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Immunity

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Review

SARS-CoV-2 in immunocompromised individuals

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SUMMARY

Immunocompromised individuals and particularly those with hematologic malignancies are at increased risk for SARS-CoV-2-associated morbidity and mortality due to immunologic deficits that limit prevention, treatment, and clearance of the virus. Understanding the natural history of viral infections in people with impaired immunity due to underlying conditions, immunosuppressive therapy, or a combination thereof has emerged as a critical area of investigation during the COVID-19 pandemic. Studies focused on these individuals have provided key insights into aspects of innate and adaptive immunity underlying both the antiviral immune response and excess inflammation in the setting of COVID-19. This review presents what is known about distinct states of immunologic vulnerability to SARS-CoV-2 and how this information can be harnessed to improve prevention and treatment strategies for immunologically high-risk populations.

INTRODUCTION

Host protection against viral infections involves a complex interplay between members of the innate and adaptive immune system working in parallel to recognize and clear pathogens. In immunocompetent hosts, the coordinated response to SARS-CoV-2 infection is generally sufficient to achieve viral clearance, with morbidity most commonly resulting from excess inflammation and resultant tissue damage (Delorey et al., 2021; Melms et al., 2021). As with other respiratory viral infections, immunocompromised individuals have demonstrated increased COVID-19-associated morbidity and mortality (von Lilienfeld-Toal et al., 2016). Many of these individuals have discrete defects in host immunity, either due to their underlying disease or receipt of targeted therapies. Studies focused on these populations have revealed the contribution of individual components of the immune response to both antiviral control and excess inflammation (Box 1). In this review, we summarize our understanding of how altered host immunity in individuals with cancer and other immunocompromising conditions impacts the prevention, susceptibility, clinical course, and long-term sequelae of SARS-CoV-2 infection and explore how these findings may provide insights into the multifaceted role of the innate and adaptive immune system in antiviral control and disease evolution. We also leverage this information to offer our perspective on how prevention and treatment of COVID-19 may be tailored to discrete immunologically high-risk populations.

Exploring immune-mediated susceptibility to SARS-CoV-2 infection

Identifying discrete risk factors that alter susceptibility to SARS-CoV-2 infection has been challenging for several reasons. Many variables that contribute to an individual's risk of acquiring COVID-19 are extrinsic, including transmissibility of viral variants, community prevalence, and social behaviors including adherence to barrier precautions. Additionally, the lack of universal and routine testing for SARS-CoV-2 in combination with the high rates of asymptomatic infection limit the ability to conclusively assess susceptibility to infection using standard epidemiologic analyses. Finally, tractable animal models to mechanistically investigate risk of acute infection are limited, largely due to the inability of SARS-CoV-2 to attach to mouse angiotensin-converting enzyme 2 (ACE2) (Muñoz-Fontela et al., 2020), although a newly developed mouse model that combines a fully humanized immune system and adenoviral delivery of human ACE2 has enabled the utilization of mice to evaluate both COVID-19 pathology and efficacy of novel treatment strategies (Israelow et al., 2021; Sefik et al., 2021; Suberi et al., 2022).

Despite these limitations, there are several reasons to suspect that individuals with cancer and other immunocompromising conditions might have increased susceptibility to viral infection even after accounting for other well-established risk factors for COVID-19 such as advanced age and male sex, both of which are more common in people with cancer. Individuals with active malignancy often have compromised epithelial barrier integrity due to chemotherapy, which has historically been associated

Box 1. What is known about COVID-19 in the immunocompromised host

- Immunocompromised individuals exhibit distinct alterations in SARS-CoV-2 susceptibility and infection due to defined immunologic deficits.
- Innate and adaptive (both T and B cells) immune populations work synergistically to prevent, limit, and clear SARS-CoV-2 infection.
- Early studies suggest that CD8+ T cells are critical for mediating the antiviral response in acute infection, while B and CD4+ T cells stand out for their role in prevention of viral infection and ultimate viral clearance.
- Receipt of active immunosuppressive therapies reduces the biologic and clinical response to SARS-CoV-2 vaccination, although incomplete responses may still provide some protection.
- Treatment options for immunocompromised individuals with either severe acute SARS-CoV-2 or prolonged SARS-CoV-2 infection remain limited.

with an increased risk of microbial translocation and infection (van Vliet et al., 2010). Additionally, cancer, rheumatologic disease, autoimmune processes, and their associated therapies can compromise innate and adaptive immune responses facilitating infection after low inoculum exposures (Figure 1A). For example, chronic steroid use in people with rheumatologic disorders was associated with development of symptomatic disease and hospitalization from COVID-19, suggesting that broad, long-term immunosuppression may increase risk of symptomatic infection (Gianfrancesco et al., 2020). Finally, individuals with altered tissue-resident immunity may be particularly vulnerable to COVID-19, a hypothesis arising from the disproportionately poor outcomes from COVID-19 among lung transplant recipients (Heldman et al., 2021). In contrast, immunocompromised individuals may be often more likely to follow strict isolation precautions, thereby reducing their overall exposures and leading to underestimation of their susceptibility to infection.

Analyses of individuals with discrete immunological defects have revealed the unique roles of arms of the immune response in protecting against primary SARS-CoV-2 infection (Box 1). The innate immune response is the first line of antiviral defense to emerge following viral infection due to recognition of conserved pathogenic elements (Iwasaki and Medzhitov, 2010). Type I interferons (IFNs) serve as central effectors for the innate immune response and impaired viral immunity is well-established in individuals with germline genetic variants that affect IFN signaling (Ciancanelli et al., 2015; Hernandez et al., 2018; McNab et al., 2015; Zhang, 2020). In line with these findings, a study of 659 individuals with severe COVID-19 infections revealed a relative increase in alleles predicted to be associated with loss of function in the type I IFN pathway compared with 534 individuals with mild or asymptomatic infections (Zhang et al., 2020). Twenty-three (3.5%) individuals in the severe group had mutations in key IFN pathways, 19 of which were autosomal dominant in nature. A smaller study of young men with severe COVID-19 identified loss-of-function mutations in toll-like receptor 7 (TLR7), which recognizes single-stranded RNA such as the SARS-CoV-2 genome within endosomes, with specific evidence of TLR7-dependent IFN activity (van der Made et al., 2020). Finally, autoantibodies that neutralize type I IFNs have been identified in individuals with severe COVID-19 (Bastard et al., 2020). IFN-neutralizing antibodies have been described in individuals with rheumatologic disorders such as systemic lupus erythematosus (SLE), which may contribute to increased disease susceptibility in this cohort (Fernandez-Ruiz et al., 2021).

Adaptive immune responses play a well-established role in both viral clearance and secondary prevention of viral infections. A potential role for adaptive immunity in primary protection against SARS-CoV-2 arose following studies identifying memory T cell and B cell responses to other coronavirus species with cross-reactive activity against SARS-CoV-2, including in unexposed and asymptomatic individuals, even in cases without a detectable serological response (Grifoni et al., 2020; Kundu et al., 2022; Mateus et al., 2020; Sekine et al., 2020). Similarly, a large population-based study found that exposure to SARS-CoV-2 in young children was associated with less severe COVID-19 illness, possibly due to cross-reactive, pre-existing immunity to other endemic human coronaviruses (Solomon et al., 2022). Whether immunocompromised individuals exhibit defects in cross-reactive immune responses to SARS-CoV-2 remains to be determined. However, one prior study of the B cell depleting therapy rituximab showed no clear loss of pre-existing antibody titers, likely due to the lack of CD20 expression on plasma cells, suggesting that cross-reactive B cell immunity may be retained in this population (Pescovitz et al., 2011). Similarly, some individuals treated with B cell depleting therapies, including anti-CD20 monoclonal antibodies or CD19-targeted chimeric antigen receptor (CAR)-T cells, retain humoral immunity to childhood vaccines and mount robust memory responses following vaccination against influenza despite substantial humoral and cellular immunodeficiencies (Walti et al., 2021).

One recent study suggests that an optimally "poised" cellular immune response may offer increased primary protection against COVID-19 (Fahrner et al., 2022). In this study, analysis of individuals following SARS-CoV-2 exposure revealed that individuals with more Th1 polarized COVID-19-specific CD4+ T cell response (marked by production of tumor necrosis factor [TNF]-alpha, IFN-gamma, and IL-2), compared with a Th2-polarized response (marked by production of IL-5), were less likely to develop symptomatic infection. The role of cross-reactivity immunity in vaccinated and previously infected individuals will be key in determining protection against future variants harboring variable SARS-CoV-2 antigens. Finally, the widespread efficacy of vaccination underscores the value of humoral immunity in reducing SARS-CoV-2 infection. Although both viral vector and mRNA vaccines elicit a polyfunctional humoral and cellular immune response in individuals unable to mount a humoral response to vaccination, prophylactic treatment with recombinant monoclonal antibodies that target the receptor-binding domain (RBD) of the S1 subunit of the SARS-CoV-2 spike protein

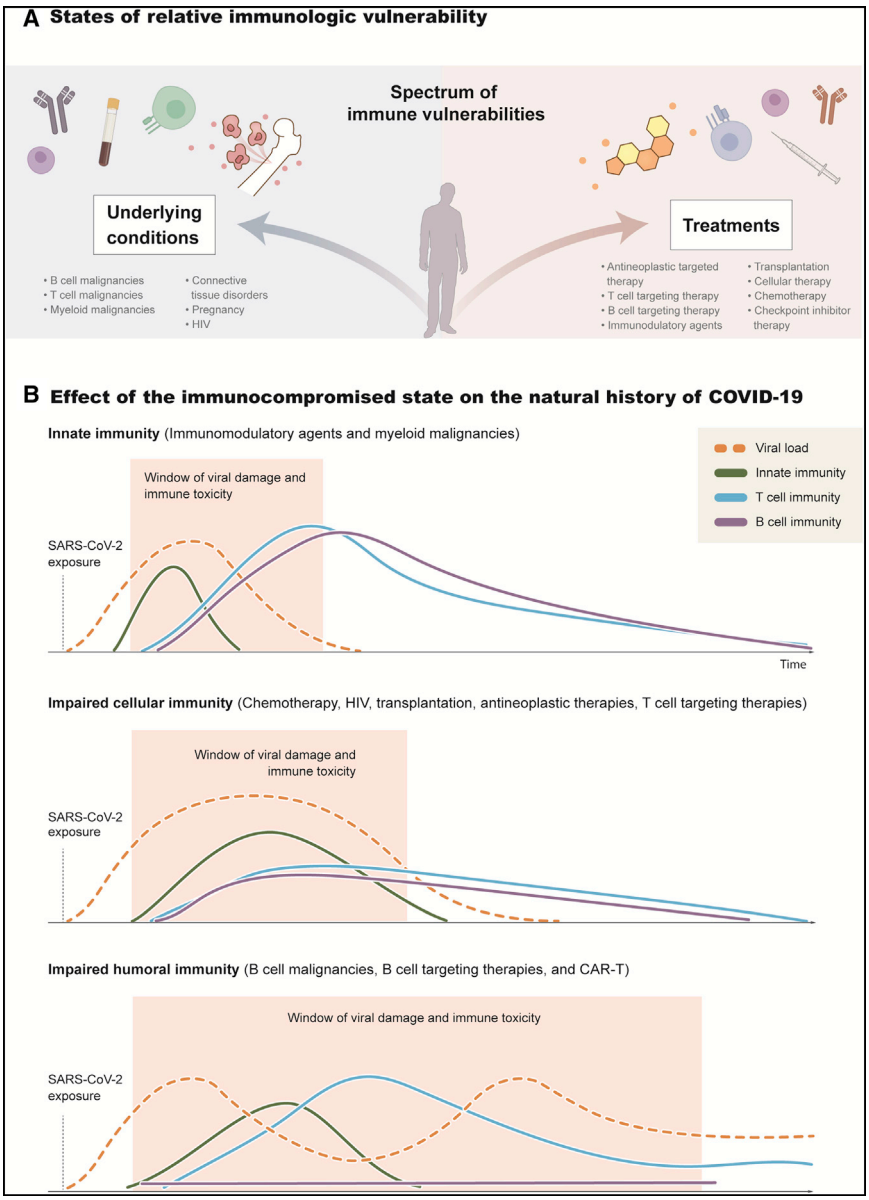

Figure 1. Investigating the immune response to COVID-19 at different states of immunity

(A) States of relative immunologic vulnerability that potentially impact the immune response to COVID-19 infection and vaccination, stratified by underlying disease and/or treatment.

(B) Specific immunocompromised states impact the natural trajectory of COVID-19 infection. Individuals with suppressed innate immunity (top) may experience a higher incidence of infection but intact adaptive immune responses enable efficient viral clearance. Patients with impaired adaptive cellular immunity (middle) demonstrate impaired acute viral clearance and have a high risk of death from acute infection. Conversely, patients with impaired adaptive humoral immunity (bottom) are relatively protected from acute infectious toxicity but have a high risk of prolonged viral shedding, viral rebound, and chronic infection.

successfully reduced the incidence of symptomatic infection before or immediately after an exposure, suggesting that circulating variant-specific neutralizing antibodies may be sufficient to reduce the risk of becoming infected (Levin et al., 2022; O'Brien et al., 2021).

Acute SARS-CoV2 infection in immunocompromised hosts: The importance of antiviral CD8+ T cell immunity

As the cancer and immunology communities worked tirelessly to care for immunocompromised individuals with acute SARS-CoV-2 infection in the beginning of the COVID-19 pandemic, an important early observation was that the clinical presentation of COVID-19 in immunosuppressed individuals was similar to that of immunocompetent individuals at time of acute infection but often was associated with more severe long-term complications.

The risk factors associated with poor outcomes following acute infection in immunocompromised individuals are heterogeneous. Advanced age is universally associated with poor outcomes in immunocompromised individuals and accordingly, pediatric cancer populations have a relatively less severe disease course (Boulad et al., 2020). Furthermore, risks of COVID-19-associated morbidity in the cancer population differ by disease type and condition. For example, individuals actively treated for solid tumors, TNF inhibitors for rheumatologic conditions, and uncomplicated bone marrow transplant recipients demonstrated relatively favorable clinical outcomes, whereas others including untreated individuals with chronic lymphocytic leukemia (CLL), those on B cell depleting agents, and hematologic malignancy with severe lymphopenia suffered from higher rates of both severe infections and long-term complications (Izadi et al., 2021; Shah et al., 2020). The association of lymphopenia with poor outcomes in COVID-19 is not unique; indeed, lymphopenia was a key predictor of severity during several prior viral pandemics, including the 2003 SARS-CoV1 (Lee et al., 2006; Poutanen et al., 2003; Tsang et al., 2003), the 2009 H1N1 influenza A (Cao et al., 2009; Perez-Padilla et al., 2009), and the 2013 MERS-CoV pandemic virus (Ko et al., 2016; Min et al., 2016) as well as for respiratory syncytial virus (Shah et al., 2014). This suggested that common immunological deficiencies might be associated with morbidity across pandemic viral infections and presented a unique opportunity for immunologists to more deeply study the natural course of COVID-19 infection in this population as a means to more broadly elucidate the role of the immune system in both antiviral control and immune-driven toxicity (Figure 1B).

In immunocompetent individuals with acute COVID-19, early pathologic analyses suggested that the majority of disease-associated morbidity resulted from an exuberant inflammatory response to viral infection. This inflammatory response was reminiscent of cytokine release syndrome, which occurs in individuals treated with cellular immunotherapies and can lead to early treatment-associated pathology, and raised the possibility that immunosuppressed individuals might be protected from COVID-19 morbidity and mortality (Giavridis et al., 2018). Unfortunately, epidemiologic studies early in the COVID-19 pandemic quickly refuted that hypothesis, as early reports demonstrated a nearly 40% hospitalization rate and nearly 10% death rate among all individuals with cancer who contracted COVID-19 (Lee et al., 2020a; Robilotti et al., 2020). Interestingly, on multivariate analysis, the most likely predictors of both hospitalization and severe disease were chronic steroid therapy, lymphopenia, and active hematologic cancer, suggesting that increased morbidity and mortality in this population might be due to adaptive immunosuppression rather than excess inflammation (Jee et al., 2020; Lee et al., 2020b; Luo et al., 2020; Robilotti et al., 2020).

The largest published cohort to date of individuals with hematologic malignancy with persistent COVID-19 presented both the clinical outcomes and immunologic profiles in a cohort over 300 individuals (Lee et al., 2022a). Greater than 80% of individuals met the criteria for severe COVID-19 with a 22% mortality rate during the initial admission and 31% requiring intensive care unit (ICU) admission. On multivariate analysis, active cancer-directed therapy, chimeric antigen receptor T cell therapy, and cardiovascular disease were each independently correlated with mortality while active receipt of CD20-targeting agents was not, implicating the key antiviral role of T cells in this population. Consistent with this, high-dimensional flow cytometry analysis of peripheral blood mononuclear cells from individuals with cancer across two institutions identified CD8+ T cells, but not CD4+ T cells or B cells, as a key determinant of outcomes during acute SARS-CoV-2 infection (Bange et al., 2021). Even in individuals treated with B cell directed agents, individuals with an adequate CD8+ T cell response did not demonstrate increased mortality, suggesting that CD8+ T cells may be sufficient for recovery from acute COVID-19 in the absence of a meaningful humoral immune response. Contemporaneous analyses of cancer populations who had received isolated B cell directed therapies such as anti-CD20 monoclonal antibodies or small molecular inhibitors of Bruton's tyrosine kinase (BTK) inhibitors support a dominant role for T cells in preventing mortality in individuals with severe COVID-19. Large cohort studies of SARS-CoV-2-infected individuals with either rheumatologic diseases or CLL in the pre-vaccination era revealed that receipt of B cell-directed therapies was associated with an increase in the occurrence of severe infection and prolonged hospital stay but not with an increase in mortality (Avouac et al., 2021; Mato et al., 2020). Taken together, these findings underscore the importance of CD8+ T cell immunity in immunocompromised individuals with COVID-19, particularly those with severe disease (Figure 1B).

The COVID-19 experience in hematopoietic stem cell transplant recipients has varied across centers with an observed higher rate of severe complications, including lower airway disease and ICU admission for those with a higher immunodeficiency scoring index (Ljungman et al., 2021). It is important to note that not all individuals exhibit poor outcomes from COVID-19 post-hematopoietic cell transplantation (HCT) and that the impact of immunosuppression may not be generalizable to all immunocompromised individuals. In the early part of the pandemic, a study of 77 individuals who had received either autologous (auto-) or allogeneic (allo-) HCT or CAR T cell therapy revealed better than expected clinical outcomes with an overall survival of 78% at 30 days following diagnosis (Shah et al., 2020). Still, 22% of all infected individuals and 50% of those admitted to the hospital developed severe disease, with 41% of admitted individuals dying during their index hospitalization. Furthermore, the median time from most recent cell therapy was 782 days in this population and analysis of lymphocyte subsets showed frequent reductions in circulating B cell populations; despite this, several individuals were still able to mount SARS-CoV-2 nucleocapsid-specific antibody responses. One potential interpretation of these findings is that many post-transplant individuals, particularly those in remission further out from transplantation and those without graft versus host disease, may achieve sufficient T cell immune reconstitution to enable an adequate antiviral T cell response despite humoral defects. This hypothesis merits further investigation, particularly in the context of developing adaptive cellular therapy strategies for SARS-CoV-2 and developing strategies for vaccination following transplantation. Similarly, not all immunosuppressive therapies have deleterious effects on acute COVID-19 infection, as several studies have identified no significant increase in COVID-19 severity in individuals receiving methotrexate, IL-6 directed therapy, or TNF inhibitors (Andersen et al., 2022; Florence et al., 2021). Whether CD8+ T cell responses are preserved in individuals receiving therapies that do not negatively impact outcomes during acute COVID-19 infection remains to be determined.

Understanding viral clearance: B cells take the stage

Immunocompetent individuals typically recover symptomatically from COVID-19 infection within 5–7 days. Viral culture remains the gold standard for definitively measuring viral viability; however, given the technical demands of viral culture, including the requirement for biosafety level 3 facilities, other diagnostic approaches such as nasopharyngeal (NP) PCR have emerged to estimate viral loads. Although PCR may capture both infectious and non-infectious viral particles, PCR cycle threshold can be used for quantifying viral burden in longitudinal samples from individuals to assess virologic control and to obtain a crude assessment for presence of viable virus (Aranha et al., 2021; Gilad et al., 2021). With this approach, an early review of randomized control trial-level data showed that 58%–83% of healthy persons achieve viral clearance by 28 days after infection and that the median time to an undetectable viral load ranged from 7 to 12 days (Farina et al., 2020). In individuals with various form of immune dysregulation, however, this window of viral shedding, including with viable virus, may persist for months (Aydillo et al., 2020; Duléry et al., 2021; Gibson et al., 2021; Lee et al., 2022a; Purpura et al., 2022; Sepulcri et al., 2021). It is important to note the discordance between persistent PCR positivity and transmissible virus, which was nicely demonstrated by contact tracing efforts among a cohort of post-symptomatic participants

with persistent PCR positivity in which no new COVID-19 diagnoses were made (Vibholm et al., 2021). However, in individuals with cancer and particularly in those with hematologic malignancies, viral cultures demonstrated that prolonged PCR positivity reflected *bona fide* culturable virus, suggesting that immune defects might significantly contribute to SARS-CoV-2 viral persistence (Aydillo et al., 2020).

Although innate immune responses play a key role in early recognition and control of viral infection, the essentiality of adaptive immune system for viral clearance has been established in both primary samples and mouse models of SARS-CoV-2 infection (Israelow et al., 2020, 2021). Virus-specific humoral and cellular components of the adaptive immune response are induced during early infection, and it is likely the coordination of virus-specific CD4+ T cells, CD8+ T cells, and antibodies which leads to effective viral clearance (Braun et al., 2020; Gudbjartsson et al., 2020; Israelow et al., 2021; Long et al., 2020; Rydyznski Moderbacher et al., 2020). Early development of cytotoxic CD8+ T cells, typically observed within 7 days and peaking at 14 days, is correlated with viral control (Notarbartolo et al., 2021). However, the numerous studies of individuals with B-lineage hematologic malignancies or autoimmune disease treated with B cell depletion who experience prolonged courses of COVID-19 with persistent viral shedding highlight the critical requirement for humoral immune responses in achieving viral clearance (Avanzato et al., 2020; Baang et al., 2021; Dispinseri et al., 2021; Guo et al., 2020; Liu et al., 2020; Tepasse et al., 2020; Zohar and Alter, 2020). For example, one longitudinal investigation of 289 individuals hospitalized with COVID-19 found that a key variable associated with viral persistence or rebound in 21 individuals was significantly lower levels of RBD-specific IgA and IgG antibodies and a greater likelihood of protracted viral detection in the gastrointestinal rather than respiratory tract (Hu et al., 2020). However, a report of two individuals with complete absence of B cells due to X-linked agammaglobulinemia who developed COVID-19 demonstrated that these individuals were able to recover from the infection, suggesting that a B cell response is not universally required for viral clearance and clinical recovery (Soresina et al., 2020).

Recurrent symptomatic disease with potential need for hospitalization and associated sequelae is of primary concern for individuals with impaired viral clearance following cell-depleting therapies. One study described an individual with mantle cell lymphoma who received the anti-CD20 monoclonal antibody rituximab and experienced four independent episodes of symptomatic COVID-19 infection. This individual demonstrated positive RT-PCR NP swabs for 268 days, with positive viral cultures and genomic analysis confirming persistent infection with the same strain (Sepulcri et al., 2021). Several small retrospective studies of B cell depleted individuals subsequently confirmed the occurrence of prolonged PCR positivity and symptomatic disease in this population (Hueso et al., 2020; Múñez-Rubio et al., 2021). In a large cohort study of 368 individuals with hematologic malignancies, Lee et al. identified persistent SARS-CoV-2 positivity via PCR in individuals with impaired immunity following B cell directed therapy and CD19-targeted CAR-T cell therapy, but not traditional parenteral cytotoxic chemotherapy (Lee et al., 2022a). Individuals with prolonged PCR positivity experienced recurrent respiratory symptoms, migratory pulmonary infiltrates, and, at times, need for rehospitalization. Viral genome sequencing demonstrated persistent SARS-CoV-2 infection with the same strain, rather than co-infection or re-infection, in these individuals. In a recent study, Lyudovyk et al. more deeply investigated how adaptive immunity contributed to SARS-CoV-2 viral clearance in individuals with cancer (Lyudovyk et al., 2022). Similar to Lee et al., the authors found that the primary predictor of prolonged SARS-CoV-2 infection in individuals with cancer was a loss of humoral immune responses, which was most potently observed in individuals who had received B cell-depleting therapies but was also seen in individuals with hematologic malignancies. Furthermore, deep immunophenotyping of these individuals revealed a broad, persistent, and functional CD8+ antiviral T cell response in individuals with prolonged disease, indicating that although CD8+ T cells are critical for surviving acute infection, they are insufficient to ensure prompt viral clearance. Intriguingly, the authors found that B cell depleted individuals who were able to efficiently clear SARS-CoV-2 exhibited a robust, clonally expanded and highly selected class II-specific CD4+ T cell response, suggesting that B and CD4+ T cell responses are key to achieving viral clearance.

The potential for intra-host viral evolution is another critical area of investigation in the context of persistent COVID-19 infection, particularly in those individuals with various forms of immune dysregulation (Choi et al., 2020; Corey et al., 2021; McCarthy et al., 2021; Pérez-Lago et al., 2021; Truong et al., 2021). A report of a solid organ transplant recipient with a detectable PCR for 138 days reported dynamic viral genetics suggestive of directed evolution over the infection course (Purpura et al., 2022). Furthermore, particularly in individuals with hematologic malignancies, several studies have found evidence for the emergence of mutations during chronic SARS-CoV-2 infection (Borges et al., 2021; Jensen et al., 2021; Kemp et al., 2021; Lynch et al., 2021). Indeed, in the study by Lee et al., analysis of longitudinal samples and 18 individuals with persistent infections demonstrated intra-host viral evolution along with evidence for increased viral entropy or diversity of detected viral strains specifically in individuals with reduced CD8 T cells (Lee et al., 2022a). A recent study demonstrated emergence of an Omicron BA.1 sub-lineage with mutations in the spike protein with persistent shedding, and the authors suggest the possibility of transmission events between a few individuals within the same healthcare facility, although direct epidemiologic links were not established (Gonzalez-Reiche et al., 2022). The risk posed by immunosuppressed individuals as reservoirs for the generation of viral escape mutants and the extent of onward transmission of these mutants remain incompletely understood at this time.

Investigating long-term sequelae

Reports documenting the phenomenon of ''long COVID'' began to appear in the literature shortly after the emergence of SARS-CoV-2 (Mahase, 2020a, 2020b; Yelin et al., 2020). Subsequent large, population-based studies have helped to elucidate the epidemiology and clinical manifestations of this entity, although definitions, at times, vary across publications limiting clear integration and interpretation of the published literature. A recent study of over a quarter million COVID-19 survivors found that a third of individuals demonstrated features of long COVID-19

between 3 and 6 months following initial COVID-19, with a higher incidence in individuals with more severe initial infections; however, close to 25% of those individuals originally had an asymptomatic presentation, supporting the notion that this clinical syndrome is likely distinct from the original acute illness (Huang et al., 2021; Taquet et al., 2021). Symptoms are heterogeneous in nature, including but not limited to cardiopulmonary and neuropsychiatric manifestations ranging from fatigue to altered mentation (Davis et al., 2021; Shoucri et al., 2021). Furthermore, post-acute COVID-19 syndrome (PACS) can manifest in seemingly disparate organ systems by mechanisms that remain poorly understood and may be difficult to differentiate from other confounding variables including stigmata of prolonged and/or ICU-level.

Although the immunologic underpinnings of the long-COVID syndrome remain incompletely understood, including the potential role of persistent virus or viral antigens, observed immune signatures in individuals with long COVID have proved distinct from those seen in individuals with either acute illness or chronic infection. In one of the first systematic studies on PACS, Su et al. identified four risk factors for PACS at time of COVID-19 diagnosis including type 2 diabetes, high SARS-CoV-2 viremia, Epstein-Barr virus reactivation, and specific autoantibodies targeting type 1 IFNs (Su et al., 2022). A recent prospective study of 31 individuals with PACS demonstrated sustained increases in activated CD14+CD16+ monocytes and plasmacytoid dendritic cells as well as persistent elevations in type I (IFN-β) and type III (IFN-λ1) IFNs 8 months post-infection (Phetsouphanh et al., 2022). Similarly, an analysis of samples obtained from 215 individuals an average of 1 year from infection demonstrated enrichment of non-classical ($CD16^{hi}$) monocytes as well as exhausted CD4+ and CD8+ T cells and elevations in activated B cells as well as SARS-CoV-2 specific humoral responses in individuals with long COVID, consistent with aberrant, chronic immune engagement (Klein et al., 2022). Persistent elevation of innate immune cell-derived cytokines may have systemic as well as organ-specific effects that are hypothesized to contribute to the development of PACS. These include altered cardiac remodeling, neuroinflammation, renal injury, persistent insulin resistance, and bone resorption (Gemayel et al., 2001; Gentile et al., 2020; Muccioli et al., 2020; Peleg et al., 2020; Salvio et al., 2020). Thus, defective resolution of inflammation may be a critical component underlying PACS pathophysiology, although the drivers of persistent innate immune reactivity remain unclear (Brunetta et al., 2020; Hadjadj et al., 2020; Lagunas-Rangel and Chávez-Valencia, 2020; Mehandru and Merad, 2022).

Another mechanism by which immune deregulation can contribute to PACS is via development of a sustained autoimmune response against self-tissue antigens that persists despite viral elimination. The intersection of SARS-CoV-2 infection and autoimmunity is likely similar to autoinflammatory pathology seen in many other viral infections and may also underly the post-COVID inflammatory condition in children known as multisystem inflammatory syndrome (Barzilai et al., 2007; Bowles et al., 2020; Panoutsakopoulou et al., 2001; Rowley, 2020; Zulfiqar et al., 2020). Proposed mechanisms for this breakdown in immunologic self-tolerance include molecular mimicry, presentation of cryptic antigens, and superantigen cross-linking (Christen, 2019; Ehl et al., 1997; Fujinami et al., 2006; Llewelyn and Cohen, 2002). Several groups have documented the presence of autoantibodies in individuals with COVID-19, with one study demonstrating that such individuals display hallmarks of extrafollicular B cell activation previously described in autoimmune settings (Bastard et al., 2020; Wang et al., 2021a; Woodruff et al., 2020). Another study found that COVID-19-infected individuals exhibited marked increase in autoantibody reactivities with a high prevalence of autoantibodies targeting both immunomodulatory proteins associated with immune function and virologic control as well as tissue compartments that are frequently implicated in PACS (Wang et al., 2021a). Detailed understanding of these deleterious autoimmune phenomena arising after acute SARS-CoV-2 infection and whether specific autoantibodies have a role in the establishment of PACS merit further investigation. Taken together, these studies add to a growing body of literature that a combination of viral and host actors, including persistent viral material, residual inflammation, autoimmune phenomena, and microvascular dysregulation may contribute to PACS (Peluso et al., 2021; Phetsouphanh et al., 2022; Pretorius et al., 2021; Seeßle et al., 2022; Zollner et al., 2022).

Given the association of long COVID with dysregulated and often persistent innate and adaptive immune responses, whether immunocompromised individuals might actually have a lower risk of long COVID is an outstanding question of considerable interest. In support of this hypothesis, several large-scale epidemiologic studies have not identified active or recent malignancy as a risk factor for long COVID despite the fact that individuals with malignancy are more likely to develop severe COVID-19 and long COVID is more prevalent in individuals with severe disease (Subramanian et al., 2022; Thompson et al., 2022; Whitaker et al., 2022). Further analysis of long COVID prevalence in immunocompromised individuals might reveal the specific contribution of innate and adaptive immune cell types to specific long-COVID-associated pathologies. Notably, although conceptually vaccination and subsequent boosting of innate and adaptive immune responses against SARS-CoV-2 might promote or worsen post-COVID-19 inflammatory sequelae, existing data suggest that vaccination decreases incidence of long COVID by decreasing the rate of primary infection (Kuodi et al., 2022).

SARS-CoV-2 vaccination in the immunocompromised

The rapid development of effective vaccines against SARS-CoV-2 represents a landmark achievement in the history of biomedical sciences. Several vaccine platforms, including mRNA, adenoviral-vectored, protein subunit, and whole-cell inactivated virus, have been approved for use in many countries. The discussion that follows focuses on the two mRNA vaccines (BNT162b2/Pfizer-BioNTech and mRNA-1273/Moderna), given their widespread international use, proven efficacy at preventing severe disease, and availability of published data regarding their immunological mechanisms.

Early reports from healthy volunteers demonstrated that the mRNA vaccines elicited high levels of IgM/IgG anti-S and anti-RBD binding titer and that plasma neutralizing activity and RBD-specific memory B cells of vaccinated volunteers were equivalent to those of individuals who had recovered from natural infection (Gaebler et al., 2021; Wang et al., 2021b). Another early study on SARS-CoV-2-naïve healthy volunteers showed

that two doses were required for the development of neutralizing titers and that memory B cells specific for spike RBD were efficiently primed by mRNA vaccination, although memory B cell responses declined slightly with age (Goel et al., 2021). Although there is a wide range in antibody titers following natural infection with SARS-CoV-2, completion of a primary vaccine series, especially with mRNA vaccines, leads to a more consistent and higher-titer initial antibody response (Israel et al., 2021; Jackson et al., 2020; Walsh et al., 2020). Immunogenicity analyses performed during phase I/III vaccine trials revealed that 100% of participants developed both binding and neutralizing antibodies following vaccination with either mRNA vaccine, whereas only 90% of participants did so following vaccination with the Janssen adenovirus vector vaccine (Jackson et al., 2020; Sadoff et al., 2021; Walsh et al., 2020).

Cell-mediated immune responses are also elicited by vaccination against SARS-CoV-2, and the use of serology as the sole measure of protection underestimates the protection afforded by vaccination. A large retrospective study from the United Kingdom during the second wave showed that those with a prior SARS-CoV-2 infection had a lower probability of a second infection compared with those without prior infection (0.9% versus 4.3%) and that this protective effect was independent of the presence of binding antibodies (Breathnach et al., 2021). Furthermore, numerous studies have demonstrated polyfunctional CD4+ and CD8+ T cells responses following vaccination (Carmen et al., 2021; Guerrera et al., 2021; Hall et al., 2022; Painter et al., 2021). Although data correlating vaccine-induced T cells with clinical efficacy against COVID-19 remain limited, a large prospective cohort study from the United Kingdom demonstrated that T cell responses were associated with protection from COVID-19 among participants with moderate serologic response (Kent et al., 2022; Wyllie et al., 2021).

Unsurprisingly, diminished SARS-CoV-2 vaccine-elicited immune responses have been reported in individuals with cancer, rheumatologic disease, and other immunocompromised individuals. The seroconversion rate of individuals with solid tumors is only mildly reduced compared with individuals without cancer (Becerril-Gaitan et al., 2022; Oosting et al., 2021; Shroff et al., 2021). However, individuals with hematologic malignancies are at especially high risk of diminished vaccine-elicited humoral immune responses (Gurion et al., 2022; Van Oekelen et al., 2021; Perry et al., 2021). Early studies reported a seroconversion rate of only 18%–25% among individuals with hematologic malignancies following the first dose of mRNA vaccine (Monin et al., 2021; Terpos et al., 2021). One prospective study of 585 individuals with cancer found that the seroconversion rate following two doses of vaccine was 85% in individuals with solid cancer and 59% in individuals with hematological malignancies (Fendler et al., 2021). Similarly, preliminary reports have shown an abrogated humoral response to vaccination against SARS-CoV-2 among individuals with inflammatory bowel disease, rheumatologic diseases, cancer, and solid organ transplant recipients (Agbarya et al., 2021; Boyarsky et al., 2021; Deepak et al., 2021; Geisen et al., 2021; Giannella et al., 2021; Ligumsky et al., 2022; Rincon-Arevalo et al., 2021; Vollenberg et al., 2022). An analysis of over six hundred solid organ transplant recipients who had received two doses of mRNA vaccine found that only 54% of participants had detectable antibodies at a median of 29 days after the second dose (Boyarsky et al., 2021).

Receipt of immunosuppressive therapies is undoubtedly a significant contributor to blunted vaccine responses in this population. An abundance of studies have identified that receipt of B cell directed therapy, specifically anti-CD20 agents, correlates with reduced mRNA vaccine response, with time from most recent treatment modulating measurable serologic activity (Bellesi et al., 2022; Ghione et al., 2021; Liebers et al., 2022; Marasco et al., 2022), irrespective of underlying disease process (Achiron et al., 2021; Furer et al., 2021; Herishanu et al., 2021). Importantly, anti-CD20 antibodies are not the only treatment that impacts humoral vaccine responses. A detailed investigation of 551 individuals with hematologic malignancies at Memorial Sloan Kettering Cancer Center (MSKCC) revealed impaired production of vaccine antibody titers and neutralizing antibodies; however, some individuals such as those with multiple myeloma on maintenance immunomodulatory drugs (for example, pomalidomide or lenalidomide) had relatively preserved responses, again highlighting the importance of considering immune-targeting agents individually (Chung et al., 2021). Limited currently available data do not suggest a clear effect of checkpoint inhibitor therapy on immune responses to COVID-19 vaccines (Lasagna et al., 2022; Niewolik et al., 2022; Waissengrin et al., 2021); this merits further evaluation given evidence for its specific effects on B cell responses to influenza vaccination (Herati et al., 2022).

Impaired host immune function likely contributes to lower clinical efficacy rates of SARS-CoV-2 vaccination in individuals with cancer and other immunocompromising conditions. Individuals with various forms of immune dysregulation were excluded from the pivotal trials that preceded regulatory approvals of the currently recommended COVID-19 vaccines. However, available data demonstrate that relative to vaccinated immunocompetent individuals, vaccinated immunocompromised individuals have an increased risk of severe COVID (Embi et al., 2021; Yek et al., 2022). A large retrospective study of 32,000 vaccinated individuals with hematologic malignancies revealed an increase in infection, hospital admission, and mortality associated with COVID-19 in comparison to a group of vaccinated controls, with an even greater risk for individuals receiving active treatment (Mittelman et al., 2021). Experience from studies in the United States demonstrates comparable findings with higher odds of breakthrough infection and a significantly higher associated risk of hospitalization (31.6% versus 3.9%), death (6.7% versus 1.3%), and severe outcomes among persons with cancers compared with other propensity score-matched individuals (Wang et al., 2022).

In a multicenter nationwide analysis of individuals with cancer, including from the VA health care system, overall vaccine effectiveness (VE) was measured in individuals with cancer compared with a matched cohort of individuals who had not yet been vaccinated (Wu et al., 2022). The VE in remotely treated individuals (>6 months), or those receiving hormonal therapy only, was comparable with the general population. However, the VE was reduced for those actively receiving chemotherapy, especially for hematological cancers (19%) and those who received chemotherapy within 3 months (VE estimates 57%). Furthermore, other population-based VE studies suggest a

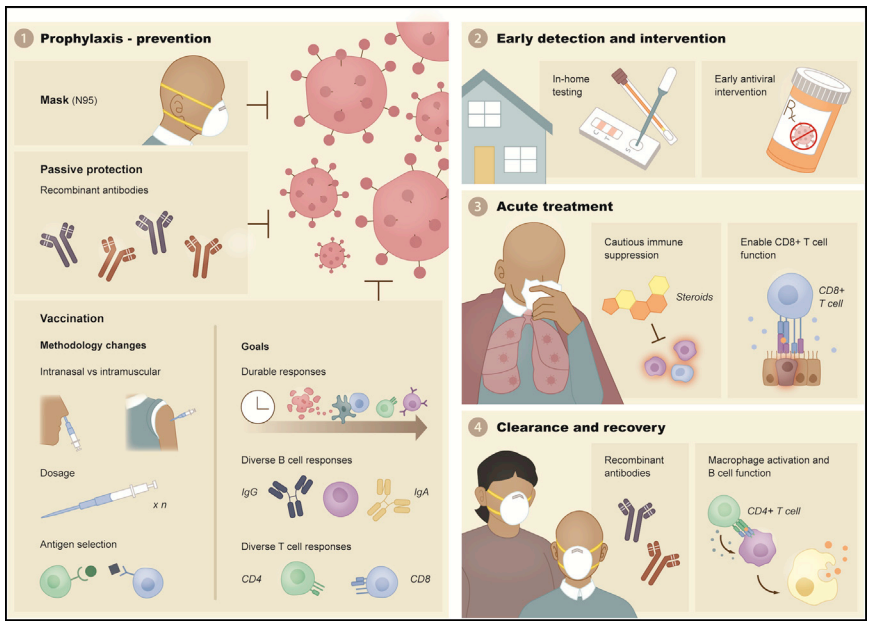

Figure 2. A multifaceted approach to preventing, managing, and treating COVID-19 in the immunocompromised

A multi-modal approach is required to limit COVID-19-associated morbidity in immunocompromised patients. This includes limiting the risk of infection via use of respirator-class masks (N95 or KN95), optimization tailoring of active and passive immunization strategies based on individual immunological vulnerabilities, including antibody therapy for patients with impaired humoral immunity and adjusting active vaccination strategies to promote broad and durable protection (#1). In addition, strategies for enhanced surveillance of high-risk patients, including access to at-home testing and facilitated early antiviral therapy, may limit the development of severe disease (#2). Finally, further investigations are required to improve immunomodulatory strategies to mitigate acute toxicity and promote long-term viral clearance and recovery in these individuals (#3–4).

disproportionately higher breakthrough infection rate among individuals with cancer over time than vaccinated non-cancer individuals. Other studies show waning VE at the three to six-month mark after completion of the primary series, with the most significant decline in those with lymphoma and leukemia (Lee et al., 2022b; Wang et al., 2022). Studies examining long-term neutralizing antibody responses against variants of concern in vaccinated individuals with cancer demonstrate significant loss (~50%) in neutralizing antibody (nAB) activity 6 months post immunization against Alpha, Beta, Gamma, and Delta variants of concern (Obeid et al., 2022).

With the emergence of the Omicron variant, the risk of breakthrough infections among vaccinated individuals rose steeply in the general population and specifically among individuals with cancer, which has been attributed to reduced neutralization from RBD mutations harbored by this strain (Mair et al., 2022). Data on the outcomes of variant-specific breakthrough infections among individuals with cancer are sparse but do not suggest higher severity or mortality in the general population or among individuals with cancer (Goga et al., 2022; Mair et al., 2022).

Another immunologically complex population is pregnant women, whose immune system undergoes significant alterations to allow for tolerance of the growing allogeneic fetus. Pregnancy stands out as a risk factor for severity of COVID-19 infection in what are often otherwise healthy, young individuals (Lokken et al., 2021). Studies to date suggest that many variables are at play in the development of the SARS-CoV-2 vaccine response, including the sex of the fetus itself (Bordt et al., 2021). Although pregnant women were not included in the original vaccine studies, invaluable safety data have now emerged, and mechanistic studies suggest distinct vaccine responses, including identifying a particularly important role for a second vaccine dose (Atyeo et al., 2021; Shimabukuro et al., 2021).

Despite reduced immunogenicity among immunocompromised populations, vaccination against SARS-CoV-2 has played an invaluable role in reducing the severity and negative sequelae of COVID-19 among individuals with various forms of immune dysregulation (Cornberg et al., 2021; Greco et al., 2021; Landewé et al., 2022). This may in part arise from potent T cell antiviral immunity, even in individuals who may not mount a clear serologic response (Liebers et al., 2022; Liu et al., 2022; Okamoto et al., 2022). For example, a single dose of mRNA vaccine has been shown to induce a polyfunctional T cell response in individuals with chronic myeloid leukemia and repeated vaccination elicits robust polyfunctional T cell response in recipients of allo-HCT (Harrington et al., 2021a, 2021b). One systematic review of 57 studies found discordant cellular and humoral immune responses among individuals with hematological malignancies following vaccination. For example, individuals treated with B cell depleting agents had lower seroconversion rates compared with individuals receiving chemotherapy whereas individuals with hematopoietic stem cell transplant had higher seroconversion rates than those after CAR T cell therapy. On the other hand, individuals who received anti-CD20 therapy within 6 months of vaccination had robust T cell responses (75%–100%), whereas individuals with hematopoietic stem cell transplant had lower response rates (27%–29%) (Piechotta et al., 2022).

How to maximize vaccination responses in individuals with immune dysfunction remains an area of active study (Figure 2), including optimizing vaccination timing and modalities. Modifying vaccine timing around cancer treatment, including immunization before commencing treatment, especially B cell depleting therapies, is not always practical but should be considered. During periods of low community SARS-CoV-2 spread, our practice is to time vaccine doses away from chemotherapy by either completing a full vaccination series prior to chemotherapy initiation or holding on initiation of vaccination for at least 6 months following completion of chemotherapy.

A large prospective cohort study of individuals with cancer assessing SARS-CoV-2 immunity following vaccination revealed

that two doses of an mRNA vaccine was associated with more potent immune responses compared with a single dose of the Janssen adenovirus vector vaccine (Naranbhai et al., 2022), supporting mRNA vaccines as the preferred approach in the United States. The addition of mRNA vaccine doses may improve the immunologic response in some individuals, especially those with rebounding immune function; extending the interval between doses may have advantages in certain situations and should be individualized (Parker et al., 2022). For example, one study demonstrated that a third dose of vaccine boosts neutralizing antibody and cellular responses in individuals with hematologic malignancies, including those who had undetectable neutralizing antibody titers following two vaccine doses or for whom titers had waned (Fendler et al., 2022), with similar findings in a cohort of renal transplant recipients (Schrezenmeier et al., 2021). Haggenburg et al. recently reported their experience with a delayed third mRNA vaccine dose in 584 immunocompromised individuals with hematologic cancers (Haggenburg et al., 2022). The third dose was given 5 months after the two-dose initial series, and the most potent immunoglobulin spike subunit one responses were observed in those with immune recovery. As anticipated, those on anti-CD20 or other B cell depleting therapies, individuals with CLL and post-CAR-T, were the least responsive.

Heterologous boosting has advantages in individuals with immune dysfunction and is frequently encouraged, given the data showing an acceptable safety profile and evidence that boosting with mRNA vaccines, regardless of primary series, is associated with better immunologic protection via increased spike (S1)-specific CD8+ T cell responses and RBD-specific memory B cell responses and has recently been shown to have improved clinical protection (Atmar et al., 2022; Reimann et al., 2022; Zuo et al., 2022). The mechanism by which additional vaccine doses promote B cell maturation and antibody production in individuals with a heavily restricted B cell compartment is also an area worthy of further investigation that may ultimately have profound implications for vaccine strategies in immunocompromised individuals.

PREVENTION AND TREATMENT OF COVID-19 IN THE IMMUNOCOMPROMISED

A definitive approach for the management of COVID-19 in immunocompromised hosts with dysregulated immunity has not yet been defined. One reason for this is that the randomized clinical trials of existing therapeutic agents for SARS-CoV-2 did not enroll a sizable number of immunocompromised individuals combined with the fact that different treatment strategies are likely needed in different states of relative immune deficiency. Given the lack of clear evidence-based studies for the treatment of COVID-19 in individuals with immunocompromising conditions, the clinical approach must be extrapolated from larger trials focusing on non-immunocompromised individuals and case studies reporting on immunocompromised hosts.

In individuals without SARS-CoV-2 infection, vaccination continues to be the consensus approach to both mitigate COVID-19 infection and, in those who do subsequently become infected, reduce COVID-19 severity. Given the cell-mediated immune responses to vaccination discussed above, vaccination may be beneficial even in individuals who do not have a detectable humoral response (Jiménez et al., 2022). It should be noted that among high-risk immunocompromised individuals, a three dose primary series followed by two boosters is the current recommended approach that is associated with the highest rates of seroconversion and neutralizing activity (Benotmane et al., 2022; Caillard et al., 2022; Kamar et al., 2021; Magen et al., 2022; Regev-Yochay et al., 2022). In some individuals with impaired vaccine immune response, our practice is to use tixagevimab/cilgavimab for pre-exposure prophylaxis against SARS-CoV-2 infection. At MSKCC, use of tixagevimab/cilgavimab is reserved for individuals who are not currently infected with SARS-CoV-2 and who have one of the following conditions: received treatment for hematologic malignancy within the past 6 months, received CAR-T cell therapy or allo-HCT within the past 2 years, moderate or severe primary immunodeficiency, or HIV infection with a CD4+ cell count <200 cells/μL. The neutralizing capacity of tixagevimab/cilgavimab and other monoclonal antibodies against various Omicron sub-lineages may differ, emphasizing the need for the development of broadly neutralizing antibody therapies that target highly conserved regions of the SARS-CoV-2 spike protein (Bruel et al., 2022; Stuver et al., 2022).

In immunocompromised individuals with recently diagnosed COVID-19, data are limited regarding the efficacy of available therapies to reduce the risk of disease progression. Accelerated viral clearance and improved outcomes from COVID-19 among immunocompromised cohorts have, however, been associated with several antiviral agents against SARS-CoV-2. For example, among B cell and antibody-deficient hosts with recurring or chronic COVID-19, remdesivir can accelerate viral clearance (Brown et al., 2022). The more recently developed oral antiviral nirmatrelvir/ritonavir has been shown to decrease the rate of progression to hospitalization/death (0.77% versus 7.01%) among symptomatic, non-hospitalized, adult individuals with at least one risk factor for severe COVID-19 (Hammond et al., 2022). We emphasize this landmark study in particular because it included individuals with HIV, cancer, and iatrogenic immunosuppression. Of note, nirmatrelvir/ritonavir is associated with a symptomatic rebound phenomenon with antigen reversion, although most individuals recover within a short timeframe (3–5 days) from recurrent symptoms (Carlin et al., 2022; Boucau et al., 2022). Molnupiravir is one of the least preferred antiviral agents against SARS-CoV-2, given its reduced efficacy compared with nirmatrelvir/ritonavir and low barrier to resistance (Jayk Bernal et al., 2021; Malone and Campbell, 2021).

The role of passive immunity for the treatment of acute COVID-19 in specific immunocompromised phenotypes remains elusive. Although general enthusiasm for convalescent plasma has waned due to contradictory and mostly negative trials, more recent studies have demonstrated signals of efficacy. For example, a review of 30 randomized clinical trials revealed reductions in mortality when neutralizing titer was high and time to randomization was rapid (Focosi et al., 2022). However, another review of 37 studies concluded that convalescent plasma did not improve clinical outcomes in critically ill individuals with COVID-19 and that the potential benefits in immunocompromised individuals with COVID-19 remain unclear (Beraud et al., 2022). Several monoclonal antibodies have received emergency use authorization for the treatment of COVID-19. We emphasize that the providers must remain informed on the latest

Food and Drug Adminstration (FDA) recommendation based on the epidemiology of SARS-CoV-2 as circulating viral variants may not be effectively neutralized by certain monoclonal antibodies. At MSKCC at present, we reserve monoclonal antibodies for the treatment of COVID-19 among individuals who are within 10 days of symptom onset with one of the following: unvaccinated (regardless of underlying cancer), receipt of allo-HCT or CAR-T therapy within the past year, acute or chronic graft versus host disease (GVHD), treatment with B cell depleting agents in the past 6 months, hypogammaglobulinemia, or acute leukemia on active treatment.

Antibody therapies may be more effective when they are delivered very early following acute infection with SARS-CoV-2 (Gupta et al., 2021; Ong et al., 2022). Animal models have highlighted the efficacy of monoclonal antibodies in controlling viral infection and immunopathology when given as part of early treatment (Sefik et al., 2021). One report of over 700 individuals with COVID-19 found that the greatest benefit of neutralizing antibody treatment was achieved when administered early in the disease course (Verderese et al., 2022). By contrast, passive immunization with monoclonal antibodies is of questionable benefit during established infection when it is known that the cellular immune response is the primary driver of clinical outcomes (Bange et al., 2021). For such individuals, methods to enhance and restore cellular immunity, such as cytotoxic T cell lymphocytes and interleukin-7 immunotherapy, hold promise as potential therapeutic strategies for immunocompromised individuals with COVID-19. It should be noted that the therapeutic efficacy of monoclonal antibodies does not always correlate with the extent of neutralization. For example, although the monoclonal antibody Sotrovimab is a relatively weak neutralizer of SARS-CoV-2, this may be offset by Fc-dependent functions (Tada et al., 2022; Winkler et al., 2021). A potential concern with monoclonal antibody use in profoundly immunosuppressed hosts is the emergence of treatment related mutations associated with viral resistance, which has now been demonstrated in multiple reports (Destras et al., 2022; Rockett et al., 2022). Despite the demonstrated high efficacy of monoclonal antibody in clinical trials, predictors of breakthrough symptomatic infection and hospitalization despite monoclonal antibody treatment in cancer or other immunocompromised individuals are not known.

Corticosteroids are the backbone of treatment for hospitalized individuals with severe COVID-19 requiring oxygen (Fernández-Cruz et al., 2021; RECOVERY Collaborative Group et al., 2021). Although precise mechanistic insights regarding efficacy are lacking, the rationale arises from mitigation of the individual's overly potent immune response in the setting of severe infection that leads to tissue damage, particularly within the lungs (Kuba et al., 2005; Lamers and Haagmans, 2022). Notably, major studies evaluating the use of corticosteroids did not consistently include or stratify individuals already receiving immunosuppressive agents, and caution must be exercised regarding how these agents may exacerbate states of underlying immunologic vulnerability (Angus et al., 2020; Dequin et al., 2020; RECOVERY Collaborative Group et al., 2021; Tomazini et al., 2020). Other agents in use to modulate inflammation for individuals hospitalized for COVID-19 are interleukin-6 inhibitors such as tocilizumab and Janus kinase (JAK) inhibitors such as baricitinib (Kalil et al., 2021; Tleyjeh et al., 2021). These agents should not be used indefinitely as long-term immunosuppression can facilitate chronic infection and potentially heighten risk of secondary infections (Leistner et al., 2022). Special consideration should be given to individuals on exogenous immunomodulatory agents for co-existing medical conditions. For example, current practice among solid organ transplant recipients is to reduce or hold antimetabolite agents such as methotrexate or mycophenolate mofetil as these drugs are likely to severely limit antiviral immunity. Withdrawal of calcineurin inhibitors was largely limited to individuals with refractory disease in one study, since these agents may limit IL-1 and IL-6-driven inflammation, which is known to contribute to COVID-19 pathology (Akalin et al., 2020; Hasbal et al., 2021).

Treatment options for immunocompromised individuals with severe COVID-19 remain limited. Immunomodulatory agents and corticosteroids are frequently used in severe cases to suppress the hyperinflammatory immune response. In our practice, we employ judicious use of these agents with tapering when possible, given the potential adverse impacts of additional long-term exogenous immunosuppression.

Preparing for the future

Further studies are urgently needed on several fronts for immunocompromised individuals including but not limited to understanding which immunocompromised phenotypes will benefit from specific therapeutics, clarifying the role of passive immunity such as convalescent and monoclonal antibodies, expanding therapeutics for individuals with active infection, and delineating the optimal timing of therapy initiation in these unique and vulnerable populations (Box 2). The development and implementation of effective prevention and mitigation strategies for individuals with underlying immune dysfunction should be made a priority as we move into the next phases of the SARS-CoV-2 pandemic. Strategies that allow for post-exposure prophylaxis, early diagnosis, and rapid treatment initiation may prove especially beneficial to immunocompromised individuals at high risk for severe outcomes from COVID-19 (Figure 2).

Careful documentation of both serologic and cellular immune responses to vaccination, particularly in immunocompromised individuals, will be of immense public benefit in determining how to maximize protection in this high-risk population. Beyond serologic measurement of antibody titers, assessment of pseudovirus neutralizing capacity, which tends to become uncoupled from antibody levels as variants emerge, is key to a complete understanding of humoral immune responses to vaccination. Similarly, routine and reproducible measurement of cellular immune responses to vaccination is increasingly possible, either via assessment of antigen-specific cytokine production or tools based on T cell receptor sequencing (Vardhana et al., 2022). These assays will be of particular utility to assess both the depth and breadth of cellular immunity in individuals incapable of mounting humoral responses to vaccination. Collaborations both across institutions and between a spectrum of physicians and scientists from expert clinicians to laboratory-based investigators will be critical to achieve comprehensive and timely characterization of immunity to novel SARS-CoV-2 variants in real time. This work must also be able to evolve dynamically as the nature and severity of the infection shifts with successive variants and as novel vaccination and treatment strategies alter

Box 2. Outstanding questions about SARS-CoV-2 in immunocompromised individuals

- What host or immune features enable primary protection and/or efficient clearance of SARS-CoV-2 in the absence of B cell function?
- What defines an effective vaccine response in individuals incapable of mounting a humoral response to vaccination?
- How does immunosuppression and cancer-directed therapy modulate tissue-resident immunity and subsequent antiviral responses?
- What is the role of persistent viral antigen in driving sustained SARS-CoV-2- associated pathology such as multisystem inflammatory syndrome in children (MIS-C) and long COVID?
- What can studies of immunocompromised individuals teach us about the pathogenesis of long COVID?
- What is the efficacy of corticosteroids, other immunosuppressant therapies, and antiviral therapies in COVID-infected immunocompromised individuals?
- What is the optimal timing and schedule of vaccination in individuals receiving lymphocyte-directed therapy or undergoing transplantation?

the course of infection (Niemann et al., 2022). Such partnerships will require strong leadership, vision, and creative funding mechanisms.

At-home rapid antigen tests are a convenient and accessible alternative to laboratory-based diagnostic testing and have transformed the landscape of community-based testing. Among persons with COVID-19-like illness, at-home tests increased from 5.7% during the Delta-variant predominant period to 20.1% during the Omicron-predominant period (Rader et al., 2022). It is hoped that a rapid test-and-treat strategy may lead to improved outcomes if therapy can be introduced prior to the development of the host inflammatory response. It must be acknowledged, however, that at-home tests for SARS-CoV-2 are not universally available and that greater efforts should be made to increase testing availability on a global scale.

Treatment strategies that do not rely on a host immune response would be uniquely beneficial for immunocompromised hosts with COVID-19. Adoptive immunotherapy in the form of cytotoxic T-lymphocytes (CTLs) is an effective therapeutic approach for other viral infections including Epstein-Barr virus and cytomegalovirus, and initial reports of CTL therapy against SARS-CoV-2 have been released (Bollard et al., 2004; Riddell and Reusser, 1991). For example, one case report of an individual with lymphoma and prolonged SARS-CoV-2 infection attributed viral clearance with the expansion of CTLs following treatment with convalescent plasma (Jassem et al., 2021). Larger trials are urgently needed to evaluate the role CTLs for the treatment of COVID-19 in individuals with cancer.

CONCLUSIONS

The global pandemic of SARS-CoV-2 has wrought massive political, economic, and social disruptions. As the world grapples with successive waves of infection fueled by the emergence of viral variants, there is a growing body of literature demonstrating that individuals with underlying immune dysfunction exhibit a distinct epidemiology, clinical course, and immune response to infection with SARS-CoV-2. For example, a notable proportion of immunocompromised individuals with COVID-19 suffer from persistent infection, which carries significant public health implications. Individuals who develop PACS display distinct immunological derangements such as persistent elevation of inflammatory cytokines, off-target autoimmune reactivity, and microvascular dysregulation. In addition, the efficacy of vaccination remains a challenge to quantify, particularly in those with impaired B cell function due to disease or treatment.

Owing to the heterogeneity of disease pathogenesis, data are lacking to guide the optimal treatment strategy for COVID-19 in individuals with immune dysfunction. Effective prevention and mitigation strategies should be made a priority as we progress into subsequent phases of the pandemic (Figure 2). Remarkable vaccination efforts have led to a marked reduction in the morbidity and mortality arising from COVID-19 for portions of the global population with access to effective vaccines. However, as viral variants continue to evade host immune defenses, development of second-generation vaccines and alternative treatment modalities such as passive immunity, post-exposure prophylaxis, and cellular therapeutics will be of increasing importance, particularly in this high-risk population.

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DECLARATION OF INTERESTS

M.-A.P. reports honoraria from Abbvie, Astellas, Bristol-Myers Squibb, Celgene, Equilium, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros, OrcaBio, Takeda, and VectivBio AG, Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, Sellas Life Sciences, and Servier, and the scientific advisory board of NexImmune. He has ownership interests in NexImmune and Omeros. He has received research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, and Novartis. He serves in a volunteer capacity as a member of the Board of Directors of the American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Executive Committee. M.V.D.B. has received research support and stock options from Seres Therapeutics and stock options from Notch

Therapeutics and Pluto Therapeutics; he is a Scientific Co-founder and consultant for Thymofox, Inc; he has received royalties from Wolters Kluwer; has consulted, received honorarium from, or participated in advisory boards for Seres Therapeutics, WindMIL Therapeutics, Rheos Medicines, Merck & Co, Inc., Magenta Therapeutics, Frazier Healthcare Partners, Nektar Therapeutics, Notch Therapeutics, Forty Seven Inc., Ceramedix, Lygenesis, Pluto Therapeutics, GlaxoSmithKline, Da Volterra, Vor Biopharma, Novartis (Spouse), Synthekine (Spouse), and Beigene (Spouse); he has IP Licensing with Seres Therapeutics and Juno Therapeutics and holds a fiduciary role on the Foundation Board of DKMS (a nonprofit organization). S.V. is an advisor for Immunai and has provided consulting services for Koch Disruptive Technologies.

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