

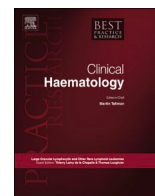


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Prevention and treatment of COVID-19 in patients with benign and malignant blood disorders

Elie A. Saade^{a,b,*}, Leila S. Hojat^{a,b}, Praveen Gundelly^{a,b}, Robert A. Salata^{a,b}^a Division of Infectious Diseases and HIV Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH, USA^b Case Western Reserve University, Cleveland, OH, USA

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ABSTRACT

Patients with moderate to severe immunosuppression, a condition that is common in many hematologic diseases because of the pathology itself or its treatment, are at high risk for COVID-19 and its complications. While empirical data are sometimes conflicting, this heightened risk has been confirmed in multiple well-done studies for patients with hematologic malignancies, particularly those with B-cell lymphoid malignancies who received lymphocytotoxic therapies, those with a history of recent hematopoietic stem cell transplant and chimeric antigen receptor T-cell therapy, and, to a lesser degree, those with hemoglobinopathies. Patients with immunosuppression need to have a lower threshold for avoiding indoor public spaces where they are unable to effectively keep a safe distance from others, and wear a high-quality well-fitting mask, especially when community levels are not low. They should receive an enhanced initial vaccine regimen and additional boosting. Therapeutic options are available and immunosuppressed patients are prioritized per the NIH.

1. Introduction

Since the initial description of Coronavirus Disease 2019 (COVID-19) in late 2020 and the identification of its causative agent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there has been a heightened concern about the vulnerability of patients with certain comorbidities, including immunocompromising conditions. The Centers for Disease Control and Prevention (CDC) identified early on a list of conditions and comorbidities thought to confer a higher risk for severe COVID-19, initially extrapolating from data on other viral illnesses, and then incorporating empirical evidence as it became available. The CDC also maintained a list of moderately to severely immunocompromising conditions (without distinction for level of risk within this group) for whom vaccination should be prioritized and, later on, an enhanced vaccination regimen was recommended, based on extrapolation from other conditions, such as influenza, as well as available empirical data (Table 1) [1]. The National Institutes of Health (NIH) further carved out a list of conditions defining patients “least likely to amount and adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes”, including certain entities of interest to hematology specialists, and recommended to prioritize limited therapeutics to this group when necessary (Table 1) [2].

In this review, we summarize the current understanding on the effect of common benign and malignant blood disorders on COVID-19 incidence and outcomes, as well as vaccine response, then we briefly review currently available SARS-CoV-2 vaccines, their

* Corresponding author. Division of Infectious Diseases & HIV Medicine, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue – Mailstop Fol. 5083, Cleveland, OH, 44106, USA.

E-mail address: elie.saade@uhhospitals.org (E.A. Saade).

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Table 1

High-risk conditions as classified by the CDC and NIH. High-risk.

CDC's moderate and severe immunocompromising conditions and treatment:

- Active treatment for solid tumor and hematologic malignancies*
- Receipt of solid-organ transplant and taking immunosuppressive therapy*
- Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic cell transplant (HCT) (within 2 years of transplantation or taking immunosuppressive therapy)*
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)*
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts less than 200/mm³, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., 20 or more mg of prednisone or equivalent per day when administered for 2 or more weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory*

National Institute of Health's prioritization list for most at risk conditions for inadequate immune response:

- Patients who are within 1 year of receiving B cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)*
- Patients receiving Bruton's tyrosine kinase inhibitors*
- Chimeric antigen receptor T cell recipients*
- Post-hematopoietic cell transplant recipients who have chronic graft-versus-host disease or who are taking immunosuppressive medications for another indication*
- Patients with hematologic malignancies who are on active therapy*
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid organ transplant (other than lung transplant)
- Solid organ transplant recipients who had recent treatment with T cell- or B cell-depleting agents for acute rejection
- Patients with severe combined immunodeficiencies
- Patients with advanced or untreated HIV

*Conditions of special interest to Hematology specialists.

indications and schedule with emphasis on the population of interest. Finally, we summarize the available therapeutic options for COVID-19 with emphasis on the population of interest as well.

2. Overview of COVID-19 risk and vaccination benefits in common hematologic conditions

2.1. Hematologic malignancies

Patients with hematologic malignancies (HM) are a heterogeneous group with a large variety of diseases and a broad spectrum of severity affecting the degree of immunosuppression and vulnerability to COVID-19; this is further compounded by the treatment received as well as age and comorbidities [3–6]. As a group, those patients are consistently shown to have a high risk of a severe and complicated COVID-19 course with high rates of hospitalization, respiratory failure, and death; the risk is particularly elevated in those with B-cell lymphoid malignancies who received lymphocytotoxic therapies. In addition, the humoral vaccine response in this high risk group is blunted and they are less likely to seroconvert after vaccination, although a relatively robust cellular immunity response to vaccine appears to be preserved; however, the data on cellular immunity is still too scarce to allow generalization [4–11]. A systematic review that identified 57 studies reporting on 7393 patients reported heterogeneous vaccine-induced seroconversion rates and cellular immunity in HM patients, but the response was in general lower than reported in healthy participants in the same studies, with the lowest immunity rates reported in CLL, and the highest in myeloproliferative disorders [6]. A meta-analysis of 64 studies (published through November 4, 2021) comprising 8546 adult patients with HM found a pooled anti-SARS-CoV-2 IgG antibody seroresponse (SR) to SARS-CoV-2 vaccination of 59%, which varied according to malignancy (myeloid having better response than lymphoid malignancies) and treatment history; the response was better in those who received stem cell transplant (SCT) or have not been treated, and poorer in those receiving chimeric antigen receptor T-cell (CAR-T) therapy or recent anti-CD20 therapy. Importantly, pooled SR to a third vaccine dose in a small subgroup of patients who didn't respond to the initial two doses was up to 55%, which supports a three-dose vaccine series [3]. Similarly, clinical data appear to confirm the vulnerability of patients with HM that persists despite vaccination. For example, a retrospective cohort study of electronic health records of more than 500,000 patients (including near 6000 with HM) from 63 healthcare organizations in the USA through October 2021 who were "fully vaccinated" for COVID-19 (defined as having received two doses of an approved mRNA vaccine or 1 dose of an adenovirus-vectored vaccine) found a cumulative risk of breakthrough of 13.4% in patients with HM, versus 4.5% for those without HM [12]. Breakthroughs frequently required hospitalizations (37.8% of cases) and resulted in a high fatality rate (5.7%). Of note, patients with HM who had breakthroughs were older and had more comorbidities than those without breakthroughs, in particular hypertension, diabetes mellitus type 2, and obesity [12]. Finally, the waning of immunity and the emergence of variants of concerns (VOC), some of which are associated with decreased neutralization effectiveness and unknown effect on cellular immune response, further supports the need for boosting and, possibly, modified formulation, especially in vulnerable groups, but further research is needed to evaluate the effectiveness of those strategies in protecting against infection, illness, and death [6].

2.2. Stem cell transplants and CAR-T cell treatment

Hematopoietic stem cell transplant (HSCT) patients are more prone to develop severe infections because of an impaired immune system. They are more susceptible to infections in the first few months after HSCT because of cytopenias and immunosuppressive medications including but not limited to tacrolimus, mycophenolate, and prednisone. Several studies early in the COVID epidemic showed increased morbidity and mortality in this group of patients. In a multicenter prospective survey involving 382 COVID-19 patients who had undergone allogenic and autologous hematopoietic stem cell transplant, 83.5% developed lower respiratory tract disease and 22.5% required admission to intensive care unit. Overall survival from the diagnosis was 77.9% and 72.1% in allogenic and autologous recipients, respectively. Factors associated with increased mortality included older age, need for intensive care unit admission, and immunocompromised status. Underlying diagnosis, time from HSCT, and graft-versus-host disease did not significantly impact the overall survival [13].

Similarly, patients receiving chimeric antigen receptor T-cell therapy (CAR-T) are also at high risk for poor outcomes from COVID-19 infection due to an immunocompromised state. They may be initially pancytopenic from lymphodepleting chemotherapy, and often remain lymphopenic and hypogammaglobulinemic for months to years after treatment which can predispose to infections. In a multicenter survey on patients with COVID-19 after CAR-T cell therapy, mortality was 44.6% (25 of 56 patients). These patients presented with various symptoms including fever, fatigue, myalgia, cough, vomiting, and diarrhea. Older age, worse performance status, and not being in clinical remission at the time of COVID diagnosis were additional risk factors associated with a poor outcome [14].

2.3. Sickle cell disease

Patients with Sickle Cell Disease (SCD) have been categorized as being at higher risk for COVID-19 severe illness and complications because of concerns about their compromised immune system related to functional hyposplenism, as well as their propensity to end organ damage, such as pulmonary and renal disease. In addition, SCD and COVID-19 are both considered to be thrombophilic conditions, with an increased risk of venous thromboembolism [15,16]. However, there is conflicting empirical evidence on whether patients with SCD experience more severe COVID-19 disease, and whether their mortality rate is greater than the general population. Some published case series and observational cohort studies reported a relatively mild and uncomplicated course [17–20] while others reported an increased risk of complications, hospitalization, and/or death [21–26]. A systematic review of case reports and observational cohort studies of patients with SCD and COVID-19 described that adults typically had a mild to moderate course, with few respiratory symptoms, similar to patients without SCD; studies that described more severe disease in patients with SCD and COVID-19 reported prolonged hospitalization with hypoxia, pneumonia, prolonged fever, multisystem inflammation, as well as complications typical in SCD, such as acute chest syndrome and severe pain crisis [26–29]. Patients with SCD had an increased risk of hospitalization (estimated at 2-to 7-fold in large cohort studies in the US and UK) and death (1.2-fold increase in mortality rate in aggregated data) [27]. However, the observed increased risk of death may have been related at least in part to the substantial comorbidity burden in patients with SCD (such as asthma, chronic obstructive pulmonary disease, hypertension, and chronic kidney disease), as the mortality risk was estimated to be no different than patients without SCD but with similar comorbidities and end organ damage [27]. Limited data from small studies suggest that hydroxyurea may have a protective effect, although others offer conflicting conclusions [23,27,28, 30].

2.4. Thalassemia

In patients with thalassemia, there is a concern for immunosuppression related to splenectomy, iron overload-related damage (to the heart and liver, among others), diabetes, and adrenal insufficiency with risk of decompensation. In addition, the thrombophilic risk of thalassemia compounds the risk of venous thromboembolism seen with COVID-19. Additional risks are associated with the use of chelation agents, such as renal toxicity and drug-induced agranulocytosis. However, there is conflicting evidence on whether thalassemia confers a higher risk of severe illness and complications with COVID-19. Data from small case series suggest a high rate of complications and hospitalizations with COVID-19 in patients with major thalassemia and in heterozygous carriers [31–36]. A systematic review series of COVID-19 and hemoglobinopathies that included articles published through October 2020 reported only 5 studies that included 63 patients with thalassemia patients, all from low-middle-income-countries, of which there were 13 (20.6%) deaths; the mortality rate was higher among patients with thalassemia and cardiovascular comorbidities [37].

3. Issues in prevention, quarantine, and isolation

3.1. Personal protective equipment

People who are immunocompromised would benefit from a lower threshold for use of personal protective equipment (PPE). The CDC provides guidance based mainly on expert opinion on recommended layers of protection stratified according to the community levels in the county, a composite of three metrics: new COVID-19 admissions per 100,000 population, the percent of staffed inpatient beds occupied by COVID-19 patients, and total new COVID-19 cases per 100,000 population [38]. When levels are high, immunocompromised patients should be counseled to avoid non-essential indoor activities in public, wear a well-fitting high-quality mask or respirator and practice physical distancing indoor in confined public spaces. Some patients and their providers may choose a lower

Table 2

ACIP recommendations for COVID-19 primary series and booster vaccination by age group.

Vaccine	Dose	Interval	
		General population	Immunocompromised
BNT162b2 and mRNA-1273 (mRNA vaccines)	Dose 1	Recommended for most.	
	Dose 2	3 (BNT162b2) or 4 (mRNA-1273), up to 8 weeks after dose 1	3 (BNT162b2) or 4 (mRNA-1273) weeks after dose 1
	Dose 3	5 months after dose 2	4 weeks after dose 2
	Dose 4	4 months after dose 2 if age >50 years	3 months after dose 3
	Dose 5	Not applicable	4 months after dose 4
Ad26.COV2.S (JNJ)	Dose 1	Limited indications (see text)	
	Dose 2	8 weeks after dose 1	An mRNA vaccine must be used; 4 weeks after dose 1
	Dose 3	4 months after dose 2 if age >50 years; only use mRNA vaccines	mRNA vaccine preferred; 8 weeks after dose 2.
	Dose 4	Not applicable	An mRNA vaccine must be used; 4 months after dose 1

threshold to practice such a level of self-protection. In addition, individuals who are immunocompromised should have easy access to rapid testing for earlier diagnosis.

3.2. Quarantine

Individuals with high-risk exposure (for example, those who are exposed for a single 15-minute exposure to one infected individual or several briefer exposures to one or more infected individuals adding up to at least 15 minutes during a 24-h period without a high-quality mask) should monitor themselves for symptoms of COVID-19 for the duration of incubation, up to 14 days. The threshold for testing immunocompromised individuals following exposure is usually lower because of the increased likelihood of infection. In general, fully vaccinated people should get tested 5–7 days after exposure and wear a mask for 14 days when in public, but do not need to quarantine. However, unvaccinated individuals should, in addition, be tested immediately and need to quarantine after exposure for 14 days or until a negative test obtained 5–7 days after the exposure. Immunocompromised persons remain at a relatively higher risk of developing infection after exposure despite vaccination, but data to make recommendation on post-exposure testing and isolation is currently lacking, and management should be individualized based on the individual's risk factors and circumstances (ability to physically distance at work, possibility of exposing high-risk individuals ...) [39].

3.3. Isolation

For most people, the recommended duration of isolation ranges from 5 to 20 days as of symptoms start (or positive test, if asymptomatic), depending on the severity of symptoms; the patient needs to be afebrile for 24 hours (without antipyretic use) and with improving symptoms, with the recognition that some symptoms (such as loss of taste or smell) may last months after recovery and do not indicate infectivity. In immunocompromised patients, a minimum of 20 days with confirmation of a negative viral testing is recommended prior to discontinuing isolation because of the concern for a prolonged shedding of replication-competent virus. Importantly, there are concerns that persistent prolonged viral replication in immunocompromised patients might facilitate the emergence of multiple mutations and, potentially, of viral strains that would be tolerant to natural or vaccine-induced immunity [40–44].

4. Vaccines

4.1. Available vaccines

At the time of this writing, there are three vaccines approved or authorized in the United States for the prevention of COVID-19: BNT162b2 from Pfizer-BioNTech, mRNA-1273 from Moderna, and the Ad26.COV2.S product from Johnson and Johnson's Janssen Pharmaceuticals (JNJ). Other vaccines are at different stages of testing or authorization in the US and internationally. All COVID-19 vaccines available in the USA to date target the spike protein of the SARS-CoV-2 virus. The mRNA vaccines use engineered lipid nanoparticles to deliver genetic material encoding for the antigens to the immune system cells; the JNJ product uses a replication-incompetent adenovirus to deliver DNA material. The mRNA vaccines are by far the most utilized in the United States; in addition to its later authorization in the U.S. relative to the mRNA vaccines, the Ad26.COV2.S product suffered from setbacks related to perceived lower efficacy in the initial clinical trials, and the post-authorization identification of a rare but potentially serious adverse

effect (vaccine-induced immune thrombotic thrombocytopenia or VITT), which led to a restriction of its authorization by the U.S. Food and Drug Administration (FDA) to individuals 18 years or older for whom other vaccines are not accessible or clinically appropriate or when the only alternative is not getting a vaccine [45].

4.2. Vaccine schedule (Table 2)

Both mRNA vaccines were initially authorized as a 2-dose regimen (separated by 3 weeks for BNT162b2, and 4 weeks for mRNA-1273), while the Ad26.COV2.S vaccine was authorized as a single injection. The ACIP then recommended an additional dose of the mRNA vaccine in adults who are immunocompromised (“in a manner similar to those who have undergone solid organ transplantation”) who initially received the 2-dose mRNA vaccine series, to be given 4 weeks after the second dose, then a booster dose 3 months later, and a fourth dose 4 months afterwards (a total of 5 doses). For those who initially received the Ad26.COV2.S vaccine, the ACIP recommended a dose of mRNA vaccine 4 weeks later, then a dose of either mRNA vaccines (preferred) or Ad26.COV2.S vaccine 8 weeks after, then a mRNA vaccine 4 months later (total of 4 doses). The current vaccine recommendations are dependent on age, comorbidities, and immune status, and are summarized in Table 2. Of note, CDC recommends not to delay vaccinations in patients who received monoclonal antibody therapy for COVID-19 infection. If a patient developed COVID-19 infection, CDC recommends postponing the next dose of COVID vaccine until symptoms resolve and patients are out of quarantine (usually 20 days).

Current guidelines recommend COVID-19 vaccine 3 months after HSCT. In addition, patients who had HSCT or CAR-T cell therapy and who have received one or more doses of COVID-19 vaccine prior to the treatment should be revaccinated (complete primary series and booster doses). However, the patient’s clinical team must make a decision regarding timing of vaccination based on immunosuppressive therapy, presence of graft versus host disease (GVHD) and local prevalence of COVID-19. A vaccine series given before recovery of the immune system may not induce a protective immune response, while delaying vaccination might place the patient at risk of infection. The long-acting monoclonal antibodies combination tixagevimab-cilgavimab, discussed below, might be administered to decrease the interim risk of infection [46]. Although they can get infected with COVID-19 in the hospital, patients with recent HSCT and CAR-T cell therapy are more likely to acquire infection from exposure to caregivers, and it is recommended that all close contacts of HSCT and CAR-T therapy patients receive COVID-19 vaccination as per CDC schedule.

4.3. Adverse effects and contraindications of interest

During the clinical trials of the SARS-CoV-2 vaccines, very few adverse effects were detected. However, during the post-marketing surveillance period, there has been an intense focus on adverse reactions. Perhaps the most notable and consequential adverse reaction is VITT, a rare complication associated with certain adenovirus-vectored SARS-CoV-2 vaccines (addressed elsewhere in this collection). In their systematic review and meta-analysis on COVID-19 vaccines in patients with HM, Piechotta et al. concluded that reported adverse events were largely consistent with the safety profile observed in the general population [6]. Adverse events of interest to the Hematology practitioners have been reported that we will briefly discuss here.

4.3.1. Secondary immune thrombocytopenia purpura (ITP)

Cases of ITP have been reported *de novo* after COVID-19 vaccination, and exacerbation of existing ITP has also been described following mRNA and adenovirus-vectored vaccines. Because of the rarity of the event and non-confirmed causal association as of yet, ITP should not be attributed to COVID-19 vaccination without the appropriate work-up for other possible etiologies. Patients with known ITP are much more likely to benefit from vaccination than developing adverse events, and vaccination is recommended for this group; ITP exacerbation, if it occurs, is usually transient and responds well to standard ITP treatment [47,48]. In conclusion, patients with prior ITP exacerbation temporarily associated with COVID-19 vaccination do not have a contraindication to receive the vaccine again as indicated, but it would be prudent to monitor their platelet count following vaccine receipt. Currently, mRNA vaccines are preferred for most groups, and the JNJ COVID-19 vaccine’s prescribing information recommends discussion of potential risks with patients with known ITP.

4.3.2. Autoimmune hemolytic anemia (AIHA)

AIHA has rarely been reported with COVID-19, and even more rarely with SARS-CoV-2 vaccination. A causal link between SARS-CoV-2 vaccination and AIHA can’t be currently established due to paucity of data, and specific recommendations for vaccinations can’t be made, although patients are more likely to benefit from vaccination in view of the rarity of any reported AE associated with AIHA [49–51].

4.3.3. Hemophagocytic lymphohistiocytosis

Case reports of hemophagocytic lymphohistiocytosis (HLH) temporally related to COVID-19 vaccination are rare, and a causal relationship is not confirmed [52–54]. A history of current or past HLH diagnosis does not preclude COVID-19 vaccination.

4.3.4. Paroxysmal nocturnal hemoglobinuria

Severe acute hemolysis induced by SARS-CoV-2 mRNA vaccines has been described in patients with paroxysmal nocturnal hemoglobinuria (PNH) [55]. This complication is also described in COVID-19, and vaccination of patients with PNH is not contraindicated as the benefits of vaccinating patients with PNH likely outweigh the risks [56].

5. Therapeutics

The major therapeutic categories which have been used in patients with COVID-19 include antivirals, antibody-based therapy, and immunomodulators. Treatment in patients with hematologic disease, however, requires special consideration, given higher risk of progression to severe disease, impaired or dysregulated immunity, impaired response to vaccination, and concomitant medication use which may interfere with COVID-19 disease or therapeutics. Immunocompromised individuals are typically underrepresented in clinical trials for COVID-19 treatment, making the results difficult to apply to this population. Moreover, no large randomized controlled trials have specifically been designed to study treatment of persistent COVID-19.

5.1. Convalescent plasma

Convalescent plasma obtained from recovering individuals, providing a passive means of protection via pathogen neutralization, was a promising early treatment for COVID-19 and an attractive approach for immunocompromised individuals unable to mount an effective immune response to the virus. However, based on the results of numerous randomized controlled trials as well as the analysis of a large, single-arm registry study, evidence suggested no benefit of convalescent plasma for patients hospitalized with COVID-19 and low-quality evidence for a marginal benefit in ambulatory patients, offset by potential harms including allergic reactions, transfusion-associated circulatory overload, and transfusion-related lung injury [57]. However, there was a suggestion that there may be a greater impact in individuals with impaired immune response, particularly if administered early in the course and utilizing plasma with high levels of antibodies specific to the SARS-CoV-2 S protein receptor-binding domain (RBD) [58]. Based on these findings, the FDA updated its EUA to restrict convalescent plasma treatment to high-titer plasma early in the disease course for hospitalized patients at high risk of progression or with impaired humoral immunity [59].

5.2. Monoclonal antibodies

A similar approach which has shown greater effectiveness in the ambulatory setting is treatment with monoclonal antibodies (mAbs). Neutralizing mAbs function by binding to the RBD, preventing viral S protein binding with the host angiotensin-converting enzyme 2 receptor. Two products previously having FDA EUA approval consisted of combinations of two mAbs with distinct target epitopes, bamlanivimab-etesevimab and casirivimab-imdevimab. However, with the emergence of new variants of concern, it has been difficult to maintain an effective mAb treatment option. Currently, the FDA has an active EUA for only one mAb agent, bebtelovimab, which retains activity against the omicron variant [60]. Several case studies, case series, and one multicenter study involving 88 patients have suggested benefit of mAb treatment of COVID-19 in patients with hematologic disease, based on successful clearance after prolonged viral shedding or improved outcomes relative to patients provided with alternative treatment [61]. These represent encouraging findings, though limited conclusions can be drawn in absence of a control group.

A unique application of a long-acting mAbs has been pre-exposure prophylaxis with tixagevimab-cilgavimab in individuals expected to have a poor response to immunization against COVID-19 [62]. This agent has been shown to have a half-life of approximately 90 days, with detectable serum levels for at least 9 months [63]. Tixagevimab-cilgavimab was shown to decrease the incidence of symptomatic COVID-19 infection for a six-month period following infusion, though there was no effect on mortality [64]. Of note, this treatment was found to retain activity against the omicron variant, though its effect was attenuated [65]. There has been a slight increase in congestive heart failure risk in patients receiving Tixagevimab-cilgavimab when compared to the placebo group but this did not reach statistical significance. This should be taken into consideration specifically when giving Tixagevimab-cilgavimab to patients who are at high risk for congestive heart failure. Monoclonal antibody prophylaxis with Tixagevimab-cilgavimab is an effective way to decrease COVID-19 infection in the first 3 months post-transplant when these patients are not eligible to receive a COVID-19 vaccine. Tixagevimab-cilgavimab provides protection for up to 6 months but COVID-19 vaccines should still be considered between 3 and 6 months depending on the patient's immunosuppressive therapy, GVHD and local COVID-19 prevalence.

5.3. Direct antiviral agents

5.3.1. Remdesivir

Remdesivir was the earliest direct-acting antiviral treatment option for COVID-19 and is still a mainstay of therapy for hospitalized patients [66]. As a nucleoside analog, the mechanism of action against SARS-CoV-2 is to serve as a substrate for RNA-dependent RNA polymerase, which leads to its incorporation into the growing RNA chain and subsequent chain termination. The standard course for remdesivir is five days of treatment, with more prolonged treatment only shown to have benefits in patients requiring mechanical ventilation [67]. Additionally, remdesivir may be administered for a three-day course in ambulatory patients at high risk for severe disease.

5.3.2. Oral antiviral agents

The first two oral antiviral agents, ritonavir-boosted nirmatrelvir and molnupiravir, emerged in late December 2021 for treatment of patients at high risk for severe disease in ambulatory settings [68,69]. Nirmatrelvir-ritonavir has proceeded to become the first-line treatment option for ambulatory patients, based on its potency, retained activity against omicron, and ease of administration, giving it at least one benefit against all other currently available outpatient treatment options. However, this treatment has many potential drug-drug interactions due to the potent cytochrome P4503A4 (CYP3A4) activity of ritonavir, limiting its use in patients requiring

transplant-related immunosuppressive treatment, such as calcineurin inhibitors and mammalian target of rapamycin inhibitors [70]. Lange et al. recommend holding tacrolimus during the 5-day treatment course, then reinitiating tacrolimus based on post-treatment levels. For cyclosporine, they recommend reducing the total daily dose by 80% for the duration of COVID-19 treatment and similarly reassessing levels following completion of the course. NIH guidelines similarly call for close monitoring of calcineurin inhibitors, and they caution that alternative therapy should be sought if close monitoring is not feasible [71]. The University Health Network/-Kingston Health Sciences Centre has developed a comprehensive guide to the management of nirmatrelvir-ritonavir drug-drug interactions in oncology, and the University of Liverpool has a drug interaction checker for all COVID-19 treatment options [72,73]. Nirmatrelvir-ritonavir is also not recommended in patients with severe renal impairment. Recently, reports have emerged of a rebound of COVID-19 symptoms and viral replication after completion of the 5-day nirmatrelvir-ritonavir treatment course [74]. No specific populations have been identified to be at higher risk for relapse, and at this time, no data are available to suggest that a longer or repeated treatment course would provide greater benefit.

5.4. Immunomodulators

The final major category of COVID-19 treatment currently in use is immunomodulatory agents. Currently recommended agents include glucocorticoids, interleukin-6 (IL-6) receptor antagonists, and Janus kinase (JAK) inhibitors.

5.4.1. Corticosteroids

Dexamethasone is thought to have benefit based on its anti-inflammatory activity in the setting of dysregulated systemic inflammation, and, in hospitalized patients requiring oxygen it has been shown to be associated with lower mortality and higher likelihood of hospital discharge at 28 days [75]. Few studies have measured the impact of dexamethasone treatment specifically on patients with hematologic disease. One single-center study noted that of approximately 800 patients with cancer and COVID-19, those with hematologic malignancy were more likely to receive corticosteroids and had a higher likelihood of mortality; however, selection bias likely was a factor as patients who were suspected to be at higher risk for decompensation may have been more likely to receive steroids [76]. Dexamethasone is a weak CYP3A4 inducer, thus, similar drug-drug interactions as nirmatrelvir-ritonavir should be considered though are not likely to be as limiting. When used as part of an induction regimen or anti-rejection agent for transplant, there are no specific guidelines or recommendations to modify this therapy in COVID-19, other than to ensure that at least the equivalent of 6 mg daily is given [77].

5.4.2. JAK inhibitors

Baricitinib and tofacitinib are JAK inhibitors which appear to possess a bifold role of both anti-inflammatory activity through mediation of cytokine signaling and antiviral activity through inhibition of receptor-mediated viral endocytosis. Benefits in clinical trials have included reduced mortality at 60 days, higher likelihood of clinical recovery, and lower likelihood of requiring mechanical ventilation [78,79]. Guidelines currently recommend baricitinib in combination with remdesivir as adjunctive therapy to dexamethasone in patients with rapidly increasing oxygen needs. On May 10, 2022, the FDA authorized baricitinib as a standalone treatment option for COVID-19, marking it as the second COVID-19 drug and first immunomodulatory agent with full FDA approval [80]. In COVID-19 clinical trials, thrombosis has been observed in similar distributions in treatment and placebo groups, in addition to lymphopenia, opportunistic infection, and major cardiac events [78,79]. While baricitinib has not been well studied in individuals with hematologic disease, the greatest safety concerns are likely related to theoretical risk of opportunistic infection and thrombosis in conditions associated with high baseline risk of thrombosis.

5.4.3. IL-6 receptor antagonists

Tocilizumab and sarilumab are IL-6 receptor antagonists and, similar to glucocorticoids and JAK inhibitors, are thought to attenuate an inappropriately robust immune response to the SARS-CoV-2 virus which may partially be mediated by the release of IL-6 and other cytokines. Tocilizumab is recommended in combination with dexamethasone for patients with COVID-19 requiring invasive mechanical ventilation or extracorporeal membrane oxygenation. It also may be considered in patients with rapidly increasing oxygen needs, though these patients would also be candidates for baricitinib. Trials have shown mixed results but have indicated a reduced likelihood of clinical deterioration; mortality benefits have been demonstrated less consistently and in more heterogeneous populations [81,82]. Moreover, patients with significant immunosuppression were not well represented in these trials. Due to the potential risk of adverse events including thrombocytopenia, anemia, opportunistic infection, and gastric perforation, this drug should be used cautiously in patients with hematologic disease.

5.5. Prioritization of therapeutic agents

Throughout the pandemic, there have been periods of supply constraint related to limitations in production, logistical issues with dissemination, and high demand resulting from COVID-19 surges. In order to ensure that available therapies are distributed to populations who would derive the greatest benefit, a means of prioritization must be established by individual centers. In these cases, it is imperative to consider the potential for intensified existing inequities in healthcare and determining how best these can be mitigated. Stratifying by diagnosis may inadvertently reverse efforts to provide fair access to treatment. The NIH has provided a management strategy which takes into consideration an individual's underlying risk of progression to severe COVID-19 disease based on age, immune status, vaccination status, and underlying medical conditions (Table 3) [83].

Table 3
NIH prioritization recommendations for COVID-19 treatment.

Tier	Risk Group
1	● Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); or ● Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥ 75 years or anyone aged ≥ 65 years with additional risk factors).
2	● Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥ 65 years or anyone aged < 65 years with clinical risk factors)
3	● Vaccinated individuals at high risk of severe disease (anyone aged ≥ 75 years or anyone aged ≥ 65 years with clinical risk factors) Note: Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.
4	● Vaccinated individuals at risk of severe disease (anyone aged ≥ 65 years or anyone aged < 65 years with clinical risk factors) Note: Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.

6. Practice points

- Patients living with blood disorders are frequently at high risk for infections because of immunosuppression related to their pathology or its treatment, such as steroids, chemotherapy, and myeloablative therapies.
- Multiple layers of protection are applied to minimize the risk, starting with avoidance of high-risk settings (poorly ventilated indoor public spaces) and using high-quality well-fitted face masks.
- SARS-CoV-2 vaccines, even though relatively less effective in the immunocompromised host, are a pillar of prevention of serious outcomes, and an enhanced regimen with additional boosting is recommended in this group.
- Passive immunization with Tixagevimab-cilgavimab is available and indicated in immunocompromised patients unable to mount a protective response.
- Multiple therapeutic agents are available and need to be prioritized to this high-risk group when the demand and supply are mismatched; resources to inform the prioritization are available from the CDC and the NIH.
- These therapies include monoclonal antibodies matched to the predominant circulating SARS-CoV-2 variant, direct intravenous (remdesivir) or oral antivirals (ritonavir-boosted nirmatrelvir and molnupiravir) and immunomodulators (corticosteroids, baricitinib, tocilizumab, and others).

7. Research agenda

- Objective evidence on the risk and severity of COVID-19 in specific hematologic disorders
- Elucidation of mechanisms underlying the vulnerability to SARS-CoV-2 in specific hematologic disorders
- Effectiveness of different SARS-CoV-2 vaccines 2 in specific hematologic disorders
- Optimal vaccination regimen in immunosuppressed patients and in specific hematologic disorders

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Conflicts of interest

The authors have no conflict of interest related to this manuscript to declare.

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