COVID-19: Management in hospitalized adults

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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 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 "COVID-19: Outpatient evaluation and management of acute illness in adults".) (Related Pathway(s): COVID-19: Initial telephone triage of adult outpatients and COVID-19: Anticoagulation in adults with COVID-19.)

The epidemiology, clinical features, diagnosis, and prevention of COVID-19 are discussed in detail elsewhere. (See "COVID-19: Epidemiology, virology, and prevention" and "COVID-19: Diagnosis" and "COVID-19: Clinical features" and "COVID-19: Infection control for persons with SARS-CoV-2 infection".)

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

- (See "COVID-19: Management of the intubated adult".)
- (See "COVID-19: Pregnancy issues and antenatal care".)
- (See "COVID-19: Clinical manifestations and diagnosis in children".)
- (See "COVID-19: Cancer screening, diagnosis, post-treatment surveillance in uninfected patients during the pandemic and issues related to COVID-19 vaccination in cancer patients".)
- (See "COVID-19: Issues related to acute kidney injury, glomerular 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 "COVID-19: Diagnosis", section on 'Diagnostic approach'.)

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)

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

- Prothrombin time (PT)/partial thromboplastin 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 "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 "COVID-19: Clinical features", 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 "COVID-19: Evaluation and management of cardiac disease in adults", section on 'Targeted cardiac evaluation'.)

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 "COVID-19: Evaluation and management of cardiac disease in adults", section on 'Troponin'.)

GENERAL MANAGEMENT ISSUES

Empiric treatment for influenza during influenza season

— The clinical features of seasonal influenza and COVID-19 overlap, and they can only be reliably distinguished by microbiologic testing. Additionally, coinfection with both is possible, so the diagnosis of COVID-19 does not rule out the possibility of influenza. We agree with the United States National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel, which recommends empiric therapy for influenza for patients hospitalized with suspected or documented COVID-19 in locations where influenza virus is circulating [4]. Antiviral therapy for influenza should be discontinued if molecular testing for influenza is negative from upper respiratory tract specimens in non-intubated patients and from both upper and lower respiratory tract specimens in intubated patients. Antiviral therapy for seasonal influenza is discussed in detail elsewhere. (See "Treatment of seasonal influenza in adults", section on 'Antiviral therapy'.)

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 "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 "COVID-19: Hypercoagulability", section on 'VTE' and "COVID-19: Hypercoagulability", section on 'Indications for full-dose anticoagulation'.)

NSAID use

— As with the general approach to fever reduction in adults, we use acetaminophen as the preferred antipyretic agent in patients with COVID-19 and, if non-steroidal anti-inflammatory drugs (NSAIDs) are needed, use the lowest effective dose to minimize common adverse effects (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).

Initial concerns about potential negative effects of NSAIDs in patients with COVID-19 [15,16] have not been supported by most observational data, which have failed to identify worse COVID-19 outcomes with NSAID use compared with acetaminophen or no antipyretic use [17-20]. As an example, in a study of patients who were hospitalized for COVID-19 in the United Kingdom, rates of in-hospital mortality, invasive ventilation, and oxygen requirement were not different among the 4205 patients who had used systemic NSAIDs the two weeks prior to hospitalization compared with propensity score-matched controls [21].

The European Medicines Agency (EMA), WHO, and the United States NIH COVID-19 Treatment Guidelines Panel do not recommend that NSAIDs be avoided when clinically indicated [4,22,23].

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 "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Aerosol-generating procedures/treatments' and "COVID-19: Respiratory care of the nonintubated critically ill adult (high flow oxygen, noninvasive ventilation, and intubation)", section on 'Nebulized medications'.)

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 [24-28]. Despite speculation that patients with COVID-19 who are receiving these agents may be at increased risk for adverse outcomes, accumulating evidence does not support an association between renin angiotensin system inhibitor use and more severe disease. This is discussed in detail elsewhere. (See "COVID-19: Issues related to acute kidney injury, glomerular disease, and hypertension", section on 'Renin angiotensin system inhibitors'.)

Statins and aspirin

— We make a point of continuing statins in hospitalized patients with COVID-19 who are already taking them. We also continue aspirin unless there are concerns about bleeding risk. A high proportion of patients with severe COVID-19 have underlying cardiovascular disease, diabetes mellitus, and other indications for use of statins and aspirin. 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. Retrospective studies have suggested that statin use is associated with a lower rate of intensive care unit admission or death in patients with COVID-19 [29-32]. 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 [33]. 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.

Similarly, observational data suggest that baseline aspirin use is associated with lower mortality among patients with COVID-19.

Although statins and aspirin might have direct benefits for COVID-19, more data are needed [34].

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.

These issues are discussed in detail elsewhere:

- (See "COVID-19: Cancer screening, diagnosis, post-treatment surveillance in uninfected patients during the pandemic and issues related to COVID-19 vaccination in cancer patients" and "COVID-19: Risks for infection, clinical presentation, testing, and approach to infected patients with cancer", section on 'Management of cancer therapy'.)
- (See "COVID-19: Issues related to solid organ transplantation", section on 'Adjusting immunosuppression'.)
- (See "COVID-19: Care of adult patients with systemic rheumatic disease", section on 'Medication management with documented or presumptive COVID-19'.)
- (See "COVID-19: Issues related to gastrointestinal disease in adults", section on 'Adjusting IBD medications'.)
- (See "COVID-19: Cutaneous manifestations and issues related to dermatologic care", section on 'Continuation of immunosuppressive therapies'.)

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 "COVID-19: Infection control for persons with SARS-CoV-2 infection".)

COVID-19-SPECIFIC THERAPY

Approach

— The optimal approach to treatment of COVID-19 is evolving. Trial data suggest a mortality benefit with dexamethasone as well as with adjunctive tocilizumab or baricitinib and a possible clinical benefit with remdesivir. Based on the pathogenesis of COVID-19, approaches that target the virus itself (eg, antivirals, passive immunity, interferons) are more

likely to work early in the course of infection, whereas approaches that modulate the immune response may have more impact later in the disease course (figure 1).

Thus, in addition to dexamethasone, baricitinib or tocilizumab, and/or remdesivir for eligible patients, we strongly recommend enrollment into a well-controlled clinical trial, when available. Our approach is consistent with recommendations from expert groups in the United States, which also endorse clinical trial enrollment [4,35].

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

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 $\leq$94 percent on room air)
- Need for oxygenation or ventilatory support

This definition is consistent with the definition used by the US Food and Drug Administration [36]. Some studies have used other features in addition to hypoxia to characterize severe disease, such as tachypnea, respiratory distress, and $>$50 percent involvement of the lung parenchyma on chest imaging [37].

Assessment of oxygen saturation in individuals with dark skin pigmentation warrants special attention, as pulse oximetry may overestimate the oxygen saturation in such patients. This is discussed in detail elsewhere, as are recommended thresholds for oxygen supplementation. (See "COVID-19: Respiratory care of the nonintubated critically ill adult (high flow oxygen, noninvasive ventilation, and intubation)", section on 'Oxygenation targets'.)

Nonsevere disease

— For most hospitalized patients with nonsevere disease, we suggest supportive care only, with close monitoring for clinical worsening. If they develop features of severe disease (eg, hypoxia or oxygen requirement (see 'Defining disease severity' above)), we treat them as described below. (See 'Severe (including critical) disease' below.)

Some patients with nonsevere disease have laboratory abnormalities that are associated with progression to severe disease (table 1). We prioritize these patients for clinical trials for treatment of nonsevere disease in addition to monitoring them closely for progression. A registry of international clinical trials can be found at covid-trials.org. Although we do not routinely use monoclonal antibody therapy for hospitalized patients, we evaluate whether patients with nonsevere disease (ie, mild to moderate COVID-19) who are hospitalized for reasons other than COVID-19 would be eligible for monoclonal antibody therapy, as with certain high-risk outpatients. This is discussed in detail elsewhere. (See "COVID-19: Outpatient evaluation and management of acute illness in adults", section on 'Monoclonal antibodies and convalescent plasma therapy'.)

In the United States, EUAs have been granted for convalescent plasma, and remdesivir is approved for hospitalized patients with COVID-19, regardless of severity. We do not use convalescent plasma outside of clinical trials for patients with nonsevere disease. We also do not routinely use remdesivir for patients with nonsevere disease, as studies suggest only a modest benefit of uncertain clinical significance in this population, and we prioritize it for patients on low-flow oxygen at baseline. (See 'Antibody-based therapies (monoclonal antibodies and convalescent plasma)' below and 'Remdesivir' below.)

We recommend not using dexamethasone in patients with nonsevere disease. (See 'Dexamethasone and other glucocorticoids' below.)

Severe (including critical) disease

— We prioritize COVID-19-specific therapy for hospitalized patients who have severe disease. The approach depends on the oxygen or ventilatory requirement:

- **Patients with hypoxia but no oxygen requirement** – For these patients, we suggest remdesivir; however, if supplies are limited, we prioritize remdesivir for patients on low-flow oxygen supplementation at baseline, as below. We suggest not using dexamethasone (or tocilizumab or baricitinib) in such patients. Trial data in this population suggest that remdesivir may improve time to recovery and that dexamethasone does not confer a mortality benefit and may cause harm.

- **Patients receiving low-flow supplemental oxygen** – For patients on low-flow supplemental oxygen, we suggest low-dose dexamethasone and remdesivir. Trial data suggest that dexamethasone improves mortality in patients who are on noninvasive oxygen supplementation; it is uncertain if there are particular patients in this relatively heterogeneous group who would benefit more than others. Subgroup analysis of trial data suggests that remdesivir improves mortality in patients who are on low-flow supplemental oxygen.

  For patients who are on low-flow supplemental oxygen but have significantly elevated inflammatory markers (eg, CRP level ≥75 mg/L) and escalating oxygen requirements despite initiation of dexamethasone, we suggest adding baricitinib or tocilizumab on a case-by-case basis. We define escalating oxygen requirements as a rapid increase of 6 L/min or more within 24 hours, a 10 L/min or more requirement, or escalating beyond nasal cannula. Trial data suggest that adding either baricitinib or tocilizumab to dexamethasone in such individuals may further reduce mortality; however, for stable patients with low expected mortality, the absolute mortality benefit may be very low and not outweigh the potential risks.

- **Patients receiving high-flow supplemental oxygen or non-invasive ventilation** – For patients on high-flow oxygen or noninvasive ventilation, we recommend low-dose dexamethasone. For those who are within 24 to 48 hours of admission to an ICU or receipt of ICU-level care, we also suggest adjunctive baricitinib or tocilizumab. Trial data suggest that dexamethasone improves mortality in patients who are on noninvasive oxygen supplementation and that the addition of baricitinib or tocilizumab further reduces mortality.

  We also suggest remdesivir in these patients but prioritize it for patients on low-flow supplemental oxygen. The clinical benefit of remdesivir is less clear in patients who need higher levels of noninvasive support.

- **Patients who require mechanical ventilation or ECMO** – For such patients, we recommend low-dose dexamethasone; for those who are within 24 to 48 hours of admission to an ICU, we also suggest adjunctive tocilizumab. Trial data suggest that dexamethasone and the addition of tocilizumab each improve mortality in this population when used early in hospitalization. We suggest not routinely using remdesivir in this population. Although it is reasonable to add remdesivir in individuals who have only been intubated for a short time (eg, 24 to 48 hours), the clinical benefit of this is uncertain. We do not routinely use baricitinib as it has not been evaluated in this population.

If dexamethasone is not available, other glucocorticoids at equivalent doses are reasonable alternatives. We only use tocilizumab in patients receiving glucocorticoids and limit it to a single dose. We do not use baricitinib in patients who have received tocilizumab and vice versa. There are no data directly comparing baricitinib with tocilizumab, and the choice between them depends on availability; if baricitinib is unavailable, tofacitinib may be a reasonable alternative.

Remdesivir is approved or available for emergency use in some countries but is not universally available [38-40]. Furthermore, some guidelines panels suggest not using remdesivir because of a lack of clear reduction in mortality [41,42]. Dosing and data on efficacy of these agents are discussed in detail elsewhere. (See 'Dexamethasone and other glucocorticoids' below and 'IL-6 pathway inhibitors (eg, tocilizumab)' below and 'Baricitinib and JAK inhibitors' below and 'Remdesivir' below.)

In addition to these therapies, we often refer patients to clinical trials of other therapies, if they allow concurrent use. Other therapies being evaluated in trials include additional antiviral agents and immunomodulatory agents. A registry of international clinical trials can be found at covid-trials.org. Detailed discussion of these agents is found elsewhere. (See 'Specific treatments under evaluation' below.)

We do not routinely use convalescent plasma or monoclonal antibodies in hospitalized patients outside clinical trials because a clear clinical benefit has not been demonstrated. (See 'Antibody-based therapies (monoclonal antibodies and convalescent plasma)' below.)

We generally suggest against off-label use of other agents. Although repurposed use of agents available for other medical indications has been described, for most of these agents there are insufficient data to know whether they have any role in treatment of COVID-19; thus, we recommend that such agents only be used in the setting of a clinical trial.

We suggest not using hydroxychloroquine or chloroquine in hospitalized patients; available data do not suggest a clear benefit and do suggest the potential for toxicity. We also suggest not using lopinavir-ritonavir in hospitalized patients.

Specific treatments under evaluation

Dexamethasone and other glucocorticoids

- **Use of** dexamethasone – We recommend dexamethasone for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support. We use dexamethasone at a dose of 6 mg daily for 10 days or until discharge, whichever is shorter. If dexamethasone is not available, it is reasonable to use other glucocorticoids at equivalent doses (eg, total daily doses of hydrocortisone 150 mg, methylprednisolone 32 mg, or prednisone 40 mg), although data supporting use of these alternatives are more limited than those for dexamethasone. In contrast, we recommend that dexamethasone (or other glucocorticoids) not be used for either prevention or treatment of mild to moderate COVID-19 (patients not on oxygen). These recommendations are largely consistent with those of other expert and governmental groups [4,35,41,43,44]. (See 'Severe (including critical) disease' above.)

- **Monitoring for adverse effects** – Patients receiving glucocorticoids should be monitored for adverse effects. In severely ill patients, these include hyperglycemia and an increased risk of infections (including bacterial, fungal, and *Strongyloides* infections); the rates of these infections in patients with COVID-19 are uncertain. Nevertheless, pre-emptive treatment of *Strongyloides* prior to glucocorticoid administration is reasonable for patients from endemic areas (ie, tropical and subtropical regions). This is discussed elsewhere (see "Strongyloidiasis", section on 'Preventive treatment'). Major side effects of glucocorticoids are also discussed in detail elsewhere. (See "Major side effects of systemic glucocorticoids".)

- **Efficacy** – Data from randomized trials overall support the role of glucocorticoids for severe COVID-19. In a meta-analysis of seven trials that included 1703 critically ill patients with COVID-19, glucocorticoids reduced 28-day mortality compared with standard care or placebo (32 versus 40 percent, odds ratio [OR] 0.66, 95% CI 0.53-0.82) and were not associated with an increased risk of severe adverse events [45]. In another systematic review and network meta-analysis of randomized trials that evaluated interventions for COVID-19 and were available through

mid-August 2020, glucocorticoids were the only intervention for which there was at least moderate certainty in a mortality reduction (OR 0.87, 95% CI 0.77-0.98) or risk of mechanical ventilation (OR 0.74, 95% CI 0.58-0.92) compared with standard care [46].

The majority of the efficacy data on glucocorticoids in these meta-analyses comes from a large, randomized open-label trial in the United Kingdom in which oral or intravenous dexamethasone reduced 28-day mortality among hospitalized patients compared with usual care alone [47]. This trial included patients with confirmed or suspected COVID-19 who had no specific indications or contraindications to dexamethasone; 2104 and 4321 patients were randomly assigned to receive dexamethasone or usual care, respectively, and the proportions of baseline comorbidities and need for oxygen or ventilatory support were comparable between the two groups. Reductions in 28-day mortality with dexamethasone in the overall trial population and in prespecified subgroups were as follows:

- Overall – 17 percent relative reduction (22.9 versus 25.7 percent, rate ratio [RR] 0.83, 95% CI 0.75-0.93).
- Patients on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at baseline – 36 percent relative reduction (29.3 versus 41.4 percent, RR 0.64, 95% CI 0.51-0.81). Age-adjusted analysis suggested a 12.3 percent absolute mortality reduction.
- Patients on noninvasive oxygen therapy (including noninvasive ventilation) at baseline – 18 percent relative reduction (23.3 versus 26.2 percent, RR 0.82, 95% CI 0.72-0.94). Age-adjusted analysis suggested a 4.1 percent absolute mortality reduction.

In contrast, a benefit was not seen among patients who did not require either oxygen or ventilatory support; there was a nonstatistically significant trend towards higher mortality (17.8 versus 14 percent, RR 1.19, 95% CI 0.91-1.55). Results were similar when analysis was restricted to the patients with laboratory-confirmed COVID-19 (89 percent of the total population).

This was a preliminary report, and some uncertainties remain. The baseline mortality rate in this report was higher than that from some other trials, and the absolute mortality benefit in other settings may not be as high as in this trial. Adverse effects (including secondary infections) were not reported.

Data on the efficacy of other glucocorticoids are limited to smaller trials, several of which were stopped early because of the findings of the trial above [48-50]. Individual trials of hydrocortisone in critically ill patients failed to demonstrate a clear benefit [48,49]; in a meta-analysis that included three trials evaluating hydrocortisone, there was a nonstatistically significant trend toward reduced 28-day mortality compared with usual care or placebo (OR 0.69, 95% CI 0.43-1.12) [45]. Trials evaluating methylprednisone have not demonstrated a clear benefit. In a randomized trial from Brazil that included 393 patients with suspected or confirmed severe COVID-19 (77 percent of whom were on oxygen or ventilatory support), there was no difference in 28-day mortality rates with methylprednisolone compared with placebo (37 versus 38 percent) [51]. It is uncertain whether the apparent difference in results compared with the larger dexamethasone trial is related to the glucocorticoid formulation and dose, other differences between the trial populations, or issues related to statistical power.

Glucocorticoids may also have a role in the management of refractory shock in critically ill patients with COVID-19. These issues are discussed elsewhere. (See "COVID-19: Management of the intubated adult", section on 'Use of glucocorticoids for non-COVID-19 reasons'.)

Baricitinib and JAK inhibitors

— Baricitinib is a Janus kinase (JAK) inhibitor used for treatment of rheumatoid arthritis. In addition to immunomodulatory effects, it is thought to have potential antiviral effects through interference with viral entry.

- **Use of** baricitinib – We suggest baricitinib as an option for patients requiring high-flow oxygen or noninvasive ventilation and for select patients who are on low-flow oxygen but are progressing toward needing higher levels of respiratory support despite initiation of dexamethasone. We do not use baricitinib in patients who have also received an IL-6 pathway inhibitor, as these agents have not been studied together and the safety of coadministration is uncertain. Baricitinib is given at 4 mg orally once daily for up to 14 days. The dose is reduced in patients with renal insufficiency, and its use is not recommended if the estimated glomerular filtration rate (eGFR) is <15 mL/min per 1.73 m^2. As with tocilizumab, we only use baricitinib with caution in immunocompromised patients. This approach is largely consistent with recommendations from the NIH COVID-19 Treatment Guidelines Panel [4]. In the United States, an emergency use authorization (EUA) was issued for baricitinib in combination with remdesivir in patients with COVID-19 who require oxygen or ventilatory support [52]; however, data also support use of baricitinib independent of remdesivir use. Tofacitinib, another JAK inhibitor, may be an alternative if baricitinib is not available. (See 'Severe (including critical) disease' above.)

- **Efficacy** – Emerging data suggest that baricitinib may provide a mortality benefit for select patients with severe disease, even if they are already on dexamethasone. In an unpublished report of a multinational placebo-controlled, randomized trial of 1525 hospitalized adults with COVID-19 who were not receiving invasive mechanical ventilation, adding baricitinib to standard of care reduced 28-day mortality (8.1 versus 13.1 percent with placebo; hazard radio [HR] 0.57, 95% CI 0.41-0.78) [53]. Most participants (79 percent) were also receiving glucocorticoids, mainly dexamethasone, and 20 percent received remdesivir. Among the subgroup of patients who were on high-flow oxygen or noninvasive ventilation at baseline, the mortality with baricitinib was 17.5 percent versus 29.4 percent with placebo (HR 0.52, 95% CI 0.33-0.80); mortality rates with baricitinib were also lower than with placebo for individuals who were not on oxygen or on low-flow oxygen at baseline, but these differences were not statistically significant.

  These data largely support earlier findings of potential benefit with baricitinib [54-56]. In a randomized trial of 1033 hospitalized adults with COVID-19, baricitinib plus remdesivir reduced time to recovery (defined as hospital discharge or continued hospitalization without need for oxygen or medical care) compared with placebo plus remdesivir (7 versus 8 days, RR for recovery 1.16, 95% CI 1.01-1.32) [54]. Among the 216 patients who were on high-flow oxygen or noninvasive ventilation at baseline, the median recovery time with baricitinib was 10 days versus 18 days with placebo (RR 1.51, 95% CI 1.10-2.08). Overall, there was also a trend toward lower 29-day mortality with the addition of baricitinib to remdesivir (5.1 versus 7.8 percent; HR 0.65, 95% CI 0.39-10.9), but this was not statistically significant. A smaller proportion of patients in this trial were also receiving glucocorticoids (approximately 20 percent) compared with the multinational trial described above. One observational study suggested that using a higher dose of baricitinib was associated with further mortality reductions, but potential confounders reduce confidence in these findings [55,56].

  Tofacitinib may also have clinical benefit, although data are more limited. In a randomized trial of 289 patients hospitalized with COVID-19, most of whom were receiving glucocorticoids, tofacitinib (10 mg twice daily for up to 14 days) reduced the combined outcome of death and respiratory failure at 28 days compared with placebo (18 versus 29 percent, relative risk 0.63, 95% CI 0.41-0.97) [57]. There was also a trend toward lower all-cause mortality (2.8 versus 5.5 percent, HR 0.49, 95% CI 0.15-1.63), but this was not statistically significant.

- **Adverse effects** – In these studies, there was no apparent increase in the rate of adverse effects, including infection rates and venous thromboembolism, with baricitinib or tofacitinib. In the large multinational trial discussed above, treatment-emergent infections (16 percent) and thromboembolic events (3 percent) occurred at similar frequencies in

both the baricitinib and placebo groups [53]. However, the number of immunocompromised patients included in this trial was not specified.

IL-6 pathway inhibitors (eg, tocilizumab)

— 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 may prevent disease progression [58]. Several agents that target the IL-6 pathway have been evaluated in randomized trials for treatment of COVID-19; these include the IL-6 receptor blockers tocilizumab and sarilumab and the direct IL-6 inhibitor siltuximab.

- **Use of** tocilizumab – We suggest tocilizumab (8 mg/kg as a single dose) as an option for individuals who require high-flow oxygen or more intensive respiratory support and who are within 24 to 48 hours of admission to an intensive care (ICU) or receipt of ICU-level care. If supplies of medication allow, we also suggest tocilizumab on a case-by-case basis as an option for select patients on low-flow oxygen supplementation if they are clinically progressing toward high-flow oxygen despite initiation of dexamethasone and have significantly elevated inflammatory markers (eg, C-reactive protein [CRP] level ≥75 mg/L). More specifically, we would give tocilizumab to such patients if they have progressively greater oxygen requirements for reasons related to COVID-19 but not if their oxygen requirement is stable or is worsening due to other causes of respiratory decompensation (eg, asthma exacerbation, congestive heart failure). (See 'Severe (including critical) disease' above.)

  We only use tocilizumab in patients who are also taking dexamethasone (or another glucocorticoid) and generally limit it to a single dose. We do not use tocilizumab in patients who are receiving baricitinib, as these agents have not been studied together and the safety of coadministration is uncertain. Tocilizumab should be avoided in individuals with hypersensitivity to tocilizumab, uncontrolled serious infections other than COVID-19, absolute neutrophil count (ANC) <1000 cells/microL, platelet counts <50,000, alanine aminotransferase (ALT) >10 times the upper limit of normal (ULN), and elevated risk for gastrointestinal perforation. Tocilizumab should be used with caution in immunocompromised individuals as very few were included in randomized trials. Data regarding sarilumab are less robust than those for tocilizumab.

  Recommendations from expert and governmental guideline groups vary slightly. The National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel recommends adding tocilizumab to dexamethasone in recently hospitalized patients who are on high-flow oxygen or greater support and have either been admitted to the ICU within the prior 24 hours or have significantly increased inflammatory markers of inflammation; some panel members also suggested adding tocilizumab to patients on conventional oxygen supplementation if they had rapidly increasing oxygen needs and a CRP level ≥75 mg/L [4]. The Infectious Diseases Society of America (IDSA) suggests adding tocilizumab to standard of care (ie, glucocorticoids) for hospitalized adults who have progressive severe or critical COVID-19 and have elevated markers of systemic inflammation [35]. The National Health Service in the United Kingdom recommends consideration of tocilizumab as an adjunct to dexamethasone in patients with severe COVID-19 [59]. These include patients who have hypoxia (oxygen saturation repeatedly <92 percent on room air) or are on supplementary oxygen and have a CRP ≥75 mg/L as well as those who started on respiratory support (high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation) in the prior 24 hours. For the latter group, sarilumab is recommended as an alternative if tocilizumab supplies are limited.

- **Efficacy** – Overall, evidence suggests a mortality benefit with tocilizumab. In a meta-analysis of eight randomized trials of patients hospitalized with COVID-19, all-cause mortality was lower among those who received tocilizumab compared with placebo or standard of care (relative risk 0.89, 95% CI 0.82-0.97) [60]. The two largest trials in that analysis were conducted in patients with severe and critical COVID-19 and support the use of tocilizumab:

- In an open-label trial in the United Kingdom that included 4116 patients with suspected or confirmed COVID-19, hypoxia (oxygen saturation <92 percent on room air or oxygenation supplementation of any kind), and a CRP level ≥75 mg/L, adding one to two doses of weight-based tocilizumab to usual care reduced the 28-day mortality rate compared with usual care alone (31 versus 35 percent, relative risk 0.85, 95% CI 0.76-0.94) [61]. Among those who were not on mechanical ventilation at baseline, tocilizumab similarly reduced the combined endpoint of progression to mechanical ventilation or death. There did not appear to be a statistically significant difference in mortality risk reduction by level of baseline respiratory support. Most of the trial participants (82 percent) were also using glucocorticoids, mainly dexamethasone, and subgroup analysis suggested that they were more likely to benefit from tocilizumab than were individuals who did not receive glucocorticoids.

- Preliminary results of another open-label international randomized trial that included 803 patients with severe COVID-19 who were admitted to the intensive care unit and required initiation of either respiratory or cardiovascular support suggested a mortality benefit of IL-6 pathway inhibitors [62]. Tocilizumab (n = 353) and sarilumab (n = 48) each reduced in-hospital mortality compared with standard of care (28 and 22 versus 36 percent; adjusted odds ratio for hospital survival 1.64, 95% credible interval [CrI] 1.14-2.35 for tocilizumab and 2.01, 95% CrI 1.18-4.71 for sarilumab). All patients were enrolled within 24 hours of admission to the intensive care unit, >80 percent received concomitant glucocorticoids, and 33 percent received remdesivir.

Several other trials failed to identify a mortality benefit or other clear clinical benefit with these agents [63-69]. As an example, one double-blind, randomized trial of 243 patients with severe COVID-19 who were not intubated but had evidence of a pro-inflammatory state (with elevations in CRP, ferritin, D-dimer, or lactate dehydrogenase) did not detect a difference in the rate of intubation or death with a single dose of tocilizumab compared with placebo (10.6 versus 12.5 percent, HR 0.83, 95% CI 0.38-1.81) [66]. Although there were more subjects older than 65 years in the tocilizumab arm, the HR was not statistically significant after adjustment for age and other clinical features. Tocilizumab also did not reduce the risk of disease progression (eg, worsening oxygen requirements). In another trial that included 389 hospitalized patients with COVID-19 who were not on ventilatory support, tocilizumab reduced progression to mechanical ventilation or death at 28 days (12 versus 19 percent; HR 0.556, 95% CI 0.33-0.97), but it did not reduce overall 28-day mortality (10.4 versus 8.6 percent) [69]. An open-label randomized trial in Brazil also failed to detect a clinical or mortality benefit among 129 patients with severe or critical COVID-19 (including those who were recently placed on mechanical ventilation); adding tocilizumab to standard of care did not reduce the risk of mechanical ventilation or death at 15 days (28 versus 20 percent, OR 1.54, 95% 0.7-3.7), and there was a trend toward higher 28-day mortality with tocilizumab (21 versus 9 percent, OR 2.7, 95% CI 0.97-8.35) [70].

The reasons for the different findings among trials are uncertain. The trials that suggested a benefit with tocilizumab reported somewhat higher overall mortality rates compared with other trials, potentially reflecting more severely ill populations. This possibility is supported by a post-hoc analysis of a trial that did not originally show a benefit, in which tocilizumab was associated with a reduction in death and mechanical ventilation only among those with a CRP level >150 mg/L [71]. Trials that suggested a benefit also reported a high rate of concomitant glucocorticoid use, which most other trials did not; whether this is a relevant factor is uncertain. Finally, some of the trials that failed to show a benefit reported non-statistically significant trends towards a benefit, and these trials may have been underpowered to identify an effect.

- **Adverse effects** – Serious adverse events in trials were not greater with IL-6 pathway inhibitors than comparators. Although use of IL-6 pathway inhibitors may be associated with an increased risk of secondary infections [72,73], this risk was not observed in several randomized trials [66-68]. However, patients with active infections other than

COVID-19 were typically excluded from trial participation. (See "Secondary immunodeficiency induced by biologic therapies", section on 'Tocilizumab'.)

Remdesivir

— Remdesivir is a novel nucleotide analog that has in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [74].

- **Use of** remdesivir – If available, we suggest remdesivir for hospitalized patients with severe COVID-19 because data suggest it reduces time to recovery, which we regard as a clinical benefit. Among patients with severe disease, we prioritize remdesivir for those requiring low-flow supplemental oxygen because it may also reduce mortality in this population. However, the optimal role of remdesivir remains uncertain, and some guidelines panels (including the World Health Organization) suggest not using it in hospitalized patients because there is no clear evidence that it improves patient-important outcomes for hospitalized patients (eg, mortality, need for mechanical ventilation) [41,42]. Other guidelines panels, including the Infectious Diseases Society of America and the National Institutes of Health, suggest using remdesivir in hospitalized patients who require supplemental oxygen [4,35]. (See 'Severe (including critical) disease' above.)

  In the United States, the Food and Drug Administration (FDA) approved remdesivir for hospitalized children ≥12 years and adults with COVID-19, regardless of disease severity [75]. The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO). If a patient is otherwise ready for discharge prior to completion of the course, remdesivir can be discontinued. 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. Given the short duration of therapy and the low concentration of the cyclodextrin vehicle, the risks in patients with renal impairment may be relatively low [76], and case series have reported safe use of remdesivir in patients with acute kidney injury and chronic kidney disease [77]. Liver enzymes should be checked before and during remdesivir administration; alanine aminotransferase elevations >10 times the upper limit of normal should prompt consideration of remdesivir discontinuation. Remdesivir should not be used with hydroxychloroquine or chloroquine because of potential drug interactions.

- **Efficacy** – Remdesivir has been evaluated for both severe and non-severe COVID-19 in hospitalized patients:

  - **Severe COVID-19** – Overall, data from randomized trials do not demonstrate a clear, major clinical benefit with remdesivir among hospitalized patients [46,78-82]. In a meta-analysis of four trials that included over 7000 patients with COVID-19, remdesivir did not reduce mortality (OR 0.9, 95% CI 0.7-1.12) or need for mechanical ventilation (OR 0.90, 95% CI 0.76-1.03) compared with standard of care or placebo [42,46]. This analysis, however, grouped patients with COVID-19 of all severities together, and based on results from one included placebo-controlled trial, there may be a mortality benefit for select patients with severe disease who only require low-flow supplemental oxygen. Results from that trial also indicate that remdesivir reduced time to recovery from severe COVID-19; in a smaller second trial that was stopped early for poor enrollment, there was also a trend toward reduced time to recovery with remdesivir, but it was not statistically significant. Data from these trials are detailed below:

    - In an interim report of the WHO-sponsored, multinational SOLIDARITY trial of patients hospitalized with COVID-19, there was no difference in overall 28-day mortality between the 2750 patients randomly

assigned to open-label remdesivir and the 2708 patients assigned to standard care (RR 0.95, 95% CI 0.81-1.11) [80]. In an accompanying meta-analysis that included data from SOLIDARITY and the trials discussed below, there appeared to be a trend toward lower mortality with remdesivir among those who were not on mechanical ventilation at baseline, but this did not reach statistical significance (RR 0.8, 95% CI 0.63-1.01). There was no mortality benefit among those on ventilation at baseline (RR 1.16, 95% CI 0.85-1.60).

- ACTT-1, a multinational, randomized, placebo-controlled trial of remdesivir (given for up to 10 days or until death or discharge) included 1062 patients with confirmed COVID-19 and evidence of lung involvement; 85 percent had severe disease and 27 percent were receiving invasive mechanical ventilation or ECMO at baseline [78]. Remdesivir resulted in a faster time to recovery, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care (median 10 versus 15 days with placebo; rate ratio for recovery 1.29, 95% CI 1.12-1.49). Remdesivir reduced time to recovery whether patients were randomized within or after 10 days of symptom onset. However, in subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on low-flow oxygen at baseline. Among the subset of patients on mechanical ventilation or ECMO at baseline, the time to recovery was similar with remdesivir and placebo (rate ratio for recovery 0.98, 95% CI 0.70-1.36), although it is possible that follow-up was too short to detect a difference.

  Overall, there was a trend towards lower 29-day mortality that was not statistically significant (11.4 versus 15.2 percent with placebo, hazard ratio [HR] 0.73, 95% CI 0.52-1.03). Among the subset of patients who were on oxygen supplementation but did not require high-flow oxygen or ventilatory support (either noninvasive or invasive), there was a statistically significant mortality benefit at that time point (4.0 versus 12.7 percent, HR 0.30, 95% CI 0.14-0.64).

- 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; HR for improvement 1.23 [95% CI 0.87-1.75]) [79]. 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. 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).

Although these trials evaluated 10 days of remdesivir, 5 days of therapy may result in similar outcomes in patients who do not need mechanical ventilation or ECMO. In an industry-sponsored, open-label randomized trial among nearly 400 patients who were hypoxic on room air or receiving noninvasive oxygen supplementation, the rates of clinical improvement and discharge by day 14 were numerically higher when remdesivir was given for 5 days (65 and 60 percent, respectively) versus 10 days (54 and 52 percent,

respectively) [83]. However, patients in the 10-day group had higher rates of invasive or noninvasive ventilation and high-flow oxygen receipt at the time of remdesivir initiation, and on adjusted analysis, the differences in outcomes were not statistically significant. Mortality rates at day 14 were 8 and 11 percent with 5 and 10 days of treatment, respectively, and varied by geographic location. In a propensity analysis of a subset of participants in this trial, the adjusted clinical improvement rate was higher and the adjusted mortality rate was lower than those in a cohort of patients who had severe COVID-19 but did not receive remdesivir [84]. However, this comparison of patients from two separate studies should be interpreted with caution because of potential confounders in patient characteristics and management approaches that cannot be fully accounted for by the propensity analysis.

- **Nonsevere COVID-19** – Among hospitalized patients with nonsevere disease, remdesivir may have a modest benefit, but the clinical significance of the benefit is uncertain. In an open-label randomized trial, 584 patients with moderate severity COVID-19 (pulmonary infiltrates on imaging but oxygen saturation >94 percent on room air) were assigned to receive remdesivir for up to 5 days, remdesivir for up to 10 days, or standard of care [85]. By day 11, the five-day remdesivir group had better clinical status according to a seven-point scale compared with standard of care (odds ratio 1.65, 95% CI 1.09 to 2.48). There was not a statistically significant difference at day 11 in clinical status between the 10-day remdesivir group and the standard of care group. Although discharge rates by day 14 were higher with remdesivir (76 percent in each of the remdesivir groups versus 67 percent with standard of care), these differences were not statistically significant. Interpretation of this trial is limited by the open-label design and an imbalance in co-therapies.

  In ACTT-1, the large trial described above, remdesivir (given for up to 10 days) did not appear to reduce time to recovery among the 119 patients with mild-moderate disease (ie, no hypoxia or tachypnea; five versus six days, recovery rate ratio 1.29, 95% CI 0.91-1.83), although the number of patients in that subgroup was underpowered to show a significant effect [78].

- **Adverse effects** – Reported side effects include nausea, vomiting, and transaminase elevations. In one trial, the most common adverse events were anemia, acute kidney injury, fever, hyperglycemia, and transaminase elevations; the rates of these were overall similar between remdesivir and placebo [78]. However, in another trial, remdesivir was stopped early because of adverse events (including gastrointestinal symptoms, aminotransferase or bilirubin elevations, and worsened cardiopulmonary status) more frequent than with placebo (12 percent versus 5 percent) [79]. Cases of bradycardia attributable to remdesivir have also been reported [86,87].

Antibody-based therapies (monoclonal antibodies and convalescent plasma)

- **Monoclonal antibodies** – Trials of monoclonal antibodies that have been developed to neutralize SARS-CoV-2 by targeting the SARS-CoV-2 spike protein and preventing viral cell entry are underway. In the United States, certain monoclonal antibodies are available for high-risk outpatients through an EUA; hospitalized patients should only receive them as part of a clinical trial or in special circumstances if they meet the EUA criteria [4]. Results from available trials thus far do not demonstrate a benefit of monoclonal antibodies in most hospitalized patients [88]. However, preliminary data suggest that a subset may benefit. In an unpublished report of an open-label randomized trial of nearly 10,000 patients hospitalized for COVID-19, nearly all of whom were receiving glucocorticoids, there was no overall difference in 28-day mortality following a single dose of casirivimab and imdevimab, a combination monoclonal antibody therapy, compared with usual care (20 versus 21 percent; relative risk 0.94, 95% CI 0.86-1.03) [89]. All participants underwent serologic testing for anti-SARS-CoV-2 antibodies at trial entry, and among the 3153 who were seronegative, 28-day mortality was lower with casirivimab and imdevimab (24 versus 30 percent; relative risk 0.80, 95% CI 0.70-0.91). While promising, we await a final report of these findings and expansion of the EUA for

casivirimab and imdevimab before routinely recommending it for seronegative patients hospitalized with COVID-19. In addition, implementation may be challenging given limited availability of highly sensitive, high-throughput serologic assays with rapid turnaround.

Evaluation of monoclonal antibodies in outpatients with mild to moderate COVID-19 is discussed in detail elsewhere. (See "COVID-19: Outpatient evaluation and management of acute illness in adults".)

- **Convalescent plasma** – Convalescent plasma from individuals who have recovered from COVID-19 has been hypothesized to have clinical benefit for COVID-19, and in the United States, emergency use authorization has been granted for high-titer convalescent plasma among hospitalized patients with COVID-19 who are early in the course of disease or have impaired humoral immunity [90]. However, the available evidence does not support a clear role for convalescent plasma in patients with severe disease, and because of the lack of evident benefit, we suggest not using convalescent plasma for mechanically ventilated patients and not using it outside the context of clinical trials for other hospitalized patients. Observational data suggest that convalescent plasma may have a role for individuals with immunocompromising conditions or deficits in antibody production (eg, those receiving anti-CD20 therapies, those with hematologic malignancies) [91,92], although randomized trial data in these populations are lacking and emerging data are more robust for monoclonal antibodies, as discussed above. Convalescent plasma is also being evaluated in outpatient populations with nonsevere COVID-19 and as post-exposure prophylaxis. (See 'Severe (including critical) disease' above and "COVID-19: Outpatient evaluation and management of acute illness in adults", section on 'Monoclonal antibodies and convalescent plasma therapy' and "COVID-19: Convalescent plasma and hyperimmune globulin" and "COVID-19: Risks for infection, clinical presentation, testing, and approach to infected patients with cancer", section on 'Convalescent plasma'.)

  Randomized trials in hospitalized patients have not demonstrated a clear clinical benefit of convalescent plasma, including large trials that stopped enrollment for lack of mortality benefit [93-99]. As an example, a meta-analysis of four published randomized trials did not detect a difference in mortality with convalescent plasma compared with placebo or standard of care (relative risk 0.93, 95% CI 0.63-1.38) [100]. There were also no differences in duration of hospitalization and mechanical ventilation use. An analysis that also included six trials that were unpublished at the time resulted in similar findings. Although there were a number of limitations with the analysis, such as inclusion of trials in which low-titer convalescent plasma was used, no individual trial demonstrated a convincing reduction in mortality in hospitalized patients. Use of convalescent plasma for severe COVID-19 has also been reported in observational studies, several of which suggest that administration of convalescent plasma with higher antibody titers and earlier in presentation are associated with a greater clinical effect [93,101-106]. As an example, in a report of 3082 patients who had or were at risk for severe COVID-19 and received convalescent plasma, receipt of plasma with higher antibody titers was associated with lower 30-day mortality rates (30, 27, and 22 percent with low-, medium-, and higher-titer plasma, respectively); however, there was no association between antibody titer and mortality among patients who were on mechanical ventilation at the time of plasma transfusion [106]. However, the clinical implications of these observational studies are uncertain given the largely negative findings from randomized trials.

  Convalescent plasma has generally been well tolerated [107]. Preparation, administration, and adverse effects of convalescent plasma are discussed in detail elsewhere. (See "COVID-19: Convalescent plasma and hyperimmune globulin".)

Others

— Many other agents with known or putative antiviral or immunomodulating effects have been proposed for use in patients with COVID-19 but have insufficient evidence of clinical benefit. Use of these agents for COVID-19 should be limited to clinical trials, if used at all; 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.

- Hydroxychloroquine/chloroquine – We suggest not using hydroxychloroquine or chloroquine in hospitalized patients given the lack of clear benefit and potential for toxicity. Several large randomized trials failed to identify a mortality or other clinical benefit for hospitalized patients with COVID-19 [108-113]. In June 2020, the US FDA revoked its EUA for these agents in patients with severe COVID-19, noting that the known and potential benefits no longer outweighed the known and potential risks [114]. The potential toxicity of hydroxychloroquine and chloroquine, including QTc prolongation and arrhythmias, is discussed in detail elsewhere. (See "COVID-19: Arrhythmias and conduction system disease", section on 'Patients receiving therapies that prolong the QT interval' and "Antimalarial drugs in the treatment of rheumatic disease", section on 'Adverse effects' and "Methemoglobinemia", section on 'Dapsone'.)

- Favipiravir – Favipiravir is an RNA polymerase inhibitor available in some Asian countries for treatment of influenza and available in India for treatment of mild COVID-19, and it is being evaluated in clinical trials for treatment of COVID-19 in the United States and elsewhere. Early trials in Russia [115] and China [116] suggested some benefit, but since other therapies (eg, immunomodulatory agents) were administered in these studies, the results should be interpreted with caution given potential confounders. Another trial in Iran suggested no benefit with favipiravir for severe COVID-19 [117].

- **Interferons** – Interferons modulate immune responses and may have antiviral effects. Interferon beta, specifically, has been reported to inhibit SARS-CoV-2 replication in vitro [118]. Defects in production of type 1 interferons (which include interferon beta), as well as autoantibodies that neutralize type 1 interferons, have been identified in patients with severe COVID-19 [119,120]. (See "Toll-like receptors: Roles in disease and therapy", section on 'Severe COVID-19'.)

  Overall, clinical data do not indicate a clear benefit of interferon beta for severe COVID-19. Interim results of a large multinational trial of patients hospitalized with COVID-19 showed no difference in 28-day mortality with subcutaneous or intravenous interferon beta compared with standard of care (2703 patients in each group; RR 1.16, 95% CI 0.96-1.39) [80]. Although some smaller trials had suggested clinical improvement, faster time to hospital discharge, and a potential mortality benefit with interferon beta, methodologic limitations reduce confidence in those findings [121].

  Inhaled interferon beta, an investigational formulation of the drug delivered by nebulizer, is also being evaluated. In a randomized trial of 101 patients hospitalized with COVID-19, inhaled interferon beta increased the likelihood of recovery by day 15 compared with placebo (OR 3.19, 95% CI 1.24-8.24); a reduction in the likelihood of severe disease or death was not statistically significant [122].

  There are also several pilot trials evaluating the use of interferon lambda for COVID-19.

- **IL-1 inhibitors** – Interleukin-1 (IL-1) is a pro-inflammatory cytokine that has been associated with severe COVID-19, and several observational studies have suggested that treatment with IL-1 inhibitors (eg, anakinra) is associated with reduced COVID-19-associated mortality [123-127]. However, in a randomized trial of 116 patients hospitalized with mild to moderate COVID-19, there was no evidence of clinical benefit of anakinra plus usual care compared with usual care alone; no difference was detected in the rates of mechanical ventilation or death at 14 days (34 versus 35 percent) [128]. Results from trials of IL-1 inhibitors in patients with severe disease are pending.

- **Other immunomodulatory agents** – In addition to IL-6 pathway inhibitors (see 'IL-6 pathway inhibitors (eg, tocilizumab)' above) and IL-1 inhibitors (discussed above), immunomodulatory agents from various other classes, including other cytokine inhibitors [129], kinase inhibitors [130-133], complement inhibitors [134,135], bradykinin pathway inhibitors [136], and hematopoietic colony-stimulating factors agonist and antagonists [137,138], are being evaluated. Their use has been described mainly in case series and other observational studies. Although an unpublished report of a randomized trial suggested a survival benefit of lenzilumab, an anti-granulocyte-macrophage colony stimulating factor (GM-CSF) monoclonal antibody, in patients with severe COVID-19, uncertainties in trial design and outcomes reduce confidence in these findings [139].

- **Azithromycin (with or without hydroxychloroquine)** – We do not use azithromycin, either alone or in combination with hydroxychloroquine, for treating COVID-19. Randomized trials and observational studies have not demonstrated a clinical benefit [112,140-145].

- **Lopinavir-ritonavir** – We suggest not using lopinavir-ritonavir for treatment of COVID-19 in hospitalized patients. Several clinical trials have failed to demonstrate efficacy [8,80,146,147]. As an example, in an open-label randomized trial of patients hospitalized with COVID-19, lopinavir-ritonavir for up to 10 days (n = 1616) did not reduce 28-day mortality (23 versus 22 percent) or need for mechanical ventilation (10 versus 9 percent) compared with usual care (n = 3424) [147]. It also did not improve 28-day hospital discharge rates. Whether lopinavir-ritonavir has a role in outpatients with nonsevere disease is uncertain; we suggest it only be used in outpatients in the context of a clinical trial. Although it has in vitro activity against SARS-CoV [148], lopinavir-ritonavir is highly protein-bound and does not appear to achieve plasma levels close to the EC50 [149,150].

- **Ivermectin** – We do not use ivermectin for treatment of COVID-19 outside of clinical trials, as with other interventions that are not supported by high-quality data, consistent with recommendations from the WHO [3]. Data on ivermectin for COVID-19 are of low quality. In a meta-analysis of 16 trials evaluating ivermectin (only four included patients with severe disease), the effects on mortality, need for invasive mechanical ventilation, and duration of hospitalization were all very uncertain because of limitations in trial design and low numbers of events [46]. In a retrospective review of 280 patients hospitalized with COVID-19, receipt of ivermectin was associated with a lower mortality rate; however, patients who received ivermectin were also more likely to receive corticosteroids, highlighting the potential for confounders to impact the findings of nonrandomized studies [151]. Ivermectin had originally been proposed as a potential therapy based on in vitro activity against SARS-CoV-2; however, the drug levels used in the in vitro studies far exceed those achieved in vivo with safe drug doses [152]. We reserve use of ivermectin for prevention of *Strongyloides* reactivation in select individuals receiving glucocorticoids. (See "Strongyloidiasis", section on 'Preventive treatment'.).

- **Vitamin D** – In patients with COVID-19, vitamin D supplementation may be appropriate to meet the recommended intake or treat deficiency. However, we do not exceed the recommended upper level of intake, and there is no clear evidence that vitamin D supplementation or high-dose vitamin D improves COVID-19 outcomes. These data are discussed elsewhere. (See "Vitamin D and extraskeletal health", section on 'COVID-19'.)

Other agents that have been proposed for COVID-19 therapy include the HCV antivirals sofosbuvir plus daclatasvir [153-155], the selective serotonin receptor blocker fluvoxamine [156], famotidine [157-159], and zinc [160]. Clinical data thus far are insufficient to support a role for these agents in hospitalized patients, and for other agents (eg, colchicine [161,162]), accumulating data suggest no clinical benefit in this population. As above, their use for COVID-19 should be limited to clinical trials.

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 "COVID-19: Respiratory care of the nonintubated critically ill adult (high flow oxygen, noninvasive ventilation, and intubation)".)

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 2). (See "COVID-19: Management of the intubated adult".)

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 "COVID-19: Arrhythmias and conduction system disease".)
- (See "COVID-19: Evaluation and management of cardiac disease in adults".)
- (See "COVID-19: Issues related to acute kidney injury, glomerular disease, and hypertension", section on 'Acute kidney injury'.)
- (See "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 "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Discontinuation of precautions'.)

Older age (eg, >65 years), underlying medical comorbidities, and discharge to a skilled nursing facility have been associated with an increased risk of readmission following hospitalization for COVID-19 [163]. Patients with COVID-19 generally warrant outpatient follow-up through telehealth or an in-person visit following discharge from the hospital. (See "COVID-19: Outpatient evaluation and management of acute illness in adults", section on 'Outpatient management following inpatient or ED discharge'.)

Patients who have recovered from COVID-19 and are interested in donating convalescent plasma 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 "COVID-19: Convalescent plasma and hyperimmune globulin", section on 'Donor recruitment'.)

INSTITUTIONAL PROTOCOLS

— Several academic medical institutions in the United States have developed COVID-19 management protocols that are publicly available:

- Brigham and Women's Hospital
- Massachusetts General Hospital
- Michigan Medicine
- Mount Sinai Health System

- 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 "COVID-19: Pregnancy issues and antenatal care".)

People with HIV

— The impact of HIV infection on the natural history of COVID-19 is uncertain. 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. (See "COVID-19: Clinical features", section on 'People with HIV'.)

Overall, 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 [164]. However, drug interactions with antiretroviral agents are important to assess before starting any new therapies.

Although certain antiretroviral agents have been hypothesized to have efficacy against SARS-CoV-2, antiretroviral regimens should not be adjusted based on concern for COVID-19. Lopinavir-ritonavir is being evaluated in trials for patients with COVID-19, although data from randomized trials do not suggest a benefit [146,165]. If a patient with HIV is not on a protease inhibitor-containing regimen, the regimen 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 [166]. One observational study of patients with HIV in Spain suggested that baseline use of tenofovir disoproxil fumarate plus emtricitabine (TDF-FTC) was associated with a lower rate of COVID-19 diagnosis and a lower COVID-19-associated mortality rate compared with other nucleoside reverse transcriptase inhibitor backbones (including tenofovir alafenamide plus emtricitabine); however, potential confounders (including underlying comorbidities and institutional differences in prescribing) were not accounted for in the analysis [167].

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: COVID-19 – Index of guideline topics".)

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 5^{th} to 6^{th} 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: COVID-19 overview (The Basics)" and "Patient education: COVID-19 and pregnancy (The Basics)" and "Patient education: COVID-19 and children (The Basics)" and "Patient education: COVID-19 vaccines (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Indications for hospitalization** – 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. Indications for hospitalization and identification of patients who can be managed in the outpatient setting are discussed in detail elsewhere. (See "COVID-19: Outpatient evaluation and management of acute illness in adults", section on 'Determine if in-person evaluation warranted'.)

- **Evaluation** – The evaluation of hospitalized patients with documented or suspected COVID-19 should assess for features associated with severe illness (table 1) and identify organ dysfunction or other comorbidities that could complicate potential therapy. (See 'Evaluation' above.)

- **Thromboprophylaxis** – 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 "COVID-19: Hypercoagulability".)

- **Antipyretics** – We suggest acetaminophen for fever reduction in patients with COVID-19 rather than non-steroidal anti-inflammatory drugs (NSAIDs) (**Grade 2C**). This approach is the same as that in the general population. If NSAIDs are needed, we use the lowest effective dose. However, we do not discontinue NSAIDs in patients who are on them chronically for other conditions if there are no other reasons to stop them. Observational data do not indicate an association between NSAIDs and poor COVID-19 outcomes. (See 'NSAID use' above.)

- **Continuing chronic medications** – 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 "COVID-19: Issues related to acute kidney injury, glomerular disease, and hypertension", section on 'Renin angiotensin system inhibitors'.)

  We continue statins in hospitalized patients with COVID-19 who are already taking them. We also continue aspirin unless there is concern for bleeding risk. (See 'Statins and aspirin' above.)

- **Approach to nonsevere disease** – For patients with nonsevere disease (O_2 saturation >94 percent and no need for oxygenation or ventilatory support), care is primarily supportive, with close monitoring for disease progression. When clinical trials for treatment of nonsevere disease are available, we prioritize those who have laboratory features associated with disease progression (table 1). Additionally, we evaluate whether patients with nonsevere disease (ie, mild to moderate COVID-19) who are hospitalized for reasons other than COVID-19 would be eligible for monoclonal antibody therapy, as with certain high-risk outpatients. (See 'Defining disease severity' above and 'Nonsevere disease'

above and "COVID-19: Outpatient evaluation and management of acute illness in adults", section on 'Monoclonal antibodies and convalescent plasma therapy'.)

- **Approach to severe disease** – For patients with severe disease (O_2 saturation ≤94 percent on room air or need for oxygenation or ventilatory support), the approach to COVID-19-specific therapy depends on the level of support (see 'Defining disease severity' above and 'Severe (including critical) disease' above):

  - For hospitalized patients with hypoxia who are not yet on oxygen, we suggest remdesivir, if available (**Grade 2C**). We suggest not using dexamethasone in such patients (**Grade 2C**).

  - For hospitalized patients who are receiving low-flow supplemental oxygen, we suggest low-dose dexamethasone and, if available, remdesivir (**Grade 2C**). For patients who have significantly elevated inflammatory markers (eg, C-reactive protein [CRP] level ≥75 mg/L) and escalating oxygen requirements despite dexamethasone, we suggest adding either baricitinib or tocilizumab on a case-by-case basis (**Grade 2C**). If supplies of tocilizumab or baricitinib are limited, we prioritize them for more severely ill patients on higher levels of oxygen support.

  - For hospitalized patients who are receiving high-flow supplemental oxygen or non-invasive ventilation, we recommend low-dose dexamethasone (**Grade 1B**). For those who are within 24 to 48 hours of admission to an intensive care unit (ICU) or receipt of ICU-level care, we suggest either baricitinib or tocilizumab in addition to dexamethasone (**Grade 2B**). We also suggest adding remdesivir (**Grade 2C**); however, if supplies are limited, we prioritize remdesivir for patients who are on low-flow oxygen supplementation at baseline.

  - For hospitalized patients with severe disease who require mechanical ventilation or extracorporeal membrane oxygenation, we recommend low-dose dexamethasone (**Grade 1B**). For those who are within 24 to 48 hours of admission to an ICU, we suggest adding tocilizumab to dexamethasone (**Grade 2B**). We suggest not routinely using remdesivir in this population (**Grade 2C**). Although it is reasonable to add remdesivir to dexamethasone in individuals who have only been intubated for a short time (eg, 24 to 48 hours), the clinical benefit of this is uncertain.

  - If dexamethasone is not available, other glucocorticoids at equivalent doses are reasonable alternatives.

- **Limited role for other therapies** – We generally do not use other agents off-label for treatment of COVID-19. In particular, we suggest not using hydroxychloroquine or chloroquine in hospitalized patients given the lack of clear benefit and potential for toxicity (**Grade 2B**). We also suggest not using lopinavir-ritonavir for COVID-19 therapy in hospitalized patients (**Grade 2B**). We suggest not routinely using convalescent plasma for hospitalized patients with severe disease outside a clinical trial because a clear clinical benefit has not been demonstrated (**Grade 2B**). (See 'Others' above and 'Antibody-based therapies (monoclonal antibodies and convalescent plasma)' above.)

- **Management of hypoxia** – 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 "COVID-19: Management of the intubated adult".)

- **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 "COVID-19: Infection control for persons with SARS-CoV-2 infection".)

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