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Review article

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Therapeutic advances in COVID-19

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Abstract

Over 2 years have passed since the start of the COVID-19 pandemic, which has claimed millions of lives. Unlike the early days of the pandemic, when management decisions were based on extrapolations from in vitro data, case reports and case series, clinicians are now equipped with an armamentarium of therapies based on high-quality evidence. These treatments are spread across seven main therapeutic categories: anti-inflammatory agents, antivirals, antithrombotics, therapies for acute hypoxaemic respiratory failure, anti-SARS-CoV-2 (neutralizing) antibody therapies, modulators of the renin–angiotensin–aldosterone system and vitamins. For each of these treatments, the patient population characteristics and clinical settings in which they were studied are important considerations. Although few direct comparisons have been performed, the evidence base and magnitude of benefit for anti-inflammatory and antiviral agents clearly outweigh those of other therapeutic approaches such as vitamins. The emergence of novel variants has further complicated the interpretation of much of the available evidence, particularly for antibody therapies. Importantly, patients with acute and chronic kidney disease were under-represented in many of the COVID-19 clinical trials, and outcomes in this population might differ from those reported in the general population. Here, we examine the clinical evidence for these therapies through a kidney medicine lens.

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Key points

- Multiple effective and safe therapeutics for COVID-19 have been developed since the start of the pandemic in early 2020, with several agents now approved for use across the spectrum of disease severity.
- COVID-19 therapeutics investigated to date include anti-inflammatory agents, antivirals, antithrombotics, therapies for acute hypoxaemic respiratory failure, anti-SARS-CoV-2 (neutralizing) antibody therapies, modulators of the renin–angiotensin–aldosterone system and vitamins.
- Patients with underlying kidney disease represent a vulnerable population at high risk of adverse outcomes from COVID-19, yet they were excluded or under-represented in many COVID-19 clinical trials.
- Additional data on the efficacy and safety of COVID-19 therapeutics in patients with chronic kidney disease are needed, as well as data on therapeutics for the prevention and treatment of COVID-19-associated acute kidney injury.

Introduction

Since the beginning of the COVID-19 pandemic in March 2020, SARS-CoV-2 has claimed the lives of millions of people worldwide, and the number of deaths continues to rise with the emergence of new variants[1]. During this time, therapeutics against COVID-19 have also advanced at an astounding pace, and clinicians are now equipped with an armamentarium of treatment options for patients across the spectrum of COVID-19 severity, ranging from mild to critical illness.

Therapeutic agents investigated during the pandemic include medications with diverse mechanisms of action, such as antiviral therapies that inhibit viral replication directly, recombinant neutralizing monoclonal antibodies that block viral entry into host cells, adjunct therapies that target the host immune response (for example, anti-inflammatory and antithrombotic therapies), and therapies targeting the renin–angiotensin–aldosterone system (RAAS) (Fig. 1). Numerous randomized clinical trials (RCTs) have tested the safety and efficacy of these agents (Fig. 2), which include both novel and repurposed drugs. Multiple therapies have obtained emergency-use authorization (EUA) and, in some cases, approval from regulatory agencies, including the FDA and the EMA (Table 1).

In this Review, we discuss the therapeutic advances in the treatment of COVID-19 since the start of the pandemic. We also emphasize their relevance to patients with kidney disease, including chronic kidney disease (CKD) and kidney failure requiring kidney replacement therapy (KRT), as well as kidney transplant recipients, who are all at increased risk of adverse COVID-19 outcomes[2,3]. These patient populations were excluded or under-represented in many of the RCTs of novel therapies for COVID-19, presumably owing to concerns regarding altered pharmacokinetics and the potential for increased toxicity. We also discuss the role of these therapies in the prevention and treatment of COVID-19-associated acute kidney injury (AKI), which is a common and important complication of COVID-19 among hospitalized[4] and critically ill patients[5].

Therapies targeting inflammation

From the early stages of the COVID-19 pandemic, hyperinflammation has been proposed to have an important role in the pathophysiology of severe COVID-19 (ref.[6]). Compared with healthy individuals, hospitalized patients with COVID-19 have elevated circulating concentrations of acute phase reactants (for example, ferritin)[7], pro-inflammatory cytokines (for example, IL-6)[8] and markers of coagulation and fibrinolysis (for example, D-dimer)[9]. Moreover, higher levels of these markers have been consistently associated with an increased risk of death in patients with COVID-19 (refs.[8,9]). Although subsequent studies found that the severity of inflammation in COVID-19 might be similar to that observed in patients with sepsis or acute respiratory distress syndrome (ARDS) but without COVID-19 (ref.[10]), the association between inflammatory markers and outcome severity prompted a series of trials of interventions that targeted inflammatory pathways.

Dexamethasone

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) group conducted the largest RCT to date of glucocorticoids in patients with COVID-19 (ref.[11]). RECOVERY randomly assigned 6,425 hospitalized adult patients with COVID-19 to receive oral or intravenous (i.v.) dexamethasone 6 mg daily for up to 10 days, or usual care. The primary outcome of mortality at 28 days was lower in the dexamethasone group (22.9% versus 25.7%; rate ratio (RR) 0.83, 95% CI 0.75–0.93). Pre-specified analyses of the primary outcome revealed significant heterogeneity according to the level of oxygen support ($P < 0.001$) — the mortality benefit with dexamethasone was greatest in patients receiving invasive mechanical ventilation (IMV) at randomization (RR, 0.64, 95% CI 0.51–0.81), whereas a trend towards harm was observed in patients not receiving oxygen at randomization (RR 1.19, 95% CI 0.92–1.55). These findings were corroborated by a meta-analysis conducted by the WHO Rapid Evidence Appraisal for COVID-19 (REACT) Working Group, which pooled data from seven RCTs of glucocorticoids in 1,703 critically ill patients with COVID-19 and found the odds ratio (OR) for 28-day mortality to be 0.66 (95% CI 0.53–0.82)[12].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. Early observational data suggested a survival benefit in hospitalized patients with COVID-19 treated with tocilizumab[13,14], particularly if administered early in the disease course. These data conflict with those of initial RCTs[15,16], which were largely negative but were also underpowered to rule out a significant clinical benefit[17]. Subsequently, two large pragmatic RCTs demonstrated a mortality benefit.

The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) randomly assigned 755 critically ill adult patients with COVID-19 to receive tocilizumab or usual care[18]. Tocilizumab was administered at a median of 1.2 days following hospital admission. In-hospital mortality was considerably lower in patients assigned to tocilizumab (28% versus 36%; median adjusted OR 1.64, 95% credible interval 1.14–2.35), as was 90-day mortality.

The RECOVERY group conducted the largest RCT of tocilizumab in COVID-19 to date[19]. A total of 4,116 adult patients hospitalized at 131 sites in the UK were randomly assigned to receive tocilizumab or usual care. Tocilizumab was administered at a median of 2 days following hospital admission. Mortality at 28 days was lower in patients assigned to tocilizumab (31% versus 35%; RR 0.85, 95% CI 0.76–0.94).

Some investigators have raised concerns regarding the lack of blinding in these large pragmatic trials[20] but the results seem to

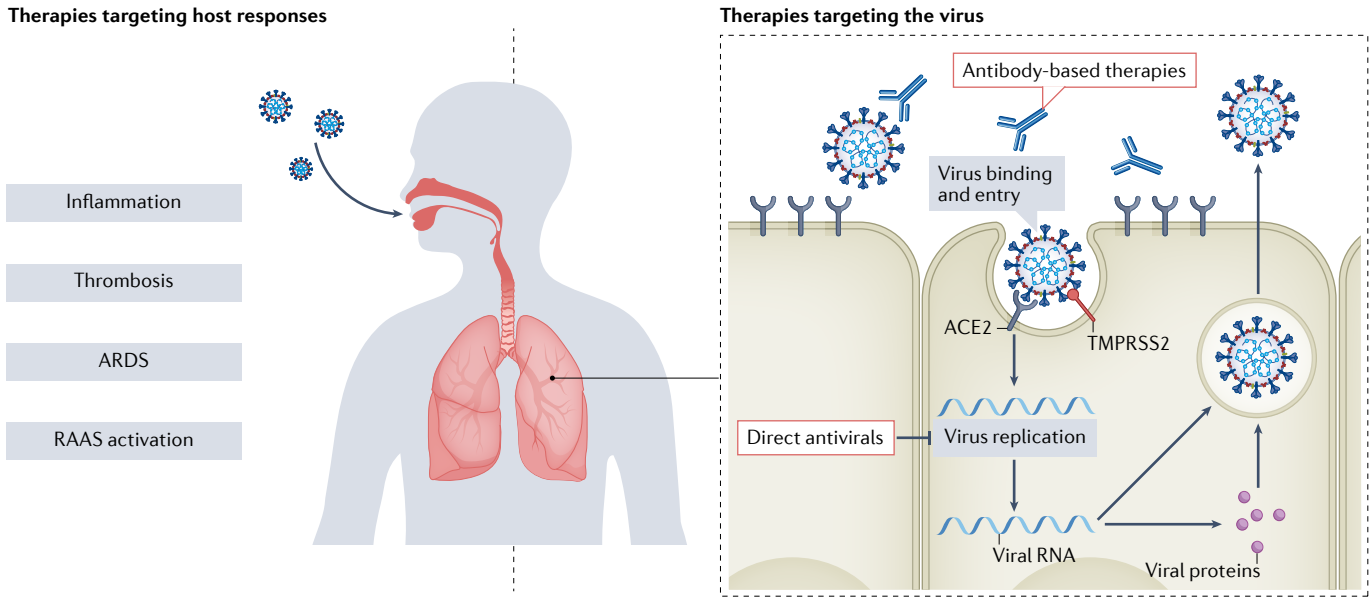

Fig. 1 | Classes of therapies for COVID-19. Therapies for COVID-19 can be broadly categorized as targeting the host response to infection (including inflammation, thrombosis, acute respiratory distress syndrome (ARDS) and renin–angiotensin–aldosterone system (RAAS) activation) or targeting the virus directly (including direct antivirals and antibody-based therapies). SARS-CoV-2 infection can lead to hyperinflammation characterized by abundant circulating levels of pro-inflammatory cytokines such as IL-6. Therapies targeting inflammation include immunosuppressive drugs such as glucocorticoids (for example, dexamethasone) and anti-IL-6 receptor antibodies (for example, tocilizumab). Several antithrombotic therapies have also been trialled to address the haemostatic and thrombotic complications associated with COVID-19, whereas different methods of oxygen delivery and intubation can be employed to treat patients with ARDS. COVID-19 can also disrupt RAAS homeostasis and drugs such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers are being investigated as potential therapies. Finally, therapies targeting SARS-CoV-2 directly include antivirals that disrupt viral replication and neutralizing antibody therapies that prevent virus entry into host cells.

be consistent across studies. Further, the findings were concordant with the results of the WHO REACT Working Group's meta-analysis, which included 10,930 adult patients with COVID-19 from 27 RCTs that assessed the efficacy of IL-6 antagonists. In this meta-analysis, the OR for 28-day mortality with IL-6 antagonists was 0.86 (95% CI 0.79–0.95)[21]. Tocilizumab received FDA EUA for COVID-19 on 24 June 2021 and is currently under priority review by the FDA for approval (Table 1); this treatment was approved by the EMA on 6 December 2021 (Table 1).

Baricitinib

Baricitinib is an oral Janus kinase 1 (JAK1) and JAK2 inhibitor with anti-inflammatory properties. An RCT conducted in 1,033 hospitalized adults found that treatment with baricitinib (4 mg daily, up to 14 days) plus the antiviral remdesivir (discussed in more detail below) was superior to remdesivir alone in reducing time to recovery[22]. In a subsequent phase III RCT, 1,525 adult patients hospitalized at 101 centres across 12 countries were assigned to baricitinib (4 mg daily) or placebo for up to 14 days[23]. Although the primary composite outcome (the proportion who progressed to high-flow oxygen, noninvasive ventilation (NIV), IMV or death by day 28) was similar between groups, 28-day mortality was notably lower in the baricitinib group than in the placebo group (8% versus 13%; hazard ratio (HR) 0.57, 95% CI 0.41–0.78). Importantly, patients receiving IMV were excluded from this study. However, a subsequent smaller RCT conducted by the same group in 101 critically ill adults with COVID-19 receiving IMV or extracorporeal membrane oxygenation (ECMO) reported a 28-day mortality benefit with baricitinib versus placebo (39% versus 58%; HR 0.54, 95% CI 0.31–0.96)[24]. In the largest RCT of baricitinib to date, the RECOVERY group randomly assigned 8,156 hospitalized adults to receive baricitinib 4 mg daily until either 10 days or hospital discharge, versus usual care. Patients who received baricitinib had lower 28-day mortality than those receiving usual care (age-adjusted RR 0.87, 95% CI 0.77–0.99)[25]. Baricitinib was approved by the FDA in May 2022 and is currently under review by the EMA (Table 1).

Relevance to patients with kidney disease

The largest RCTs that assessed dexamethasone and tocilizumab in COVID-19 included patients with AKI, CKD and kidney failure requiring KRT, as well as kidney transplant recipients. No dose adjustments are required for the use of these agents in patients with kidney dysfunction (Fig. 3). By contrast, the baricitinib dose is reduced to 2 mg daily in patients with estimated glomerular filtration rate (eGFR) 30–59 ml/min/1.73 m^2, and to 1 mg daily in patients with eGFR 15–29 ml/min/1.73 m^2 (Fig. 3). Whether the magnitude of benefit of anti-inflammatory therapies in patients with COVID-19 differs according to the level of kidney function at baseline has not been assessed.

The use of anti-inflammatory agents such as tocilizumab or dexamethasone could potentially increase the risk of secondary infection, especially in patients with kidney failure or in kidney transplant recipients. Of note, although the aforementioned RCTs of tocilizumab did not report an increased risk of secondary infection[18], solid organ transplant recipients might have been under-represented in these trials.

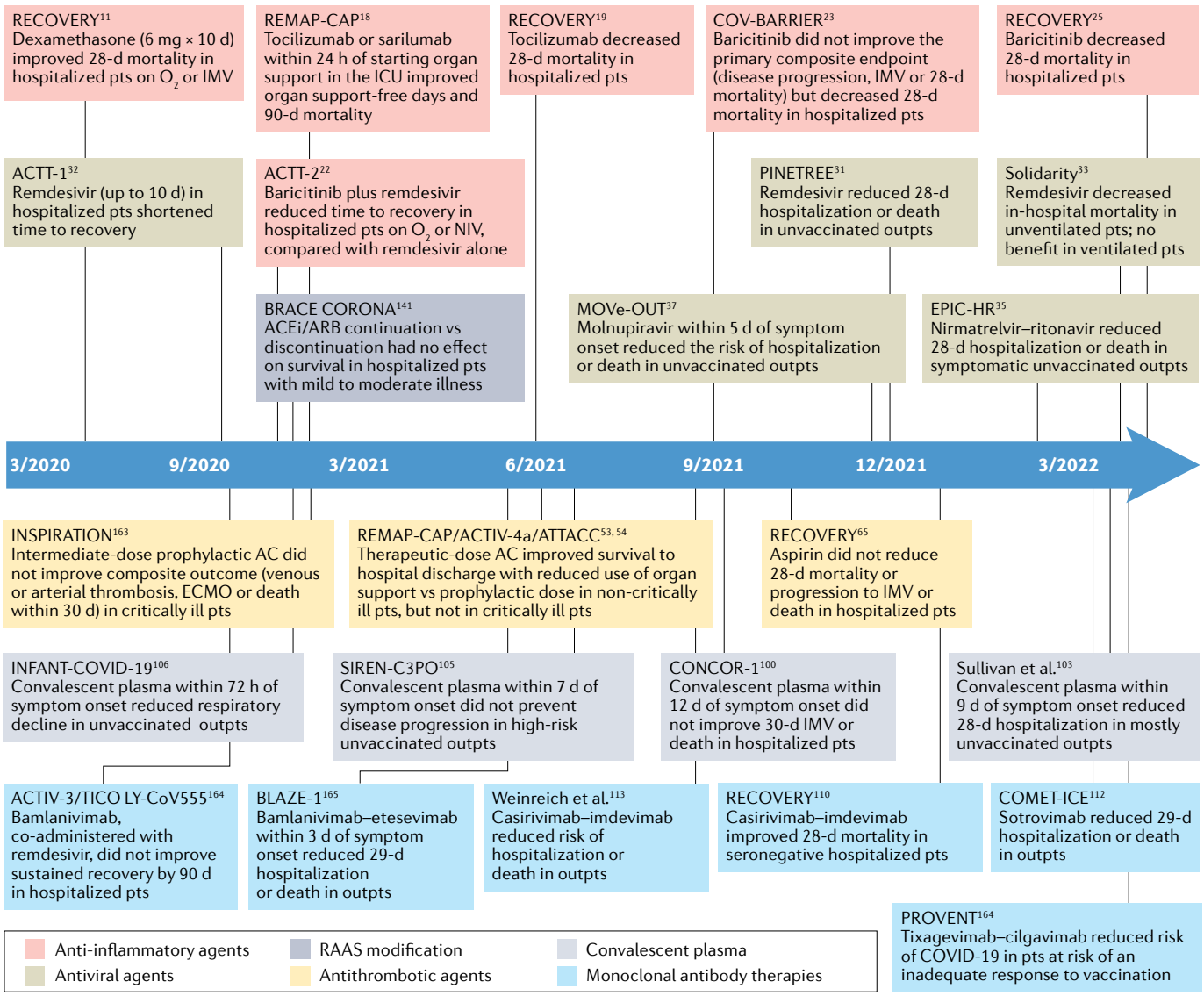

Fig. 2 | Timeline of publication of pivotal phase III randomized clinical trials of COVID-19 therapies. Timeline of publication and key features of pivotal phase III randomized clinical trials of COVID-19 therapies. These trials are categorized into six treatment categories: anti-inflammatory agents, antivirals, renin–angiotensin–aldosterone system (RAAS) modification, antithrombotic agents, convalescent plasma and monoclonal antibody therapies. AC, anticoagulation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; d, days; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; outpts, outpatients; pts, patients. This timeline reflects published data as of 29 May 2022.

Finally, whether glucocorticoids, IL-6 antagonists and other anti-inflammatory therapies reduce the risk of AKI in patients with COVID-19 has not been rigorously examined. However, the effect of dexamethasone and tocilizumab on the most severe form of AKI (that is, AKI requiring KRT) was assessed by the RECOVERY group trials of these agents and, in both cases, treatment reduced the incidence of KRT considerably[11,19].

Antiviral therapies

At the outset of the COVID-19 pandemic, no antiviral agents were licensed for the treatment of this disease. Consequently, numerous repurposed therapies with in vitro antiviral activity entered clinical use and were tested in clinical trials. However, many widely used agents such as hydroxychloroquine, lopinavir or ritonavir, and ivermectin were shown to be ineffective COVID-19 therapies when studied in adequately powered RCTs[26–28]; more effective antivirals are now available.

Remdesivir

Remdesivir is a prodrug nucleoside analogue — its active metabolite reduces genome replication by inhibiting RNA-dependent RNA polymerase — and has antiviral activity against many RNA viruses in vitro, including SARS-CoV-2 (refs.[29,30]). Remdesivir has been studied in patients with COVID-19 in both the outpatient and inpatient settings. In the PINETREE study, a 3-day course of i.v. remdesivir among unvaccinated outpatients with COVID-19 at a high risk of disease progression

reduced 28-day hospitalization or death by 87% compared with placebo (0.7% versus 5.3%; HR 0.13, 95% CI 0.03–0.59)[31]. By contrast, remdesivir's magnitude of benefit was modest among hospitalized patients. The pivotal ACTT-1 trial, which enrolled 1,062 patients, showed that the time to recovery was shorter with remdesivir than with placebo (10 days versus 15 days), and there was a trend towards lower 29-day mortality (11.4% versus 15.2%; HR 0.73, 95% CI 0.52–1.03)[32]. The WHO Solidarity trial, which is the largest RCT of remdesivir to date, randomly assigned 8,275 hospitalized patients to remdesivir or no study drug. Overall, treatment with remdesivir did not affect hospital mortality compared with control (14.5% versus 15.6%; RR 0.91, 95% CI 0.82–1.02), although it reduced hospital mortality modestly in patients who were not ventilated at study entry (11.9% versus 13.5%; RR 0.86, 95% CI 0.76–0.98); there was no benefit in patients who were already ventilated at the start of treatment[33]. Remdesivir was approved by the FDA on 22 October 2020 and by the EMA on 3 July 2020 (Table 1).

Table 1 | Authorized or approved therapeutics for COVID-19

Drug	Setting	Patient population	Dosing regimen	Dose adjustment for kidney dysfunction	Date of FDA EUA or approval	Date of EMA authorization
Anti-inflammatory agents						
Tocilizumab	Inpatient	Patients receiving corticosteroids and on supplemental oxygen, a ventilator or ECMO	8 mg/kg i.v. once (max dose: 800 mg)	None	EUA, 24 June 2021[a]	6 December 2021
Baricitinib	Inpatient	Patients on supplemental oxygen, IMV or ECMO	4 mg once daily	eGFR ≥ 60: 4 mg daily; eGFR 30–59: 2 mg daily; eGFR 15–29: 1 mg daily; eGFR < 15: NR	EUA, 19 November 2020; FDA approved, 10 May 2022	Under review
Antiviral agents						
Remdesivir	Inpatient and outpatient	Symptoms (mild to moderate) for < 7 days	200 mg i.v. on day 1, then 100 mg i.v. daily from day 2 (3 days for non-hospitalized, 5 days or until discharge for hospitalized)	eGFR < 30: NR	EUA, 1 May 2020; FDA approved, 22 October 2020	3 July 2020
Nirmatrelvir–ritonavir (Paxlovid)	Outpatient	Symptoms (mild to moderate) for < 5 days	300 mg/100 mg oral twice daily for 5 days	eGFR 30–59: 150/100 mg twice daily for 5 days; eGFR < 30: NR	EUA, 22 December 2021	28 January 2022
Molnupiravir	Outpatient	Symptoms (mild to moderate) for < 5 days	800 mg orally twice daily for 5 days	None	EUA, 23 December 2021	Under review
Antibody-based therapies						
Convalescent plasma	Inpatient and outpatient	Hospitalized patients receiving supplemental oxygen, noninvasive ventilation or IMV, or ECMO	~200 ml IV	None	EUA, 23 August 2020	ND
Bamlanivimab/etesevimab[a]	Outpatient	Symptoms (mild to moderate)	700 mg/1400 mg i.v. once	None	EUA, 9 February 2021	Withdrawn from review 29 October 2021
Casirivimab/imdevimab[a]	Outpatient	Symptoms (mild to moderate) for < 10 days	600 mg/600 mg s.c. once	None	EUA, 21 November 2020	12 November 2021
Sotrovimab[b]	Outpatient	Symptoms (mild to moderate) for < 7 days	500 mg i.v. once	None	EUA, 26 May 2021	17 December 2021
Bebtelovimab	Outpatient	Symptoms (mild to moderate) for < 7 days and at a high risk of severe illness	175 mg i.v. once	None	EUA, 11 February 2022	ND
Tixagevimab/cilgavimab (Evusheld)	Outpatient	Pre-exposure prophylaxis and with moderate to severe immune compromise due to a medical condition or immunosuppressive medication	300 mg/300 mg i.m. once	None	EUA, 8 December 2021	25 March 2022

ECMO, extracorporeal membrane oxygenation; EUA, Emergency Use Authorization; eGFR, estimated glomerular filtration rate; i.m., intramuscular; IMV, invasive mechanical ventilation; i.v., intravenous; ND, not discussed; NR, not recommended; s.c., subcutaneous. [a]Currently under priority review for FDA approval. [b]Use terminated in the USA owing to high frequency of the Omicron SARS-CoV-2 variant. [c]Use suspended in certain US states owing to lack of efficacy against the BA.2 variant.

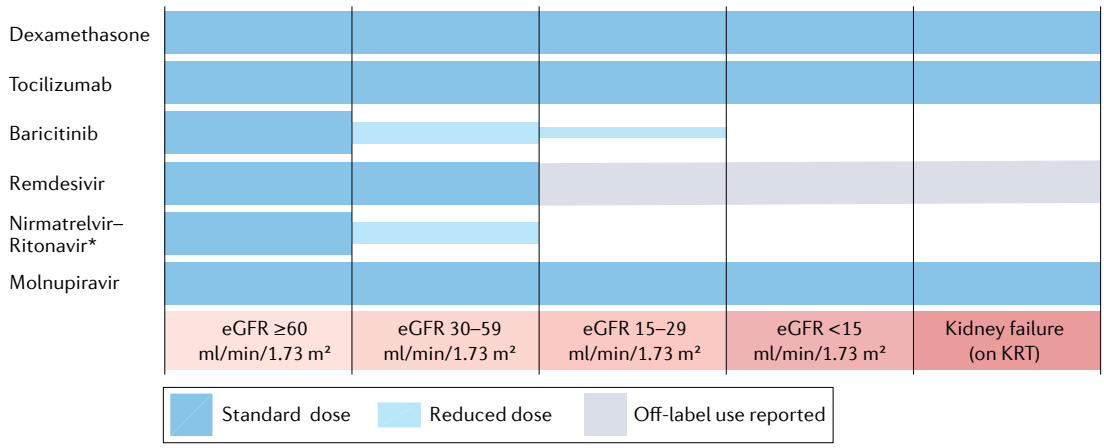

Fig. 3 | Anti-inflammatory and antiviral agents for COVID-19 including dose adjustment for kidney function impairment. The immunosuppressive therapies dexamethasone and tocilizumab can be used without dose adjustments in patients with kidney disease, including those with kidney failure. However, the anti-inflammatory agent baricitinib must be administered at reduced doses in patients with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. In the case of antivirals used to treat SARS-CoV-2 infection, molnupiravir can be used without dose adjustments and remdesivir, although currently not recommended for use in patients with eGFR < 30 ml/min/1.73 m^2, has been reportedly used in patients across the spectrum of kidney dysfunction, including in patients with kidney failure who require kidney replacement therapy (KRT). By contrast, nirmatrelvir–ritonavir is contraindicated in patients with eGFR <30 ml/min/1.73 m^2 and, given its potential to increase exposure to calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors, must be used with extreme caution in recipients of solid organ transplants, and only if CNI and/or mTOR levels can be monitored closely. The asterisk indicates that in patients with eGFR 30–59 ml/min/1.73 m^2, the dose of nirmatrelvir is reduced by 50% but the ritonavir dose remains unchanged.

Nirmatrelvir–ritonavir

Nirmatrelvir–ritonavir (also known as Paxlovid) is a combination therapy consisting of nirmatrelvir, an oral 3C-like protease inhibitor that is active against the main viral protease that cleaves SARS-CoV-2 polyproteins during viral replication, and ritonavir, a strong cytochrome P450 3A4 (CYP3A4) inhibitor and pharmacokinetic boosting agent[34]. In the EPIC-HR trial, which enrolled 2,246 unvaccinated adult outpatients with COVID-19 at a high risk of disease progression, nirmatrelvir–ritonavir reduced the risk of 28-day hospitalization or death by 89% compared with placebo (0.7% versus 6.5%; difference of −6.32 percentage points, 95% CI −9.04 to −3.59)[35]. Nirmatrelvir–ritonavir received EUA from the FDA on 22 December 2021, and approval from the EMA on 28 January 2022 (Table 1).

Molnupiravir

Molnupiravir is an oral pro-drug of β-D-N4-hydroxycytidine (NHC), which is a cytidine analogue that has broad-spectrum antiviral activity against SARS-CoV-2 in vitro[36]. NHC is incorporated into new RNA strands of the SARS-CoV-2 genome as they are synthesized, causing an accumulation of deleterious mutations that is termed lethal mutagenesis. In the MOVe-OUT trial, which enrolled 1,433 adult outpatients with mild-to-moderate COVID-19, molnupiravir reduced 29-day hospitalization or death by approximately one-third compared with placebo (6.8% versus 9.7%; HR 0.69, 95% CI 0.48–1.01), which was an effect of lesser magnitude than that observed with other antivirals[37].

Relevance to patients with kidney disease

Most RCTs of remdesivir excluded patients with an eGFR <30 ml/min/1.73 m^2 (refs.[31–33]). Remdesivir is formulated with sulfobutylether β-cyclodextrin sodium, which is a solubility enhancer that is eliminated by the kidney and is nephrotoxic in rats at high doses[38]. However, whether the doses of sulfobutylether β-cyclodextrin sodium administered during short courses of remdesivir represent a substantial safety concern is unclear, and remdesivir use in patients with severely impaired kidney function has been reported[39–43]. Nonetheless, remdesivir is not currently recommended in patients with eGFR <30 ml/min/1.73 m^2 (Fig. 3), although a phase III RCT is ongoing to evaluate its efficacy and safety in that population[44].

The EPIC-HR trial of nirmatrelvir–ritonavir described above excluded patients with an eGFR <45 ml/min/1.73 m^2 (ref.[35]). Nonetheless, nirmatrelvir–ritonavir can be used in patients with moderate CKD — a 50% dose reduction of nirmatrelvir is recommended in patients with an eGFR 30–59 ml/min/1.73 m^2 (ref.[45]) (Fig. 3). Nirmatrelvir–ritonavir is contraindicated in patients with eGFR <30 ml/min/1.73 m^2, as well as in those with severe hepatic impairment. Importantly, ritonavir is a potent inhibitor of CYP3A and would therefore increase exposure to calcineurin inhibitors and mammalian target of rapamycin inhibitors, which are immunosuppressive drugs commonly used to prevent graft rejection in kidney transplant recipients. Accordingly, nirmatrelvir–ritonavir should be used with extreme caution in recipients of kidney and other solid organ transplants, and only if calcineurin inhibitors and/or mammalian target of rapamycin levels can be monitored closely[46].

The MOVe-OUT trial of molnupiravir excluded patients with eGFR <30 ml/min/1.73 m^2, and only 5.9% of participants had CKD[37]. However, because NHC is metabolized through an endogenous pyrimidine pathway[47], the EUA for molnupiravir does not restrict its use in patients with advanced CKD or kidney failure requiring KRT, and no dose adjustment is required for patients with kidney disease (Fig. 3).

In summary, antiviral therapy now has an established role in preventing disease progression when used for early treatment of symptomatic patients at risk of poor outcomes (for example, unvaccinated patients and those with comorbidities such as CKD). Whether the remdesivir, nirmatrelvir–ritonavir and molnupiravir RCT data can be

extrapolated to vaccinated populations, patients infected with new SARS-CoV-2 variants or patients with advanced CKD is unclear. Notably, all three drugs have limitations: remdesivir requires i.v. infusion, nirmatrelvir–ritonavir has important interactions with other drugs that might restrict or complicate its use, and the efficacy of molnupiravir is modest. Evidence directly relevant to patients with CKD or kidney failure and kidney transplant recipients is scarce and eagerly awaited.

Antithrombotic therapies

Hospitalized patients with COVID-19 experience relatively high rates of morbid and potentially fatal haemostatic and thrombotic complications, particularly venous thromboembolism (VTE)[48,49]. These complications result from a state of dysfunction in the thromboinflammatory coagulation system, sometimes referred to as 'COVID-19-associated coagulopathy'[50]. The pathogenesis of this coagulopathy is incompletely understood and seems to be multifactorial. Contributing factors include endothelial injury (induced by the virus and/or the anti-viral immune response), a hypercoagulable state induced by elevated levels of acute-phase reactant coagulation factors (particularly fibrinogen and factor VIII) and other pro-inflammatory mechanisms, including the formation of neutrophil extracellular traps[49–52]. Consequently, empirical use of antithrombotic therapies, including empirical administration of anticoagulant or antiplatelet agents in the absence of a standard clinical indication, and empirical dose escalation to a dose higher than that otherwise indicated in patients who would typically receive prophylactic dosing, has been under investigation in patients with COVID-19 since the early days of the pandemic.

Importantly, the use of antithrombotic therapies requires careful balancing of thrombotic and bleeding risks. In most patient populations, major bleeding is associated with a higher mortality risk than VTE, including in patients with COVID-19 (ref.[48]). The risks of both bleeding and thrombosis escalate with worsening illness, but not always in equal proportions, and the relative contribution of thrombotic injury to morbidity might depend on the phase of illness[53,54]. The potential benefit of empirical use or dose-escalation of anticoagulation or antiplatelet therapy in COVID-19 has been evaluated across different phases of illness (that is, in critically ill inpatients, non-critically ill inpatients, and outpatients) and at varying dose levels, particularly for anticoagulation (prophylactic, intermediate and therapeutic doses)[55] (Table 2); several clinical trials are ongoing. Patients with COVID-19 and an existing indication for therapeutic anticoagulation (for example, VTE) or antiplatelet therapy (for example, coronary artery disease) should receive antithrombotic therapy as indicated by American Society of Hematology guidelines[56].

At present, the accumulated body of evidence suggests that antithrombotic management of patients with COVID-19 should not differ substantially from that of other populations with similar degrees of illness. However, where no contraindications exist, all hospitalized patients with COVID-19 should receive pharmacological thromboprophylaxis (in contrast to mechanical thromboprophylaxis alone)[56], and empirical therapeutic anticoagulation can be considered in non-critically ill hospitalized patients, particularly in those with a high thrombosis risk (that is, patients with elevated D-dimer levels) and a low bleeding risk[57,58]. Importantly, although two large RCTs reported a benefit for therapeutic anticoagulation in non-critically ill hospitalized patients[53,59], two others did not report a beneficial effect[60,61]. However, of the two trials that did not find a benefit, one was stopped early owing to feasibility (although data showed that therapeutic anticoagulation significantly reduced 28-day mortality compared with prophylactic anticoagulation)[60], and the other investigated rivaroxaban, which is a factor Xa inhibitor[61] (whereas other RCTs evaluated the use of unfractionated or low-molecular-weight heparin (LMWH)). Finally, patients at high risk of VTE might benefit from post-discharge pharmacological thromboprophylaxis[62,63], which also applies to patients who were hospitalized without COVID-19 (ref.[64]).

In contrast to therapeutic anticoagulation, empirical antiplatelet therapy does not seem to be beneficial at any stage of COVID-19 (refs.[65–67]), including the RECOVERY trial of aspirin versus usual care in 14,892 hospitalized patients[65], which is the largest trial of any agent in patients with COVID-19 to date. One trial found a reduction in 90-day

Table 2 | Summary of evidence from major RCTs evaluating the use of empirical antithrombotic therapy in COVID-19

Disease severity	Therapy	RCT	Summary of current evidence and recommendations
Inpatient, critically ill (severe illness)	Anticoagulation (heparin-based)	ACTIV-4a–ATTACC–REMAP-CAP[a,54] INSPIRATION[163]	Critically ill patients with COVID-19 should receive pharmacological thromboprophylaxis with unfractionated or low molecular weight heparin Multiple RCTs show no benefit from intermediate- or therapeutic-dose anticoagulation over standard prophylactic-dose thromboprophylaxis, and potential for harm with dose escalation owing to higher bleeding rates Prophylactic dosing should be adjusted for weight and eGFR
	Aspirin or P2Y12 inhibitor[b]	RECOVERY[65] REMAP-CAP[67]	No clear benefit, and higher rates of major bleeding with empirical use of antiplatelet agents in critically ill patients with COVID-19
Inpatient, not critically ill (moderate illness)	Heparin-based anticoagulation or rivaroxaban	REMAP-CAP–ACTIV-4a–ATTACC[53] ACTION[61]; RAPID[60]; HEP-COVID[59]	Moderately ill patients with COVID-19 should receive at least pharmacological thromboprophylaxis Empirical therapeutic-dose anticoagulation might benefit certain individuals with high thrombosis and low bleeding risk, but data are conflicting
	Aspirin	RECOVERY[65]	No clear benefit for empirical use of aspirin in moderately ill patients with COVID-19
Outpatient, no hospitalization	Apixaban	ACTIV-4B[66]	No clear benefit for empirical use of apixaban in outpatients with COVID-19
	Aspirin	ACTIV-4B[66]	No clear benefit for empirical use of aspirin in outpatients with COVID-19
Outpatient, following hospital discharge	Anticoagulation (apixaban, rivaroxaban, or enoxaparin)	MICHELLE[63]	Possible benefit for prophylactic-dose rivaroxaban post-discharge in certain patients hospitalized for COVID-19 who have high thrombosis and low bleeding risk

eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial. [a]ATTACC–ACTIV-4a–REMAP-CAP was a multiplatform trial of anticoagulation in hospitalized patients with COVID-19. [b]Clopidogrel, prasugrel or ticagrelor.

mortality with antiplatelet therapy (aspirin or a P2Y12 inhibitor) in critically ill patients with COVID-19 (ref.[67]), although this was a secondary end point and additional trials are ongoing to address this question[68]. Conversely, several trials have reported increased rates of major bleeding in patients treated with empirical antiplatelet versus no antiplatelet therapy, and in patients treated with therapeutic- versus prophylactic-dose anticoagulation therapy[53,54,61,67]. Importantly, given the substantial contribution of inflammation to COVID-19-associated coagulopathy, the development of anti-inflammatory therapies to treat COVID-19 might attenuate or nullify any potential benefit of escalated anticoagulation, leaving only elevated bleeding risk. This risk is particularly important to consider when assessing trials of antithrombotic therapies conducted before the routine use of anti-inflammatory therapies.

Relevance to patients with kidney disease

In general, the aforementioned conclusions regarding antithrombotic therapies apply to patients with advanced kidney disease, with slight modifications. Patients with CKD or kidney failure requiring KRT are at an increased risk of both bleeding[69] and clotting[70] at baseline compared with patients with normal kidney function. These risks must be considered when evaluating non-critically ill patients for empirical therapeutic-dose anticoagulation and when evaluating hospitalized patients for post-discharge pharmacological thromboprophylaxis. Most major trials of anticoagulation in hospitalized patients with COVID-19 enrolled patients with advanced kidney disease, but dose-reduced LMWH or mandated the use of unfractionated heparin rather than LMWH in these patients. Although LMWH is usually preferred over unfractionated heparin, given its much lower risk of heparin-induced thrombocytopenia[71] and ease of administration, LMWH must be used with caution and at lower doses in patients with advanced kidney disease owing to the potential increased risk of bleeding given that LMWH is excreted in the kidney[72]. Finally, although empirical dose escalation of prophylactic anticoagulation does not seem to be beneficial in critically ill patients with COVID-19 (ref.[54]), patients receiving continuous KRT who experience recurrent clotting of the circuit filter might benefit from therapeutic-dose anticoagulation to prevent further clotting[73]. Of note, some small studies suggest that argatroban, which is a direct thrombin inhibitor, might be useful to prevent circuit filter thrombosis in these patients[74,75] but high-level evidence to support its use is lacking. Importantly, in any critically ill patient with multi-organ system failure, acquired antithrombin deficiency might render heparin ineffective. This effect can be countered with either antithrombin repletion or a switch to a direct thrombin inhibitor, which would act independently of antithrombin[76].

Finally, whether therapeutic anticoagulation can attenuate the risk of COVID-19-associated AKI is unknown. The pathophysiology of AKI in COVID-19 is complex and involves inflammation, endothelial injury, and microvascular thrombosis[77]. Although acute tubular injury is the most common finding at autopsy in patients with COVID-19-associated AKI, platelet-rich peritubular fibrin microthrombi in the kidney microcirculation have also been reported[78]. Therapeutic anticoagulation with heparin might mitigate microvascular thrombosis and attenuate ischaemia–reperfusion injury[79] thereby preventing AKI, but supporting clinical trial data are lacking.

Therapies for acute respiratory failure

COVID-19 might cause critical illness through a variety of mechanisms, but acute hypoxaemic respiratory failure remains the leading cause[7]. In addition to decisions regarding the use of antivirals, immunomodulators and anticoagulants, which might benefit patients across the spectrum of illness, the treatment of COVID-19-induced respiratory failure requires special consideration of the method of oxygen delivery, timing of intubation, and the use of prone positioning or of adjuvant therapies for refractory hypoxaemia.

Oxygen delivery

Three noninvasive methods of oxygen delivery can be used in patients who require more oxygen than can be delivered by a standard nasal cannula — conventional oxygen therapy (usually a mask with an oxygen reservoir, termed a 'non-rebreather mask'), a high-flow nasal cannula (HFNC), which delivers warmed and humidified oxygen through large-bore nasal cannulas at flow rates that exceed the patient's peak inspiratory flow rate, or NIV, whereby a tight-fitting mask connected to a noninvasive ventilation machine provides continuous positive airway pressure or bilevel positive airway pressure.

Initially, concerns surrounding the use of HFNC or NIV included a potential increase in the risk to health-care workers owing to aerosolization of SARS-CoV-2 and potential exacerbation of lung injury owing to increased transpulmonary pressures from vigorous respiratory effort (so-called patient self-induced lung injury), which might be avoided with intubation and sedation[80,81]. During the first wave of COVID-19, these concerns led to the intubation of patients who had only moderate hypoxaemia[82]. Earlier intubation, however, potentially exposes patients to other risks, such as ventilator-induced lung injury and sedation-associated delirium. Accordingly, some studies showed that the outcomes of hospitalized patients improved as the use of HFNC and NIV became more liberal, and the approach to intubation became more conservative[83]. Furthermore, the availability of highly effective vaccines and research suggesting that HFNC and NIV do not significantly increase aerosolization of virus particles have allayed concerns regarding the risk to health care workers[84].

Although the use of HFNC and NIV are now more common in the treatment of COVID-19 than earlier in the pandemic, their relative effectiveness remains unclear. The RECOVERY-RS trial compared available methods for oxygen delivery by randomly assigning 1,237 hospitalized adults with COVID-19-related acute hypoxaemic respiratory failure to conventional oxygen therapy, HFNC or NIV (specifically, continuous positive airway pressure). The study found that NIV led to lower rates of intubation than conventional oxygen delivery or HFNC, but mortality was not significantly different among the three groups. However, the interpretation of the study is complicated by a high rate of crossover between groups[85].

Prone positioning

Prone positioning is one of the few interventions shown to reduce mortality among patients intubated for non-COVID-19 ARDS[86]. However, adoption of proning in patients with COVID-19 ARDS has been incomplete based on ongoing concerns regarding its effectiveness, resource utilization and the risk of dislodging support devices; reports show wide inter-hospital variation in the use of proning[7]. No RCT has evaluated proning in patients intubated owing to COVID-19 but observational studies suggest that early proning of these patients is associated with reduced mortality[87].

Since the early days of the pandemic, some experts have proposed extending the use of proning to non-intubated spontaneously

breathing patients (that is, awake proning). However, results of trials evaluating the use of awake proning have been mixed – some showed benefit[88], whereas others showed no effect[89] or even potential harm[90].

Adjunctive therapy for hypoxemia

In the years leading up to the COVID-19 pandemic, the use of neuromuscular blockade in ARDS had been hotly debated. The Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial, reported in 2019, showed that 48 h of neuromuscular blockade in patients with a partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio <150 mmHg did not improve 90-day mortality[91]. No trials have specifically evaluated neuromuscular blockade in patients with COVID-19 but, based on the results of the ROSE trial, no major medical society has recommended the routine use of neuromuscular blockade. However, many patients with COVID-19 develop refractory hypoxaemia despite maximal ventilatory support, and both neuromuscular blockade and inhaled pulmonary vasodilators are routinely used in this setting despite a lack of evidence that they affect clinical outcomes in either COVID-19 or non-COVID-19 ARDS.

ECMO

For patients with refractory hypoxaemia despite maximal ventilatory support, proning, neuromuscular blockade, and inhaled pulmonary vasodilators, ECMO might be a life-saving therapy[92,93]. The ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, published in 2018, suggested a mortality benefit in patients with non-COVID-19 ARDS with severe hypoxaemia[94], and the use of ECMO increased dramatically during the COVID-19 pandemic.

No RCTs have evaluated the efficacy of ECMO in patients with COVID-19 ARDS. However, two target trial emulation analyses, as well as a pseudo-randomized study that used a period of resource limitation as a natural experiment, suggested a robust mortality benefit from ECMO in patients with COVID-19 (refs.[92,93,95]). In one target trial analysis, which used data from 55 geographically diverse sites from across the USA, patients with severe hypoxaemia (defined as PaO_2 to FiO_2 ratio <100 mmHg while receiving IMV) in whom ECMO was initiated within 7 days following intensive care unit admission, had a considerably lower mortality than similarly ill patients at ECMO-capable centres who were not treated with ECMO (34.6% versus 47.4%; HR 0.55, 95% CI 0.41–0.74)[92]. Similar findings were observed in a larger subsequent study, which used data from 7,345 adults admitted to intensive care units in 30 countries[93]. In the pseudo-randomized study, mortality among patients who qualified for ECMO but did not receive it owing to resource limitations was ~90%, compared with 43% among patients for whom those resources were available[95]. Although the data from these observational studies are compelling, they should nonetheless be interpreted cautiously, as they might have been affected by residual confounding (for example, disease severity and mortality risk might have affected treatment selection).

Relevance to patients with kidney disease

ARDS is independently associated with a higher risk of AKI in critically ill patients, and the combination of both syndromes portends a particularly poor prognosis in both COVID-19 and non-COVID-19 settings[7,96]. Crosstalk between injured lungs and kidneys has been well recognized in both animal models and human studies, and multiple mechanisms have been proposed to explain this pathophysiology (reviewed previously[97]).

Glossary

Pseudo-randomized study
The use of naturally occurring variation in an exposure to identify its effect on an outcome of interest; also known as a natural experiment.

Target trial emulation analyses
The application of principles from randomized clinical trials to observational studies.

Neutralizing antibody therapies

Antibodies have a key role in the adaptive immune response and are crucial to protecting the host from pathogens. Passive administration of pathogen-specific polyclonal or monoclonal antibodies (mAbs) has been used to control viral infections, with the goal of neutralizing a target virus by targeting it for elimination and preventing its entry into host cells, thereby eliminating the infection-associated disease[98]. Pathogen-specific neutralizing antibodies can either be transferred from patients who have recovered from a viral infection (that is, convalescent plasma) or synthesized as recombinant neutralizing mAbs through established molecular engineering techniques.

The use of convalescent plasma was rapidly implemented in the early phase of the pandemic in the absence of alternative treatment options[99]; since then, several studies have investigated the efficacy of this therapy. Multicentre, open-label RCTs repeatedly demonstrated a lack of benefit for convalescent plasma in hospitalized patients with COVID-19 (refs.[100–102]). In non-hospitalized and mostly unvaccinated adults, a double-blind RCT of convalescent plasma versus control plasma administered within 8 days of symptom onset reduced hospitalization (2.9% versus 6.3%; absolute risk reduction, 3.4 percentage points, 95% CI 1.0–5.8)[103]. By contrast, two RCTs in adult patients with mild or moderate COVID-19 symptoms for less than 1 week[104,105] or 72 h[106] failed to demonstrate any benefit from the administration of convalescent plasma. Lack of efficacy of convalescent plasma for adult patients with mild to moderate COVID-19 was further confirmed by a patient-level meta-analysis of 782 patients from two RCTs[107]. The emergence of new variants of SARS-CoV-2 added further uncertainty to the potential benefit of convalescent plasma therapy. Currently, the use of convalescent plasma collected prior to the Omicron (B1.1.529/BA1 and BA2) surge is not recommended by the FDA[108] and has not been considered by the EMA.

Recombinant neutralizing mAbs have been the focus of a large number of studies[109]. These neutralizing mAbs are developed to target the receptor-binding spike protein of SARS-CoV-2, which mediates viral entry into host cells by binding to angiotensin-converting enzyme 2 (ACE2). Five mAb agents are currently available in the USA under EUA: bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab, bebtelovimab, and tixagevimab plus cilgavimab (Table 1). One large RCT found that casirivimab plus imdevimab reduced 28-day mortality in hospitalized patients who were seronegative at baseline compared with standard of care (24% versus 30%; RR 0.79, 95% CI 0.69–0.91)[110]. Furthermore, several RCTs in non-hospitalized adults from high-risk groups with mild or moderate COVID-19 demonstrated that early treatment with recombinant neutralizing mAbs reduced the risk of hospitalization or death, particularly in patients who were seronegative[111–113]. Recombinant mAbs are highly effective at preventing hospitalization when given early but they are highly susceptible to loss of neutralizing activity as novel virus variants emerge[114]. Currently, in the USA, only bebtelovimab is recommended in non-hospitalized adult

patients with COVID-19 at risk of disease progression when antiviral treatment is unavailable or contraindicated[108].

The NIH COVID-19 treatment guideline panel recommends pre-exposure prophylaxis with tixagevimab plus cilgavimab (Evusheld) in moderately to severely immunocompromised adults without active SARS-CoV-2 infection[108]. These specific recombinant neutralizing mAbs carry a modification of the fragment crystallizable (Fc) region that prolongs their half-life and hence their potential protective effect for up to 6 months. A double-blind RCT conducted in 5,197 patients at a high risk of severe outcomes demonstrated that tixagevimab plus cilgavimab reduced the incidence of COVID-19 infection (0.2%) compared with placebo (1.0%) (relative risk reduction 76.7%; 95% CI 46.0–90.0)[115]. Of note, tixagevimab plus cilgavimab have neutralizing activity against Omicron sub-variants BA1.1.529 (refs.[114,115]).

Overall, based on these pharmacological, epidemiological and clinical trial data, recommendations for the use of convalescent plasma and recombinant neutralizing mAbs for COVID-19 treatment or prevention are necessarily fluid, as they require frequent updates depending on the resistance patterns of prevalent virus variants and the results of ongoing research.

Relevance to patients with kidney disease

Kidney transplant recipients and patients with CKD or kidney failure requiring KRT are at a high risk of progression to severe illness and death from COVID-19 (refs.[2,116]) and could theoretically benefit from early treatment with convalescent plasma or recombinant neutralizing mAbs. Convalescent plasma has been examined in these populations and, although several observational studies suggested some benefit[117–120], clinical trial data to support the routine use of convalescent plasma in patients with COVID-19 with underlying kidney disease are lacking. Similarly, no high-grade evidence supports the use of convalescent plasma as pre-exposure prophylaxis in these populations.

Of note, small observational studies suggested that early treatment with recombinant neutralizing mAbs might be beneficial in patients with kidney failure requiring KRT or in kidney transplant recipients with mild COVID-19 (refs.[121,122]). Additionally, data from several observational studies suggested that kidney transplant recipients might benefit from pre-exposure prophylaxis with tixagevimab plus cilgavimab[123,124]. Importantly, given that mAbs are metabolized via target-mediated elimination, no dose adjustment is required in patients with kidney impairment (Table 1). However, conclusive data from RCTs conducted in this patient population are lacking and the existing studies were conducted before the emergence of the Omicron variant, which was resistant to most neutralizing mAbs[125–127].

Therapies targeting the RAAS

Interest in the effects of SARS-CoV-2 on the host RAAS emerged early in the pandemic[128]. The RAAS has key roles in the regulation of vascular tone, electrolyte balance, inflammation, thrombosis and response to injury, and might be dysregulated in COVID-19 (ref.[129]). Moreover, ACE2, which converts angiotensin II into angiotensin (1–7), is the functional host receptor for SARS-CoV-2 (ref.[130]). ACE2 is abundantly expressed on the surface of nasopharyngeal and lung alveolar epithelial cells, and throughout the vascular endothelium; soluble ACE2 is also present in the circulation[131]. Angiotensin II increases vascular tone, upregulates inflammation, increases capillary permeability and activates clotting and profibrotic responses, whereas angiotensin (1–7) provides counter-regulatory functions to angiotensin II[132].

COVID-19 might disrupt ACE2 homeostasis via several mechanisms, and lead to a maladaptive increase in angiotensin II and a reduction of protective angiotensin (1–7). These mechanisms include direct binding to virus particles, which might reduce the bioavailability of ACE2, as well as COVID-19-mediated destruction of alveolar epithelial cells, which are a primary source of ACE2 (ref.[133]). These observations led to the hypothesis that attenuating angiotensin II activity and augmenting angiotensin (1–7) might be beneficial in COVID-19. Therapies being evaluated in RCTs include those that inhibit angiotensin II production (ACE inhibitors), inhibit angiotensin II binding to the angiotensin type I receptor (angiotensin II receptor blockers (ARBs)), accelerate conversion of angiotensin II to angiotensin (1–7) (recombinant ACE2) or activate angiotensin (1–7) signalling (investigational drugs, including TRV-027 and TXA-127). Recombinant ACE2 might confer the additional advantage of serving as a decoy for SARS-CoV-2, potentially limiting viral invasion[134].

These hypotheses are supported by observations that ACE inhibitors or ARBs mitigate the severity of acute lung injury in experimental models of COVID-19 (ref.[135]), as well as models of acute lung injury induced by sepsis, chemical aspiration, SARS-CoV-1 or ventilation[136]. Observational studies suggested that the use of ACE inhibitors and ARBs is associated with improved outcomes in pneumonia[137], influenza[138] and sepsis[139]. Among patients with COVID-19, a meta-analysis of 52 observational studies found that antecedent ACE inhibitor or ARB use was associated with improved survival[140]. By contrast, an RCT in 659 hypertensive adults hospitalized for mild or moderate COVID-19 who were already taking an ACE inhibitor or an ARB prior to hospitalization found that continuation of ACE inhibitors and ARBs resulted in a similar number of hospital-free days compared with discontinuation[141]. However, whether initiating RAAS modulators in the setting of acute COVID-19 is beneficial is unclear and is being evaluated in several RCTs. Notably, as with other COVID-19 treatments, the risk–benefit balance might depend on the stage and/or severity of COVID-19, as the potential for these agents to cause or worsen hypotension, hyperkalaemia and/or kidney impairment might increase with greater illness severity. The benefits of these therapies remain uncertain owing to the limited number of published RCTs and their modest sample sizes[142,143]. Therefore, initiating these treatments in patients with COVID-19 who do not have accepted clinical indications is not recommended outside of RCT settings.

Vitamin supplements

In addition to the COVID-19 therapeutics discussed above, the potential benefits of several vitamin and nutritional supplements — including vitamin D, nicotinamide and vitamin C — have been investigated.

Biologically active vitamin D (1,25-dihydroxyvitamin D (1,25D)) exerts immunomodulatory effects by binding to the cytoplasmic vitamin D receptor (VDR) that is expressed in T, B, and antigen-presenting cells. The 1,25D–VDR complex translocates to the nucleus, where it binds to DNA sequence elements in vitamin D-responsive genes[144]. Over 200 vitamin D target genes have been identified, including genes that encode antimicrobial peptides (for example, cathelicidin) with broad activity against a range of bacteria and viruses[145].

This established biological process, in combination with the epidemiological data linking vitamin D deficiency to adverse health outcomes across multiple clinical settings, generated enthusiasm for a potential therapeutic role for vitamin D long before the COVID-19 pandemic. However, two RCTs found that administration of high-dose vitamin D_3 did not reduce hospital length of stay or mortality compared with placebo in non-COVID-19 critically ill patients with vitamin D

Table 3 | Major COVID-19 RCTs that assessed AKI outcomes

Trial name	No. of patients	Treatment arms	Patient population	Definition of AKI	AKI outcome
Anti-inflammatory therapies					
RECOVERY (dexamethasone)[11]	6,425	Dexamethasone versus usual care	Hospitalized adults	Receipt of KRT	RR 0.61 (95% CI 0.48–0.76)
RECOVERY (tocilizumab)[19]	4,116	Tocilizumab versus usual care	Hospitalized adults	Receipt of KRT	RR 0.72 (95% CI 0.58–0.90)
RECOVERY (baricitinib)[25]	8,156	Baricitinib versus usual care	Hospitalized adults	Receipt of KRT	RR 0.78 (95% CI 0.59–1.03)
ACTT-2 (ref.[22])	1,033	Baricitinib + RDV versus placebo + RDV	Hospitalized adults	AKI or kidney failure[a]	Baricitinib + RDV: 5/507 (1.0%) Placebo + RDV: 16/509 (3.1%)
Antiviral therapies					
ACTT-1 (ref.[32])	1,048	RDV versus placebo	Hospitalized adults	GFR decreased, AKI or failure[a]	RDV: 14/532 (2.6%) Placebo: 17/516 (3.3%)
Antithrombotic therapies					
INSPIRATION[163]	562	Intermediate- versus standard-dose anticoagulation	Critically ill adults	Receipt of KRT	OR 1.49; (95% CI 0.58–3.86)
RECOVERY (Aspirin)[65]	14,892	Aspirin versus usual care	Hospitalized adults	Receipt of KRT	RR 0.99 (95% CI 0.84–1.17)
Anti-SARS-CoV-2 (neutralizing) antibody therapies					
CONCOR-1 (ref.[100])	938	Convalescent plasma versus standard of care	Hospitalized adults	Receipt of KRT	RR 0.83 (95% CI 0.31–2.27)
RECOVERY (casirivimab/imdevimab)[110]	9,785	Casirivimab/imdevimab versus usual care	Hospitalized adults	Receipt of KRT	RR 1.04 (95% CI 0.86–1.28)
Therapies targeting the RAAS					
BRACE-CORONA[141]	659	Discontinuing versus continuing ACEi/ARB	Hospitalized adults	Receipt of KRT	RR 2.0 (95% CI 0.80–5.37)

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; KRT, kidney replacement therapy; RAAS, renin–angiotensin–aldosterone system; RCT, randomized controlled trial; RDV, remdesivir; RR, relative risk. [a]Definitions not available.

deficiency[146,147]. In patients with COVID-19, an RCT conducted in 240 hospitalized adults with moderate to severe illness found that a single dose of vitamin D_3 (200,000 IU) had no effect on the length of hospital stay compared with placebo[148]. Of note, the study had several important limitations, including being underpowered[149]. The Vitamin D for COVID Trial (VIVID) is an ongoing phase III RCT that will enrol 1,880 outpatients with newly diagnosed COVID-19 to assess whether a 28-day course of vitamin D_3 improves outcomes compared with placebo[150].

Nicotinamide is a vitamin B_3 analogue that attenuates AKI in pre-clinical models through its effects on mitochondrial oxidation and prostaglandin production[151], and also attenuated AKI in a pilot RCT in adults undergoing cardiac surgery[152]. Several RCTs are currently ongoing to investigate nicotinamide for AKI prevention in various non-COVID-19 settings, including in patients undergoing aortic aneurysm repair[153] and those with septic shock[154]. In patients with COVID-19, data are more limited, although a prospective cohort study conducted in 201 hospitalized adults with COVID-19 found that administration of nicotinamide was associated with a lower risk of KRT or death compared with control individuals (HR 0.64, 95% CI 0.40–1.00)[155]. Ongoing RCTs of nicotinamide in patients with COVID-19 are investigating several outcomes, including AKI[156] and cognitive function[157].

Administration of vitamin C (ascorbic acid) has been investigated in several non-COVID-19 clinical settings, including in critically ill patients with sepsis or septic shock, given its antioxidant, anti-inflammatory and free radical scavenging properties. However, a meta-analysis of 11 RCTs concluded that use of high-dose i.v. vitamin C does not improve survival in patients with sepsis[158]. Furthermore, the 2022 LOVIT trial found that administration of i.v. vitamin C in critically ill patients with sepsis who were receiving vasopressor therapy increased the risk of death or persistent organ dysfunction at 28 days compared with placebo[159]. In the setting of COVID-19, an open-label 2 × 2 factorial RCT tested the efficacy of a 10-day course of oral vitamin C (8,000 mg) and zinc gluconate (50 mg) in non-hospitalized adults. The study was stopped early for futility after enrolling 214 patients[160]. Moreover, a pilot trial conducted in China randomly assigned 56 critically ill patients with COVID-19 to receive 24 g vitamin C daily for 7 days or placebo but the study was terminated early and found no effect of vitamin C on mortality or duration of IMV[161]. In summary, despite the interest in several vitamin supplements for the treatment of COVID-19, data to support their efficacy are currently lacking, although several RCTs are ongoing.

Conclusions

Multiple effective and safe therapeutics for COVID-19 have been developed during the past 2 years, with several agents now having been approved for use across the spectrum of disease severity. The extraordinarily rapid pace of drug development for this disease represents an incredible feat for the global scientific community. In addition to the development of direct antiviral agents and recombinant neutralizing mAbs with activity against SARS-CoV-2, anti-inflammatory, immunomodulatory, and antithrombotic agents that target the host immune

response to COVID-19 have also been introduced and have a crucial role in preventing severe illness and death. Indeed, although few direct comparisons have been performed, anti-inflammatory therapies appear to be among the most effective in improving outcomes, at least among hospitalized patients. Efforts to develop effective therapies to treat emerging novel variants of SARS-CoV-2 are also underway. In combination with mass vaccination campaigns, the development of highly efficacious therapies to treat COVID-19 has undoubtedly contributed to the lower rates of hospitalization, critical illness and death that are observed today compared with earlier stages of the pandemic[162].

Despite these impressive therapeutic advances for the general population, patients with kidney disease, including CKD or kidney failure, and kidney transplant recipients, are often excluded or underrepresented in clinical trials. This patient population is immunocompromised and often has multiple comorbidities, such as hypertension, diabetes mellitus, coronary artery disease and cancer, and is therefore at a high risk of developing severe COVID-19 and death. Accordingly, greater efforts are needed to include these high-risk populations in RCTs of COVID-19 therapeutics. Additionally, more studies are needed to understand the impact of novel and repurposed agents on the prevention and treatment of COVID-19-associated AKI, which is linked to high mortality[5]. Many of the larger RCTs investigating COVID-19 therapeutics failed to collect or report data on AKI, or only recorded whether patients received KRT (Table 3), which represents a missed opportunity.

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