Clinical course and management of COVID-19 in the era of widespread population immunity

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Abstract

The clinical implications of COVID-19 have changed since SARS-CoV-2 first emerged in humans. The current high levels of population immunity, due to prior infection and/or vaccination, have been associated with a vastly decreased overall risk of severe disease. Some people, particularly those with immunocompromising conditions, remain at risk for severe outcomes. Through the course of the pandemic, variants with somewhat different symptom profiles from the original

SARS-CoV-2 virus have emerged. The management of COVID-19 has also changed since 2020, with the increasing availability of evidence-based treatments in two main classes: antivirals and immunomodulators. Selecting the appropriate treatment(s) for patients with COVID-19 requires a deep understanding of the evidence and an awareness of the limitations of applying data that have been largely based on immune-naïve populations to patients today who most likely have vaccine- and/or infection-derived immunity. In this Review, we provide a summary of the clinical manifestations and approaches to caring for adult patients with COVID-19 in the era of vaccine availability and the dominance of the Omicron subvariants, with a focus on the management of COVID-19 in different patient groups, including immunocompromised, pregnant, vaccinated, and unvaccinated patients.

Table of content blurb (~50 words max.)

In this Review, Meyerowitz, Scott, Richterman, Male and Cevik examine the clinical presentations of COVID-19 in the era of widespread population immunity and explore current approaches to managing COVID-19 across different patient groups. **[Au:OK?]**

[H1] Introduction

With widespread population immunity, resulting from vaccination and prior infection or both, and new SARS-CoV-2 variants, the disease trajectory and clinical outcomes have vastly changed since the beginning of the pandemic. While the basic illness course and the risk factors for severe disease have remained the same, immune status plays an increasingly important role in defining risk for severe disease, with increasing reinfections mostly mild and self-resolving, and

not requiring medical attention or hospitalization[1–4]. Vaccination remains the key intervention to reduce the risk of severe COVID-19 in all population groups. However, because of the differential protection provided by vaccination between immunocompromised and immunocompetent populations, additional booster vaccine doses are recommended for some individuals[5]. A variety of immunocompromising conditions have been associated with a greater risk of COVID-19-related complications, particularly in the context of sub-optimal vaccine- or infection-derived immunity [6,7]. Similarly, pregnancy has also been associated with an increased risk of severe outcomes[8]. Certain highly immunocompromised individuals including those with hematologic malignancies may remain at high risk for death even following vaccination and are at risk for high SARS-CoV-2 respiratory viral loads and prolonged viral positivity.

A major challenge in the era of widespread immunity is the lack of clinical trial data supporting the use of COVID-19 therapeutics in populations with immunity. Treatments commonly given earlier in the pandemic to prevent hospitalization and death are now mostly used for immunocompromised individuals and others with severe disease.

Taken together, clinical outcomes and management of COVID-19 have changed over time, and there is a need for an up-to-date understanding of the available evidence regarding the care of adult patients with COVID-19 in the era of high population immunity. This Review will focus on the changing disease manifestations, due to variants and host factors, and the management of COVID-19, with a focus on different patient groups, including immunocompromised, pregnant, vaccinated, and unvaccinated patients. We will place particular emphasis on COVID-19 agents that are most strongly backed by clinical evidence and that remain relevant during the current stage of the pandemic.

[H1] Clinical manifestations of COVID-19

[H2] COVID-19 illness course

The COVID-19 illness course for most immunocompetent individuals is defined by an incubation period, a brief symptomatic period, and recovery, influenced by host factors including immune status, and the infecting SARS-CoV-2 variant (FIG. 1)[9]. The mean incubation period has shortened for newer variants compared with the wildtype SARS-CoV-2 (Wuhan-Hu-1)[10]. With earlier symptom onset, rapid antigen tests (RAT) may be negative if obtained immediately after symptom onset for Omicron infections, before the viral load has risen sufficiently to meet the threshold for positivity[11]. Duration of symptoms differs by variant as well. For instance, while the mean duration is 6 to 9 days, it was longer for Delta than for Omicron[12]. Vaccination status, including total number of vaccine doses received and interval between vaccination and infection, also impacts symptom severity and duration of illness[9].

Viral rebound (an increase in upper respiratory tract viral load after an initial decline), with or without symptom rebound, may occur in both treated and untreated individuals, with the precise prevalence of rebound not yet well-defined[13,14].

Severe COVID-19 requiring hospitalization is generally preceded by a mild illness. Hospitalisation occurred a median of 6 days from symptom onset in the pre-Delta period[15]. Among those hospitalized, the duration of hospitalisations has decreased throughout the course of the pandemic, with a mean length of stay of 8.0 days in the pre-Delta period, 7.6 days during Delta, and 5.5 days during Omicron BA.1 circulation in the United States[16]. The reasons

for the decreased hospital duration are multifactorial and include improvements in medical management of COVID-19.

Severely immunocompromised individuals may develop persistent SARS-CoV-2 infection[17]. This stands in stark contrast to the vast majority of people, for whom the period of active viral replication in the respiratory tract is quite brief (FIG. 2)[18]. Persistent SARS-CoV-2 infection has been described in individuals with profound B- and T-cell immunodeficiencies, including hematologic malignancy and advanced HIV and those receiving immunosuppressing agents for other health conditions[19,20]. It thus remains an extremely challenging clinical entity whose ideal management is currently unknown[21–23].

Additionally, a subset of individuals may continue to experience persistent or new symptoms such as fatigue, dyspnoea, and anosmia in the months after acute SARS-CoV-2 in what has been referred to as long COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), or post-COVID conditions (PCC) (BOX 1).

[H2] Heterogeneity of symptoms

Heterogeneity in symptoms and disease severity is a hallmark of COVID-19. Individuals with SARS-CoV-2 infection may experience mild symptoms, critical illness, or no symptoms at all (FIG. 1). While there is significant heterogeneity in the literature, around 20% of infections with pre-Delta variants remained symptom-free (asymptomatic) for the duration of infection[24,25]. The most common symptoms in people with COVID-19 are those that are also seen in other common respiratory viruses, including nonspecific manifestations like fever, myalgia, sore throat, and runny nose. The exact symptom profile depends on the SARS-CoV-2 variant. For

instance, while sore throat was unusual in the Delta era, it became more common during Omicron, which may explain the differences in symptom recognition[12].

SARS-CoV-2 may affect any organ system and in most critical cases multiorgan failure occurs[26] (FIG. 3). Pneumonia is the most common pulmonary manifestation, presenting with cough, fever, and radiographic opacifications, often with hypoxemia (low levels of oxygen in the blood)[15,27]. Many people with severe COVID-19 have cardiac abnormalities, and elevated serum troponin — a protein that appears in the blood when the heart muscle is damaged, for example during a heart attack— is an important marker of disease severity[28]. Myocarditis, arrhythmias, and myocardial infarctions can be seen with SARS-CoV-2 infection[29,30]. The vast majority of individuals with SARS-CoV-2-related myocarditis present within a week after symptom onset[31]. Acute kidney injury is another marker of severe COVID-19[32]. A variety of neurologic manifestations are associated with COVID-19, ranging in severity from syncope to strokes[33,34]. An elevated risk of arterial and venous thromboembolism, highest in the first week after a positive SARS-CoV-2 test, persists for at least a year after infection[33]. Many skin lesions and rashes have been described in people with SARS-CoV-2 infection; the most characteristic skin lesion is pernio, which appears as oedematous, erythematous plaques and patches most commonly seen on fingers and toes[35].

[H2] Risk factors for severe disease

Increasing age is the host factor with the strongest association with severity. Prior to widespread infection-derived immunity, infection fatality rate (IFR) among unvaccinated individuals was 0.002% at age 10 and 15% at age 85[36]. This steep age gradient explains most of

the variation in mortality between different age groups and geographic regions with varied demographics.

Besides age, a variety of other medical comorbidities have been consistently associated with more severe outcomes, although to a much lesser extent, including obesity, diabetes mellitus, renal disease, cardiac disease, active cancer, pre-existing lung disease, and dementia[37]. Pregnancy increases the risk of severe COVID-19 disease[8], and social determinants of health like poverty and structural racism are also strongly associated with increased COVID-19 severity[37].

Immunity from vaccination or prior infection has repeatedly been shown to reduce the severity of COVID-19. For instance, among adults in the United States with SARS-CoV-2 infection during the Omicron period, hospitalisations were 10.5 and 2.5 times higher among unvaccinated and vaccinated individuals without a booster dose, respectively, compared with individuals who had received a booster dose[38]. While protection against infection wanes with increasing time following infection or vaccination, protection from severe outcomes is more durable[39,40].

Viral factors are also associated with the severity of COVID-19. Higher respiratory tract viral load has been associated with more severe outcomes after controlling for the number of days from symptom onset[41]. Detectable SARS-CoV-2 RNA in the blood has been shown to be a marker of severe COVID-19[42]. Additionally, among hospitalized patients, those with higher SARS-CoV-2 nucleocapsid antigen (NAg) levels have been shown to have worse outcomes[43]. While plasma NAg levels are important, they are generally not clinically available and therefore not useful for clinicians to triage patients in real time.

It is also clear that certain SARS-CoV-2 variants may be associated with more severe outcomes. A United States-based matched cohort study in veterans found fewer moderate, severe, or

160 critical Omicron compared with Delta infections, 9.5% versus 15.3% ($p<0.001$)[44]. A large study
161 from England similarly found a lower risk for hospitalisation and death with Omicron versus
162 Delta variant, with adjusted hazard ratios of 0.41 (95% confidence interval, 0.39-0.43) and 0.31
163 (0.26-0.37), respectively[45].
164
165 **[H1] Clinical manifestations in immunocompromised individuals**
166 Among a variety of immunocompromised conditions, cancer (and immunosuppression
167 associated with cancer therapeutics) has been among the most widely studied in the context of
168 COVID-19. A systematic review that included over 60,000 patients with cancer prior to the
169 widespread availability of vaccines or antiviral therapies found a nearly 70% increased risk of
170 COVID-19 mortality after age and sex matching, with particularly high risks of death among
171 people with lung and haematological cancers[46]. A pre-vaccine era study covering 40% of
172 patients in England showed an approximately 80% increased risk of COVID-19 death associated
173 with recently diagnosed non-haematological cancer, and about a 300% increased risk
174 associated with recently diagnosed haematological cancer. Notably, outcomes in people with
175 cancer began improving even prior to the availability of vaccines, likely related to
176 improvements in care and management. To illustrate this point, a registry study from six
177 European countries showed improved mortality among people with cancer over the course of
178 the first year of the pandemic[47].
179 Even after the availability of vaccines, people with cancer continue to have increased risk for
180 infections and severe outcomes. A national cohort from the United States found that about
181 one-fifth of breakthrough infections (SARS-CoV-2 infection that occurs after completion of a

recommended COVID-19 vaccine series) occurred in patients with cancer, with solid and haematological cancer patients both having significantly higher risks for breakthrough infection and severe outcomes[7]. Similarly, a study using electronic health record data from over 600,000 vaccinated people found significantly higher risk for breakthrough infection among cancer patients relative to propensity score-matched patients without cancer[6]. This analysis found substantial heterogeneity by cancer type, with the most prominent risks seen in patients with active cancer in the last year.

Despite this, as in immunocompetent populations, there has been a notable reduction in disease severity since the emergence of Omicron in people with cancer. For example, an update from the previously mentioned registry study from six European countries showed a 68% reduction in the COVID-19 case fatality rate among cancer patients relative to the pre-vaccine era, a 78% reduction in requirements for COVID-19-specific therapies and a 76% reduction in the need for oxygen therapy relative to the Alpha-Delta phase, with the highest risks for death among those receiving active chemotherapy[48]. Importantly, unvaccinated patients with cancer and Omicron infection showed similar death and hospitalisation rates to patients diagnosed during the Alpha-Delta period, indicating the ongoing importance of vaccination even with widespread population immunity.

In the setting of other immunocompromising conditions, there are notable similarities in risk for COVID-19-related outcomes. For example, according to a study in the United States, solid organ transplant recipients had case fatality rates of 20% during the beginning of the pandemic, that decreased to 13.7% by the end of 2020 with new therapies like dexamethasone[49]. In the vaccine era, prior to Omicron, another single-centre study in the United States found a

hospitalisation rate of 60% and a death rate of 10% among solid organ transplant recipients, which declined during the Omicron era to 26% and 2%, respectively[50]. Receipt of other immunosuppressive drugs, in particular B-cell depleting agents like rituximab, are also associated with more severe outcomes, including after vaccination[51–53]. Finally, people living with HIV, particularly those with a lower $CD4^+$ T-cell count, also have greater risks of severe illness and death that persist after vaccination[20,54–58].

Evidence about vaccine effectiveness (VE) among general immunocompromised populations in the Omicron era is still limited. Consistent with overall changes in VE seen in other populations[59], a study of adults with immunocompromising conditions in ten United States states during a period dominated by Omicron found that two doses of a monovalent mRNA vaccine had a VE against hospitalisation of only 36%, though this was somewhat mitigated by a third dose of a monovalent booster, increasing to 67%[5]. An analysis of solid organ transplant recipients in England during a period dominated by Omicron found no protection by the vaccine against infection, but incremental protection against hospitalisation (VE of 38% with three doses, 61% with four doses) and death (VE of 54% with three doses, 82% with four doses)[60].

[H1] Interpretation of repeated positive SARS-CoV-2 RT-PCR tests

A repeat positive polymerase chain reaction (PCR) test may indicate either ongoing RNA shedding (without replication-competent virus), reinfection with a new SARS-CoV-2 virus (after the clearance of previous infection), persistent active viral replication from a prolonged infection, or viral rebound that either occurs spontaneously or following treatment with

nirmatrelvir–ritonavir (NMV–r). Distinguishing between these possibilities is required in clinical settings to manage patients appropriately (FIG. 4).

[H2] Prolonged RNA shedding

RNA shedding indicates that viral RNA continues to be detected from patient samples. Shedding of viral RNA or DNA is commonly seen in many infections. It most likely indicates ongoing release of RNA from inactive virus during convalescence or, less likely, low level, ongoing viral replication below the minimum inoculum needed for positive culture or secondary transmission[9]. While the median duration of RNA shedding (and therefore of positive PCR tests) is 11 days (interquartile range (IQR) 8-14 days)[61], some individuals may continue to shed viral RNA in the respiratory tract for weeks or even months after illness onset. However, this does not necessarily indicate an ongoing active infection. Therefore, patients need to be assessed clinically and virologically to distinguish between reinfection and persistent infection. Prolonged RNA shedding is more likely in individuals with more severe COVID-19, though it can be seen in some individuals with very mild disease[61]. In those with prolonged RNA shedding, it is possible to see an intervening negative PCR test, usually at a high PCR cycle threshold (Ct) —a proxy for low viral load levels— indicating later stages of infection[62]. Unless confirmed as reinfection or persistent infection, prolonged RNA shedding does not require ongoing treatment or special management.

[H2] Reinfection

An early reinfection may be indicated by recurrent shedding of replication-competent virus with a distinct genotype. Viral culture is the most commonly used method to confirm

247 replication-competent virus, though this is not feasible in most clinical settings, as it requires
248 safety infrastructure not available in most clinical laboratories[9]. Subgenomic RNA is also used to
249 assess for the presence of active viral replication, though it, too, tends to be primarily used in
250 research settings[63]. In clinical settings, low Ct values (indicating high viral loads) can be used as
251 a proxy for the likelihood of the presence of infectious virus, though with some important
252 caveats and limitations. First, Ct values are dependent on the timing and quality of sample
253 collection, with sampling during the early stages of infection (viral phase) associated with lower
254 Ct values. Second, a low Ct may indicate either reinfection or persistent infection, with the
255 likelihood of the latter based on the patient's immune function. For instance, among 14
256 individuals with repeat positive SARS-CoV-2 PCR who underwent viral genomic analysis, clinical
257 and Ct value assessment miscategorized 2 of 6 reinfections[64]. Therefore, any positive SARS-CoV-
258 2 test requires a consideration of the patient's history, immune status, and ideally, an
259 assessment of the Ct from the sample for a robust (though imperfect) interpretation.
260 For most immunocompetent individuals, reinfections are mild, may not be of clinical
261 importance, and may be discovered incidentally. Some studies suggest an association between
262 increased risk of a variety of sequelae, including diabetes and PCC, although these studies
263 should be interpreted with caution because they use routinely collected clinical data and are
264 therefore highly susceptible to ascertainment bias[65]. The incidence and timing of SARS-CoV-2
265 reinfections (defined as a positive test 90 days after the initial positive test) are still being
266 described. The current literature is limited since milder reinfections are less likely to be
267 recognized, tested, and subsequently recorded in most studies and by public health
268 surveillance. Early reinfections (before 60 days) are unusual but well documented, and are

more likely to occur during times of transition between dominant SARS-CoV-2 variants, such as between Delta and Omicron[66]. Among other coronaviruses, seasonal reinfections are common at one year and it is possible that the same may be true for SARS-CoV-2 as it transitions to endemicity[67].

[H2] Persistent infection

Persistent infection is defined as ongoing viral replication without the clearance of initial infection. It is difficult to confirm clinically, since it, too, requires genomic analysis. However, it should be suspected in individuals with profound B- and/or T-cell immunodeficiencies who present with repeatedly positive SARS-CoV-2 PCR, typically with low Ct values (less than 30) indicating high viral loads. Importantly, not all individuals with persistent infections have symptoms throughout the course of infection[68]. Considering persistent infection is important in clinical settings since transmission risk may persist, requiring adjusted infection control protocols, and it may require extended or combination treatments. However, the optimal clinical management of persistent SARS-CoV-2 infection is unknown, with multiple strategies reported in case reports such as prolonged remdesivir (10 days or longer) and dual antiviral therapy with remdesivir and NMV–r[22,69]. It is important to note that viral evolution may occur during persistent infections, with mutations accumulating over time in immunocompromised hosts, which may contribute to the development of new SARS-CoV-2 variants[70,71].

[H2] Viral rebound

Viral rebound occurs when the upper respiratory tract viral load rises following an initial decline. After day five from diagnosis, around 10% of individuals may have spontaneous

transient viral rebound that declines rapidly. Around 1% overall may have spontaneous viral rebound that persists, though it is very unusual beyond day 10 after diagnosis and the risk of prolonged transmission for these individuals is unknown[13].

On the other hand, rebound after treatment with NMV–r is far more common. A prospective cohort study found viral rebound in 14% of patients on NMV–r (n = 127) compared to 9% of controls (n = 43), and symptom rebound in 19% and 7%, respectively[72]. Another study showed increased rebound in the NMV–r group, 10% compared to 1% in the no study drug group[73]. Rebound following NMV–r is associated with prolonged shedding of infectious virus and transmission risk[74].

The degree to which RATs can be used to determine prolonged risk of transmission is not well defined. RATs are more likely to be positive when viral loads are higher and are associated with positive viral cultures early after symptom onset[75]. Some immunocompetent adults had prolonged positive RATs out to at least 14 days from symptom onset, though few documented transmissions occurred after 7 days from symptom onset[76,77]. In general, it is safest to assume transmission risk if a RAT is positive, though more work is needed in this area.

[H1] Management of COVID-19

COVID-19 therapeutics include antiviral and immunomodulatory agents. Antivirals inhibit viral replication during the early stage of illness. Therefore, when antiviral treatment is indicated, it should be initiated as early as possible, and ideally within 5 to 7 days of symptom onset. When indicated, immunomodulators are given after the viral replication stage to blunt hyperinflammatory processes, such as acute respiratory distress syndrome (ARDS). While these

fundamental principles of COVID-19 therapeutics remain unchanged, the optimal utilization of these drugs continues to evolve. In the following sections, we will focus on COVID-19 therapies that are best supported by clinical evidence and that remain relevant to the current stage of the pandemic (Table 1).

[H2] Antiviral agents

[H3] Remdesivir

Remdesivir is an adenosine nucleotide analogue prodrug[78] that acts by competitively incorporating into RNA chains synthesized by the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), resulting in delayed chain termination during viral replication[79].

The randomized controlled trials (RCTs) that evaluated remdesivir for the treatment of COVID-19 were all conducted prior to the widespread availability of vaccines. Therefore, the clinical benefit of remdesivir in vaccinated patients remains unknown[80–86]. The adoption of remdesivir for hospitalized COVID-19 patients was based on the results of the National Institutes of Health-sponsored Adaptive COVID-19 Treatment Trial (ACTT-1)[82]. In this study, patients who received a 10-day course of remdesivir within 10 days of symptom onset had a faster time to recovery compared to those who received placebo (10 days versus 15 days (rate ratio for recovery, 1.29; 95% CI 1.12-1.49; P<0.001)). This benefit was most prominent in those who required low-flow supplemental oxygen at baseline, although the trial was not powered to detect differences in mortality or differences between subgroups. In addition, remdesivir reduced the need for respiratory support in those who did not require high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygen (ECMO) at baseline[82]. A

subsequent study showed that 5 days of remdesivir is as effective as 10 days for hospitalized patients on supplemental oxygen but not mechanical ventilation[85,87]. Guidelines have since recommended remdesivir for a course of 5 days to treat patients in the early stages of the disease (that is, 7 to 10 days of symptom onset) who require low-flow oxygen. Remdesivir can be combined with immunomodulators for patients that require high-flow oxygen or non-invasive ventilation. However, it is not recommended to use remdesivir for patients who require mechanical ventilation[87,88].

The results of the SOLIDARITY trial[84] demonstrated no significant difference in mortality between patients who received remdesivir and those who received standard-of-care treatment. Similarly, there was no difference in ventilation requirement or time to hospital discharge. Based on these findings, the World Health Organization (WHO) made a conditional recommendation against the use of remdesivir in patients hospitalized for COVID-19, regardless of the severity of illness[89]. However, the trial was criticized due to a missing key determinant of treatment response: time from symptom onset. As shown in ACTT-1, antiviral agents work best during the period of viral replication, soon after symptom onset, and without this critical piece of information, the SOLIDARITY results should be interpreted with caution.

Another key study, the PINETREE trial, tested a 3-day course of remdesivir for the treatment of high-risk, unvaccinated outpatients prior to the emergence of the Omicron variant[86]. This double-blinded RCT found that patients who received remdesivir had an 87% lower risk in hospitalisation compared to those who received the placebo. There were no deaths reported in either group after 28 days. Based on the trial's data, high risk individuals who are not on

supplemental oxygen may be treated with a 3-day course of remdesivir. However, the data are based on unvaccinated individuals and should be interpreted with caution.

More recently, a systematic review and meta-analysis using individual patient data from 9 RCTs, including 10,480 hospitalized participants, found that remdesivir has a mortality benefit for patients who received no oxygen or low-flow oxygen at baseline[90]. Remdesivir has been consistently shown to be well tolerated and serious adverse events have been rare[82,91].

In summary, current recommendations suggest the use of remdesivir within 5 to 10 days of symptom onset for adult patients with severe COVID-19 not requiring mechanical ventilation. While the parenteral administration of remdesivir limits its widespread use in the outpatient setting, the PINETREE trial demonstrated its potential use there, and oral analogues of remdesivir have recently shown promise[86,92]. Although in vitro studies have demonstrated that remdesivir activity is retained against the Omicron subvariants, clinical data from randomized, placebo-controlled trials are lacking[93–95].

[H3] Nirmatrelvir–ritonavir

Nirmatrelvir–ritonavir (NMV–r, co-packaged as Paxlovid) is a combination of orally administered viral protease inhibitors. Nirmatrelvir targets the SARS-CoV-2 main protease (M^{pro}) also called the 3C-like protease ($3CL^{pro}$) enzyme, which plays an essential role in viral replication[96]. Ritonavir inhibits the cytochrome P4503A4 (CYP3A4) isoenzyme responsible for metabolizing nirmatrelvir in the body, thus boosting nirmatrelvir plasma concentrations[97].

The Evaluation of Protease Inhibition of COVID-19 in High-Risk Patients (EPIC-HR) trial is an outpatient RCT conducted on 2,246 unvaccinated, high-risk adults with mild to moderate

COVID-19 that evaluated the efficacy of a 5-day course of NMV–r given within 5 days of symptom onset compared to placebo. The results from the trial showed that NMV–r was associated with an 88% relative risk reduction in hospitalisation or death at 28 days. Only 8 out of 1,039 patients (0.77%) in the NMV–r group were hospitalized, compared with 66 out of 1,046 patients (6.31%) in the placebo group (P<0.001)[98]. Participants were enrolled during a period of Delta predominance and those with previous confirmed SARS-CoV-2 infection were excluded. While these results are impressive, the benefits provided by NMV–r treatment in the context of baseline immunity are uncertain. Evaluation of Protease Inhibition of COVID-19 in Standard-Risk Patients (EPIC-SR) was a double-blinded RCT that tested the efficacy of NMV–r treatment among unvaccinated individuals considered to be low-risk for hospitalisation and death, and vaccinated individuals with at least one risk factor for progression to severe COVID-19 during the Delta-predominant period. According to a press release, the trial failed to demonstrate a significant difference in self-reported sustained symptom alleviation through day 28 as compared with the placebo[99]. Although there was a numerical difference in COVID-19-related hospitalisations (0.9% in the NMV–r group, compared with 1.9%in the placebo group) and death from any cause (0 in the NMV–r group and 1 in the placebo group), these differences were not statistically significant. While there are no RCTs reporting the effectiveness of NMV–r in patients with Omicron infection, antiviral activity of NMV–r is expected to be retained based on in vitro assays[93,94,100,101]. Multiple observational studies of vaccinated individuals have attempted to determine the effect of NMV–r in this population[87,102–105], yet such studies are intrinsically susceptible to various biases, including confounding by indication, residual confounding by vaccine and prior infection status, and immortal time bias (Immortal time bias,

also referred to as time-dependent bias, occurs when an analysis does not account for a time-dependent intervention, such as the receipt of a medication, that requires that the patient survive long enough to receive the intervention). Accordingly, any interpretations or conclusions drawn from observational studies of NMV–r should be taken with caution. An ongoing trial known as Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC) and sponsored by the National Health Services (NHS) is currently evaluating the impact of NMV–r on all-cause, non-elective hospitalisation and/or death within 28 days of randomization in adults who were recently infected with SARS-CoV-2 and have high levels of baseline immune protection[106]. The results of the trial are still pending. According to another press release, NMV–r failed to show a statistically significant benefit when used as post-exposure prophylaxis, and is therefore not recommended for this purpose[107].

In summary, NMV–r is generally recommended for use in symptomatic adults at high risk of progression to severe disease, although EPIC-SR did not demonstrate a statistically significant benefit in vaccinated individuals. While NMV–r is relatively safe with a good side effect profile, the co-administration of NMV–r with other medications can potentially cause significant drug–drug interactions, primarily due to the ritonavir component. Although this short course of ritonavir does not typically lead to major contraindications, it is important that clinicians carefully review any concomitant drugs prior to prescribing NMV–r, including over-the-counter, recreational drugs, and herbal supplements[108].

[H3] Other antiviral agents

Molnupiravir is the oral prodrug of β-D-N4-hydroxycytidine, a nucleoside analogue that becomes incorporated into new strands of RNA and causes lethal viral mutagenesis[109]. While in vitro and early clinical studies demonstrated that molnupiravir has antiviral activity against SARS-CoV-2 viruses[93,110,111], the placebo was favoured over molnupiravir in the subgroup of the MOVeOUT trial (in high-risk, unvaccinated outpatients who had positive baseline nucleocapsid antibodies), raising questions about its efficacy in people with baseline immunity (vaccine-derived, infection-derived, or hybrid)[112]. While the PANORAMIC study, the largest RCT to date, showed no reduction in the risk of hospitalisation or death among high-risk, mostly vaccinated adults, the study did show a faster time to symptom improvement and viral load reduction among those receiving molnupiravir[113]. As this was an open-label, unblinded, and not placebo controlled study, these findings should be interpreted with caution. A recent study found evidence of onward-transmission of molnupiravir-mutated viruses, which raises concern about its potential deleterious effect on a population level , with questionable clinical benefits[114].

Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein were effective for the outpatient treatment and prevention of infection caused by pre-Omicron variants[115–118]. Ongoing use of mAbs has been substantially limited by the persistent genetic drift of SARS-CoV-2[119,120].

Early administration of convalescent plasma (CCP) was shown to reduce the risk of COVID-19-related hospitalisation among relatively low-risk unvaccinated outpatients in one RCT study[121]. High-titre CCP is sometimes considered as an alternative treatment for some severely immunocompromised patients[122], yet other studies have failed to demonstrate any significant

benefit[123,124]. The feasibility of this treatment remains a significant issue because it is resource-intensive and has limited availability outside of research setting.

The selective-serotonin reuptake inhibitor fluvoxamine exhibited possible benefit in a single RCT conducted prior the emergence of the Omicron variant when administered to high-risk, unvaccinated adults[125]. However, ACTIV-6, a high-quality outpatient RCT including vaccinated individuals with mild to moderate Omicron infection, failed to demonstrate any benefit of fluvoxamine in terms of time to sustained recovery[126].

Several other agents that have been studied for the treatment of COVID-19 either lacked any benefit or were harmful, and are therefore not recommended. Examples include inhaled glucocorticoids[127], pegylated interferon lambda[128], hydroxychloroquine[129], azithromycin[130], lopinavir[131], ivermectin[132], colchicine[133], and aspirin[134].

[H2] Immunomodulators

The risk of progressive respiratory failure related to the hyperinflammatory state that can sometimes complicate COVID-19 pneumonia may be reduced with certain immunomodulators. Dexamethasone is a glucocorticoid that was shown to significantly reduce 28-day mortality in patients hospitalized with severe or critical COVID-19 in the landmark RECOVERY trial[135]. In this study, dexamethasone was associated with a 36% relative reduction in mortality compared with usual care among patients on invasive mechanical ventilation or ECMO at baseline and an 18% relative reduction among patients requiring non-invasive oxygen therapy at baseline. This monumental finding led to the widespread adoption of dexamethasone, dosed at 6 milligrams

per day, as the standard-of-care for patients hospitalized with severe COVID-19 requiring respiratory support.

Early in the pandemic, some studies found an association between patients with clinical evidence of hyperinflammatory states with elevated interleukin-6 (IL-6) levels and more severe disease[136]. When administered soon after the onset of rapidly progressive respiratory failure, a single dose of intravenous tocilizumab, a monoclonal anti-IL-6-receptor blocking antibody, significantly reduces the risk of progression to mechanical ventilation or death[137–139]. Since this beneficial effect of tocilizumab was most apparent in patients who received concurrent glucocorticoids, coadministration is recommended[119,140].

Janus kinase (JAK) inhibitors interfere with the phosphorylation of certain proteins involved in the JAK-STAT signalling pathway, which can lead to a hyperinflammatory state[141,142]. Baricitinib, an oral JAK inhibitor that may also prevent viral endocytosis[143,144], has been shown to accelerate the time to recovery in hospitalized patients when combined with remdesivir[145], and has also been shown to improve survival, particularly in patients who are receiving high-flow oxygen or non-invasive ventilation at baseline[146,147]. Similar to tocilizumab, the use of baricitinib is recommended in combination with dexamethasone[119,148]. The co-administration of IL-6 blockers and JAK inhibitors is not recommended[119,149].

In summary, the use of glucocorticoids and adjunctive immunomodulators should be limited to the hospital setting for patients who require supplemental oxygen, as they may cause harm outside this population[150]. Since these immunomodulatory agents suppress the patient's hyperinflammatory state, clinical judgment is crucial to ascertain whether a hypoxemic patient

may have an alternative diagnosis, such as bacterial pneumonia or an acute exacerbation of congestive heart failure.

[H1] Management of COVID-19 in pregnancy

Pregnancy, although not an immunocompromising state[151], leads to a somewhat modified immune response which, together with the associated increased strain on the heart and lungs, makes it a risk factor for severe COVID-19. Among those previously naïve to SARS-CoV-2, pregnant patients are at increased risk of admission to intensive care, invasive ventilation and ECMO compared to patients of the same age and sex who are not pregnant[8]. Furthermore, the foetus is also at risk when SARS-CoV-2 infection occurs during pregnancy. The virus can infect the placenta, leading to stillbirth[152] and for this reason infection increases the risk of stillbirth in pregnant individuals that are naïve to SARS-CoV-2[153]. Infection also increases the risk of premature delivery, largely driven by iatrogenic deliveries, in which doctors opt to deliver the infant in order to improve the mother's chances of survival[153]. Babies born to infected mothers are more likely to be admitted to neonatal intensive care[8].

In the era of widespread immunity, these risks are likely to be lower, but to which extent is not clear. Of note, no cases of SARS-CoV-2 stillbirth have been reported in vaccinated individuals[154]. However, SARS-CoV-2 infection continues to put pregnant individuals at increased risk of morbidity and mortality and their babies at risk of severe perinatal morbidity and mortality, and this is largely driven by those who remain unvaccinated[155]. Because of the continuing risk of SARS-CoV-2 infection during pregnancy, and the extensive epidemiological evidence supporting vaccines safety and effectiveness[154,156], vaccination in pregnancy is now the frontline defence

against COVID-19 in pregnant individuals. Some countries offer additional boosters during pregnancy, even though others in the same age group are not eligible.

Pregnancy is a hypercoagulable state[157], as is moderate to severe SARS-CoV-2 infection[158,159]. Consequently, pregnant patients with COVID-19 who have been admitted to the hospital, and those at high risk of thrombosis who are still well enough to be managed in the community, will often be given a prophylactic dose of low molecular weight heparin as an anticoagulant, although the evidence that this significantly improves outcomes is uncertain[158,160]. While several antiviral medications are commonly used to treat early SARS-CoV-2 infection, there is limited data on the safety of these drugs in pregnancy. Guidance on whether and when to deploy these differs by country, depending on the balance between the risk of severe disease and the potential side effects of antiviral drugs. Available data on remdesivir[161,162] and NMV–r[163,164] are reassuring. However, pregnant rats receiving molnupiravir exhibited fetal abnormalities, leading to the recommendation against its use during human pregnancy[165]. Guidance on the treatment of pregnant patients with COVID-19 who are experiencing a deterioration in their health also differs by country. In the United States, pregnant COVID-19 patients who require supplemental oxygen are treated with dexamethasone, in line with the treatment guidelines for non-pregnant patients[149]. However, repeated exposure of the foetus to corticosteroids is associated with adverse neonatal outcomes[166]. Therefore, in the United Kingdom, prednisolone or hydrocortisone that minimally transferred to the foetus, are preferred over dexamethasone[167]. The exception is in cases where early delivery is planned, when dexamethasone serves the dual purpose of treating COVID-19 and promoting foetal lung maturation[167]. Monoclonal antibodies have a good safety profile in pregnancy, so pregnant

patients who meet the eligibility criteria are offered the monoclonal IL-6 inhibitor tocilizumab[168–170]. Baricitinib causes reproductive toxicity and teratogenicity in rats and rabbits, so its use is contraindicated in pregnant patients[171].

[H1] Conclusions and outlook

While there has been significant progress in understanding the disease course and management of COVID-19, important research gaps in patient management remain. Particularly, more up-to-date research into the risks and benefits of COVID-19 therapeutics are needed in populations with prior immunity. For instance, the clinical benefit of remdesivir in immune populations remains unknown, as the risk of progression to severe or critical COVID-19 is substantially reduced by immune protection[172]. Similarly, the impact of NMV–r treatment on rates of hospitalisation and death is expected to be lower in immune populations. It is also unclear exactly how research findings supporting the use of immunomodulators can be generalized to the highly immune population.

Perhaps most urgently, high-quality studies involving groups at increased risk of severe COVID-19 are critically needed. More information about the safety of antiviral drugs in pregnancy are needed to better inform risk-benefit analysis. In non-pregnant populations, patient safety data can be reasonably extrapolated from studies conducted in immune-naïve individuals, but cost effectiveness data in immune populations are needed, especially as the expenses of many antiviral drugs shift from governments to individuals. Since COVID-19-related hospitalisations and deaths have been disproportionately higher in members of racial and ethnic minorities[173], and antiviral dispensing rates have been lower in high-vulnerability populations[174], more

equitable access to diagnostic tests and treatments is imperative for reducing health disparities as we move forward.

Given the reduced incidence of severe COVID-19, it is crucial to define minimum clinically important differences other than decreased in severe outcomes. When considering outcomes such as improvements in viral clearance and duration of illness, it is important to also carefully consider the costs of the drugs, potential harms, and population-level impacts. While faster viral clearance may be correlated with a lower risk of disease progression and onward transmission, these benefits may be offset by virological rebound and mutations. Further investigations into the clinical and epidemiological impacts of these outcomes are needed.

The current understanding of the prevalence and the treatment approaches for PCC remains inadequate (BOX 1). To date, there are limited treatment options for PCC with strong evidence (that is, RCT) to support their use. Similarly, the management of persistent infection and reinfection is mostly guided by expert opinion and evidence based on case reports. While in this Review we aimed at providing guidance for these populations, the use of real-world observational and clinical trial data remains crucial to improving patient outcomes.

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Author contributions

The authors contributed equally to all aspects of the manuscript.

Competing interests

M.C. is a member of SAGE-NERVTAG. All other authors declare no competing interest.

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Related links

COVID-19 drug interaction checker: https://www.covid19-druginteractions.org/checker
NIH COVID-19 treatment guidelines: https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy/pregnancy-lactation-and-covid-19-therapeutics/

Display items

Table 1. COVID-19 management strategies.

	Antiviral	Immunomodulator
Outpatient with mild to moderate COVID-19 (not requiring supplemental oxygen)		

No risk factors	None	None, steroids may cause harm (RECOVERY study)[15]
more than 1 high risk factor(s)[a]	Nirmatrelvir–ritonavir[b] (within 5 days of symptom onset)[98] or intravenous remdesivir[c] (within 7 days of symptom onset)[79]	None, steroids may cause harm[15]
Inpatient		
Not requiring supplemental oxygen, more than 1 high risk factor(s)	Consider remdesivir if within 7 days of symptom onset[79]	None[15]
Stable and minimal supplemental oxygen (2 litres nasal cannula)	Remdesivir recommended if initiated within 7 days of symptom onset[75,78,80,81]	None[15]
Worsening respiratory status while on 2-4 litres nasal cannula	Remdesivir recommended if initiated within 7 days of symptom onset[75,78,80,81]	Dexamethasone[d,15]
HFNC, NIV, or invasive ventilation (within 24 hours)	Remdesivir may be considered if initiated within 7 days of symptom onset[75,78,80,81]	Dexamethasone[15] plus tocilizumab (RECOVERY-TOCI study)[110,119-122], or baricitinib[145,146]
HFNC, NIV, or invasive ventilation (after 24-48 hours of requiring this level of support)	Remdesivir may be considered if initiated within 7 days of symptom onset but is not routinely recommended[75,78,80,81]	• Dexamethasone[15] • Consider tocilizumab[e,110,119-122] or baricitinib[f] if within 72 hours of admission[145,146]
Mechanical ventilation or ECMO (within 24-48 hours)	Remdesivir may be considered if initiated within 7 days of symptom onset, but it is not routinely recommended[75,78,80,81]	• Dexamethasone[15] • Consider tocilizumab[110,119-122] or baricitinib if within 72 hours of admission[145,146]
Pregnant	Consider intravenous remdesivir if initiated within 7 days of symptom onset[75,144] or nirmatrelvir–ritonavir if initiated within 5 days of symptom onset[91,145,146] when meets eligibility criteria	• Dexamethasone in some countries, for example, United States (see NIH COVID-19 treatment guidelines) **[Au:OK? This is a general website, and needs to be in the 'Related links' section. I've removed it from the references list. Please check the reference numbers are accurate and in order.]** • Prednisolone or hydrocortisone is preferred over dexamethasone in some countries, for example United Kingdom[167] • Dexamethasone, when early delivery is planned[167]

		• Tocilizumab, when meets eligibility criteria[170] • Baricitinib is contraindicated[171]

HFNC, high flow nasal cannula; NIV, noninvasive ventilation; ECMO, extracorporeal membrane oxygenation.

[a]Age ≥65, body-mass index (BMI) ≥25, pregnancy, chronic kidney disease, diabetes, immunosuppression, cardiovascular disease, hypertension, chronic lung disease, sickle cell disease, neurodevelopmental disorder, medical-related technological dependence. Data on benefits of COVID-19 treatment are primarily based on unvaccinated individuals.

[b]Ritonavir-boosted nirmatrelvir has potential significant drug–drug interactions. Clinicians should carefully review concomitant medications. See COVID-19 Drug Interaction checker. Renal dose adjustment is required if the estimated glomerular filtration rate (eGFR) is less than 60 millilitres per minute. Not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

[c]Remdesivir is given as 200 milligrams intravenously on day 1, then 100 milligrams daily on days 2 and 3 for mild disease. For severe disease, it is continued for a total of 5 days. No renal dose adjustment is required. Food and Drug Administration (FDA)-approved as of 14th of July 2023 for patients with severe renal impairment, including those on dialysis.

[d]Dexamethasone is given as 6 milligrams orally or intravenously daily for up to 10 days. Consider Strongyloides Immunoglobulin G (IgG) for patients who were born or lived in an endemic country.

[e]Tocilizumab is given as 8 milligrams per kilogram (maximum 800 milligrams) intravenously once. Use with caution in immunocompromised patients, those with hepatic impairment, and in patients with suspected concurrent bacterial or fungal infection.

[f]Baricitinib is given as 4 milligrams via oral route daily for up to 14 days. Contraindicated in pregnancy. Use with caution in immunocompromised patients, those with hepatic impairment, and in patients with suspected concurrent bacterial or fungal infection.

Fig. 1. Illness course and severity spectrum for unvaccinated individuals with Wuhan-Hu-1 virus. SARS-CoV-2 generates a diverse range of clinical manifestations, ranging from mild infection (dark blue) to severe disease (blue) accompanied by critical illness including high mortality (light blue). All patients go through a pre-symptomatic phase (yellow) initially. Then, approximately 20% of patients experience asymptomatic infection, 64% have mild illness (dark blue) and the remaining 16% experience dyspnoea/hypoxemia (red) requiring hospital admission with severe (12%, blue) or critical illness (4%, light blue). In patients with mild infection, initial host immune response is capable of controlling the infection. In severe disease, excessive immune response leads to organ damage, intensive care admission, or death.

Fig. 2. Clinical course of disease in relation to viral load. After the initial exposure to the virus, patients typically develop symptoms within 5 to 6 days (incubation period). The upper

respiratory tract viral load (green curve) peaks in the first week of infection and declines thereafter, whereas the viral load in the lower respiratory tract (red curve) peaks in the second week of infection. At the time when patients present to the hospital with symptoms of severe or critical disease (shortness of breath, acute respiratory distress syndrome (ARDS)) and require admission to the intensive care unit (ICU), **[Au:OK?]** the viral load in the upper respiratory tract will usually be on the decline. The blue curve highlights the mild disease course, and the red curve shows the progression to severe and critical disease. The table shows the treatment options recommended according to the timing of symptoms, some being recommended early in the course of illness, whereas others recommended during hospitalisation. The graph was adapted with permission from reference[5].

Fig. 3. Clinical manifestations of COVID-19 in different patient groups. COVID-19 typically presents with generalised non-specific symptoms in most immunocompetent patient. However, patients that are immunocompromised due to pre-existing diseases (for example, neurological, respiratory, cardiac or renal diseases) or are pregnant will have worse symptoms and a minority will progress to serious illness with multiorgan failure. In addition to risk of serious illness, immunocompromised patients generally have higher risks for breakthrough infection, prolonged infection, severe outcomes and increased fatality rate. Pregnant women with COVID-19 have risk of stillbirth, premature delivery and high risk of thrombosis. On the left general symptoms of COVID-19 are shown with the arrow representing that these symptoms may worsen to severe disease (dark grey box). Light grey boxes on the left explain the severity markers in individuals developing severe illness, with an emphasis on risks explained in immunocompromised individuals and pregnant women. Light grey boxes on the right summarise the organ specific symptoms. Dark grey box on the bottom left summarises the risk factors for severe disease.

Fig. 4. The four scenarios for repeated SARS-CoV-2 polymerase chain reaction positivity. A repeat positive test may indicate either ongoing RNA shedding (without replication-competent virus), persistent active viral replication from a prolonged infection, reinfection with a new SARS-CoV-2 virus (after the clearance of previous infection), or viral rebound that either occurs spontaneously or following treatment with nirmatrelvir–ritonavir (NMV–r). Distinguishing between these possibilities in clinical settings is crucial to manage patients appropriately. The first graph represents prolonged RNA shedding. In this scenario, after the initial period of infectiousness, patients continue to shed RNA. However, this represents unviable virus picked up by real-time polymerase chain reaction (RT-PCR). The second graph corresponds to persistent infection, in which after the initial period of infectiousness, infection is not resolved

and there is an ongoing replication of viable virus. The third graph represents reinfection, a new infection after the period of complete resolution of the first infection. Patients do not shed viable virus in between infections. Finally, the last graph depicts viral rebound; in this case, we see an increase in viral load following initial decline, which is seen more often after antiviral treatment.

Box 1. Post-COVID conditions.

While there are different time frames considered by various definitions of post-COVID conditions (PCC), PCC is often defined as persistent symptoms for at least 12 weeks after acute infection. In the context of PCC, numerous, non-specific, and overlapping symptom combinations have been described, implying that PCC may in fact be comprised of disparate syndromes with distinct pathophysiologic processes. To address this possibility, investigators have attempted to characterize different symptom clusters associated with PCC, including tiredness and fatigue, respiratory symptoms, and neurocognitive features[175–179]. Many of these studies have been significantly limited by selection or ascertainment bias.

The challenges in study design limitations, along with difficulties in defining a suitable control group, have made it challenging to conduct high-quality evaluations to estimate the prevalence or risk of PCC. In addition, PCC occurring after severe COVID-19 must be differentiated from post-intensive care syndrome (PICS), which occurs after a variety of severe illnesses[180]. An ongoing population-based cohort study in the Netherlands compared symptoms between participants with COVID-19 matched to contemporaneous COVID-19-negative controls early in the pandemic, and corrected for symptoms present before COVID-19 and symptom dynamics in the uninfected population during the pandemic[181]. They found that 12.7% of COVID-19 patients had worsening symptoms at 90 to 150 days after COVID-19 that could be attributed to

the infection, with COVID-19 patients experiencing more ageusia and anosmia (loss of taste and smell, respectively), painful muscles, and general tiredness. A study using data from 1.2 million people with symptomatic COVID-19 from 22 countries, adjusting for symptoms in control groups and self-reported health status prior to COVID-19, found that 6.2% experienced at least 1 of 3 PCC clusters, with about 1% continuing to experience symptoms at 12 months[182]. Studies using routinely collected clinical data and comparator groups have found similar[183], modestly higher[184], or lower[185] risk of persistent symptoms among survivors of COVID-19 relative to those with other respiratory infections.

Evidence suggests that the risk of PCC has decreased over time, as illustrated by an observational cohort study of 2,560 regularly tested Italian health care workers that was ongoing from March 2020 to 2022 — the prevalence of PCC decreased from 48.1% in their first wave, to 35.9% in their second wave, to 16.5% in their third wave[186]. Other studies have demonstrated a similar phenomenon over time[185,187].

This is likely related in part to growing population immunity, including through vaccination. A case-control study in the United Kingdom using data from a symptom tracking app found that symptoms lasting 28 days or more were less frequent among vaccinated participants[188], with other studies showing similar findings[186]. Some studies also suggest that vaccination after infection might reduce symptoms and risk of PCC[189].

There is limited evidence supporting treatment for PCC. The COVID-OUT trial was a placebo-controlled randomized controlled trial of early outpatient treatment of SARS-CoV-2 among adults with overweight and obesity with over ten months of follow-up. This study showed a reduction in the self-reported receipt of a PCC diagnosis from a medical provider after a 14-day

course with metformin[190]. Given the decreasing incidence of PCC over time, the overall risk-benefit for metformin use remains uncertain.