Coronavirus Disease-2019 in the Immunocompromised Host

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Immunocompromised host • Pneumonia • Hematologic malignancy • Immunosuppression

KEY POINTS

- Immunocompromise refers to a host's inability to combat infections from a variety of partial or total immune defects and can occur in the setting of diseases such as hematologic malignancies, immunosuppression use, primary immunodeficiency syndromes, and human immunodeficiency virus infection.
- Hospitalization risk, intensive care unit admission, and mortality are substantially higher after severe acute respiratory syndrome coronavirus 2 pneumonia in immunocompromised hosts.
- Immunocompromised hosts are underrepresented in clinical trials of vaccines and other treatments, and therefore efficacy data are often inferred or based upon small studies.
- Vaccines and treatments are often effective in immunocompromised hosts, but persistent viral replication due to impaired immunity can hinder the efficacy of these interventions.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory virus that originated in Wuhan, China in 2019. Since that time, SARS-CoV-2 has been responsible for over 6 million deaths from coronavirus disease-2019 (COVID-19).[1] Respiratory viral infections, in general, place an outsized burden on immunocompromised hosts, and increase the mortality.[2] Therefore, there was significant concern from the outset of the pandemic that SARS-CoV-2 infection would similarly impact immunocompromised patients disproportionately. This review focuses on the specific impact of COVID-19 on immunocompromised patients.

The term "immunocompromise" describes patients who have an impaired or absent immune system, limiting a host's ability to combat pathogens. Immunodeficiencies are classified as either primary or secondary. Primary immunodeficiencies (PIDs) are intrinsic to the immune system. Examples include congenital conditions such as severe combined immunodeficiency (SCID), caused by various mutations which can impact many immune cell lineages, and common variable immune deficiency (CVID), which is caused by a diverse array of genetic conditions that result in varying degrees of hypogammaglobulinemia.[3] Secondary immunodeficiencies refer to those acquired through conditions that depress the immune system. These include

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hematological malignances, solid and hematopoietic transplantation, infection with the human immunodeficiency virus (HIV), chronic immunosuppressive medication use, and others. In these cases, the period of immunocompromise may be limited in duration; for example, a patient with leukemia may no longer be immunocompromised once their disease is in remission and leukocyte counts recover, or a patient receiving biologic immunosuppressive therapy may no longer be immunocompromised once therapy has completed and enough time has lapsed to allow for immune recovery. On the contrary, comorbidities that may impact immune function, such as diabetes, do not necessarily connote an immunocompromised state, but are worthy of consideration because they are often independently associated with poor outcomes after COVID-19.[4,5] **Table 1** shows examples of high-risk groups who we consider to be immunocompromised and their attendant immune deficits.

Immunocompromised hosts are at considerable risk for a variety of infections. For example, bacterial pneumonia has been estimated to account for 30% of intensive care unit (ICU) admissions in patients with cancer.[6] In another study of severe influenza pneumonia, 12.5% of patients admitted to the ICU were immunocompromised, indicative of a higher propensity toward critical illness after infection.[7] Indeed, mortality was over twofold higher among immunocompromised patients with influenza pneumonia. Other respiratory viruses also affect the immunocompromised; a recent retrospective cohort study of 1643 hematopoietic cell transplant (HCT) patients found increased mortality in allogeneic recipients infected with human rhinovirus (HRV) and adenovirus lower respiratory infections.[2] Finally, human herpesvirus-6 (HHV-6) and cytomegalovirus (CMV) have long been associated with increased mortality amongst HCT recipients.[8]

Considering that over 500 million cases of COVID-19 have been reported worldwide since the pandemic began, it is likely that several million immunocompromised hosts were infected, extrapolating from the estimate that 2.7% of the American adult population are immunocompromised.[9] Research within this specific vulnerable population has not been commensurate to the substantial body of literature for COVID-19 in general. This review will summarize the current scientific literature that discusses the impact of COVID-19 on immunocompromised hosts. We will discuss mechanisms for COVID-19's affinity for the

Table 1
Examples of immunocompromised conditions and possible mechanisms of immunocompromise

Immunocompromised Condition	Mechanism of Immunocompromise	Immune Deficits
Hematologic malignancies	Marrow infiltration and cytotoxic chemotherapy	Lymphopenia Neutropenia Impaired cellular immunity Impaired humoral immunity
Hematopoietic cell transplantation	Corticosteroid use, immunosuppressive medications (eg, tacrolimus, sirolimus, and ibrutinib)	Lymphopenia Neutropenia Impaired cellular immunity Impaired humoral immunity
Solid organ transplant (kidney, lung, and heart)	Corticosteroid use, immunosuppressive medications (eg, tacrolimus, sirolimus, and cyclosporine)	Impaired cellular immunity Impaired humoral immunity
Human immunodeficiency virus (HIV)	Apoptosis of T cells	Lymphopenia Impaired cellular immunity Impaired humoral immunity
Autoimmune rheumatology diseases requiring immunosuppressive drug therapy	Use of immunosuppressive agents (eg, methotrexate, TNF-alpha inhibitors, and specific interleukin inhibitors)	Lymphopenia Impaired cellular immunity Impaired humoral immunity Impaired innate immunity
Primary immunodeficiency syndromes	Hereditary agammaglobulinemia, defective phagocytosis, and impaired leukopoiesis	Lymphopenia Neutropenia Impaired cellular immunity Impaired humoral immunity Impaired innate immunity

immunocompromised, compare clinical data between immunocompromised and immunocompetent hosts, and examine the evidence supporting treatment strategies within immunocompromised hosts who develop COVID-19.

MECHANISMS OF IMMUNOCOMPROMISE

The innate immune response is driven by cells such as neutrophils, macrophages, and natural killer cells. The innate immune response is evolutionarily ancient and is often the first defense against many pathogens, including SARS-CoV-2. Impaired innate immunity may be correlated with COVID-19 severity. For example, in a study of 84 COVID-19 patients, of whom 44 were critically ill, the presence of immature neutrophils, defined by low CD13 expression and characterized by diminished antimicrobial and phagocytic activity, was associated with a critical illness.[10] Similar findings were seen in monocytes, and the diminished functional capacity of monocytes was correlated with increased risk for septic shock rate and mortality. Impaired type 1 interferon responses measured in the peripheral blood were also associated with severe illness in 50 patients with COVID-19 of variable severity.[11] On the contrary, more exuberant type 1 interferon responses that occur later in the course of infection have been associated with a worsening of lung injury, indicating that these innate immune responses may have salutary or harmful roles depending upon when they occur within the course of disease.[12] Of note, these studies were conducted in immunocompetent hosts and were performed during an acute infection, and although the findings indicate that innate immune impairments are associated with higher COVID-19 severity, these findings require validation in immunocompromised hosts who are evaluated before the onset of disease.

Cellular, or cell-mediated, immunity, typically refers to host response involving T cells, though notably many innate immune cells also have a direct cell-mediated anti-pathogen response. In many immunocompromised hosts, cellular immunity can be impaired and lead to worsened outcomes after COVID-19. In a study comparing over 1400 immunocompetent COVID-19 patients to 166 immunocompromised patients, lymphopenia was associated with threefold mortality increase in the latter.[13] The immunocompromised cohort consisted of patients with autoimmune rheumatologic diseases (ARD) (39.2%) as well as patients with hematologic malignancies (21.1%), solid malignances (19.3%), and solid organ transplant (SOT) recipients (18.1%). Specifically, CD8 cells may have an important role in determining outcomes after COVID-19. In a prospective cohort study of 106 patients with cancer, lower peripheral blood CD8 T-cell counts were correlated with a higher COVID-19 viral load and associated with higher mortality.[14] However, hematologic patients with cancer with preserved CD8 counts had low viral loads and decreased mortality, even among patients with impaired humoral immunity. Of note, 23% of patients with hematologic malignancy had no detectable anti-SARS-CoV-2 T-cell responses. In another cohort of 79 COVID-19 patients, 36 immunocompromised hosts had significantly fewer CD3+ T -cells and CD3+/CD4+ T cells compared with 20 patients above age 60 and 23 patients with diabetes.[15] T cells from immunocompromised patients produced less interferon-gamma compared with elderly patients, but there was no difference in interferon production between diabetic and immunocompromised patients. However, this study included patients with renal disease and cirrhosis as part of its definition of immunocompromised hosts. Further detailing the role CD8 cells play, a retrospective case-control study of 174 COVID-19 hospitalized patients in Spain showed that patients admitted to the ICU had lower CD8 counts compared with patients admitted to the general wards.[16] CD4 counts did not vary between ICU and non-ICU admitted patients. However, in general, the classification of immunocompromise should precede the infection, and in this study, most of the patients did not have a disease that would indicate immunocompromise.

In addition to impaired cellular immunity, immunocompromised hosts may have diminished humoral immunity, defined by an impaired ability to produce pathogen-specific antibodies against COVID-19 and other pathogens. For example, a study of 103 patients with cancer showed that delayed viral clearance was associated with loss of antibody production, despite adequate T cell response to infection.[17] Prolonged viremia was driven by B-cell depletion, potentially indicating that the resolution of infection depends upon adequate humoral immunity. In a study of lymphoma patients, B-cell-depleting therapies, such as rituximab, were associated with higher rates of hospital readmission and persistent SARS-CoV-2 positivity.[18] This diminished humoral response may increase the risk in for adverse outcomes; a study of 111 patients with lymphoma admitted to French hospitals for the treatment of COVID-19 found that anti-CD20 therapies increased the risk of mortality by over two-fold.[19] With regards to the development of humoral immunity after infection, Wunsch and colleagues[15] found in a cohort of 70 patients with SARS-CoV-

2 infection IgG ELISA antibody responses measured after infection that 16 patients lacked antibodies. Of these 16 patients, 11 were immunocompromised. This lack of humoral immunity can in rare instances lead to immune escape by SARS-CoV-2 variants.

Long-term shedding of COVID-19 in immunocompromised patients has been well described in transplant recipients and patients with cancer with B cell depletion.[20–24] Many of these cases describe changes in viral spike protein despite repeated treatment with antivirals. For example, one renal transplant patient with COVID-19, over a 145-day course of infection, SARS-CoV-2 viral spike proteins showed increased resistance to neutralizing antibodies.[20] These mutations have been shown to mimic variants from Brazil and the United Kingdom, though no clear link between long-term shedding and the evolution of COVID-19 variants have been identified.[20] In addition to the potential for mutations in the spike protein, resistance to antiviral agents may also arise in patients with long-term shedding[24]; this was most recently described in a cancer patient with B cell depletion.[24] These examples cite the risk long-term shedding of COVID-19 poses in immunocompromised patients and the need for effective prevention and treatment methods.

Clinical Outcomes After Coronavirus Disease-2019 Infection in Immunocompromised Hosts

Immunocompromised patients generally develop more severe illness after SARS-CoV-2 infection than immunocompetent patients. However, the studies discussed here need to be interpreted in the context of which variants dominated during the time of study and the availability of vaccines and effective therapies. We will discuss COVID-19 disease severity in the immunocompromised and considerations amongst different types of immunocompromised patients.

Immunocompromised patients may have a higher ICU admission rate and longer hospital lengths of stay. A Turkish retrospective case-control study reported a 22% ICU admission rate among 156 immunocompromised patients compared with 9% ICU admission rate among 312 nonimmunocompromised patients between April 2020 and October 2020.[25] Length of stay was longer in the immunocompromised cohort as well. The immunocompromised cohort included people living with HIV (PLWH), cancer, rheumatologic disease, and those who were on immunosuppressive medications. Immunocompromised patients may also have higher mortality rates compared with those in the immunocompetent. For example, a separate Korean retrospective cohort study of 871 immunocompromised patients and 5564 nonimmunocompromised patients found that immunocompromised patients had a mortality of 9.6%, over four times higher than the 2.3% mortality rate observed in immunocompetent patients.[26] Immunocompromised patients included those with HIV/AIDs, malignancy, SOT, and immunosuppressive medication use. Smaller cohort studies have also shown a mortality rate three to four times higher in immunocompromised patients.[25]

Immunocompromised patients who are mechanically ventilated often present with more severe acute respiratory distress syndrome (ARDS). For example, a retrospective cohort of 1594 patients with COVID-19, of whom 166 were immunocompromised, found that the mean Sap02/Fi02 ratio was 251 in immunocompromised patients, compared with 276 in immunocompetent patients.[13] Mild ARDS (Sap02/FiO2 >235 mm Hg) occurred in 42.3% of the immunocompetent grouped, compared with 33.7% of the immunocompromised group, and moderate ARDS (Sap02/FiO2 >160 mm Hg) occurred in 25.6% of the immunocompetent group compared with 33.1% of the immunocompromised group. No significant difference was observed in the rate of severe ARDS (Sap02/FiO2 <100 mm Hg) between the two groups. Immunocompromised patients had higher mortality, and among immunocompromised patients, older age, the presence of ARDS, and severe lymphopenia were predictors of mortality. These studies show the shift to a higher disease severity among COVID-19 patients.

Hematologic malignancy

Patients with hematologic malignancy have been shown to have high rates of hospitalization for COVID-19. For example, a European multicenter analysis of 3801 patients with hematologic malignancies who developed COVID-19 reported a hospitalization rate of 74%.[27] Other studies have also reported high hospitalization rates; for example, Mato and colleagues[28] reported a 25% admission rate among 174 patients with chronic lymphocytic leukemia (CLL). ICU admission rate has high as 18% have been observed, with a median length of stays as long as 15 days.[27] Mortality is often high in hematologic patients with cancer. For example, in 174 patients with CLL, 33% of patients died during the analysis.[28] Similarly, a study of 3801 patients with hematologic malignancies showed a mortality rate of 31%, with the highest found in patients with AML or myelodysplastic syndrome (~40%).[27] Smaller cohort studies have confirmed a case fatality rate of about 40%

among patients with hematologic malignancy. Lastly, patients with hematologic malignancies often require vasopressor support and renal replacement; in a cohort of patients with CLL, 27% required vasopressor support and 11% required hemodialysis.[28] Reassuringly, survival in patients with CLL may be improving with newer variants.[29]

Solid malignancy

Several studies have shown that solid malignancy COVID-19 patients have a high hospitalization rate. A French retrospective cohort study of 212 solid tumor patients with cancer, of whom about 75% were undergoing active treatment of cancer, found a similar 70% rate of hospitalization, but a lower rate of ICU admission (12%).[30] Half of this cohort had undergone chemotherapy in the first 3 months, and overall mortality was 30%.

Furthermore, Dai and colleagues[31] showed an ICU admission rate of 20% for 105 hospitalized patients with cancer, compared with 8% in 536 non-patients with cancer, and ICU survivors with cancer had a mean 27-day length of stay compared with 17 in ICU survivors without cancer. The cancer cohort in this study included patients with lung, breast, thyroid, blood, cervical and esophageal cancer. In addition, death occurred in 11% of the cancer cohort compared with 4% in the noncancer cohort. Of all the cancers, hematologic and lung cancers had the highest mortality rates at 33% and 18%, respectively. This suggests that though patients with lung cancer usually do not meet the definition of immunocompromise, their risk of death is substantially higher than in non-patients with cancer. Though it is not clear how lung cancer increases mortality in patients with COVID-19, it is possible that this is either due to the extent of preexisting lung disease or a direct effect from smoking.[32] Further work is necessary to understand the mechanisms driving increased in mortality in lung patients with cancer with COVID-19.

In general, patients with hematologic and lung cancers or metastatic cancers had more severe COVID-19 illness. To wit, Dai and colleagues[31] found that 10% of patients with cancer required mechanical ventilation, compared with less than 1% of non-patients with cancer. The authors also found that patients with cancer had higher rates of renal replacement therapy and extracorporeal membrane oxygenation compared with non-patients with cancer, in addition to symptoms such as fever or chest pain.

Risk factors that have been reported to correlate with disease severity in immunocompetent patients have been validated in patients with cancer.[33] For example, a Chinese comparative study showed that old age, d-dimer, elevated tumor necrosis factor (TNF) alpha and N terminal pro-brain natriuretic peptide (pro-BNP) may be correlated worsening hypoxemia in solid and hematological patients with cancer admitted with COVID 19.[34] Furthermore, in an analysis of 218 solid and hematologic patients with cancer, D-dimer levels were twice as high in patients with cancer who died; serum lactate and lactate dehydrogenase were also higher among decedents.[35] Furthermore, CRP and ferritin have been shown to be higher in immunocompromised patients compared with immunocompetent patients.[25] This suggests that serum biomarkers which correlate with disease severity in non-patients with cancer are also applicable to patients with cancer.

Hematopoietic cell transplantation

A study of 382 HCT recipients in Europe during the first few months of the pandemic showed a mortality of 22% in allogeneic transplant recipients and 28% in autologous transplant recipients; children had a mortality of 7%, lower than adults but exponentially higher than the mortality observed in children who were not HCT recipients.[36,37] Older age and more severe immunodeficiency were associated with a higher chance for death. Furthermore, an observational cohort study of 86 HCT recipients in Brazil showed that 70% required hospitalization and 14% required ICU admission.[38] Mortality in this cohort was 30%, with a 34% mortality rate among the 62 adult patients compared with 21% in the 24 pediatric patients. In general, large studies of HCT recipients who are infected with SARS-CoV-2 are lacking.

Solid organ transplant

SOT recipients also have poorer outcomes after COVID-19. In over 17,000 patients with SOT, of whom 1682 developed COVID-19, COVID-19 increased the rate of death by nearly ten-fold, and SOT recipients hospitalized with COVID-19 were about 2.5 times more likely to die than those hospitalized with non-SARS-CoV-2 pneumonia.[39] In-hospital mortality among those who developed COVID-19 was 17%, and 21% required ICU admission. SOT recipients with COVID-19 had an increased length of stay (LOS) compared with SOT patients with non-COVID-19 pneumonia (6 vs. 4 days). Similar to the general population, certain comorbidities increase hospitalization risk in SOT recipients. For example, a case-control series of 47 SOT recipients found that chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM), and hypertension (HTN) were more prevalent in

the hospitalized patients compared with the non-hospitalized control group.[40]

In 49 advanced heart failure (HF) patients admitted for COVID-19, heart transplant (HTx) patients had worse mortality compared with left ventricular assist device (LVAD) and HF patients.[41] Specifically, mortality for the HTx group was 18.9% compared with 12.5% for LVAD and 11.5% for HF, respectively. Similarly, HTx patients, who are often on immunosuppressive medications, have been shown to have higher ICU LOS compared with HF patients. Kidney transplant recipients (KTx) show similar vulnerability to COVID-19. An international registry of 9845 KTx recipients reported that 144 patients required hospitalization.[42] The mortality rate was 32%; 29% were intubated and 52% developed acute kidney injury. Lymphopenia, elevated lactate dehydrogenase and elevated procalcitonin were all correlated with increased mortality. Outcomes may be more severe among lung transplant (LTx) recipients, as a French cohort analysis of 35 LTx patients with COVID-19 reported a hospitalization rate of 88.6%.[43] 42% were admitted to the ICU, and 52% required mechanical ventilation. 14% of the 35 LTx patients died after COVID-19.

People living with human immunodeficiency virus

COVID-19 may more severely affect PLWH who have uncontrolled HIV as compared with their well-controlled counterparts. For example, in an Italian study of 69 PLWH, 38 hospitalized patients had an average nadir CD4 count of 167 compared 399 in those who were not hospitalized.[44] However, the hospitalization rate remains high even among PLWH on antiretroviral therapy (ART). In a large Spanish cohort of 77,590 PLWH on ART, 63% of the 236 PLWH diagnosed with COVID-19 required hospitalization.[45] Of those 151 hospitalized patients, the ICU admission rate was about 9% and the mortality rate was 11%. Of the 15 PLWH admitted to the ICU, the mortality rate was 33%. The median LOS for 116 patients who survived to hospital discharge was 7 days. Similar to the general population and other immunocompromised patients, age and number of comorbidities were highly correlated with hospitalization, ICU admission, and death rates.

Autoimmune rheumatologic disease

Patients with rheumatologic illness are also at high risk for severe complications from COVID-19. For example, a cohort of 58,052 Danish patients with inflammatory rheumatologic diseases had a 50% higher probability of admission compared with the general Danish population of 4.5 million.[46] The risk was 30% higher for patients with rheumatoid arthritis and over 80% higher for patients with vasculitis. However, the use of immunosuppressive agents (TNF-alpha inhibitors and steroids) surprisingly did not impact admission rate. Hospitalized patients with rheumatoid arthritis, particularly those with lung or cardiovascular disease, may have the more severe infection than hospitalized patients without ARD. In a case-control study comparing 2,379 patients with ARD to those without, ARD increased the risk of hospitalization by 14%, ICU admission by 32%, acute kidney injury by 81%, and venous thromboembolism by 74%, but did not increase the risk for mechanical ventilation or death.[47] Severe outcomes were more common for patients on glucocorticoids, but not DMARDs (disease-modifying antirheumatic drugs). In a study of 52 patients with systemic ARD, of whom 75% were on immunosuppressive therapy and 31% on biologic therapies, the requirement for mechanical ventilation was threefold higher in patients with rheumatologic disease compared with matched controls. However, mortality was indistinguishable between the two groups. Similar to other patients, a greater number of comorbidities increases the likelihood of severe COVID-19 in patients with ARD. For example, in patients with inflammatory bowel disease with two or more comorbidities, such as heart disease, diabetes, and kidney disease, severe COVID-19 was more common than in patients with one or zero comorbidities.[48]

Primary immunodeficiency

Little data exist for patients who have non-HIV immunodeficiency. In an Italian case series of seven patients with PIDs, six were hospitalized, and three were admitted the ICU.[49] Of the hospitalized patients at time of publication, 1 patient died in hospital, three were discharged and two were still being treated. The length of stay ranged between 3 days to 25 days.

TREATMENT

In general, there is a paucity of randomized controlled trial data examining the efficacy of anti-SARS-CoV-2 treatments in immunocompromised hosts. For example, in a recent randomized controlled trial of high-risk individuals who developed COVID-19 and were randomized to nirmatrelivir/ritonavir or placebo, fewer than 30 patients met any criteria for immunocompromise as we outline above.[50] Most data comes from observational or case-control studies. In this section, we will discuss studies that show the efficacy of antiviral, monoclonal antibodies, and convalescent

plasma to treat, preempt, or prevent COVID-19 in immunocompromised patients.

Little data exist regarding antiviral therapy and its efficacy specifically in the immunocompromised. One challenge with the use of antiviral therapy is that the kinetics of viral replication necessitate prompt therapy to ensure an adequate outcome[51]; there is no clear evidence that replication is more rapid in immunocompromised hosts, despite the possibility due to impaired innate and cellular immunity. In one series of 31 ARD patients treated with nirmatrelivir/ritonavir (29) and molnupilavir during the first 5 days of COVID-19 diagnosis, no patients were hospitalized, but most (94%) were fully vaccinated,[52] and no comparator arm was studied. Little efficacy data is available for remdesivir in immunocompromised hosts; a case study suggested that remdesivir can reduce viral load in immunocompromised patients with persistent infections.[53] A recent randomized, double-blind, placebo-controlled trial found that a 3-day course of remdesivir in non-hospitalized patients with COVID-19 with high-risk conditions reduced the risk for hospitalization or death by 87%; however, only 4% of patients were immunocompromised.[54] Given the possibility of prolonged viral replication, multiple courses or longer courses of remdesivir may be necessary in immunocompromised hosts, but prospective studies comparing these strategies to usual care are necessary. In general, the evidence for the efficacy of antiviral therapy in immunocompromised hosts is lacking, but antiviral therapies are reasonable to use given the high probability of adverse outcomes in immunocompromised hosts.

It is unclear as to whether anti-inflammatory drugs are as effective in immunocompromised COVID-19 patients as in the general population. For example, a multicenter cohort study of 80 KTx patients showed that the mortality rate among patients treated with the interleukin-6 inhibitor tocilizumab was around 33%,[55,56] whereas the overall mortality rate for KTx patients with COVID-19 has been estimated to be around 24%. However, it is likely there is a selection bias as sicker patients tend to be treated with monoclonal antibodies, and prospective studies with appropriate controls are lacking. Similarly, studies regarding the use of the interleukin-6 inhibitor sarilumab have also excluded patients on immunosuppressive medications. The Infectious Disease Society of America (IDSA) does not promote nor discourage the use of tocilizumab and sarilumab in immunocompromised due to lack of available evidence.[57] Janus Kinase Inhibitors such as baricitinib have not been well studied in the immunocompromised. Both the RECOVERY trial and COV-BARRIER trial showed that baricitinib reduced risk of death in COVID-19 patients; however, only RECOVERY included immunocompromised patients, whereas COV-BARRIER excluded them.[58,59] The IDSA points out that data supporting the use of Janus kinase inhibitors in immunocompromised hosts is lacking.

COVID-19 convalescent plasma (CCP) has been used in immunocompetent patients with variable evidence for efficacy. Although this may be useful in immunocompromised patients who cannot generate a humoral response, high-quality randomized, placebo-controlled trials have shown no benefit.[60] Lower quality studies have suggested efficacy under some circumstances. For example, in a propensity score-matched analysis of 112 patients with hematologic malignancies, most of whom received other nonplasma therapies, the use of convalescent plasma decreased mortality by 63% among patients who were exposed to anti-CD20 antibodies in the subgroup of patients with B-cell neoplasms.[61] Transfusion reactions were rare. A Swedish cohort of 28 immunocompromised COVID-19 patients showed that 46% had clinical improvement by at least one score one WHO scale on week after convalescent plasma administration.[62] No comparator arm was studied. The United States Food and Drug Administration Emergency Use Authorization authorizes CCP use in patients with immunosuppressive conditions, but data is limited and caution is necessary when extrapolating data from immunocompetent hosts.[57]

VACCINATION

Vaccinations are effective for reducing mortality in immunocompromised patients. For example, a retrospective British study examining vaccine efficacy in SOT patients including 39260 double vaccinated patients, 1141 single vaccinated patients and 3080 unvaccinated patients showed a 20% reduction in risk of death in vaccinated patients.[63] However, vaccination may not effectively decrease risk of positive SARS-CoV-2 test, as the risk-adjusted infection incidence rate was 1.29. Moreover, although two doses of ChAdOx1-S vaccines reduced the risk of death, similar efficacy was not observed with BNT162b2.

However, vaccines may be less effective for the immunocompromised compared with the immunocompetent. For example, one comparison prospective study detailing humoral immune response between 54 immunocompetent patients and 57 immunocompromised patients showed

that some immunocompromised patients, namely patients with PIDs and rheumatologic disease, show declining immunity to COVID-19 as time progresses after two administrations of BNT162b2 vaccine.[64] Among the immunocompetent patients, PLWH and CKD patients, all had detectable antibodies at 2 weeks and 3 months post vaccination. The mean CD4 count for the PLWH was 254. However, subgroup analysis showed that 50% of the rheumatologic patients and 94.5% of the (PID) group had antibodies at two weeks. An inferior response to SARS-CoV-2 vaccination in immunocompromised patients has been shown in other studies. For example, an Austrian prospective cohort studied antibody response to COVID-19 vaccination in 15 healthy controls compared this to 74 patients previously treated with rituximab.[65] All healthy patients developed antibodies, but only 39% of the rituximab group developed antibodies to spike proteins following vaccination.

Lastly, COVID-19 hospitalization following vaccination, commonly referred to as "breakthrough cases," are more frequent in the immunocompromised. For example, an American study of 45 vaccine breakthrough COVID-hospitalizations reported that 44% were immunocompromised, and an Israeli cohort of 152 hospitalized fully vaccinated patients reported that 40% were immunocompromised.[66,67] Of the 60 immunocompromised fully vaccinated patients in the Israeli cohort, 18 had a poor outcome, which was defined as either requiring mechanical ventilation or death. Knowing that the prevalence of immunocompromise in the United States is around 2%, it follows that breakthrough infection seems to occur much more frequently among immunocompromised patients. Two studies prove this point more definitively. In a study of 6,860 cases of breakthrough COVID-19 after vaccination, patients with hematologic malignancies had over a four-fold higher risk for breakthrough infection,[68] with the highest rates seen in patients with leukemia or myeloma. Proteasome inhibitors and other immunomodulators significantly increased the risk for breakthrough infection. Similarly, in a study of over 45,000 patients with cancer, primarily with solid tumors, the overall incidence of breakthrough COVID-19 was 13.6%.[69] Mortality rate may be higher after breakthrough infection in immunocompromised patients. A cohort study of 54 fully vaccinated hematologic and solid tumor patients with cancer who developed breakthrough COVID-19 reported a 65% hospitalization rate, 19% ICU admission rate and 13% mortality rate,[70] not markedly different from adverse event rates among unvaccinated patients with cancer.

Pre-Exposure Prophylaxis

A preexposure prophylaxis strategy may be effective to mitigate COVID-19 severity in the immunocompromised. The PROVENT trial is a 2:1 randomized double-blind placebo-controlled study of 5197 patients investigating the use of tixagevimab and cilgavimab, a cocktail of two monoclonal antibodies that bind to non-overlapping sites from the SARS-CoV-2 spike protein, in preventing symptomatic COVID-19 in the at-risk patients, such as those with chronic obstructive pulmonary disease, immunocompromise, or elderly. Results show that the medication has a 77% risk reduction compared with placebo and 83% reduction at 6 months analysis.[71] As a result, the Infectious Diseases Society of America guidelines and US Food and Drug Administration agree about its use for the immunocompromised to provide further protection. However, only 7.4% of the cohort had any cancer, only 3.3% were receiving immunosuppressive therapies, and only 0.5% had a PID; therefore, these results are not necessarily indicative of efficacy in all immunocompromised hosts. Nevertheless, the use of tixagevimab and cilgavimab is reasonable given the frequent lack of humoral response to vaccination in immunocompromised hosts.

Post-Acute Sequelae of Coronavirus Disease-2019

Post-acute Sequelae of COVID-19 (PASC) refer to a range of ongoing health problems that people experience usually in the weeks and months following SARS-CoV-2 pneumonia,.[72] PASC refers to symptoms that are not explained by an alternative diagnosis, including fatigue, shortness of breath, anosmia, chest pain, diarrhea, and fever.[73,74] In immunocompromised patients, persistent respiratory symptoms and fatigue may be the most common.[74] These symptoms can persist for an extended period of time and, in some cases, may persist indefinitely.

PASC presents unique challenges to immunocompromised patients. A study of 1557 COVID-19 survivors with cancer showed that 15% reported PASC symptoms at a median of 44 days after COVID-19 diagnosis, suggesting a higher incidence than in the general population.[74] The study also reported a higher hospitalization rate and mortality rate due to PASC, but this must be interpreted in the context of other factors related to cancer, such as the discontinuation of cancer treatment which was independently associated with mortality. Lastly, the analysis revealed a few characteristics that were more frequent in the 234 patients with PASC as compared with the 1323 patients without

PASC. Compared with patients without COVID-19 sequalae, a larger portion of the PASC group was male (54.5% vs 47.2%), over the age 65 (55.1% vs 48.1%), and had two or more comorbidities (48.4% vs 36.4%).[74]

One possibility for why immunocompromised patients may experience PASC is the possibility of delayed viral clearance. Some reports have shown that immunocompromised patients may display persistent viral infection well after initial COVID-19 diagnosis. For example, in addition to prior examples, one follicular lymphoma patient showed an increase in SARS-CoV-2 viral load 54 days after symptoms onset, whereas another patient receiving showed persistent RT-PCR (reverse transcription polymerase chain reaction) positivity 238 days following SARS-Cov-2 diagnosis.[53,75] A recent report suggested that the presence of spike proteins could be associated with PASC; in a recent study of 37 PASC patients, 84% had evidence of circulating spike protein, as compared with 0 in 26 recovered COVID-19 patients.[76] Whether the circulating spike protein represents active SARS-CoV-2 replication or simply viral remnants is unclear. Further work is needed to understand PASC in patients with or without immunocompromise.

SUMMARY

COVID-19 often results in more severe infections in immunocompromised patients. Hospitalization rate, disease severity, and mortality rates are generally higher for the immunocompromised, especially those with hematologic malignancies, SOT recipients, and patients with ARD. Treatment strategies for these patients are similar to those in the immunocompetent, but high-quality data are lacking. Vaccinations are recommended but less effective in immunocompromised patients. As the pandemic continues, the vulnerability of immunocompromised patients should garner the attention of the medical and scientific communities. Studies focusing on immunocompromised patients will help illuminate the best strategies to mitigate harms in these high-risk patients.

CLINICS CARE POINTS

- Immunocompromised patients have often develop severe SARS-CoV-2 pneumonia, and the threshold to escalate the level of care should be low given the possibility for rapid deterioration.
- Despite the possibility of inferior rates of response to vaccination, vaccinatiion is recommended in most immunocompromsied patients.
- Though most antiviral and anti-inflammatory agents have not been specifically tested in immunocompromised hosts, these should be initiated early given the possibility for clinical worsening without prompt intervention.

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