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RAPID RECOMMENDATIONS

Remdesivir for severe covid-19: a clinical practice guideline

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ABSTRACT

CLINICAL QUESTION

What is the role of remdesivir in the treatment of severe covid-19? This guideline was triggered by the ACTT-1 trial published in the *New England Journal of Medicine* on 22 May 2020.

CURRENT PRACTICE

Remdesivir has received worldwide attention as a potentially effective treatment for severe covid-19. After rapid market approval in the US, remdesivir is already being used in clinical practice.

RECOMMENDATIONS

The guideline panel makes a weak recommendation for the use of remdesivir in severe covid-19 while recommending continuation of active enrolment of patients into ongoing randomised controlled trials examining remdesivir.

HOW THIS GUIDELINE WAS CREATED

An international panel of patients, clinicians, and methodologists produced these recommendations in adherence with standards for trustworthy guidelines using the GRADE approach. The recommendations are based on a linked systematic review and network meta-analysis. The panel considered an individual patient perspective and allowed contextual factors (such as resources) to be taken into account for countries and healthcare systems.

THE EVIDENCE

The linked systematic review (published 31 Jul 2020) identified two randomised trials with 1300 participants, showing low certainty evidence that remdesivir may be effective in reducing time to clinical improvement and may decrease mortality in patients with severe covid-19. Remdesivir probably has no important effect on need for invasive mechanical ventilation. Remdesivir may have little or no effect on hospital length of stay.

UNDERSTANDING THE RECOMMENDATION

Most patients with severe covid-19 would likely choose treatment with remdesivir given the potential reduction in time to clinical improvement. However, given the low certainty evidence for critical outcomes and the fact that different perspectives, values, and preferences may alter decisions regarding remdesivir, the panel issued a weak recommendation with strong support for continued recruitment in randomised trials.

As of July 2020, more than 15 million people worldwide have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and covid-19 has led to more than 600 000 deaths.[1] No specific therapeutic agent had demonstrated efficacy in treating patients with covid-19 until recently. This is reflected in multiple clinical practice guidelines that almost exclusively recommend supportive therapy alone, outside the context of a clinical trial.[2-4] Remdesivir is a novel monophosphoramidate adenosine analogue prodrug that impedes viral RNA synthesis and has in vitro antiviral activity against several viral agents.[5] Two recently published clinical practice guidelines have addressed remdesivir, both with recommendations for administration (table 1).[6,7]

Table 1 | Current guidelines on use of remdesivir for treating covid-19

Guideline	Recommendation
US National Institutes of Health	Strong recommendation in favour of remdesivir for severe covid-19
Up to Date	Weak recommendation in favour of remdesivir for severe covid-19
Australian National Guidelines	Weak recommendation in favour of remdesivir for severe covid-19

This clinical practice guideline was triggered by publication of the ACTT-1 randomised controlled trial (RCT) of remdesivir in the *New England Journal of Medicine* on 22 May 2020, which reported a reduction

This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

in time to recovery from severe covid-19 among those patients randomised to remdesivir compared with those randomised to placebo, but did not find important differences in mortality or need for ventilation.[8]

The covid-19 pandemic—which can also be characterised as an infodemic, given the explosion of research combined with misinformation and hoaxes—has demonstrated a need for trustworthy, accessible, and regularly updated guidance[9] to place emerging findings into context and give clear recommendations for clinical practice. This guideline is based on a living network meta-analysis tracking the development of evidence from randomised controlled trials.[10] This living review will continuously search for and rapidly incorporate new evidence into the network meta-analysis. As the living network meta-analysis is updated with new evidence about different treatments and patient populations, guidelines addressing other interventions, such as dexamethasone will follow. This *BMJ* Rapid Recommendation represents the first in a series of recommendations for the management of covid-19 (box 1). The main infographic provides an overview of the effects of remdesivir on severe covid-19.

Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster

- Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. *BMJ* 2020;370:m2924
  - Summary of the results from the Rapid Recommendation process
- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
  - Review and network meta-analysis of all available randomised trials that assessed drug treatments for covid-19
- MAGICapp (https://app.magicapp.org/#/guideline/j1W7rn)
  - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Although the incremental value of the network meta-analysis over a simple direct comparison of remdesivir and control is at this point limited because the network is sparse, as new trials are reported its value will grow. The guideline was developed using the GRADE approach with the objective of providing clinicians, patients and other stakeholders with guidance for the use of remdesivir in patients with severe covid-19 (see box 2).

Box 2: How these recommendations were developed

The covid-19 pandemic has demonstrated a need for trustworthy, accessible, and continually updated guidance. This has triggered the MAGIC Evidence Ecosystem Foundation to focus their *BMJ* Rapid Recommendations on covid-19, starting with treatments that hold the potential to change clinical practice, informed by a living systematic review and network meta-analysis. The recent publication of a randomised controlled trial comparing remdesivir with placebo in patients with covid-19 triggered this guideline.[8] The Rapid Recommendations team felt that the results of this study, interpreted in the context of existing evidence, might change practice.

Our international panel was selected to maximise multidisciplinary and regional representation—including covid-19 survivors, intensivists, internists, infectious disease specialists, public health specialists, family physicians, pharmacists, and methodologists (see appendix 2 on bmj.com for details). The panel decided on the scope of the recommendation and the outcomes that are most important to patients. The panel met to discuss the evidence and formulate a recommendation. No panel member had any relevant financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 3 on bmj.com). The World Health Organization (WHO) advised in recruiting panel experts to ensure regional representation, gender balance, and appropriate technical expertise as well as patient representation, according to their criteria. This contribution reflects a plan from the WHO to use the MAGIC platform and *BMJ* Rapid Recommendations, among other sources, to inform their own covid-19 guidance.

The panel followed the *BMJ* Rapid Recommendations procedures for developing trustworthy guidelines[9 12] with standards, methods, and processes as detailed in MAGICapp (https://app.magicapp.org). The panel applied the GRADE approach to critically appraise the evidence and create recommendations.[13] The panel considered the balance of benefits, harms, and burdens of remdesivir, the quality of the evidence for each outcome, typical and expected variations in patient values and preferences, and acceptability.[14] Recommendations can be strong or weak, for or against a course of action.

Visual summary of recommendation

Population

This recommendation applies only to people with these characteristics:

Disease severity

Mild | Moderate | Severe

Does not apply to:

- ✖ Patients with mild or moderate covid-19
- ✖ Pediatric patients

Applies to people with at least one of:

- ✔ Respiratory rate >30
- ✔ Respiratory distress
- ✔ SpO_2 <94% on room air
- ✔ Requires intensive care admission

Resource limited settings

Remdesivir is a new drug with uncertain benefits and undetermined cost-effectiveness, not yet approved for marketing or reimbursed for use in many countries. The significant opportunity costs and potential to exacerbate existing health inequities in resource-limited settings may well justify policy decisions not to offer remdesivir to patients until more conclusive evidence is available

Recommendation 1

Usual supportive care		Remdesivir
No remdesivir	or	100 mg intravenously daily for 5-10 days
Strong / Weak		Weak / Strong

We suggest remdesivir rather than no remdesivir in patients with severe covid-19

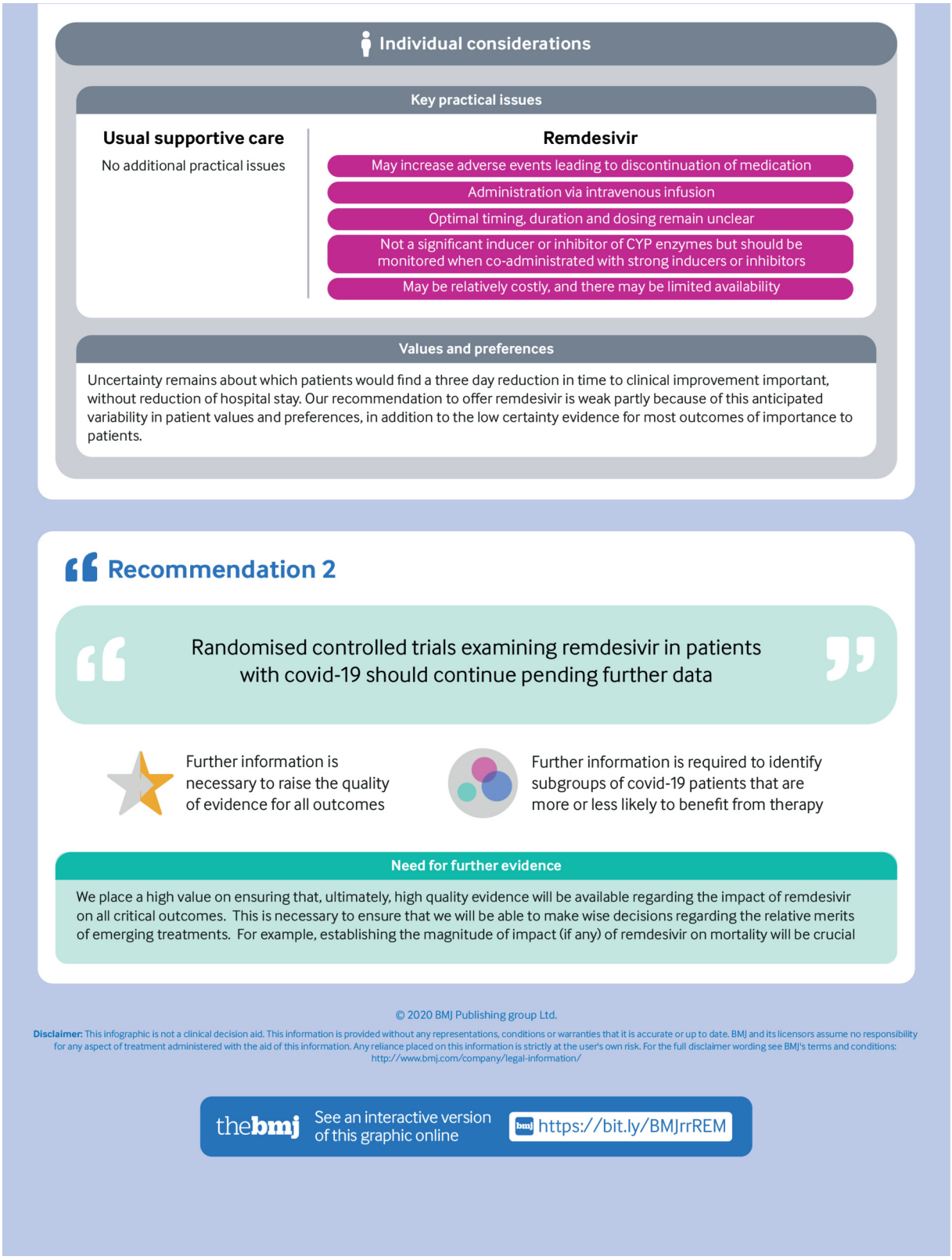
Evidence profile

Usual supportive care | No important difference | Remdesivir

	Events per 1000 people			Evidence quality
Mortality	330	85 fewer	245	★★☆☆ Low
Mechanical ventilation risk	116	No important difference	119	★★☆☆ Low
Serious adverse events	80	19 fewer	99	★★☆☆ Low

	Median days			Evidence quality
Hospitalisation duration	24	No important difference	25	★★☆☆ Low
Mechanical ventilation duration	16	4 lower	7	★★☆☆ Low

	Mean days			Evidence quality
Time to clinical improvement	19	3 lower	16	★★☆☆ Low
Length of stay in intensive care	Not measured			



The evidence

To date, two RCTs have evaluated remdesivir versus placebo in severe covid-19 (fig 2).[8 11] The study by Wang et al enrolled 237 patients in China, all with severe disease, of whom 16.1% were critically ill at baseline.[11] The ACTT-1 trial enrolled 1063 patients across 13 countries including those in North America, Europe, and Asia.[8] Most of these patients experienced severe disease, but the trial also included some (11.9%) with mild/moderate disease. Both trials evaluated remdesivir given intravenously at a dose of 100 mg per day for 10 days. Gilead Sciences, the manufacturer of remdesivir, provided the drug free for both trials and was involved in protocol

development in the ACTT trial. Patients in both trials were randomised approximately 9-11 days after initial symptom onset and were predominantly male (60-65%) with a mean age between 58 and 65 years old. These two trials together addressed the critical outcomes for treatment of covid-19 as defined by the panel, including mortality, mechanical ventilation, time to clinical improvement, duration of hospitalisation, and adverse events related to drug administration.

Fig 2 | Characteristics of patients and trials included in systematic review of effects of remdesivir for severe covid-19

We included data from both trials in the network meta-analysis[10] to generate pooled estimates of effect (see main infographic for summary of findings). For outcomes in which the networks were too sparse to generate trustworthy effect estimates (need for and duration of mechanical ventilation, time to clinical improvement), we generated pooled estimates based on direct pairwise meta-analysis. We used the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) dataset,[15] prospectively collected data from over 15 000 hospitalised patients with covid-19 from 36 countries, to calculate the baseline risk for outcomes of mortality (33%) and mechanical ventilation (11.6%). The baseline risk from the ISARIC data was then used, along with the pooled relative risk from the network meta-analysis, to calculate the absolute effect estimates presented in our evidence summaries. We generated baseline risk for the other outcomes of interest based on the control arms of the two included trials.

Remdesivir may decrease mortality (network meta-analysis odds ratio 0.66 (95% confidence interval (CI) 0.40 to 1.14), absolute effect estimate 8.5% reduction (95% CI 16.5% reduction to 3.0% increase)), but this is based on low certainty evidence with very serious imprecision.

Remdesivir may reduce time to clinical improvement (mean difference 3.04 days fewer (0.89 to 5.19 days fewer), mean in supportive care group 19 days, mean in remdesivir group 16 days); this result also has low certainty due to imprecision and indirectness. Clinical improvement was measured using an ordinal scale, in which the importance of individual components varies (see appendix 1 on bmj.com for the ordinal scales and definitions for clinical improvement used by both studies). In general, both studies used similar definitions and ones that would probably be consistent with what patients or clinicians would expect (that is, no longer requiring life support, no longer requiring oxygen therapy, no longer requiring hospitalisation). However, we did still lower the certainty in this outcome for indirectness, as not all aspects of clinical improvement (such as symptom resolution and functional status) were considered. The panel concluded that a three day reduction in time to clinical improvement would likely be important to most individuals; however, as the clinical importance of the individual components of the scale vary, the overall interpretation of this outcome remains somewhat uncertain.[16 17]

Remdesivir may have little to no effect on risk for mechanical ventilation (network meta-analysis odds ratio 1.03 (0.50 to 2.13), absolute effect estimate 0.3% more (5.4% fewer to 10.2% more), low certainty), or duration of hospitalisation (mean difference 0 days fewer (4 days fewer to 4 days more), low certainty). Decisions regarding discharge may not track closely with clinical improvement: Wang et al reported no difference in the duration of hospitalisation,[11] and the ACTT-1 trial did not report hospital duration.[8]

Remdesivir may increase the risk of serious adverse events leading to drug discontinuation (network meta-analysis odds ratio 1.26 (0.52 to 3.94), absolute effect estimate 1.9% more (3.7% fewer to 17.5% more), low certainty).

Wang et al[11] reported that those who received remdesivir within 10 days of symptom onset may have benefited most in terms of time to clinical improvement; however, the credibility of this subgroup hypothesis is low as this analysis was not pre-specified and chance can easily explain the apparent difference between subgroups. The ACTT trial suggested that those requiring mechanical ventilation may have benefited less from remdesivir.[8] However, this subgroup analysis was also of low credibility given the hypothesised direction of effect were not specified a priori; it was one of seven subgroup hypotheses examined in the trial (increasing the likelihood the findings were due to chance alone); and chance can easily explain the apparent difference between subgroups.

Understanding the recommendations

- *Recommendation No 1*—We suggest remdesivir rather than no remdesivir for the treatment of patients with severe covid-19 infection (weak recommendation).
  - The panel made its recommendation on the basis of the low certainty evidence of a modest reduction in time to clinical improvement and no effect on duration of hospitalisation. We made this recommendation despite an uncertain impact on survival. Following GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidance, a weak recommendation implies that most patients with severe covid-19 infection would choose to take remdesivir; a minority will, depending on individual shared decision making, decline. The panel was reassured that the risk for adverse effects with remdesivir seems minimal (4 out of 1063 patients randomised in the ACTT trial, 2 in each group, had severe adverse events judged to be secondary to remdesivir or placebo), although a full safety analysis will require documentation of adverse effects in much larger numbers of patients.[18] Potential adverse events associated with remdesivir include hyperglycaemia, liver dysfunction, and renal failure. Administration of remdesivir should always be in addition to, and not instead of, routine supportive therapy.
- *Recommendation No 2*—Randomised controlled trials examining remdesivir in patients with covid-19 should continue.
  - Although the panel made a weak recommendation for remdesivir, uncertainty regarding any mortality benefit, possible reduction in hospitalisation, and the magnitude of any benefit in time to clinical improvement can only be resolved by continuing enrolment in RCTs examining remdesivir in comparison with placebo or usual care for patients with severe covid-19 (See box 3). Clarification of the benefits and harms of remdesivir is even more important in economically constrained hospital systems.

Box 3: Future research priorities

Key research questions to inform decision makers and future guidelines are:

- Low certainty evidence suggests 10 days of remdesivir treatment may improve time to clinical improvement. Larger scale RCTs must clarify effects on time to clinical improvement and further evaluate the safety of remdesivir and its effects on other patient-important outcomes such as mortality, need for invasive mechanical ventilation, duration of hospitalisation, and quality of life
- If remdesivir is to be used in patients with severe covid-19, what is the optimal dose, time of starting treatment, and duration of therapy? Is it best given alone or in combination with other interventions?
- Are there specific subgroups of patients most likely to receive benefit with remdesivir therapy?

Who does it apply to?

Recommendation 1 applies to all adult patients with severe confirmed covid-19. As criteria for hospitalisation vary among jurisdictions, we anchored our definition of severe infection to the initial WHO criteria, which specifies one or more of respiratory rate

>30 breaths per minute, respiratory distress, or SpO2 <94% on room air.[19] In most treatment centres, need for hospitalisation or oxygen therapy are reasonable surrogates for severe covid-19. However, as some centres have admitted less sick patients with covid-19 (even those not requiring oxygen therapy) or don't have the ability to provide oxygen therapy, the panel was more comfortable using objective clinical criteria in order to maximise applicability.

The panel's plan to address several subgroups—including (*a*) critically ill versus non-critically ill, (*b*) early initiation of remdesivir versus later initiation, and (*c*) patients with evidence of pneumonia not requiring oxygen versus those requiring supplemental oxygen—proved unfeasible because of lack of informative data. The subgroup findings from the two trials were deemed of very low credibility, and the panel based recommendations on the entire population with severe covid-19.

Values and preferences

We did not perform a systematic review of patient values and preferences for this guideline and therefore views expressed are those of the panel members, which included covid-19 survivors and patient partners. As with other Rapid Recommendations, the panel took an individual patient perspective to values and preferences. The panel felt that uncertainty remains regarding the extent to which patients would find a three day reduction in time to clinical improvement, in the absence of reduction in hospital stay, important. This anticipated variability in patients' values and preferences, combined with the low certainty evidence for most outcomes, resulted in a weak recommendation to offer remdesivir to patients.

Resource considerations

The panel also considered the impact of resource allocation in economically constrained health systems when generating this recommendation, a perspective in which widespread provision of novel therapies for covid-19 may require higher quality evidence of important benefits. Resource constrained environments exist in low and middle income countries, as well as, to varying degrees, in high income countries. In such environments, opportunity costs—that is, drawing resources away from alternative, perhaps more worthwhile, expenditures—become a particularly salient concern. This is especially relevant in covid-19, as even centres in high resource settings may experience resource constraints with diversion of time, funds, attention, and workforce during a pandemic surge.

Guidance for remdesivir also has implications for priority setting in health systems with limited resources, as the opportunity cost of remdesivir may be associated with exacerbation of health inequities. Under these circumstances, widespread use may indeed be unwise. Some on the panel were sufficiently worried about this contribution to health inequities, an issue magnified by the covid-19 pandemic, as to consider only recommending remdesivir in the context of clinical trials. Ultimately, however, the panel achieved consensus regarding a weak recommendation in favour.

Practicalities

Some practicalities in the administration of remdesivir may limit its use. To date, it can only be administered intravenously, and it is relatively costly with, at least for now, limited availability. Remdesivir is contraindicated in patients with liver dysfunction (alanine aminotransferase >5 × normal at baseline) or renal dysfunction (Estimated glomerular filtration rate <30 mL/minute). See fig 3 for other issues related to practicalities.

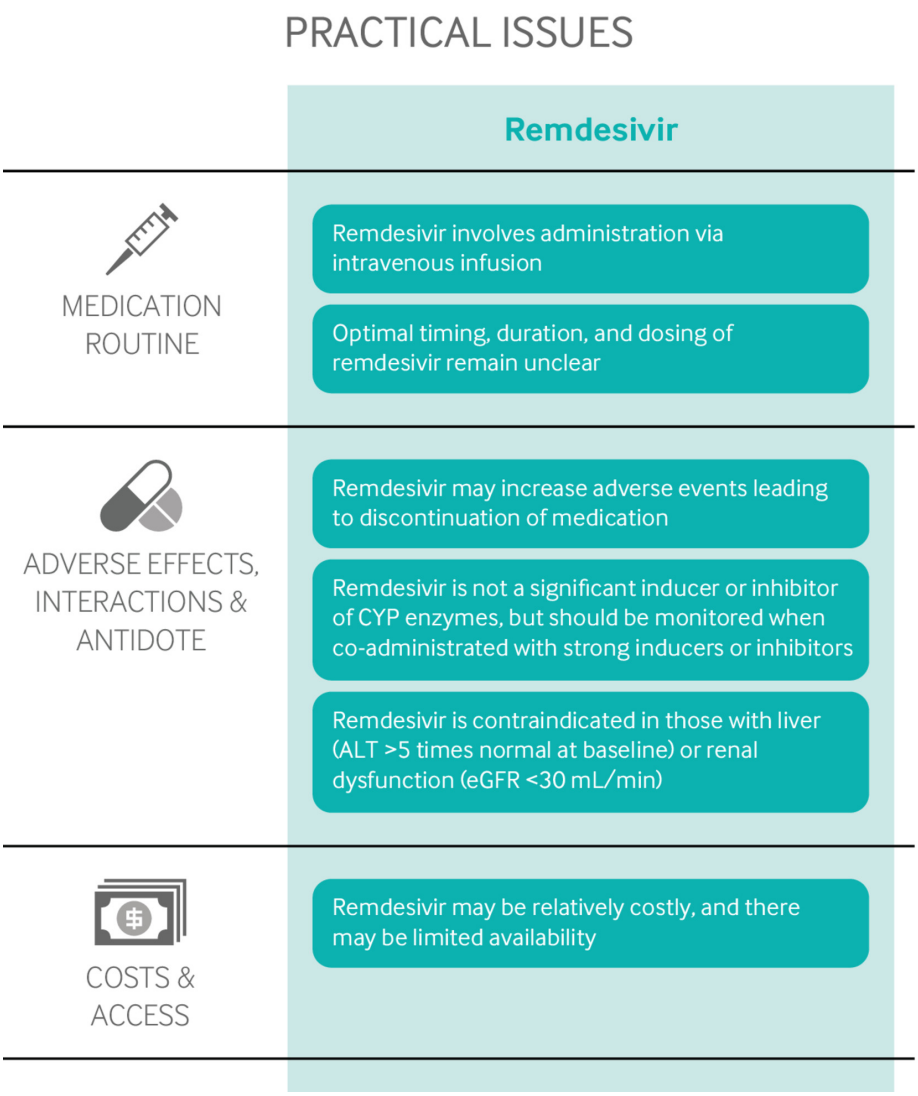


Fig 3 | Practical issues about use of remdesivir for patients with severe covid-19

Ongoing uncertainty

Important uncertainties remain, including:

- The impact of remdesivir on mortality
- The effect of remdesivir on time to clinical improvement, duration of hospitalisation, and long term morbidity
- The effect of remdesivir in combination with other agents
- The optimal timing of drug initiation, dose, and duration of remdesivir. A recently completed RCT compared a 10 day course versus a five day course of remdesivir and found no difference in patient-important outcomes,[20] but the trial had important methodological limitations
- Whether there are specific subgroups of patients with covid-19 who may benefit more or less from remdesivir
- Generalisability of study results to other regions and populations
- The long term safety of remdesivir
- The impact of remdesivir on patient-reported outcomes such as symptom burden.

We anticipate more evidence on the effect of remdesivir from RCTs and on long term safety from observational studies with sufficient length of follow-up (see table of ongoing trials in appendix 4 on bmj.com).[21 22] The largest ongoing trials examining remdesivir include WHO SOLIDARITY, DISCOVERY (NCT04315948), and SIMPLE (NCT04292899). The living network meta-analysis associated with this guideline[10] will incorporate new data as the evidence base increases and allow for analysis of many different interventions within the same analytic model.

Updates to this article

Table 2 shows evidence that has emerged since the publication of this article, informed by our living systematic review and network meta-analysis. As new evidence is published, the *BMJ* Rapid Recommendations collaboration will assess the new evidence and make a judgment on the extent that it is expected to alter the recommendation. Updated recommendations will appear in The BMJ and in MAGICapp subsequently.

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

How patients were involved in the creation of this article

The Rapid Recommendation panel included two patients who have experienced covid-19.

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Competing interests: All authors have completed the BMJ Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 3 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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