Australian National Clinical Evidence Taskforce COVID-19 drug treatment guidelines: challenges of producing a living guideline

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The National Clinical Evidence Taskforce (NCET) established coronavirus disease 2019 (COVID-19) drug treatment guidelines in March 2020 to provide clinicians with living evidence-based recommendations for the care of patients with COVID-19. These guidelines have been widely used and have informed practice in Australia and beyond. However, there are limitations to the available evidence, and, as the COVID-19 pandemic has progressed, the NCET has had to address a number of challenges. This perspective article discusses these limitations and challenges and the strategies developed to ensure that the guidelines remain relevant and useful for clinicians (Box).

The guideline development process

The NCET evidence team conduct daily searches of the literature to identify relevant studies, which, for drug treatments, is limited to randomised controlled trials (RCTs). Studies are evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology,[1] and an evidence summary is produced for each intervention. Where evidence for an intervention already exists, a meta-analysis is performed so that each evidence summary incorporates all available data. The evidence summaries are presented to an expert clinical panel, who develop recommendations that are then discussed by the Guidelines Leadership Group, which is the NCET's senior clinical body.[2] Once the Guidelines Leadership Group approves them, the recommendations are reviewed by the NCET Steering Committee, comprised of representatives from all 35 member organisations, for final 100% consensus approval, with recommendations and evidence summaries then published and clinical flow charts updated. Further details on the guideline development process have been previously published[3,4] and are available on the NCET website.[2]

Applicability of data from randomised controlled trials

Evidence-based guidelines are limited by the quality and applicability of the studies on which recommendations are based. Applicability has been a particular challenge for the NCET, particularly as the COVID-19 pandemic has progressed. Most of the studies that have informed the current guidelines were conducted in unvaccinated patients and before the emergence of the Omicron variants. For example, the recommendations for nirmatrelvir/ritonavir and remdesivir for patients with mild or moderate COVID-19 were based on the EPIC-HR[5] and PINETREE[6] studies respectively. Both studies were conducted before the emergence of the Omicron variants and both excluded patients who had had any COVID-19 vaccination. For the prevention of COVID-19-related hospitalisation or death from any cause, the relative risks in the EPIC-HR and PINETREE studies were 0.12 (95% CI, 0.06–0.25) and 0.28 (95% CI, 0.11–0.75) respectively.[2] With COVID-19-related hospitalisation rates of 6.5% and 5.3% in the respective placebo groups, this amounted to absolute risk reductions of 46 and 55 fewer hospitalisations per 1000 patients,[2] sufficient to be considered clinically important and resulting in conditional recommendations supporting the use of these agents in unvaccinated patients with mild or moderate COVID-19. Given the exclusion of vaccinated patients from the studies, the recommendations to use these agents in vaccinated patients are given as consensus recommendations (based on expert opinion); additionally, the accompanying remark states that the efficacy of these treatments for the Omicron variants is unknown. Despite these caveats, nirmatrelvir/ritonavir and remdesivir have been adopted as standard treatments across Australia for patients with mild or moderate COVID-19 and risk factors for disease progression, generally regardless of vaccination status or variant. However, with high vaccination coverage and the emergence of the Omicron variants, the risk of progression to severe disease is now substantially reduced. Thus, even if the relative risk for the interventions remains the same in these lower risk populations, the absolute risk reduction may be minimal.

In a recently published open-label RCT of molnupiravir versus standard of care — the PANORAMIC study, which involved 25 054 participants from a highly vaccinated population predominantly infected with the Omicron variant — the hospitalisation rate overall was only 1%.[7] No difference in hospitalisation rate or death was demonstrated, and, thus, the NCET now recommends against the routine use of molnupiravir for the treatment of COVID-19. However, it is worth noting that even if a significant relative risk reduction had been demonstrated, it is likely that the absolute risk reduction would be so small that it would not be considered clinically important. Clearly, this will be an important consideration when the results of the PANORAMIC nirmatrelvir/ritonavir RCT are published.

An additional consideration is that a relative risk that translates to a negligible absolute risk reduction at a population level may still represent a clinically important difference for a particularly high risk individual. This is illustrated by a recent RCT of pegylated interferon-λ for mild or moderate COVID-19.[8] The study included vaccinated and unvaccinated patients with Delta and Omicron variants, and the hospitalisation rate in the placebo arm was 3.9%. Combining these data with data from

Challenges faced by the National Clinical Evidence Taskforce (NCET) and strategies developed to adress them

Challenges	Strategies
Most RCTs evaluating treatments for mild COVID-19 were conducted before the emergence of the Omicron variants and excluded vaccinated patients	• Conditional recommendations for nirmatrelvir/ritonavir and remdesivir apply only to unvaccinated patients • Consensus recommendation developed for high risk vaccinated patients • Comment added to state that the effectiveness of agents for patients with Omicron variants is unknown
No head-to-head studies of antiviral agents for the treatment of mild COVID-19	• Clinical flow charts developed to illustrate the various treatment options • Comment added to state that the relative efficacy of the recommended antiviral agents is unknown
No head-to-head studies of various immunomodulators (eg, tocilizumab *v* bariticitinib) for the treatment of severe COVID-19	• Clinical flow charts developed to illustrate the various treatment options • Comment added to state that the relative efficacy of the recommended immunomodulators is unknown • Information box and table developed to provide additional information about the available immunomodulators
Lack of data regarding the use of immunomodulator agents in combination for the treatment of severe COVID-19	• Comment added to state that few studies have evaluated the efficacy of immunomodulators in combination and, due to concerns regarding adverse effects, the NCET recommends the use of dexamethasone and one other immunomodulator
In vitro data demonstrate that available monoclonal antibodies have reduced activity against emerging Omicron variants	• Working group convened to evaluate *in vitro* data and advise on clinical relevance • Conditional recommendations withdrawn and replaced with consensus recommendations against the use of monoclonal antibodies for treatment of COVID-19

COVID-19 = coronavirus disease 2019; RCT = randomised controlled trial. ◆

two previous smaller studies[9,10] produced a relative risk of 0.61 (95% CI, 0.37–0.99) and an absolute risk reduction of 11 fewer hospitalisations per 1000 (95% CI, 0–25), which was considered by the NCET to be not clinically important.[2] Thus, a recommendation has been made to not use pegylated interferon-λ outside of RCTs. However, with a relative risk of about 0.61, a clinically important difference in a particularly high risk patient cannot be completely excluded, highlighting that guidelines developed for populations may obscure benefits for certain individual patients.

The evolution of the COVID-19 pandemic may also have affected the applicability of the NCET recommendations for treatments of severe COVID-19. Currently, for patients with severe COVID-19, the NCET recommends the use of remdesivir (unless mechanically ventilated), in addition to dexamethasone and an immunomodulator such as tocilizumab or baricitinib, based on relative reductions in 28-day mortality of about 16–19% for each of these immunomodulatory agents.[2] The studies on which these recommendations are based were conducted during the time of the Delta variant and when vaccination rates were low and mortality rates were generally higher (23% in the placebo group in the initial RECOVERY dexamethasone RCT[11]). As with the treatments for mild COVID-19, the absolute benefit for treatments for severe COVID-19 are likely to have fallen with reduced mortality rates. Although even modest relative risk reductions may still translate into clinically important differences for patients with severe COVID-19, whether the reduced pathogenicity of the Omicron variants modifies the effect of the immunomodulatory agents is unknown.

Lack of head-to-head studies and lack of studies evaluating therapeutic agents in combination

At the time of writing, the NCET has developed conditional recommendations supporting the use of two antiviral agents for the treatment of mild COVID-19, nirmatrelvir/ritonavir and remdesivir. However, there has been no head-to-head study comparing these two antivirals, and no study evaluating the effectiveness of the combination. The latter is particularly relevant for patients who are highly immunosuppressed and have long periods of persistent viraemia. Although a number of case reports support the use of both nirmatrelvir/ritonavir and remdesivir in these patients,[12,13] RCTs are needed to address this important evidence gap.

For severe COVID-19, the NCET has developed recommendations for six immunomodulators, including dexamethasone, tocilizumab, baricitinib, sarilumab (not available in Australia), abatacept and infliximab. However, there are limited data evaluating the relative effectiveness of these agents and the use of these agents in combination. Although the RECOVERY trial demonstrated a mortality benefit of baricitinib in combination with both dexamethasone and tocilizumab,[14] the use of baricitinib and tocilizumab together has not been widely adopted, likely due to clinician concerns regarding adverse events. A recent article reported data from an RCT evaluating dexamethasone versus baricitinib (both in combination with remdesivir) for patients with severe COVID-19;[15] further RCTs comparing immunomodulators and evaluating immunomodulator combinations are required to determine the most effective treatment strategies for patients with severe COVID-19.

Reduced activity of monoclonal antibodies against emerging Omicron variants

Perhaps the greatest challenge faced by the NECT has been the emergence of variants that are less susceptible *in vitro* to previously recommended monoclonal antibodies. These monoclonal antibodies include casirivimab/imdevimab (previously

recommended for mild or moderate COVID-19 and seronegative patients with severe COVID-19), regdanvimab and sotrovimab (previously recommended for mild or moderate COVID-19) and tixagevimab/cilgavimab (previously recommended for mild or moderate COVID-19 and for patients with severe COVID-19 but not mechanically ventilated). All recommendations were based on RCTs, and amending the recommendations based on *in vitro* data represented a substantial change to the NCET guideline development process. This change has been facilitated by a new NCET working group, convened to evaluate and advise on the clinical relevance of the available *in vitro* data. As a result, previous conditional recommendations have been replaced with consensus statements recommending against the routine use of monoclonal antibodies for the treatment of COVID-19.

Conclusion

The NCET guidelines have been a valuable resource for clinicians across Australia. However, the ability of the guidelines to make strong, evidence-based recommendations is limited by the applicability of RCTs to current populations, the lack of data evaluating relative effectiveness of agents and the use of agents in combination, and the rapid emergence of new COVID-19 variants. Continued efforts by the NCET to respond and adapt to these challenges will be essential to ensuring the ongoing relevance of the guidelines. Many of these challenges may be relevant for other living guidelines. Finally, ongoing efforts are required to support additional RCTs to address the remaining evidence gaps in the management of people with COVID-19.

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