortality in patients with influenza and delayed viral clearance in patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Although they were widely used in management of SARS, there was no good evidence for benefit, and there was persuasive evidence of adverse short- and long-term harm [21]. (See "Treatment of seasonal influenza in adults", section on 'Adjunctive therapies' and "Middle East respiratory syndrome coronavirus: Treatment and prevention", section on 'Treatment'.)

The approach to glucocorticoids among critically ill patients with COVID-19 is discussed elsewhere. (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues", section on 'Glucocorticoids'.)

Managing chronic medications

ACE inhibitors/ARBs — Patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should continue treatment with these agents if there is no other reason for discontinuation (eg, hypotension, acute kidney injury). This approach is supported by multiple guidelines panels [22-26]. There has been speculation that patients with COVID-19 who are receiving these agents may be at increased risk for adverse outcomes, but this has not been supported by findings from observational studies. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Issues related to kidney disease and hypertension", section on 'Renin angiotensin system inhibitors'.)

Conversely, ARBs have also been proposed to have potential protective effects based on their mechanism of action [27], but there is no trial evidence to support this hypothesis. We do not use ACE inhibitors or ARBs as potential COVID-19 treatment.

Statins — We make a point of continuing statins in hospitalized patients with COVID-19 who are already taking them. A high proportion of patients with severe COVID-19 have underlying cardiovascular disease, diabetes mellitus, and other indications for use of statins. Moreover, acute cardiac injury is a reported complication of COVID-19. Although clinicians may be concerned about hepatotoxicity from statins, particularly since transaminase elevations are common in COVID-19,

most evidence indicates that liver injury from statins is uncommon. (See "Statins: Actions, side effects, and administration", section on 'Hepatic dysfunction'.)

Whether statins could impact the natural history of SARS-CoV-2 infection is not clear. Statins are known inhibitors of the MYD88 pathway, which results in marked inflammation, and have been reported to stabilize MYD88 levels in the setting of external stress in vitro and in animal studies [28]. Dysregulation of MYD88 has been noted and associated with poor outcomes in SARS-CoV and MERS-CoV infections, but this has not been described with SARS-CoV-2. Although statins might be of benefit in patients with COVID-19, more data are needed.

Immunomodulatory agents — Use of immunosuppressing agents has been associated with increased risk for severe disease with other respiratory viruses, and the decision to discontinue prednisone, biologics, or other immunosuppressive drugs in the setting of COVID-19 must be determined on a case-by-case basis. (See "Coronavirus disease 2019 (COVID-19): Cancer care during the pandemic", section on 'Patients with COVID-19 symptoms or a known COVID-19 exposure' and "Coronavirus disease 2019 (COVID-19): Issues related to solid organ transplantation", section on 'Adjusting immunosuppression'.)

For individuals with underlying conditions who require treatment with these agents and **do not** have suspected or documented COVID-19, there is no evidence that routinely discontinuing treatment is of any benefit. In addition, discontinuing these medications may result in loss of response when the agent is reintroduced. The approach of continuing immunomodulatory therapy in patients without infection is supported by statements from dermatology, rheumatology, and gastroenterology societies [29-32].

Infection control — Infection control is an essential component of management of patients with suspected or documented COVID-19. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Patients with suspected or confirmed COVID-19'.)

COVID-19-SPECIFIC THERAPY

Specific treatments — Several treatments are being evaluated for COVID-19. Although some of these treatments are clinically available for other indications, their use for COVID-19 remains investigational.

Remdesivir — Remdesivir is a novel nucleotide analogue that has activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro [33]. In the United States, the Food and Drug Administration (FDA) has issued an emergency use authorization for remdesivir for

hospitalized children and adults with severe COVID-19 (SpO_2 ≤94 percent on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]) [34]. The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 10 days total in patients on mechanical ventilation or ECMO and 5 days total in other patients (with extension to 10 days if there is no clinical improvement). Remdesivir is not recommended in patients with an alanine aminotransferase ≥5 times the upper limit of normal (and should be discontinued if it rises above this level during treatment or if there are other signs of liver injury). The pharmacokinetics of remdesivir in the setting of renal impairment are uncertain, and it is prepared in a cyclodextrin vehicle that accumulates in renal impairment and may be toxic; thus, remdesivir is not recommended in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 unless the potential benefit outweighs the potential risk.

Data from comparative, randomized trials are needed to define the effect of remdesivir in COVID-19; these data are emerging but remain limited and mixed. Overall, if preliminary results are confirmed, there is likely some clinical benefit to remdesivir, although the patient population most likely to benefit remains uncertain.

The United States National Institute of Allergy and Infectious Diseases announced preliminary results of a multinational, randomized, placebo-controlled trial of remdesivir among 1063 patients with confirmed COVID-19 and evidence of lung involvement [35]. On interim analysis, remdesivir resulted in a faster time to recovery, defined as being discharged from the hospital or no longer requiring supplemental oxygen (median 11 versus 15 days with placebo, p<0.001). There was also a trend towards lower mortality that was not statistically significant (8 versus 11.6 percent with placebo, p = 0.059). Final analysis and peer review of these data are pending.

In contrast, in a double-blind randomized trial in China of 237 patients with severe COVID-19 (hypoxia and radiographically confirmed pneumonia), time to clinical improvement was not statistically different with remdesivir compared with placebo for 10 days (median 21 versus 23 days; hazard ratio for improvement 1.23 [95% CI 0.87-1.75]) [36]. Clinical improvement was defined as discharge from the hospital or a two-point improvement on a six-point clinical score that ranges from death to mechanical ventilation to lower levels of oxygen support to discharge. This study only included one patient who was on mechanical ventilation at baseline. Mortality at 28 days was also similar with remdesivir or placebo (14 versus 13 percent); there was also no difference in time to viral clearance. Among patients who had received treatment within 10 days of symptom onset, there were trends towards lower mortality and more rapid clinical improvement with remdesivir, but these differences were not statistically significant. Remdesivir was stopped early because of adverse events (including gastrointestinal symptoms, aminotransferase or bilirubin elevations, and worsened cardiopulmonary status) in 12 percent, compared with 5 percent in the placebo group. Several limitations reduce confidence in the finding of no effect; concomitant therapies (lopinavir-ritonavir,

interferon alpha-2b, and/or corticosteroids) were used by most study participants, patients in the remdesivir group had a higher proportion of comorbidities (hypertension, diabetes mellitus, and coronary heart disease), and the study was stopped early for poor enrollment (the target enrollment pre-determined to demonstrate effect was 435 patients).

Early data suggest that 5 days of remdesivir result in similar outcomes as 10. In a preliminary report from the manufacturer of a randomized, open-label trial among nearly 400 patients with severe COVID-19 who were not on mechanical ventilation, the rates of clinical recovery and discharge by day 14 were not statistically different when remdesivir was given for 5 days (65 and 60 percent, respectively) versus 10 days (54 and 52 percent, respectively) [37]. Mortality rates at day 14 were 8 and 11 percent with 5 and 10 days of treatment, respectively, and varied by geographic location.

Use of remdesivir has also been described in several case series [38-40]. In one multicenter, multinational series, 53 patients with severe COVID-19 and hypoxia received compassionate-use remdesivir for up to 10 days and had a median of 18 days of follow-up; 68 percent had clinical improvement (decreased requirement for oxygen support or hospital discharge), and 13 percent died [40]. Of the 30 patients who were mechanically ventilated at baseline, 17 (57 percent) were extubated, and three of four patients on extracorporeal membrane oxygenation (ECMO) were taken off it.

Reported side effects include nausea, vomiting, and transaminase elevations. In a preliminary report from a trial of remdesivir among patients with severe COVID-19, grade 3 aminotransferase elevations occurred in 7 percent and led to drug discontinuation in 3 percent [37]. Other adverse events described in patients who received remdesivir include worsening kidney injury, multiple organ failure, and worsened cardiopulmonary status [36,40].

Convalescent plasma — In the United States, the FDA is accepting investigational new drug applications for use of convalescent plasma for patients with severe or life-threatening COVID-19 [41]; pathways for use through these applications include clinical trials, expanded access programs, and emergency individual use. Use of convalescent plasma has been described in case series [42-44]. One case series described administration of plasma from donors who had completely recovered from COVID-19 to five patients with severe COVID-19 on mechanical ventilation and persistently high viral titers despite investigational antiviral treatment [42]. The patients had decreased nasopharyngeal viral load, decreased disease severity score, and improved oxygenation by 12 days after transfusion. However, these findings do not establish a causal effect, and the efficacy of convalescent plasma remains unknown. In another case series of six patients who received convalescent plasma late in the course of illness, five died despite SARS-CoV-2 viral clearance within three days of treatment [44]. Finding appropriate donors and establishing testing to confirm neutralizing activity of plasma may be logistical challenges. In the United States, the

American Red Cross is helping to collect and distribute convalescent plasma throughout the country [45]. (See "Clinical use of plasma components", section on 'Convalescent plasma'.)

The FDA is also facilitating the evaluation of hyperimmune globulin for patients with COVID-19 [45].

IL-6 pathway inhibitors — Markedly elevated inflammatory markers (eg, D-dimer, ferritin) and elevated pro-inflammatory cytokines (including interleukin [IL]-6) are associated with critical and fatal COVID-19, and blocking the inflammatory pathway has been hypothesized to prevent disease progression. Tocilizumab is an IL-6 receptor inhibitor used for rheumatic diseases and cytokine release syndrome and is being evaluated in randomized trials for treatment of COVID-19. Case reports and observational studies have described use of tocilizumab in patients with COVID-19 [46-53]. As an example, in a study of 63 patients with severe COVID-19 who had laboratory results suggesting a pro-inflammatory and pro-thrombotic state, no major adverse events were thought to be directly related to tocilizumab (given intravenously or subcutaneously), which was associated with a decrease in C-reactive protein, D-dimer, and ferritin levels; overall, there was a 14-day mortality rate of 11 percent [51].

Sarilumab and siltuximab are other agents that target the IL-6 pathway and are also being evaluated in clinical trials.

Hydroxychloroquine/chloroquine — There are insufficient data thus far to know whether hydroxychloroquine **or** chloroquine **has a role in treatment of COVID-19. For this reason, we strongly recommend that patients should be referred to a clinical trial whenever possible.** In the United States, the FDA has issued an emergency use authorization to allow the use of these agents in adolescents or adults hospitalized for COVID-19 when participation in clinical trials is not feasible [54]. When a clinical trial is not available, we suggest not routinely using hydroxychloroquine or chloroquine given the lack of clear benefit from limited data and potential for toxicity. If drugs are used for COVID-19 outside a clinical trial, the Infectious Diseases Society of America (IDSA) encourages creation of a registry, when possible, to systematically evaluate their safety and efficacy [55].

Additionally, if hydroxychloroquine or chloroquine is used outside of a clinical trial, the potential for adverse effects should be carefully assessed. In particular, these agents can prolong the QT interval and should be avoided in patients with prolonged baseline QTc interval or on other agents that affect cardiac conduction, and otherwise should be used with close monitoring. The American College of Cardiology has suggested QTc monitoring parameters in this setting [56]. QTc monitoring in this setting is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Arrhythmias and conduction system disease", section on 'Monitoring for QT prolongation'.)

Other risks (eg, retinopathy or cardiomyopathy) are primarily with longer-term use and higher cumulative doses, but should be a consideration when deciding to use these agents. Catastrophic outcomes have been reported with hydroxychloroquine or chloroquine overdose; no individual should use these medications without medical supervision [57,58]. (See "Antimalarial drugs in the treatment of rheumatic disease", section on 'Adverse effects'.)

Both chloroquine and hydroxychloroquine have been reported to inhibit SARS-CoV-2 in vitro, although hydroxychloroquine appears to have more potent antiviral activity [59]. Randomized trials evaluating their clinical use are underway. However, published clinical data on either of these agents are limited, have methodologic problems, and do not suggest a clear benefit [60-65]. In an open-label randomized trial of 150 hospitalized patients with mild to moderate COVID-19 (either no pneumonia or pneumonia without hypoxia), adding hydroxychloroquine to standard of care did not improve the rate of SARS-CoV-2 clearance (84 versus 81 percent with standard of care alone) or result in symptomatic improvement (60 versus 66 percent) by 28 days [64]. Methodologic concerns with this trial include concomitant co-therapies, baseline differences between the groups, and lack of blinding or placebo control.

Available evidence does not suggest a benefit for patients with severe COVID-19, although data in this population are limited to observational studies. In an observational study of nearly 1400 patients with COVID-19 admitted to a hospital in New York, hydroxychloroquine use was reported in 811 patients and was associated with a higher risk of intubation or death (hazard ratio [HR] 2.37) [62]. Patients who received hydroxychloroquine were older, were more likely to have comorbidities, and had more severe illness than those who did not, which were likely confounding variables; in a multivariate analysis comparing those patients with a propensity score-matched subset of 274 patients who did not receive hydroxychloroquine, there was no association between hydroxychloroquine use and intubation or death (adjusted HR 1.04). In another observational study from France of 180 patients with severe COVID-19 who required oxygen supplementation but not critical care, the rates of transfer to the intensive care unit or death were similar among those who did and did not receive hydroxychloroquine [65].

Studies have, however, highlighted the potential for toxicity of hydroxychloroquine or chloroquine. One trial comparing two doses of chloroquine for COVID-19 was stopped early because of a higher mortality rate in the high-dose group [66]. In an observational study in which 84 patients received hydroxychloroquine, 10 percent had electrocardiographic changes that prompted discontinuation [65]. QTc prolongation with hydroxychloroquine and chloroquine are discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Arrhythmias and conduction system disease", section on 'Patients receiving QT-prolonging treatments (eg, hydroxychloroquine, chloroquine, azithromycin, etc)'.)

The evidence on the combination of hydroxychloroquine and azithromycin is discussed elsewhere. (See 'Others' below.)

Others — Many other agents with known or putative antiviral or immunomodulating effects have been proposed for use in patients with COVID-19 [67-71], and some are in preclinical or clinical evaluation. Use of these agents for COVID-19 should be limited to clinical trials; their efficacy has not been proven, and extensive off-label use may result in excess toxicity and critical shortages of drugs for proven indications. A registry of international clinical trials can be found at covid-trials.org, as well as on the WHO website and at clinicaltrials.gov.

- **Favipiravir** – Favipiravir is an RNA polymerase inhibitor that is available in some Asian countries for treatment of influenza, and it is being evaluated in clinical trials for treatment of COVID-19 in the United States. In a study of patients with non-severe disease (including oxygen saturation >93 percent), use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days) and more frequent radiographic improvement (in 91 versus 62 percent by day 14) compared with lopinavir-ritonavir [72]. However, other therapies were administered in this non-randomized, open-label study, so the results should be interpreted with caution given potential confounders.

- **Interferon beta** – Interest in interferon beta for SARS-CoV-2 was spurred by evidence suggesting in vitro activity against Middle East respiratory syndrome coronavirus (MERS-CoV) and good outcomes in an animal model of MERS-CoV infection [73-75]. In one open-label randomized trial from Hong Kong, 127 adults hospitalized with primarily nonsevere COVID-19 were randomly assigned 2:1 to a combination intervention (interferon beta, ribavirin, plus lopinavir-ritonavir if symptom onset was within 7 days or ribavirin plus lopinavir-ritonavir if symptom onset was between 7 to 14 days) versus control (lopinavir-ritonavir alone) [76]. Patients in the intervention group had more rapid times to a negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab (median 7 versus 12 days), clinical improvement (median 4 versus 8 days), and hospital discharge (median 9 versus 15 days); in a subgroup analysis, the differences were only observed among patients with symptom onset within 7 days who thus received interferon beta as part of the intervention. Adverse effects were similar between the intervention and control groups. No hemolysis was detected with ribavirin (400 mg orally twice daily). Further study is needed to clarify the role of interferon beta in COVID-19 therapy.

- **Other immunomodulatory agents** – Because of the observation that some patients have a clinical presentation that resembles cytokine release syndrome and the association between severe disease and a number of pro-inflammatory markers, interrupting the inflammatory cascade has been proposed as a potential therapeutic target for severe COVID-19. In addition

to IL-6 pathway inhibitors (see 'IL-6 pathway inhibitors' above), immunomodulatory agents from various classes, including IL-1 inhibitors, kinase inhibitors, and complement inhibitors, are being evaluated. Their use has been described in case series and other observational studies [68,77-80]. As an example, in a retrospective study of patients with COVID-19, acute respiratory distress syndrome (ARDS) requiring non-invasive ventilation, and markedly elevated C-reactive protein (CRP) or ferritin, receipt of high-dose anakinra in 29 patients (in addition to hydroxychloroquine and lopinavir-ritonavir) was associated with a lower 21-day mortality rate compared with a historical cohort of 16 patients who received only hydroxychloroquine and lopinavir-ritonavir (10 versus 44 percent); however, the historical group was older, and the likelihood of other, unmeasured confounders makes the findings difficult to interpret [77]. Results of randomized trials are necessary to determine the effect of these agents.

- **Azithromycin and hydroxychloroquine** – We do not use azithromycin in combination with hydroxychloroquine for treating COVID-19. Use of the combination has been described in observational studies [60,63,81,82]. Although one study suggested the use of azithromycin in combination with hydroxychloroquine was associated with more rapid resolution of virus detection than hydroxychloroquine alone [60], this result should be interpreted with caution because of the small sample size, substantial methodologic concerns [83], and unclear biologic plausibility. Another small observational study in patients with more severe illness did not suggest rapid viral RNA clearance with the combination [81]. Furthermore, both azithromycin and hydroxychloroquine are associated with QTc prolongation, and combined use may potentiate this adverse effect. In a large observational study of patients hospitalized with COVID-19 in New York, the adjusted mortality rate among those who received azithromycin plus hydroxychloroquine was similar compared with those who received neither agent, but the rate of cardiac arrest was higher [63].

- **Lopinavir-ritonavir** – This combined protease inhibitor, which has primarily been used for HIV infection, has in vitro activity against the SARS-CoV [84] and appears to have some activity against MERS-CoV in animal studies [73]. However, lopinavir-ritonavir appears to have minimal to no role in the treatment of SARS-CoV-2 infection outside of a clinical trial. The WHO has launched a multinational trial to further evaluate remdesivir, hydroxychloroquine/chloroquine, and lopinavir-ritonavir with and without interferon beta [85].

  Results from a randomized trial do not demonstrate a clear benefit of lopinavir-ritonavir. In a randomized trial of 199 patients with severe COVID-19, the addition of lopinavir-ritonavir (400/100 mg) twice daily for 14 days to standard care did not decrease the time to clinical improvement compared with standard care alone [86]. There was a trend towards decreased mortality with lopinavir-ritonavir (19 versus 25 percent), and the numerical difference in

mortality was greater among those who were randomized within 12 days of symptom onset, but neither difference was statistically significant. The rate of SARS-CoV-2 decline was similar in the group that received lopinavir-ritonavir and the group that did not. Lopinavir-ritonavir was stopped early in 14 percent because of adverse effects.

If lopinavir-ritonavir is used, the patient's HIV status should be known. If the patient has HIV, lopinavir-ritonavir should be used as a standard combination antiretroviral regimen.

Approach — The optimal approach to treatment of COVID-19 is uncertain. Although some trial data suggest a benefit with remdesivir, these data are very preliminary and have not been formally peer reviewed or reported, and there are otherwise no therapies that have clearly proven effective; for most potential therapies, evidence for their use comes primarily from observational case series and anecdotal use based on in vitro or extrapolated indirect evidence.

Thus, when available, we strongly recommend enrollment into a well-controlled clinical trial. Our approach is consistent with recommendations from expert groups in the United States. The IDSA recommends that COVID-19-specific therapy be given in the context of a clinical trial and additionally recommends certain therapies (including hydroxychloroquine plus azithromycin, lopinavir-ritonavir, and tocilizumab) only be administered in the context of a clinical trial because of a greater level of uncertainty or potential for toxicity [55]. Similarly, the NIH COVID-19 Treatment Guidelines Panel notes there is insufficient evidence to recommend for or against any antiviral or immune-based therapy and specifically recommends against using certain therapies (including hydroxychloroquine plus azithromycin, HIV protease inhibitors, interferons, and Janus kinase inhibitors) outside the context of a clinical trial [4].

A registry of international clinical trials can be found at covid-trials.org, as well as on the WHO website and at clinicaltrials.gov.

We use a risk-based approach to try to enroll those patients who may be most likely to benefit. The approach is dependent on local availability of clinical trials and may not be universally applicable. Clinicians should consult their own local protocols for management.

Defining disease severity — Mild disease is characterized by fever, malaise, cough, upper respiratory symptoms, and/or less common features of COVID-19, in the absence of dyspnea. Most of these patients do not need hospitalization.

If patients develop dyspnea, that raises concern that they have at least moderate severity disease, and these patients often warrant hospitalization. Patients can have infiltrates on chest imaging and still be considered to have moderate disease, but the presence of any of the following features indicates severe disease:

- Hypoxia (oxygen saturation ≤93 percent on room air or PaO_2/FiO_2 <300 mmHg)
- Tachypnea (respiratory rate >30 breaths per minute) or respiratory distress
- More than 50 percent involvement of the lung parenchyma on chest imaging

These features were used in China to characterize severe disease in a large cohort of patients [87] and are consistent with the United States NIH COVID-19 Treatment Guidelines Panel definition of severe infection [4].

We also treat patients who have certain laboratory abnormalities (table 1) similar to patients who have severe disease, because these abnormalities have been associated with disease progression in several studies.

Nonsevere disease — For most patients with nonsevere disease, we suggest supportive care only, with close monitoring for clinical worsening. If they develop features of severe disease (eg, hypoxia, tachypnea, or respiratory distress (see 'Defining disease severity' above)), or if they have any laboratory features associated with disease progression (table 1), we treat them as described below. (See 'Severe (including critical) disease' below.)

Some clinical trials may be available for patients with nonsevere disease. If so, we prioritize patients who have epidemiologic risk factors associated with development of severe illness (table 2). We generally do not treat patients with nonsevere disease with experimental agents outside the context of a clinical trial.

Severe (including critical) disease — We prioritize COVID-19-specific therapy for hospitalized patients who have severe disease or laboratory risk factors for disease progression (table 1).

For hospitalized patients with severe COVID-19, we recommend remdesivir, if available. In the United States, remdesivir can be obtained through the FDA's emergency use authorization, although availability is limited to hospitals designated for distribution by the federal government [88]. For pregnant individuals, remdesivir may also be obtained through a compassionate use program. (See 'Remdesivir' above.)

For patients with severe disease or laboratory risk factors for disease progression (table 1) who cannot get remdesivir through these routes, we recommend referral to a clinical trial for treatment. We also refer patients who are able to get remdesivir through emergency use authorization to clinical trials for other agents, if they allow concurrent use of remdesivir. In addition to remdesivir, therapies being evaluated in trials include convalescent plasma and hydroxychloroquine. Patients who have features similar to cytokine release syndrome (eg, persistent fevers with elevated cytokine levels, ferritin, D-dimer, and/or other inflammatory markers) may also be eligible for clinical trials of IL-6 pathway inhibitors or other immunomodulators. A registry of international clinical trials

can be found at covid-trials.org. Detailed discussion of these agents is found elsewhere. (See 'Specific treatments' above.)

If neither a clinical trial nor emergency-use remdesivir is an option, clinicians may be able to obtain convalescent plasma for investigational treatment of COVID-19; in the United States, this may be accessed through the FDA's investigational new drug application or expanded access program [41]. (See 'Convalescent plasma' above.)

Although treatment is hypothesized to have greater impact when given early in the course of disease, the optimal timing for implementation of any of these therapies remains unknown. Until more data are available, it is uncertain which patients would benefit the most and how to best allocate potentially limited clinical trial slots or emergency use agents.

Several agents being investigated for treatment of COVID-19 are available for other medical indications, and repurposed use for COVID-19 has been described. There are insufficient data to know whether these agents have any role in treatment of COVID-19; thus, **we strongly recommend that patients be referred to a clinical trial whenever possible**.

When a clinical trial is not an option and remdesivir or convalescent plasma cannot be obtained, we favor supportive care rather than off-label use of available agents with unknown efficacy for COVID-19. In particular, we suggest not routinely using hydroxychloroquine or chloroquine outside of a clinical trial; limited available data do not suggest a clear benefit and do suggest the potential for toxicity. However, we acknowledge that, in the absence of other options, some clinicians may choose to use certain agents (eg, hydroxychloroquine, or IL-6 pathway inhibitors in patients with evidence of a severe pro-inflammatory state) for severely ill patients. If drugs are used for COVID-19 outside a clinical trial, the IDSA encourages creation of a registry to systematically evaluate their safety and efficacy [55].

MANAGEMENT OF HYPOXIA, ARDS, AND OTHER COMPLICATIONS

Patients with severe disease often need oxygenation support. High-flow oxygen and noninvasive positive-pressure ventilation have been used, but the safety of these measures is uncertain, and they should be considered aerosol-generating procedures that warrant specific isolation precautions. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues", section on 'Respiratory care of the nonintubated patient'.)

Some patients may develop acute respiratory distress syndrome (ARDS) and warrant intubation with mechanical ventilation. Management of ARDS in patients with COVID-19 and other critical care

issues are discussed in detail elsewhere (table 3). (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues".)

In addition to ARDS, other complications of infection include arrhythmias, acute cardiac injury, acute kidney injury, thromboembolic events, and shock. Management of these complications is discussed elsewhere.

- (See "Coronavirus disease 2019 (COVID-19): Arrhythmias and conduction system disease".)
- (See "Coronavirus disease 2019 (COVID-19): Myocardial injury".)
- (See "Coronavirus disease 2019 (COVID-19): Issues related to kidney disease and hypertension", section on 'Acute kidney injury'.)
- (See "Coronavirus disease 2019 (COVID-19): Hypercoagulability".)

DISCHARGE

The decision to discharge a patient with COVID-19 is generally the same as that for other conditions and depends on the need for hospital-level care and monitoring.

Continued need for infection control precautions should not prevent discharge home if the patient can appropriately self-isolate there; long-term care facilities may have specific requirements prior to accepting patients with COVID-19. Criteria for discontinuing precautions and infection control issues in long-term care facilities are discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Discontinuation of precautions' and "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Long-term care facilities'.)

Patients with COVID-19 generally warrant outpatient follow-up through telehealth or an in-person visit following discharge from the hospital. (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults", section on 'Outpatient management following inpatient or ED discharge'.)

We encourage patients who have recovered from COVID-19 to consider donating convalescent plasma. Interested patients can be referred to their community blood center or, in the United States, to the American Red Cross to determine whether they meet eligibility criteria for donation. (See "Clinical use of plasma components", section on 'COVID-19 pandemic'.)

INSTITUTIONAL PROTOCOLS

Several academic medical institutions in the United States have developed COVID-19 management protocols that are publicly available. Given the paucity of high-quality clinical evidence on the

management of COVID-19, the safety and efficacy of these strategies are uncertain:

- Brigham and Women's Hospital
- Massachusetts General Hospital
- Michigan Medicine
- Nebraska Medicine
- Penn Medicine
- University of Washington Medicine

Partners in Health has also released resources for clinicians and organizations in resource-limited settings.

SPECIAL SITUATIONS

Pregnant and breastfeeding women — The management of pregnant and breastfeeding women with COVID-19 is discussed elsewhere. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Pregnant and breastfeeding women'.)

People with HIV — Data on the impact of HIV infection on the natural history of COVID-19 are limited [89,90]. However, many of the comorbid conditions associated with severe COVID-19 (eg, cardiovascular disease) occur frequently among patients with HIV, and these, in addition to CD4 cell count, should be considered in risk stratification. Additionally, drug interactions with antiretroviral agents are important to assess before starting any new therapies. Otherwise, the management of COVID-19 in patients with HIV is the same as in patients without HIV; HIV should not be a reason to exclude a patient from clinical trials or other interventions [91].

Lopinavir-ritonavir is being used in trials for patients with COVID-19, although data from one randomized trial do not suggest a benefit [86]. If a patient with HIV is not on a protease inhibitor-containing regimen, it should not be changed to include a protease inhibitor outside the context of a clinical trial and without consultation with an expert in the management of HIV [92].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – International and government guidelines for general care" and "Society guideline links:

Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Resources for patients".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Coronavirus disease 2019 (COVID-19) overview (The Basics)" and "Patient education: Coronavirus disease 2019 (COVID-19) and pregnancy (The Basics)" and "Patient education: Coronavirus disease 2019 (COVID-19) and children (The Basics)")

SUMMARY AND RECOMMENDATIONS

- A novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China at the end of 2019; it has subsequently spread rapidly, resulting in a global pandemic. The disease is designated COVID-19, which stands for coronavirus disease 2019. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

  The optimal approach to treatment of COVID-19 is uncertain. Our approach is based on limited data and evolves rapidly as clinical data emerge. (See 'Introduction' above.)

- Many patients with known or suspected COVID-19 have mild disease that does not warrant hospital-level care. Having such patients recover at home is preferred, as it prevents additional potential exposures in the health care setting and reduces burden on the health care system. Identification of patients who can be managed in the outpatient setting is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults".)

- The evaluation of hospitalized patients with documented or suspected COVID-19 should assess for features associated with severe illness and identify organ dysfunction or other comorbidities that could complicate potential therapy (table 2). (See 'Evaluation' above.)

- Patients hospitalized with COVID-19 should receive pharmacologic prophylaxis for venous thromboembolism (algorithm 1). COVID-19 has been associated with thromboembolic complications. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Hypercoagulability".)

- There are minimal data informing the risks of non-steroidal anti-inflammatory drugs (NSAIDs) in the setting of COVID-19. We suggest acetaminophen as the preferred antipyretic agent, if possible (**Grade 2C**). If NSAIDs are needed, we use the lowest effective dose. We do not discontinue NSAIDs in patients who are on them chronically for other conditions if there are no other reasons to stop them. (See 'Uncertainty about NSAID use' above.)

- Specific concern for COVID-19 should not impact the decision to start or stop angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). People who are on an ACE inhibitor or ARB for another indication should not stop their medication. (See "Coronavirus disease 2019 (COVID-19): Issues related to kidney disease and hypertension", section on 'Renin angiotensin system inhibitors'.)

- We make a point of continuing statins in hospitalized patients with COVID-19 who are already taking them. (See 'Statins' above.)

- The optimal use of COVID-19-specific therapy is uncertain; very preliminary, unpublished trial data suggest a benefit of remdesivir, but no other agent has clearly proven effective. For most potential therapies, evidence on their use is low quality. For this reason, patients should be referred to clinical trials whenever possible. Clinicians should consult their own local protocols for management. (See 'Approach' above.)

    - For patients with nonsevere disease who have no laboratory features associated with severe disease (table 1), care is primarily supportive, with close monitoring for disease progression. If a clinical trial is available for such patients, we prioritize those with advanced age (eg, >65 years) and other comorbidities associated with risk of progressive disease (table 2). (See 'Defining disease severity' above and 'Nonsevere disease' above.)

    - For hospitalized patients with severe disease, we recommend remdesivir, if available (**Grade 1C**). In the United States, remdesivir may be available through a US Food and Drug Administration (FDA) emergency use authorization. (See 'Remdesivir' above.)

- For hospitalized patients with severe disease or with laboratory features associated with severe disease (table 1) who cannot get remdesivir through emergency use authorization, we recommend referral to a clinical trial (**Grade 1C**). Clinical trials of remdesivir are ongoing; other investigational therapies include convalescent plasma, hydroxychloroquine, interleukin (IL)-6 pathway inhibitors, and other immunomodulatory agents. We also refer patients who are able to get remdesivir through emergency use authorization to clinical trials for other agents, if they allow concurrent use of remdesivir. (See 'Severe (including critical) disease' above.)

  If neither a clinical trial nor remdesivir through emergency use authorization is available, clinicians may be able to obtain convalescent plasma for investigational use in patients with severe disease; in the United States, this can be requested through the FDA's expanded access program. (See 'Convalescent plasma' above.)

  When none of these options is available, we favor supportive care. In particular, we suggest not routinely using hydroxychloroquine or chloroquine outside the context of a clinical trial given the lack of clear benefit from limited data and potential for toxicity (**Grade 2C**). We also suggest not using lopinavir-ritonavir for COVID-19 therapy outside of a clinical trial (**Grade 2B**). (See 'Hydroxychloroquine/chloroquine' above and 'Others' above.)

- Patients with severe disease often need oxygenation support. Some patients may develop acute respiratory distress syndrome (ARDS) and warrant intubation with mechanical ventilation. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues".)

- Infection control is an essential component of management of patients with suspected or documented COVID-19. This is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Patients with suspected or confirmed COVID-19'.)

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