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A practical update on the management of patients with COVID–19

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ABSTRACT

While vaccines against COVID-19 are being rolled out, an ongoing need remains for therapies to treat patients who have symptomatic COVID-19 before vaccination or in whom breakthrough infection develops. Dexamethasone and interleukin-6 inhibitors have been the mainstay of treatment for severe to critical COVID-19 requiring hospitalisation. However, in the previous few months, several therapies have been approved in the UK for hospitalised and non-hospitalised patients with COVID-19. In particular, the development of neutralising monoclonal antibodies and novel antivirals represents a welcome expansion in the armamentarium against COVID-19, not only therapeutically to reduce mortality but also because they can be used in mild or moderate disease to prevent hospitalisation. This update is based on guidance from NHS England as well as the World Health Organization, and provides practical support and guidance to all clinicians involved or interested in the management of COVID-19 patients, whether based in community, outpatient or inpatient settings.

KEYWORDS: COVID-19, treatments, monoclonal antibodies

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Introduction

While vaccines against COVID-19 are being rolled out, an ongoing need remains for therapies to treat patients who have symptomatic COVID-19 before vaccination or in whom breakthrough infection develops. Dexamethasone and interleukin (IL)-6 inhibitors have been the mainstay of treatment for severe to critical COVID-19 requiring hospitalisation.[1] However, in the previous few months, several therapies have been approved in the UK for hospitalised and non-hospitalised patients with COVID-19. In particular, the development of neutralising monoclonal antibodies (nMABs) and novel antivirals represent a welcome expansion in the armamentarium against COVID-19, not only therapeutically to reduce mortality but also because they can be used in mild or moderate disease to prevent hospitalisation.[2] Ronapreve (casirivimab and imdevimab) was the first monoclonal antibody to gain approval in August 2021, specifically for hospitalised patients, but is now no longer approved for use due to its lower efficacy against the Omicron variant. Sotrovimab is now the only nMAB therapy available for non-hospitalised patients who are considered to be at highest risk of progression to severe disease, hospital admission or death.[2] In January 2022, the UK Medicines Health Regulatory Authority (MHRA) also approved the use of the oral antiviral Paxlovid (nirmatrelvir (PF-07321332) and ritonavir) for patients with mild–moderate disease, which is a joint first-line agent with sotrovimab.[2] Remdesivir and molnupiravir are also recommended for use in the outpatient setting, as second- and third-line treatments, respectively.[2] For patients hospitalised with acute COVID-19 infection, baricitinib has been added to the list of recommended treatments by both NHS England (NHSE) and the World Health Organization (WHO) as an alternative anti-inflammatory to IL-6 inhibitors.[1,3] Remdesivir is also recommended for use by NHSE in this setting, but not by WHO, since evidence of its efficacy has been conflicting.[4–8]

COVID-19, in its various variant forms, is a rapidly changing landscape with new therapies becoming available in community, outpatient and inpatient settings. This update is based on guidance from NHSE as well as WHO, and provides practical support and guidance to all clinicians involved in the management of patients with COVID-19, whether they are based in primary care, local COVID-19 medicine delivery units (CMDUs) or in hospitals.[1,2,9–12] A summary schematic of treatment options now available in the different phases of COVID-19 infection is shown in Fig 1.[1,13]

Treatments for non-hospitalised patients

Several treatments are now approved in the UK for use in non-hospitalised patients at high risk of progression to severe disease, as outlined in Fig 2 and Table 1.[2] High-risk characteristics are outlined in detail in supplementary material S1 and also available in government guidance (www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report/defining-the-highest-risk-clinical-subgroups-upon-community-infection-with-sars-cov-2-when-considering-the-use-of-neutralising-monoclonal-antibodies#recommendations).[14] These include patients with Down syndrome, sickle cell disease, solid cancers, haematologic malignancy, renal disease, liver disease, immune-mediated inflammatory disorders, primary immune deficiencies, HIV/AIDS, solid-organ transplant and neurological conditions (such as multiple sclerosis, motor neurone disease, myasthenia gravis and Huntington's disease).

Both Paxlovid and sotrovimab can be used in non-hospitalised, high-risk patients as first-line agents, as clinically indicated.

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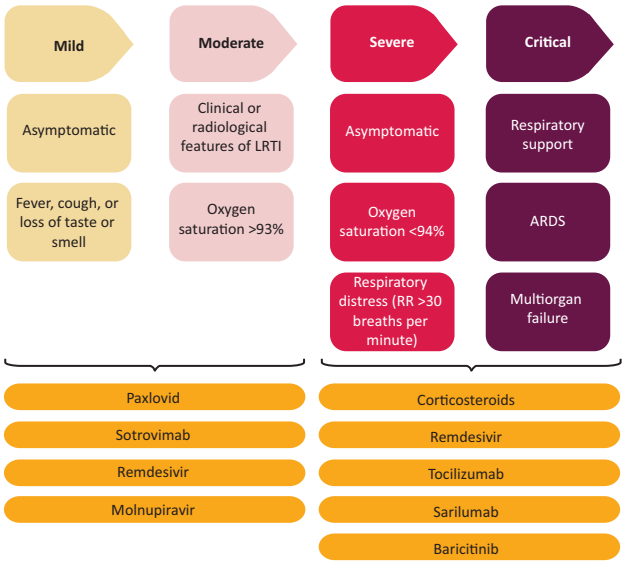

Fig 1. Spectrum of severity in COVID-19, clinical features and drugs approved for the management at each stage of infection. ARDS = acute respiratory distress syndrome; LRTI = lower respiratory tract infection; RR = respiratory rate.

Paxlovid is a combination of nirmatrelvir (PF-07321332) and a low dose of ritonavir, which disrupts the replication of SARS-CoV-2 in the body by binding to the 3CL-like protease, an enzyme crucial to the virus' function and reproduction. The EPIC-HR trial of 1,379 patients in the modified intention-to-treat population showed an 89% relative risk reduction in hospital admission or death from any cause (when given within 3 days of symptom onset) and 88% reduction when given within 5 days of symptom onset.[15] Paxlovid cannot be used in pregnancy, patients aged <18 years old, or in those with chronic kidney disease (CKD) stage 4–5, on dialysis and with advanced decompensated liver cirrhosis. In CKD stage 3, Paxlovid may be used with a dose adjustment. As a CYP3A inhibitor, the use of Paxlovid also carries a risk of serious adverse reactions due to interactions with other medicinal products. Many of these drugs are commonly prescribed in the following groups: statins, anticoagulants, inhalers for asthma and chronic obstructive pulmonary disease (COPD), antiepileptics, hormonal contraception, immunosuppressants and chemotherapy, as well as several other classes of drugs. This underscores the importance of checking for drug interactions in a systematic way. A COVID-19 drug interaction checker has been developed in order to aid clinicians assessing patients for eligibility and an exhaustive list of drugs that may interact with Paxlovid is provided in the NHSE guidance.[2,16] Chemotherapy agents are often not found in the drug interaction checkers and will require further thought and discussion with the relevant specialist pharmacist.

Sotrovimab is an immunoglobulin (Ig) G1-kappa monoclonal antibody that acts by binding an epitope located on the spike protein receptor-binding domain of SARS-CoV-2, which in turn is necessary for entry into human cells. It has been approved for use in the UK in non-hospitalised patients with mild–moderate COVID-19 and at an increased risk of developing severe disease. In a seminal study investigating the use of sotrovimab in 583 non-hospitalised symptomatic patients (<5 days) with at least one risk factor, 1% of patients in the sotrovimab group, compared with 7% in the placebo group, had disease progression leading to hospitalisation or death (relative risk reduction 85%; p=0.002).[17] No statistically significant difference in adverse events was noted between the two groups. However, there are concerns that sotrovimab is less effective at binding and neutralising the Omicron BA.2 variant and, in the USA, it is no longer authorised to treat COVID-19 in any region as BA.2 becomes the dominant

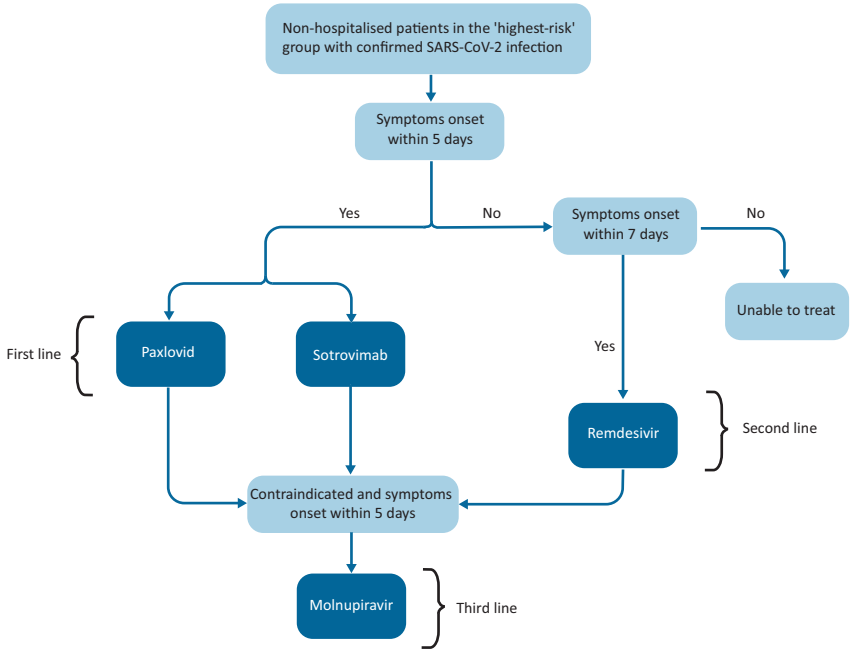

Fig 2. Pathway for the management of non-hospitalised patients with mild–moderate COVID-19. Refer to Table 1 for contraindications and full eligibility criteria.

Table 1. Drugs used to treat COVID-19: doses, eligibility criteria and contraindications or cautions

Medication	Route	Dose	Indication	Contraindications
Dexamethasone	Oral or IV	6 mg OD for up to 10 days	PCR-confirmed infection. Features of severe or critical COVID-19 (Fig 1).	Avoid live virus vaccines. Systemic infection (unless specific therapy is given). Use with caution in a patient with coexisting heart failure, diabetes mellitus, diverticulitis, epilepsy, glaucoma, steroid myopathy, tuberculosis, hypertension, hypothyroidism, peptic ulcers, psychiatric reactions, recent intestinal anastomosis, recent myocardial infarction, severe affective disorders, thromboembolic disorders or ulcerative colitis.
Tocilizumab	IV	8 mg/kg (max dose 800 mg) stat dose	Hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support and CRP >75 ng/mL. Within 48 hours of respiratory support (high-flow nasal oxygen, CPAP, NIV or IMV) regardless of CRP level.	Children aged under 12 years old. Patients weighing less than 40 kg. Known hypersensitivity reaction to tocilizumab. Caution if: › co-existing infection which might be worsened by IL-6 inhibitor therapy › baseline ALT or AST >5 times the upper limit of normal › pre-existing condition or treatment resulting in immunosuppression. Not to be used in pregnancy unless clinically necessary.
Sarilumab	IV	400 mg stat dose	As per tocilizumab. To be considered if tocilizumab is not available.	As per tocilizumab plus: › platelets <150 x 10^9/L › known hypersensitivity reaction to sarilumab.
Baricitinib	Oral	4 mg OD for up to 14 days	Requiring respiratory support (high-flow nasal oxygen, CPAP, NIV or IMV). To be given as an alternative to tocilizumab or sarilumab.	Lymphocyte count <0.5 x 10^9/L. Neutrophil count <1 x 10^9/L. Haemoglobin less than 8 g/dL. Active tuberculosis.
Remdesivir	Oral	200 mg loading dose followed by 100 mg OD for 3 days with mild–moderate disease and for 5 days with severe disease.	Onset of symptoms within 7 days (outpatient) or 10 days (hospitalised due to COVID-19). On low-flow supplemental oxygen.	Children aged under 12 years. Patients weighing less than 40 kg. eGFR <30 mL/min (unless known end-stage renal failure or dialysis). ALT >5 times the upper limit of normal.
Paxlovid	Oral	300 mg nirmatrelvir (PF-07321332) and 100 mg ritonavir BD for 5 days	Adults who do not require supplemental oxygen and are at increased risk for progression to severe COVID-19. Onset of symptoms within 5 days.	Children aged under 18 years. Severe renal or hepatic impairment. Pregnancy. Hypersensitivity to the active substances (nirmatrelvir (PF-07321332) or ritonavir). Concomitant use of drugs highly dependent on CYP3A for clearance or potent inducers of CYP3A, eg amiodarone, apixaban, rivaroxaban, dabigatran, warfarin, clopidogrel, simvastatin, rosuvastatin, digoxin and phenytoin.
Molnupiravir	Oral	800 mg BD for 5 days	Aged ≥18 years. PCR-confirmed infection within 5 days. Onset of symptoms within 5 days. Member of the 'highest-risk' group.	Pregnancy. Breastfeeding (to be interrupted during treatment and resumed 4 days after last dose).

Table 1. Drugs used to treat COVID-19: doses, eligibility criteria and contraindications or cautions (Continued)

Medication	Route	Dose	Indication	Contraindications
Sotrovimab	IV	500 mg stat dose	PCR-confirmed infection within 5 days. Onset of symptoms within 5 days. Member of the 'highest-risk' group	Children aged under 12 years. Patients weighing less than 40 kg. A pattern of illness that suggests recovery rather than risk of deterioration. Likely to require hospitalisation in the next 24 hours. Requiring supplemental oxygen for the management of COVID-19 symptoms or increase in baseline oxygen flow rate due to COVID-19. Known hypersensitivity reaction to sotrovimab.

ALT = alanine transaminase; AST = aspartate aminotransferase; BD = twice daily; CPAP = continuous positive airways pressure; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; NIV = non-invasive ventilation; OD = once per day.

sub-variant.[18] The MHRA is reviewing its position of sotrovimab and the guidance may change in the near future.

In the UK, sotrovimab is delivered by CMDUs. Commonly reported side effects include diarrhoea and hypersensitivity reactions. Administration should also be under conditions where management of hypersensitivity, including anaphylaxis, is possible.

Pre-hospitalised patients are eligible for treatment with sotrovimab if they:

- have PCR-confirmed SARS-CoV-2 infection or positive lateral flow test (LFT) within 5 days
- have onset of symptoms of COVID-19 within 5 days
- are a member of the 'highest-risk' group.[2]

Exclusion criteria are detailed in Table 1 but, importantly, if a patient is displaying a pattern of illness that suggests recovery or, conversely, is likely to require hospitalisation in the next 24 hours, then they should not receive treatment with sotrovimab.

When sotrovimab and Paxlovid cannot be administered because they are contraindicated, eligible patients can be considered for treatment with remdesivir.[2]

Remdesivir is an adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate that inhibits SARS-CoV-2 RNA polymerase and disrupts viral replication. Both NHSE and WHO support its use in non-hospitalised patients following recent data from 562 patients that showed an 87% risk reduction in hospitalisation or death from COVID-19 compared with a placebo.[4] Treatment is intravenously for 3 days, administered within 7 days of symptom onset, providing the exclusion criteria are not met (Table 1).

Molnupiravir is the third-line treatment option for patients. This is an oral antiviral that acts by increasing the frequency of viral RNA mutations and, therefore, inhibiting SARS-CoV-2 replication. In a study of 1,433 patients, the risk of hospitalisation for any cause or death by day 29 was lower with molnupiravir (7.3%) than with placebo (14.1%; p=0.001).[19]

Molnupiravir may be administered if a patient fulfils the following criteria:

- aged ≥18 years old
- PCR-confirmed SARS-CoV-2 infection or positive LFT within 7 days
- symptomatic for <7 days
- not pregnant
- a member of the 'highest-risk' group.[2]

Commonly reported side effects of molnupiravir (>1 in 100) include diarrhoea, nausea, dizziness and headache. Molnupiravir is not recommended during pregnancy, and women of child-bearing potential should be advised on use of effective contraception during treatment and 4 days after the last dose. Breastfeeding should be interrupted during treatment and should resume 4 days after the last dose. These recommendations follow laboratory studies in animals showing that molnupiravir can cause developmental delay in fetuses.

Approved treatments for hospitalised patients

Several options for treatment are now available to those with severe COVID-19 requiring hospitalisation (Fig 3 and Table 1). Dexamethasone and IL-6 inhibitors have been in use for several months and will be discussed briefly, both targeting the inflammatory response that accompanies severe infection and leads to hypoxaemic respiratory failure.

As per the REACT meta-analysis aggregating seven randomised controlled trials (RCTs), including the RECOVERY and REMAP-CAP trials, dexamethasone is now the standard of care in all patients with severe–critical COVID-19 requiring supplemental oxygen therapy or other features of respiratory distress.[12,20–22]

IL-6 inhibitors (tocilizumab and sarilumab) have also been approved for use for severe–critical COVID-19.[10] IL-6 is released in response to infection and stimulates inflammatory pathways as part of the acute-phase response. Tocilizumab and sarilumab are monoclonal antibodies that inhibit both membrane-bound and soluble IL-6 receptors and dampen the inflammatory response in COVID-19. Promising data supporting their use came from the REMAP-CAP and RECOVERY trials with significant reduction in organ-free support at 21 days or mortality at 28 days, respectively.[23,24] IL-6 inhibitors have been approved for use specifically when either:

- there is hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support and C-reactive protein (CRP) >75 ng/mL
- patients are within 48 hours of respiratory support (high-flow nasal oxygen, continuous positive airway pressure, non-invasive

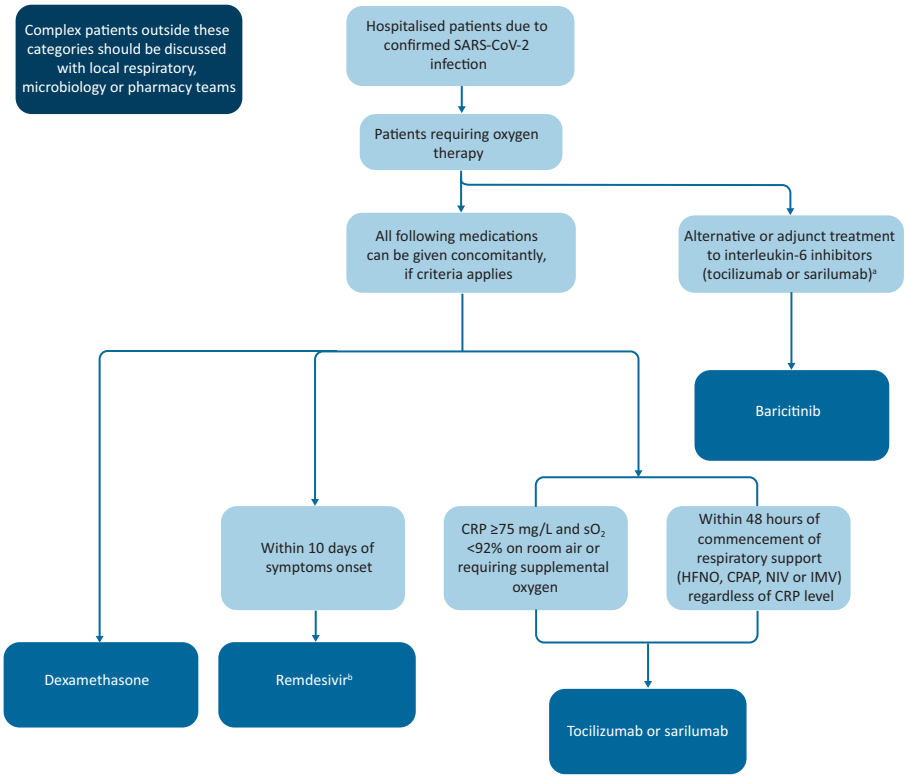

Fig 3. Pathway for the management of patients admitted for the acute symptoms of COVID-19 pneumonia. Refer to Table 1 for contraindications and full eligibility criteria. [a]Not to be used simultaneously with interleukin-6 inhibitors except in life-threatening disease. [b]Remdesivir is a recommendation made in NHS guidelines but not the World Health Organization guidelines. ALT = alanine transaminase; AST = aspartate aminotransferase; CPAP = continuous positive airways pressure; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HFNO = high-flow nasal oxygen; IMV = invasive mechanical ventilation; NIV = non-invasive ventilation; sO_2 = oxygen saturation.

ventilation, or invasive mechanical ventilation) regardless of CRP level.[10]

It is important to consider whether patients have a co-existing bacterial infection that may be worsened by IL-6 inhibitor therapy. A procalcitonin assay may be helpful as part of the assessment.

Remdesivir also now appears on the NHSE guidance for the management of patients with COVID-19 requiring low-flow supplemental oxygen therapy within 10 days of symptom onset and there are no contraindications to its use. Treatment is for 5 days, except for those who a severely immunocompromised where treatment can be extended to 10 days.[11] Evidence supporting its use comes from the ACTT-1 trial, which showed that remdesivir improved time to recovery in patients hospitalised with COVID-19 by 5 days compared with a placebo.[6] However, data from other trials are conflicting; the WHO Solidarity trial indicated that remdesivir did not improve overall mortality, initiation of ventilation or duration of hospitalisation.[8] Therefore, remdesivir does not feature in the WHO guidance for the management of patients hospitalised due to COVID-19.

Baricitinib is an oral selective Janus kinase 1/2 inhibitor with anti-inflammatory properties. It has recently been recommended for use as an alternative to IL-6 inhibitors for severe–critical COVID-19. The RECOVERY trial of 8,156 patients randomly allocated to receive either baricitinib or placebo in conjunction with the standard of care drugs (dexamethasone, tocilizumab and remdesivir), showed that treatment with baricitinib significantly reduced deaths at 28 days with a relative reduction of 13% (age-adjusted rate ratio 0.87; 95% confidence interval (CI) 0.77–0.98; p=0.026).[25] Baricitinib, like tocilizumab and sarilumab, should be used in conjunction with dexamethasone. NHSE suggests that the use of baricitinib in the treatment of COVID-19 should be considered as 'additive' to the use of an IL-6 inhibitor (tocilizumab or sarilumab) rather than an alternative. A patient may, therefore, be given an IL-6 inhibitor after treatment with baricitinib has been commenced (or vice versa), according to clinical judgement. Baricitinib should not routinely be given simultaneously with an IL-6 inhibitor except for a life-threatening disease requiring critical care support when clinical judgement may consider this necessary.[3]

There are no available nMABs for patients admitted with COVID-19 pneumonia since this class of drug is now reserved for those with early mild–moderate disease in order to prevent the need for hospitalisation and supplemental oxygen requirement.

Nosocomial acquisition of COVID-19

Patients who acquire COVID-19 infection after hospitalisation for the management of other conditions may require treatment if they are symptomatic for COVID-19, they are a member of the 'highest-risk' group, or COVID-19 might compromise their recovery from a pre-existing illness or procedure. The following are considered symptoms of COVID-19: fever, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhoea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomachache, rash, sneezing, sputum or phlegm, and runny nose.

In this setting, the first line of treatment is Paxlovid delivered within 5 days of symptom onset. If treatment with Paxlovid is not possible, second-line treatment is with remdesivir within 7 days of symptom onset. Sotrovimab is a third-line therapy when given within 5 days of symptom onset (Fig 4 and Table 1). Where

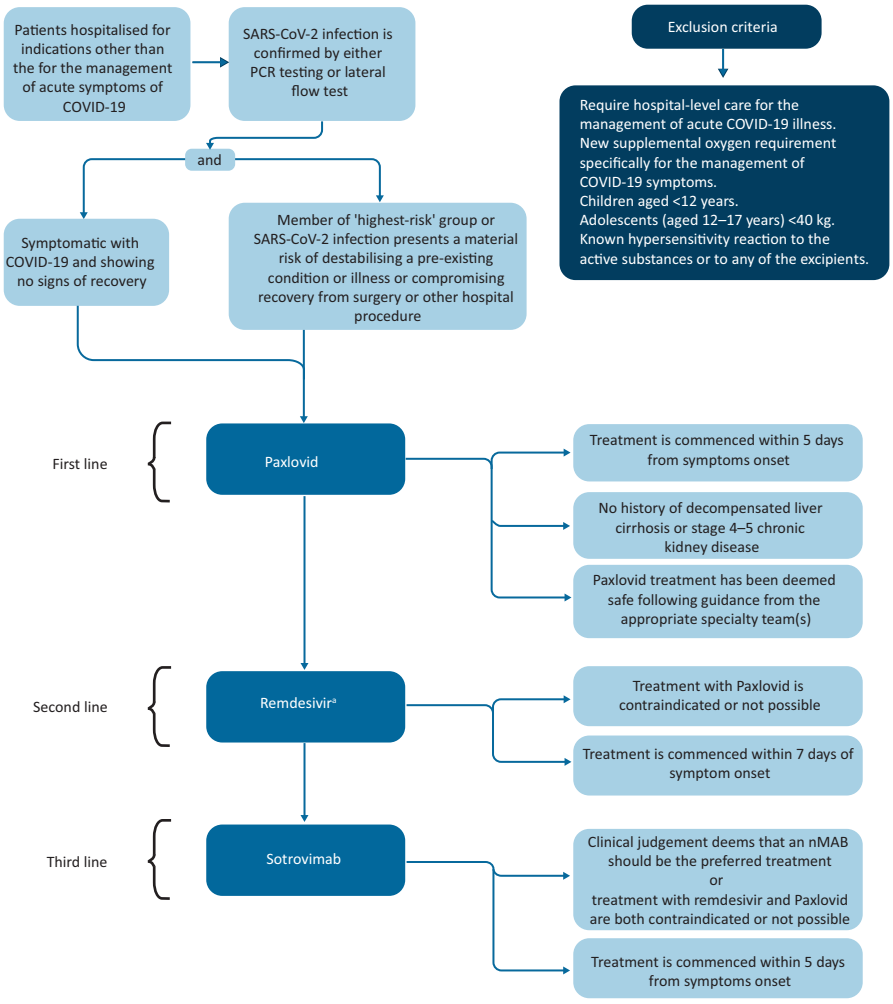

Fig 4. Pathway for the management of patients who acquire COVID-19 in hospital. Refer to Table 1 for contraindications and full eligibility criteria. [a]Remdesivir is a recommendation made in NHS guidelines but not the World Health Organization guidelines. nMAB = neutralising monoclonal antibody.

possible, all patients being considered for treatment with antivirals or nMABs should have samples taken for serology (anti-spike antibody) prior to treatment.

Those acutely unwell requiring supplemental oxygen specifically for the management of COVID-19 should continue to receive dexamethasone, IL-6 inhibitors, remdesivir and baricitinib if they meet the eligibility criteria. Patients who are asymptomatic or improving from COVID-19 infection do not require treatment.

Conclusion

The recent approval of sotrovimab for use in non-hospitalised patients, together with Paxlovid, remdesivir and molnupiravir, are important developments in the fight against COVID-19. Their rapid provision and delivery have the potential to reduce hospitalisations, severe disease and death, while also reducing pressure on other NHS services. The therapies available for the treatment of hospitalised patients have become increasingly complex. We hope this rapid update provides useful guidance on the management of COVID-19 to physicians across the healthcare spectrum.

Key points

- Sotrovimab, Paxlovid, remdesivir and molnupiravir has been approved for non-hospitalised, high-risk patients with mild–moderate COVID-19.
- In addition to dexamethasone and IL-6 inhibitors, patients hospitalised with COVID-19 can be treated with remdesivir and baricitinib.
- Patients who acquire COVID-19 during their hospital admission and are high risk for further deterioration can be treated with Paxlovid, remdesivir or sotrovimab. ■

Supplementary material

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:
S1 – List of conditions that place patients in the 'high-risk' group for deterioration with COVID-19.

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