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COVID-19 in patients with B cell immune deficiency

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ABSTRACT

This article aims to describe the clinical manifestations and management of COVID-19 in patients with primary and secondary B cell deficient states. We describe the epidemiologic and clinical features as well as unique management paradigm including isolation precautions with COVID-19. We then focus upon primary and secondary preventive approaches including vaccination and pre- as well as post-exposure prophylaxis. Further, we elaborate upon the important disease specific risk factors in these patients and the need to conduct prospective clinical trials to develop individualized management strategies in this population.

1. Epidemiology of COVID-19 in patients with B cell deficiency

As of February 25, 2022, there have been 430 million confirmed cases of COVID-19 worldwide, including 5.9 million deaths, as reported to World Health Organization (World Health Organization). In 2013, it was estimated that primary immunodeficiencies disorders (PIDD) affected up to 6 million people worldwide (Bousfiha et al., 2013), with humoral immunity deficiencies accounting for about half of those (Woroniecka and Ballow, 2000). Primary B-cell immunodeficiency disorders can be categorized into the following groups: (i) Severe reduction in serum immunoglobulin isotypes with profoundly decreased or absent B-cells (i.e., agammaglobulinemia), (ii) Severe reduction in at least 2 serum immunoglobulin isotypes with normal or low B-cells (e.g., common variable immunodeficiency), (iii) Severe reduction in serum IgG and IgA with normal/increased IgM (ie, hyper IgM syndrome), (iv) Antibody deficiency with normal B cells (e.g., selective IgA deficiency, isolated IgG subclass deficiency) (Smith and Cunningham-Rundles, 2019). At this time, the incidence and mortality of COVID-19 in the humoral immunity deficiency population remains unknown. Lack of data may reflect the overall infrequency of people living with immunodeficiency, as well as relative scarcity of infected PIDD patients as they have increased awareness of protective, non-pharmacological measures including hand hygiene, masking, and social distancing, or characteristics of certain PIDD or PIDD therapies providing protection (Marcus et al., 2020). PIDD patients may also present with chronic or relapsing COVID-19 infection (Delavari et al., 2021). Furthermore, B-cell deficient patients may develop re-infection or persistent infections (Brown et al., 2022a), albeit at low rates (Delavari et al., 2021; Cavanaugh et al., 2021; Malhotra et al., 2022; Pilz et al., 2021; Slezak et al., 2021). In a prospective study of a national pediatric registry, death from COVID-19 in patients with PIDD (which included B cell and other immune deficiencies) was found to be 10-fold higher compared to the general population (Delavari et al., 2021). The highest mortality rate was observed among patients with severe combined immunodeficiency and familial hemophagocytic lymphohistiocytosis. There was no mortality among predominantly antibody deficiencies. Based on a review of the literature, patients with common variable immunodeficiency are probably more susceptible to severe COVID-19 than patients with other primary forms of humoral immunodeficiency (Jones et al., 2021).

In addition to primary B cell deficiency states, there is a growing population of secondary B cell deficiency, with medication associated B cell depletion (e.g. rituximab, ocrelizumab, etc.) where the risk of COVID-19 and COVID-19-associated outcomes are 1.7–5.5 higher than in patients with normal B cell states (Boekel and Wolbink, 2022; Andersen et al., 2022; Simpson-Yap et al., 2021).

In the interest of this growing population and similarities with intrinsic B cell deficient states, we shall focus this review to encompass both primary and secondary B cell immunodeficient states with COVID.

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2. Pathophysiology of COVID-19

SARS-CoV-2 is highly contagious and is transmitted primarily via direct person-to-person respiratory transmission through respiratory droplets (Meyerowitz et al., 2021), by inhalation, exposure of mucous membranes to virus carried in droplets, and touching mucous membranes with hands contaminated with virus. Transmission can occur from people with a range of symptoms, including those without symptoms (*Scientific Brief: SARS-CoV-2 Transmission*, 2022). Incubation time ranges from 2 to 14 days, with a median of 5 days (*Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)*, 2022).

It is historically known that patients with humoral immune deficiency (B cell deficiency) are less prone to serious viral infections than those with cellular or combined immunodeficient states. That does not necessarily reflect a lack of importance of B cells in antiviral immunity, but rather highlights the importance of T helper cells in priming humoral immunity, via the generation of memory B cells and long-lived plasma cells (Grammatikos et al., 2021). Humoral immunity is effective in neutralizing viral particles and thus preventing their spread through tissues but once an infection is established, cellular immunity is more important via its role in eliminating virally infected cells. Besides their role in humoral immunity, B-cells are also regarded as antigen-presenting cells that activate T-cells.

3. Clinical manifestations and diagnosis of COVID-19 in patients with B-Cell deficiency

Acute presentation of COVID-19 is similar to the general population. Typically, symptoms will include a combination of cough, fever, myalgias, headache and dyspnea (Stokes et al., 2020). Essentially, symptomatic disease is clinically indistinguishable from other upper respiratory tract infections. The likelihood that any of these symptoms indicate COVID-19 depends on the predominant circulating viral respiratory infections at a given time. The most important difference between immunocompromised and non-immunocompromised hosts is the increased risk of disease progression (Fung and Babik, 2021). Antigen testing and nucleic acid amplification detection remain the mainstay of testing in acute illness (Simioli et al., 2021).

Immunosuppressed patients may incidentally test positive for SARS-CoV-2 through shedding. Viral shedding is not associated with disease progression or transmission. However, in the B-cell deficient population, prolonged active infection has been reported. A case report analyzed a patient with malignant B cell lymphoma on chemotherapy who had active virus recovered over three months, with interval evolution of the viral strain during that time in that individual (Kemp et al., 2021). In another case report, a patient receiving rituximab had initially asymptomatic infection, which progressed to symptomatic disease over several weeks in a delayed presentation (Rodriguez-Pla et al., 2021). The lack of an effective immune response appears to prolong illness in many other B-cell depleting conditions as well (Brown et al., 2022). It has been our experience that patients with chronic or relapsing infection are often misdiagnosed as having post-infectious sequelae (such as organizing pneumonia) when their disease reflects active viral replication. As such, a patient with compatible symptoms and positive antigen or nucleic acid amplification testing should be considered infected and potentially infectious, even if outside of traditional windows for illness duration. No test currently exists to distinguish shedding from active infection, and the evaluation is based mainly on clinical evaluation, radiographic findings and timing of symptom onset (Widders et al., 2020) which is less reliable in this population

4. Management of COVID-19

The current management of COVID-19 involves different aspects of the pathogenesis and its sequalae of SARS-CoV-2 infection. Antivirals and passive antibody therapies (monoclonal antibodies and convalescent plasma (CP)) are effective early in the course of COVID-19 infection, while immunomodulation (with glucocorticoids or anticytokine therapies) is more suitable later in the course of the disease. The management of COVID-19 is guided by data from randomized trials (Bhimraj et al., 2022). Patients with underlying immunodeficiency disorders (including B-cell immune deficiency) have not been adequately represented in these trials. The existing evidence indicates that glucocorticoids improve outcomes in hospitalized patients with severe COVID-19 presumably due to a mitigation in the systemic inflammatory response and associated lung injury. The combination of glucocorticoid treatment with immunomodulators (such as tocilizumab or baricitinib) has demonstrated benefit in patients who are advancing to early critical illness. Caution should be exercised in the use of these immunomodulatory agents in patients with underlying B-cell immunodeficiency due to the potential risk of secondary bacterial or fungal infections.

4.1. Antivirals

At this time (July 2022), there are several antivirals (nirmatrelvir/ritonavir, molnupiravir, and remdesivir) used for treatment of non-hospitalized patients with COVID-19, (Lee et al., 2022). Currently, remdesivir remains the most commonly used antiviral medication for hospitalized patients who have already developed severe disease or critical illness. For hospitalized patients with severe disease combination therapy is typically employed (ie, remdesivir plus dexamethasone). In patients with significant immune compromise, particularly those with humoral immunodeficiency, antiviral therapy may be combined with monoclonal antibody or convalescent plasma therapy (Palomba et al., 2021; Baang et al., 2021; Brown et al., 2022b; Casarola et al., 2021; Malsy et al., 2021).

4.1.1. Nirmatrelvir/ritonavir (Paxlovid)

Nirmatrelvir/ritonavir is currently under Emergency Use Authorization (EUA) for adults and children ($\geq$ 12yo and $>$ 40 kg) with mild to moderate illness who are at high risk of progression to severe COVID-19, including individuals with primary or acquired immunodeficiency. It is typically used for outpatients, though may be used in the inpatient setting if the patient was admitted for a reason *other* than COVID-19. (US Food and Drug Administration, 2021) Nirmatrelvir inhibits the *Mpro* SARS-CoV-2 protease, while ritonavir inhibits CYP450 3A4 allowing for a longer nirmatrelvir half-life. Because of ritonavir's CYP450 "pharmacokinetic booster" effect, all concomitant medications (including supplements and over-the-counter medications) should be carefully reviewed prior to prescription. The Infectious Diseases Society of America (IDSA) recommends nirmatrelvir/ritonavir for high-risk outpatient adults and children $\geq$12yo/$>$40 kg with mild to moderate disease within 5 days of COVID-19 symptom onset (Bhimraj et al., 2022). There have been limited clinical trials to date. Nirmatrelvir/ritonavir did have efficacy in decreasing severity and reducing all-cause mortality in pharmaceutical-sponsored adult clinical trials (Wen et al., 2022).

4.1.2. Molnupiravir (Lagevrio)

Molnupiravir is an oral nucleoside analogue that inhibits viral replication by inducing progressive mutagenesis via incorporation into viral RNA; it is currently under FDA EUA for outpatients $\geq$18 years old at risk of severe disease progression in situations where no alternative treatment (e.g., bebtelovimab, remdesivir, or nirmatrelvir/ritonavir) are available (Bhimraj et al., 2022). Because of the mechanism of action of introducing genetic code errors, these is significant risk of teratogenicity and fetal harm, pediatric bone and cartilage side effects, and other adverse events related to potential for mutagenesis. In immune compromised patients who cannot clear infections with SARS-CoV-2 (Duléry et al., 2021), there is a theoretical concern about SARS-CoV-2 ongoing mutation which could lead to longer duration of infection or

emergence/selection of variants resistant to other therapies (i.e. variants of concern). Thus, while molnupiravir has been shown to be effective for preventing disease progression when used early in infection in several clinical trials (Jayk Bernal et al., 2022a; Fischer 2nd et al., 2022; Jayk Bernal et al., 2022b), it is currently recommended for use only when other outpatient therapies for prevention of disease progression are contraindicated or unavailable.

4.1.3. Remdesivir (Veklury)

Remdesivir is an intravenous nucleotide analogue that inhibits viral replication by blocking SARS-CoV-2 RNA-dependent polymerase. This causes premature termination of viral transcription. It is currently under EUA for children (> 3.5 kg) and FDA approved for older children (≥12yo/>40 kg) and adults with severe disease, hypoxia, or risk of progression to severe disease. Most experts recommend remdesivir for patients hospitalized requiring supplemental oxygen requirement, including those with progression to respiratory failure. It is also recommended for patients hospitalized without oxygen requirement but with underlying risk factors for severe progression (Bhimraj et al., 2022). A randomized double-blind study demonstrated that remdesivir, as compared to placebo led to reduction in hospitalization among high-risk adult outpatients (Gottlieb et al., 2022). This led to the recommendation to consider 3 days of remdesivir in high-risk outpatients with COVID-19. Multiple animal models have demonstrated that remdesivir reduces SARS-CoV and SARS-CoV-2 viral loads, as well as progression of disease, and work best during early disease when viral replication is high (Sheahan et al., 2017; Williamson et al., 2020). A number of randomized controlled trials have demonstrated that in hypoxic hospitalized patients, remdesivir may reduce mortality as well as duration of hospitalization (Beigel et al., 2020; Wang et al., 2020; Goldman et al., 2020). There is a less certain effect in non-hypoxic patients, but in those that are at risk of progression to severe disease (for example, patients with severe immune compromise) experts continue to consider remdesivir as a reasonable therapy (Bhimraj et al., 2022). There is unclear evidence regarding 5 versus 10 days duration of treatment during severe illness (Goldman et al., 2020). However, for patients who are requiring supplemental oxygen alone, 5 days duration appears to offer the clearest benefit. The strongest effect has been seen early in severe disease, when used prior to requirement for invasive ventilation or ECMO. Remdesivir can cause nausea and vomiting, elevate transaminases and cause transient hepatotoxicity. Additionally, the package insert recommends it be discontinued in patients with creatine clearance <30 mL/min. However, observational data suggest that significant toxicity with a short duration of therapy is unlikely in patients with impaired renal function (Adamsick et al., 2020; Pettit et al., 2021) and experts have approved the use in patients on renal replacement therapy (Bhimraj et al., 2022). Multiple animal models have demonstrated that remdesivir reduces SARS-CoV and SARS-CoV-2 viral loads, as well as progression of disease, and works best during early disease when viral replication is high (Sheahan et al., 2017; Williamson et al., 2020).

4.2. Passive antibody therapies

4.2.1. Anti-SARS-CoV-2 monoclonal antibody treatment

A novel approach in the combat against SARS-CoV-2 has been the development of neutralizing monoclonal antibodies. The spike protein of the coronavirus is divided into 2 subunits (S1 and S2). S1 attaches to the angiotensin-converting enzyme 2 receptor through its receptor binding domain (RBD) thus allowing viral entry into the host cell. Monoclonal antibodies bind to the RBD and prevent viral binding and fusion with the host cell. When used in combination, antibodies bind to non-overlapping epitopes of the RBD. These antibodies are engineered but derived from either convalescent plasma or humanized mice exposed to SARS-CoV-2 antigens (Taylor et al., 2021).

Anti SARS-CoV-2 monoclonal antibodies that received EUA have been studied in the early treatment of non-hospitalized patients with mild to moderate disease who have at least one risk factor for progression to severe disease such as older age, obesity and diabetes mellitus. A small percentage of immunocompromised individuals was included in these trials. Bamlanivimab-etesevimab was given within 3 days of laboratory diagnosis (Dougan et al., 2022), casirivimab-imdevimab within 72 h of diagnosis or 7 days of symptom onset (Weinreich et al., 2021) and sotrovimab within 5 days of symptom onset (Gupta et al., 2021). Treatment was shown to decrease the risk for hospitalization or death from any cause compared to placebo. The currently used monoclonal antibody bebtelovimab is active against all Omicron variants and has received EUA after being studied in a phase 2 clinical trial (Dougan et al., 2022). These monoclonal antibodies are administered as intravenous infusion. Infusion-related reactions have been reported. Adverse events are typically mild.

Anti-SARS-CoV-2 monoclonal antibody therapy was studied in a cohort of 180 patients receiving rituximab or obinutuzumab who developed mild-to-moderate COVID-19 (Yetmar et al., 2022). Only 12.2% progressed to severe disease (hypoxia or hospitalization). No deaths were reported within 30 days and only 1.8% developed persistent COVID-19 within 90 days.

In an open-label platform trial (RECOVERY), hospitalized patients with COVID-19 were randomly assigned to casirivimab-imdevimab (n = 4839) versus usual care alone (n = 4946) (Group RC, 2022). The proportional effect on mortality differed significantly between seronegative and seropositive patients (p value for heterogeneity = 0.002). Among seronegative individuals, 28-day mortality was 24% for those who received casirivimab-imdevimab and 30% for those assigned to usual care (rate ratio 0.80; 95% CI 0·70–0·91; p = 0.001). In a pre-specified analysis treatment was beneficial in seronegative patients if given ≤7 days after symptom onset. In summary, the study suggests that treatment was beneficial to patients lacking humoral immunity. This has implications for patients with B-cell deficient disorders who are typically unable to mount an adequate antibody response after natural infection or vaccination. While the combination of casirivimab and imdevimab has no activity against the currently circulating variants of concern, the novel monoclonal antibody bebtelovimab retains activity against all Omicron subvariants. Currently, monoclonal antibodies are not authorized for use in hospitalized patients but may be available through expanded access programs.

4.2.2. Convalescent plasma

Plasma collected from patients who have recovered from COVID-19 containing high-titer of anti-SARS-CoV-2 antibodies has been hypothesized to inhibit viral replication. Results from 3 randomized open-label trials showed no benefit in regard to mortality or need for mechanical ventilation among hospitalized patients (Recovery Collaborative Group, 2021a; Begin et al., 2021; Writing Committee for the REMAP-CAP Investigators et al., 2021). Most patients enrolled in these studies did not have an underlying immunocompromising condition. A re-analysis of the RECOVERY trial data suggested that convalescent plasma reduces mortality in patients who present within 7 days of symptom onset and those who are seronegative at the time of presentation (Hamilton et al., 2021). In a prespecified subgroup analysis, the REMAP-CAP investigators noted a trend towards improved survival and/or more organ support-free days in immunocompromised patients (Writing Committee for the REMAP-CAP Investigators et al., 2021). Convalescent plasma is available under EUA for children of all ages. Similar to adults there is limited evidence to date of improved outcomes (Zaffanello et al., 2021).

Patients treated with anti-CD20 monoclonal antibodies may develop chronic or relapsing infection. We have noticed this particularly in patients receiving rituximab for B-cell malignancies and less commonly in those treated for rheumatologic conditions. We have also seen occasional cases of prolonged COVID-19 in patients with multiple sclerosis receiving ocrelizumab. In a retrospective cohort study from Spain, 13.5% (57/422) of patients treated with anti-CD20 monoclonal antibodies developed infection. Of those who survived, 17.3% (9/52) had

COVID-19 relapse (Calderon-Parra et al., 2022). Notably, all of them received the last dose of anti-CD20 monoclonal antibody <6 months from the COVID-19 episode.

In a published case series, clinical improvement was observed in 16 of 17 B-cell-depleted patients within 48 h following plasma transfusion (Hueso et al., 2020). All these patients were seronegative and had RNAemia on presentation. In another series, 4 of 5 rituximab-treated, seronegative patients with chronic COVID-19 improved clinically after receiving convalescent plasma (Betrains et al., 2021). All patients had detectable SARS-CoV-2 IgG antibody immediately following transfusion. Even though antibodies were absent at later follow-up in all 4 surviving patients, no disease relapse was observed. Successful outcomes were also reported in 3 patients with X-linked agammaglobulinemia following plasma transfusion (Jin et al., 2020). Despite these findings, there is currently insufficient evidence to recommend for or against the use of convalescent plasma in patients with B-cell deficiency presenting with either acute or chronic/relapsing infection.

4.3. Immunomodulation

4.3.1. Glucocorticoids

In a controlled, open-label trial conducted within the National Health Service in the United Kingdom, patients with confirmed or suspected COVID-19 were randomly assigned to receive dexamethasone (n = 2104) or usual care alone (n = 4321) (Recovery Collaborative Group et al., 2021). Dexamethasone was used at a dose of 6 mg daily orally or intravenously for up to 10 days. The primary outcome was 28-day mortality. No survival benefit was observed among patients who did not require supplemental oxygen. For patients on noninvasive oxygen therapy at baseline, there was significant reduction in mortality (23.3% vs. 26.2%, relative risk 0.82, 95% CI 0.72–0.94). Age-adjusted analysis suggested a 4.1% absolute mortality reduction. Similarly, for patients on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at baseline, mortality was decreased in those treated with dexamethasone (29.3% vs. 41.4%, relative risk 0.64, 95% CI 0.51–0.81). Age-adjusted analysis suggested a 12.3% absolute mortality reduction. A prospective meta-analysis of pooled data from 7 randomized clinical trials similarly supports the use of glucocorticoids (WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group et al., 2020). Based on these findings, treatment with dexamethasone is recommended for severe COVID-19 (oxygen saturation $\leq$ 94% on room air or need for oxygenation or ventilatory support).

4.3.2. Interleukin-6 (IL-6) inhibitors

In acute COVID-19, a heightened cytokine release is indicated by elevated levels of c-reactive protein (CRP), ferritin and the pro-inflammatory cytokine interleukin-6 (IL-6). Tocilizumab and sarilumab are IL-6 receptor antagonists that have not been specifically studied in immunocompromised individuals.

In the open-label RECOVERY trial conducted in the United Kingdom, patients with suspected or confirmed COVID-19, who had hypoxemia (oxygen saturation < 92% on room air or oxygenation supplementation), and CRP $\geq$75 mg/L were randomized to receive tocilizumab (n = 2022) or usual care alone (n = 2094) (Recovery Collaborative Group, 2021b). Tocilizumab significantly reduced the 28-day mortality rate (31% vs. 35%, relative risk 0.85, 95% CI 0.76–0.94). Among those who were not on mechanical ventilation at baseline, tocilizumab reduced the combined endpoint of progression to mechanical ventilation or death. Subgroup analysis suggested that patients who were receiving glucocorticoids (mainly dexamethasone) were more likely to benefit from tocilizumab than those who did not receive glucocorticoids.

In the international REMAP-CAP trial, patients were enrolled within 24 h after starting organ support in the intensive care unit (ICU) (REMAP-CAP Investigators et al., 2021). Patients were randomized to tocilizumab (n = 353) or sarilumab (n = 48), or standard of care (n = 402). Improved outcomes were demonstrated in patients treated with IL-6 receptor antagonists in terms of respiratory and cardiovascular organ support-free days as well as 90-day mortality. The RECOVERY and REMAP-CAP trials were the two largest, randomized trials on the use of IL-6 inhibitors in hospitalized patients with COVID-19 and demonstrated a survival benefit. Several other trials that failed to demonstrate a clinical benefit may have been underpowered (Rosas et al., 2021; Salama et al., 2021; Salvarani et al., 2021; Stone et al., 2020). Another possible explanation of the conflicting results is that glucocorticoids were not consistently used in the initial trials.

Based on the existing evidence from studies in the general population, tocilizumab should be considered for patients with B-cell immune deficiencies who require high-flow oxygen or non-invasive ventilation and have rapidly increasing oxygen needs and systemic inflammation. The selected CRP cut-off of 75 mg/dL in the RECOVERY trial is arbitrary. Tocilizumab is also recommended for patients requiring mechanical ventilation or ECMO within 24 h of ICU admission. Tocilizumab should always be used in combination with dexamethasone (or another glucocorticoid). In the published trials, most patients were treated with a single dose of 8 mg/kg (max 800 mg). There is not enough evidence for or against administering a second dose. Data on sarilumab are less robust.

4.3.3. Janus kinase (JAK) inhibitors

Baricitinib is a Janus kinase (JAK) inhibitor that interferes with phosphorylation of signal transducer and activator of transcription (STAT) proteins involved in immune activation and inflammation. In the international, multicenter, double-blind, placebo-controlled COV-BARRIER trial patients with COVID-19 pneumonia and elevation in one or more inflammatory markers were randomized to baricitinib (n = 764) or placebo (n = 761) for up to 14 days (Marconi et al., 2021). Most participants were receiving glucocorticoids (mainly dexamethasone). Adding baricitinib to standard of care reduced mortality at 28 days. The difference was most pronounced in patients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% vs. 29.4%, hazard ratio 0.52, 95% CI 0.33–0.80). In the previous ACCT-2 trial, baricitinib combined with remdesivir reduced time to recovery compared with placebo plus remdesivir (Kalil et al., 2021).

Similar to IL-6 inhibitors, baricitinib should be considered for patients with B-cell immune deficiencies who require high-flow oxygen or non-invasive ventilation and have rapidly increasing oxygen needs and systemic inflammation. Limited data suggest a possible benefit in patients requiring mechanical ventilation. Like tocilizumab, it should be used in combination with dexamethasone. Baricitinib is administered at a dose of 4 mg po daily (if estimated GFR >60 mL/min/1.73 m^2) for 14 days or until hospital discharge. Data on the JAK inhibitor tofacitinib are limited. No head-to-head comparisons have been conducted between different immunomodulatory agents in a clinical trial setting and their relative efficacy is not known. IL-6 inhibitors should not be used concomitantly with JAK inhibitors.

Chronic use of JAK inhibitors has been associated with increased risk of cardiovascular events, cancer and thrombosis. The FDA has therefore required a Black Box warning. However, data from short-term use of JAK inhibitors for the treatment of COVOID-19 have not revealed significant safety signals.

4.4. Anticoagulation

There has been a substantial improvement in our understanding of the role of anticoagulation in improving outcomes among hospitalized COVID-19 patients over the past 2 years of this global pandemic (Angelini et al., 2022; Flumignan et al., 2022). From the early days of the pandemic, it became quite obvious that COVID-19 was associated with significant endothelial injury/activation with marked elevations in D-dimer and fibrinogen degradation product levels especially in patients with critical illness in the ICU. This was associated with high rates of both venous thromboembolism (VTE) as well as arterial

thromboembolic events (ATE) as compared to patients with severity matched non-COVID illnesses with odds ratio (OR) for VTE ranging from 2.8 to 5.9 for non-severe and severe COVID respectively (Angelini et al., 2022; Li et al., 2021). Published rates of VTE among hospitalized COVID-19 patients have varied widely and probably reflect factors such as severity of illness, hospital length of stay, VTE prophylaxis strategies and whether active surveillance for VTE was performed etc. VTE rates have ranged anywhere from 10 to 70% with meta-analyses of individual studies placing the rate closer to 31% (Di Minno et al., 2020). Autopsy studies have also shown a 60% rate of VTE in patients in whom it was not suspected clinically prior to death (Wichmann et al., 2020). Given these high rates of VTE; many algorithms were implemented worldwide where critically ill patients and those with high D-dimer levels ($>$ 2000 or $>$ 3000 for example in different algorithms) were treated with therapeutic anticoagulation to proactively prevent VTE. These types of algorithms also received support from early retrospective studies that showed improved outcomes with therapeutic anticoagulation (Tang et al., 2020).However, these algorithms were based on clinical reasoning that therapeutic anticoagulation would decrease the high rates of VTE and death in these subgroups of patients. However, the initial hopes that therapeutic anticoagulation would improve COVID-19 outcomes by preventing VTE as well as tissue level microthrombi and endothelial/organ dysfunction were not supported by data from randomized clinical trials (RCTs). Since the start of the COVID pandemic, at least 8 RCTs have been performed to look at the impact of either intermediate or full dose therapeutic anticoagulation in $>$5500 hospitalized COVID-19 patients. A systematic review and meta-analysis summarize the results of these trials and provide an opportunity to focus on broad principles while deciding on anticoagulation strategies in hospitalized COVID-19 patients (Reis et al., 2021). The most important message from the available evidence is that clinicians should base anticoagulation strategies on COVID-19 disease severity as a guide to treatment rather than basing these decisions on levels of individual biomarkers such as CRP, D-dimer etc.

The first recommendation that one can extrapolate from the trial data is that critically ill COVID-19 patients NOT be placed on therapeutic levels of anticoagulation proactively without actual evidence for VTE. The levels of D-dimer in these patients can often fluctuate greatly from day to day and sometimes a sudden spike and D-dimer levels along with worsened clinical status can point towards a new VTE event. The second recommendation is to individualize anticoagulation decisions in hospitalized patients with non-critical illness (i.e., patients not receiving vasopressor support, high-flow nasal cannula oxygen support, noninvasive ventilation or invasive mechanical ventilation). Non-critically ill COVID-19 patients do appear to benefit from therapeutic anticoagulation, with reduced thrombotic events as well as death but at the expense of increased bleeding events. Non-critically ill patients should receive at least prophylactic levels of anticoagulation and therapeutic anticoagulation can be offered to certain individuals after an individualized risk assessment. Thus, it appears that conventional wisdom regarding the plausible benefits of therapeutic anticoagulation especially in critically ill COVID-19 patients were proved wrong by subsequent randomized controlled data. A more nuanced understanding of the role of anticoagulation in moderate intensity COVID-19 illness is warranted with a risk-benefit analysis and discussion in each patient.

5. Isolation precaution and personal protective equipment

Our knowledge of respiratory disease transmission continues to grow throughout the COVID-19 pandemic, including understanding of appropriate PPE (personal protective equipment). SARS-CoV-2 is transmitted via a combination of larger infectious droplets and smaller infectious aerosols, which exist on a spectrum of size. Transmission generally occurs within 6 ft of an individual, though aerosolization of smaller wafting particles can occur beyond that distance, particularly during certain procedures (e.g., including intubation, bag mask ventilation) often termed “aerosol-generating procedures” (AGPs). Masking is a safe and effective way to reduce transmission in a variety of settings, including both healthcare settings and the community (Chu et al., 2020; Eikenberry et al., 2020; Tomshine et al., 2021).

For healthcare workers, the same PPE is recommended for caring for immunocompetent and immunocompromised patient populations. A layering approach (admission screening, healthcare worker vaccination, increased facility ventilation, and PPE tiered for a variety of factors) has generally been found to be most effective for transmission prevention (Klompas and Karan, 2022). At this time, the CDC recommends use of either N95s or well-fitted surgical masks while caring for known COVID positive patients or persons under investigation (PUIs) for COVID-19 (Healthcare Workers: Information on COVID-19, 2022). Healthcare worker type of mask may be based on the types of care being performed (e.g. AGPs like intubation for which respirators are recommended), patient or healthcare worker specifics (such as vaccination status or immune status), and facility-parameters like ventilation (Klompas et al., 2020; Klompas et al., 2021). Eye protection should be worn during COVID-19 or PUI care. While cloth masks may be more comfortable and are sometimes worn in a non-hospital setting, they are less effective than medical grade masks and should not be used for clinical care (Ueki et al., 2020). Increased permeability of cloth masks may also mean the patient is less protected from asymptomatic transmission from the healthcare worker. Guidance continues to evolve, and we recommend following local infection control guidelines which may be based, in part, upon local COVID-19 prevalence.

In terms of patient-specific recommendations for community masking, wearing a well-fitted face mask in indoor settings, particularly during periods of high prevalence, is the most reliable way to prevent transmission. Patients with significant humoral deficiencies or immune compromise may be advised to be more vigilant about community masking than the general population, particularly because a “layering” approach, which includes vaccine response after vaccination, may be less effective in this population. Reliable masking is of highest priority as compared to the specific mask type; in other words, the “best” mask is a mask that is actually worn consistently (Tomshine et al., 2021; Leung et al., 2020). If the patient inquiries about type of mask, an N95, KN95, or similar “respirator” are thought to be most effective at prevention transmission in the setting of unmasked very close proximity community contacts. A surgical mask is also considered very protective, while cloth masks, particularly “single ply” or “breathable material” may be more permeable and provide less protection (Tomshine et al., 2021).

Typical isolation following COVID-19 infection is $<$10 days, for non-immune compromised individuals with mild to moderate COVID-19. Although individuals may PCR test positive for weeks after infection when tested via molecular methods (‘shedding’), it has not clearly been correlated with replicative virus. In studies using viral culture, probability of infectiousness dropped drastically by day 10. However, replication competent virus was more commonly identified $>$10 days in studies including immune compromised individuals (Walsh et al., 2020). Another review reported replication competent virus not being detected $>$20 days after symptom onset among immune compromised individuals (Rhee et al., 2020). These data support the current recommendations of 10 days of isolation for most patients, and 20 days beyond symptom onset for those with critical illness or immune compromise (Centers for Disease Control and Prevention, 2022).

Despite these findings and more conservative approach to immune compromised patients generally, patients with B-cell disorders merit additional consideration. A case report documented a post stem cell transplant patient with persistent fever and PCR positivity for $>$60 days, only defervescing after an infusion of convalescent plasma and subsequently testing negative (Karataş et al., 2020). A similar report was described in a chronic lymphocytic leukemia patient, where symptoms, radiographic findings, and laboratory findings all supported an ongoing infection for several weeks (Ye et al., 2020). These case reports highlight timing of those with immune compromise- particularly humoral

immune compromise- needing careful attention paid not only to how long since symptom onset, but also cessation/improvement of symptoms. Patients with B-cell disorders and ongoing symptoms without sustained improvement should be considered potentially infectious beyond 20 days. The decision to remove isolation should be informed by symptoms and time since symptom onset. In the future, repeat testing may have a role, but shedding of replication incompetent virus is prolonged in this demographic as well (Walsh et al., 2020), and thus is not presently part of the current approach to ending isolation.

6. Vaccination and booster vaccination

COVID-19 vaccination is the most effective measure to prevent morbidity and mortality. Since Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines have been most studied in the immunocompromised population, they will be more extensively covered below. In December 2020, 2 dose series of Pfizer-BioNTech and Moderna received EUA for people 16 years and older and 18 years and older, respectively (*FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine*, 2022; *FDA Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine*, 2022). By May 2021, the FDA expanded Pfizer-BioNTech vaccine EUA down to people aged 12 years and older and by October 2021 included children 5 through 11 years of age (*FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Adolescents in Another Important Action in Fight Against Pandemic*, 2022; *FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age*, 2022).

It is known that vaccine effectiveness in all people declines over several months (Tartof et al., 2021; Pegu et al., 2021) and unsurprisingly, vaccine effectiveness is lower in immunocompromised individuals (Tenforde et al., 2021).Trials for COVID-19 booster immunizations were expedited and in August 2021 booster immunizations were endorsed for immunocompromised individuals, and by November 2021 the FDA expanded booster eligibility for all adults over the age of 18 (*FDA Authorizes Additional Vaccine Dose for Certain Immunocompromised Individuals*, 2022; *FDA Expands Eligibility for COVID-19 Vaccine Boosters*, 2022).In January 2022, FDA cleared Pfizer-BioNTech boosters for children 12 to 15 years and the CDC recommended that immunocompromised 5- to 11-year-olds also receive an extra Pfizer-BioNTech primary dose (*CDC Recommends Pfizer Booster at 5 Months, Additional Primary Dose for Certain Immunocompromised Children*, 2022). Expanded authorization for a second booster dose for older and immunocompromised individuals occurred in March 2022 (*FDA Authorizes Second Booster Dose of Two COVID-19 Vaccines for Older and Immunocompromised Individuals*, 2022). In June 2022, the FDA authorized emergency use of both Pfizer-BioNTech and Moderna vaccines to include use in children down to 6 months of age. A third primary series dose of Moderna vaccine was also authorized for immunocompromised individuals 6 months to 17 years (*FDA Authorizes Moderna and Pfizer-BioNTech COVID-19 Vaccines for Children Down to 6 Months of Age*, 2022).

In a multistate analysis performed January to September 2021 (Embi et al., 2021) (during a period of Delta variant spread) designed to assess the effectiveness of 2 dose vaccination with mRNA COVID-19 vaccines, over 20,000 immunocompromised adults (defined as solid malignancies, hematologic malignancies, rheumatologic or inflammatory disorders, other intrinsic immune conditions or immunodeficiencies, organ transplants, and stem cell transplants) were included. Vaccine effectiveness against COVID-19-associated hospitalization was lower among immunocompromised adults (70%) compared to immunocompetent adults (90%). Of the nearly 3000 adults with immunodeficiency who were included, vaccine efficiency was 73%. In another multistate analysis performed August to December 2021 (a period of Delta and Omicron variants), effectiveness of a third dose of mRNA COVID-19 vaccine was examined, including around 1000 immunocompromised adults (defined as active cancer, HIV, congenital immunodeficiencies, prior splenectomy, prior transplants, immunosuppressive medication, rheumatologic conditions, and inflammatory bowel disease), which showed higher vaccine effectiveness of 88% with 3 doses of vaccine compared to those who had received 2 doses (69%) (Tenforde et al., 2022).

However, large-scale studies in patients with specifically B cell immunodeficiencies addressing SARS-CoV-2 mRNA vaccine antibody production and vaccine efficiency are lacking. In a study from Israel, Hagin et al. (Hagin et al., 2021) reported that 70% (18 of 26 adult patients) with mostly antibody deficiency generated specific humoral and T-cell responses after 2 doses of Pfizer-BioNTech, with 4 of the 8 who did not respond were, unsurprisingly, patients with XLA. In a European study which included 21 patients with inborn errors of immunity mostly impairing the B-cell compartment, 16 patients (76%) showed an overall significant increase in SARS-CoV-2 antibodies after the second Pfizer-BioNTech dose as well as expansion of antigen-specific CD4 + CD40L+ T cells (Amodio et al., 2021). In one of the largest studies to date, Delmonte et al. (Delmonte et al., 2021) showed antibody response in 85.1% (63 of 74) of fully immunized patients, with a lower rate of seroconversion in patients with APCED (Autoimmune Polyendocrinopathy, candidiasis, ectodermal dystrophy). Finally, in an interventional study from Italy, Pulvirenti et al. (Pulvirenti et al., 2021) showed that COVID-19 infection of 72 patients with primary antibody deficiencies followed by immunization resulted in boosted immune response.

In the immunocompromised patient population, COVID-19 vaccines may provide some protection. Therefore, these patients should be vaccinated with a consideration to monitoring T cell responses to SARS-CoV-2 (Amodio et al., 2021; Ameratunga et al., 2021; Salinas et al., 2021). Multiple studies focusing on patients with immunodeficiencies have reported safety with COVID-19 vaccines (Hagin et al., 2021; Amodio et al., 2021; Delmonte et al., 2021).

Fig. 1 shows the current mRNA vaccination strategy for patients (>12 yrs. old) with B cell defects

7. Pre-exposure prophylaxis

Since many patients with intrinsic or acquired B cell defects may not mount a robust and long lasting immune response (Bitoun et al., 2022; Graalmann et al., 2021) to the current COVID-19 vaccines, EUA was approved for the use of combination of two monoclonal antibodies: Evusheld (Tixagevimab co-packaged with cilgavimab) on December 8, 2021 (*Coronavirus (COVID-19) Update: FDA Authorizes New Long-Acting Monoclonal Antibodies for Pre-exposure Prevention of COVID-19 in Certain Individuals*, 2022a). It has a prolonged half-life and may provide protection for 6 months after administration. It was also noted that the current dose of Evusheld may be less active against certain Omicron subvariants, hence, on February 24,2022, FDA authorized a revised dosing regimen to double the dose 150 mg of Tixagevimab and 150 mg of Cilgavimab administered as two separate consecutive intramuscular injections to 300 mg of each (*FDA authorizes revisions to Evusheld dosing*, 2022). Cardiac side effect events were rare (1 in 200 injections) (*Coronavirus (COVID-19) Update: FDA Authorizes New Long-Acting Monoclonal Antibodies for Pre-exposure Prevention of COVID-19 in Certain Individuals*, 2022b) and likely reflective of patients with pre-existing cardiac diseases. The recommended timing of administration is as below in Table 1.

8. Post-exposure prophylaxis

Casirivimab/imdevimab (*Regen-Cov*) and bamlanivimab/etesevimab were previously authorized for post-exposure prophylaxis (PEP) in patients at high risk for disease progression including individuals with significant immunocompromise. Unfortunately, neither of these monoclonal antibodies are effective against the Omicron variant and so are considered ineffective during the current COVID-19 variant wave. While sotrovimab appears to retain activity and is still being used for

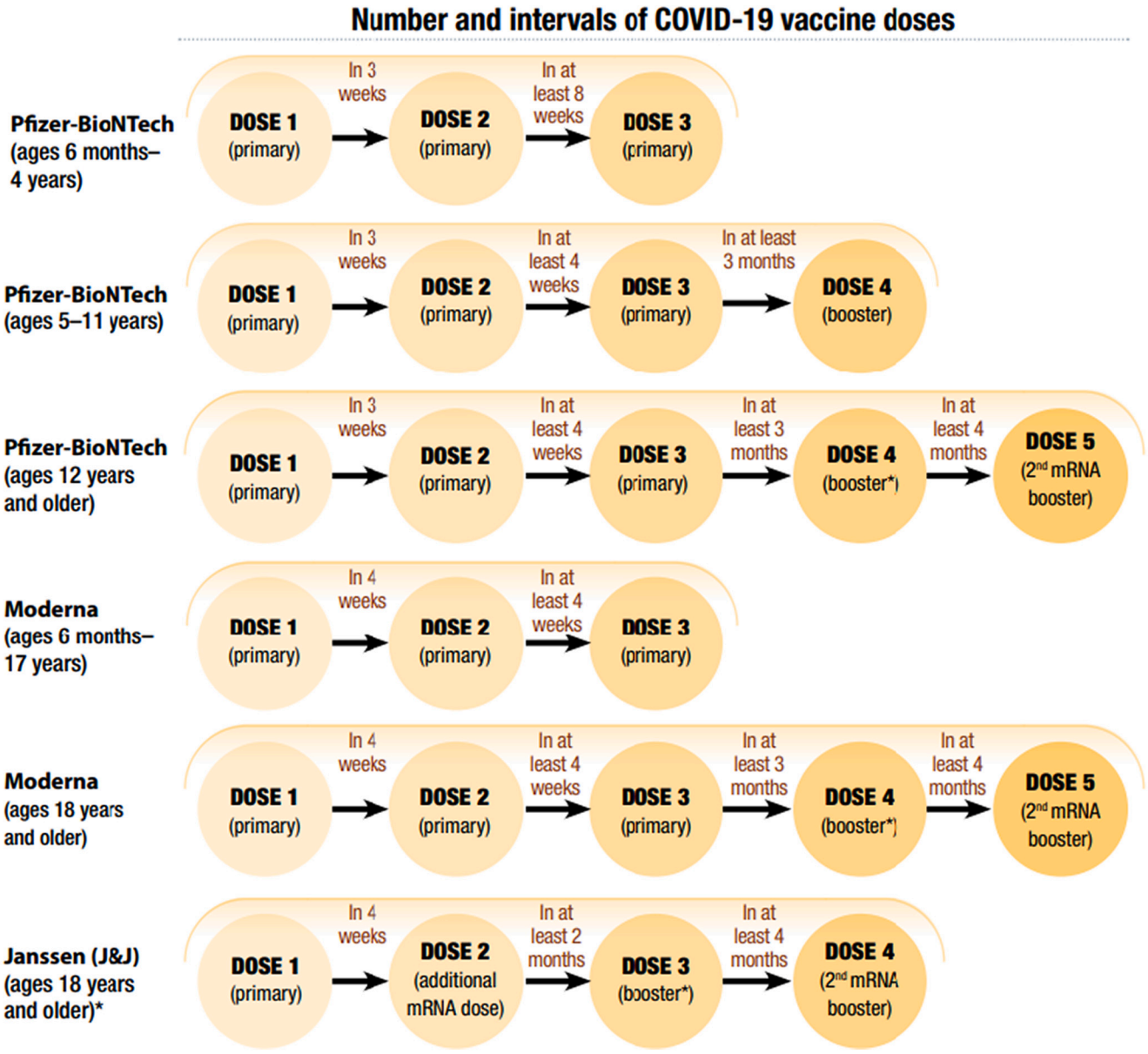

Fig. 1. mRNA vaccination strategy for B cell immunodeficient patients per CDC guidance.

Table 1
Timing of Pre-exposure prophylaxis in B cell immunodeficient patients.

Event	Timing
Active COVID infection	>20 days after symptom onset
Exposure to confirmed case (without symptoms)	>14 days after exposure
Receipt of COVID vaccine	>14 days after the last dose
Receipt of Sotrovimab Monoclonal Antibody therapy	>90 days
Other monoclonal antibody therapies	No restrictions

treatment, it has not been authorized for PEP. Thus, no PEP is being offered to individuals at high risk for progression at this time in regions with predominant Omicron variant circulation. (EUA Fact Sheet: https://www.fda.gov/media/149533/download, accessed 2/20/2022).

9. Conclusions

Our understanding of the COVID-19 in patients with B cell defects

Table 2
Risk profile of COVID-19-associated morbidity and mortality in patients with B cell defects.

Are patients with B cell defects at	Higher	Lower	Risk Unknown
Risk of COVID-19 infection (Boekel and Wolbink, 2022)	++		
Risk of re-infection/persistent infection (Tay et al., 2022)	++		
Risk of Severe COVID-19 infection (Boekel and Wolbink, 2022)	++		
Risk of Long COVID (Glynne et al., 2022; Leipe et al., 2020; Nussenblatt et al., 2021)			++
COVID vaccine responses (Bitoun et al., 2022; Jinich et al., 2022)		++	
Durability of COVID vaccine responses (Tay et al., 2022)		++	
Mortality with COVID (Boekel and Wolbink, 2022)	++		

continues to evolve. We have learned some unique aspects of the disease as shown in Table 2 below, but more needs to be understood.

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The authors declare that they have no conflict of interest.

Patients with defects in humoral immune system are associated with poor prognosis with COVID-19. These defects affect short- and long-term anti SARS-CoV-2 immunity as well as vaccine responses. There is also a risk of emergence of SARS-CoV-2 genomic variants in these patients, hence consideration of combination treatment regimens, including immuno-modulation and prolonged antiviral treatment may be needed and likely be better defined through dedicated prospective clinical trials.

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