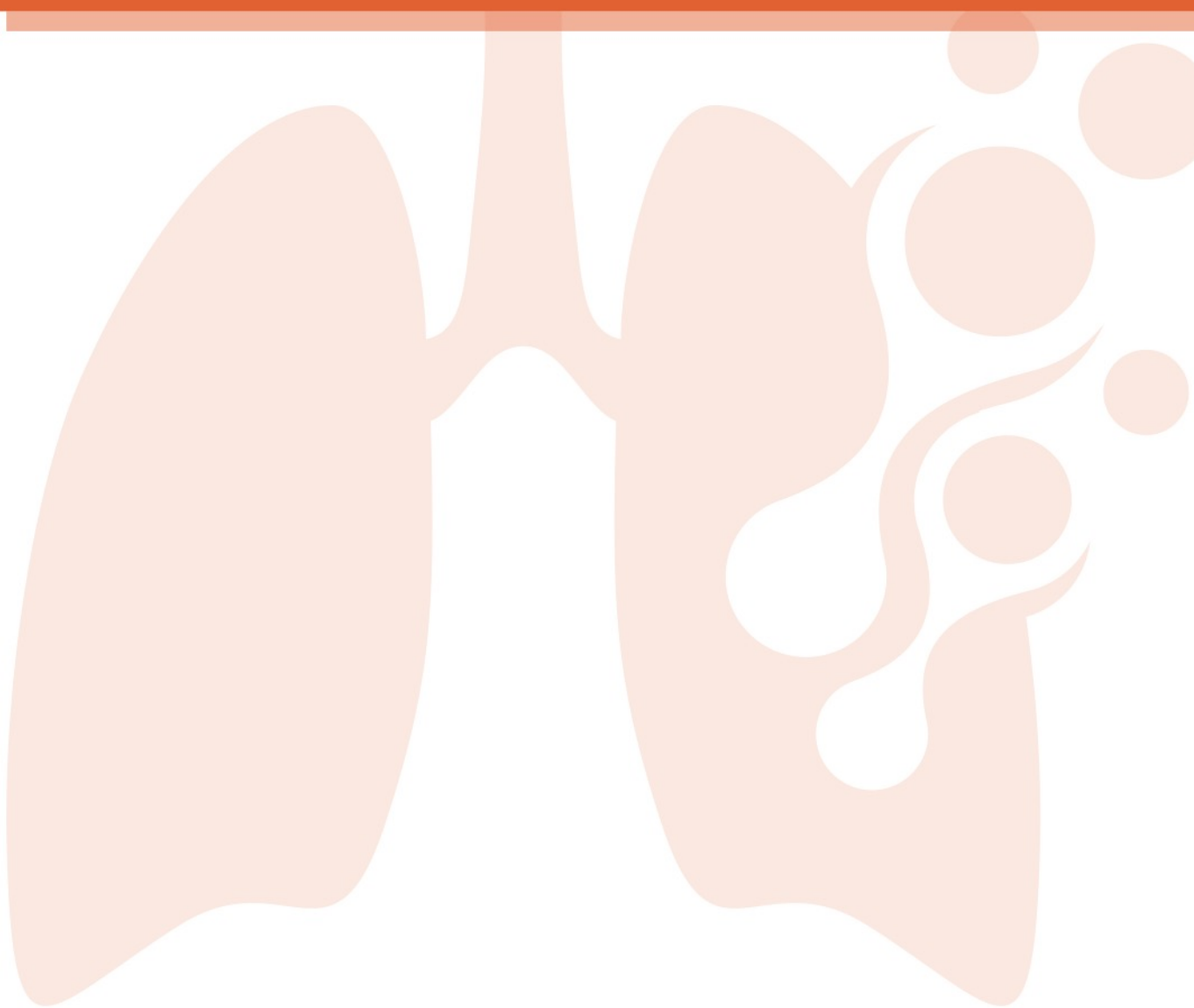
Corticosteroids for COVID-19

LIVING GUIDANCE
2 SEPTEMBER 2020

World Health Organization



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Abbreviations

ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MAGIC	Magic Evidence Ecosystem Foundation
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SEA	serious adverse event
WHO	World Health Organization

Summary

Clinical question: What is the role of systemic corticosteroids in the treatment of patients with COVID-19?

Target audience: The target audience consists primarily of clinicians, and, secondarily, health care decision-makers.

Current practice: Corticosteroids have received worldwide attention as a potentially effective treatment for COVID-19. This guideline was triggered on 22 June 2020 by the publication of the preliminary report of the RECOVERY trial *(1, 2)*, which has now been published as a peer-reviewed paper. Corticosteroids are listed in the World Health Organization (WHO) model list of essential medicines, readily available globally at a low cost, and of considerable interest to all stakeholder groups.

How this guideline was created: This guideline reflects an innovation from the WHO, driven by an urgent need for global collaboration to provide trustworthy and living COVID-19 guidance informing policy and practice worldwide during an outbreak of an emerging infectious disease, such as this pandemic. For this purpose, WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support, to develop and disseminate living guidance for COVID-19 drug treatments. WHO also partnered with investigators of seven trials on corticosteroids to conduct a prospective meta-analysis of randomized trials for corticosteroid therapy for COVID-19 (PMA), in order to rapidly provide additional evidence to build on RECOVERY data and inform guidance development. Drawing on these data, an international panel of content experts, patients, clinicians and methodologists (no conflicts of interest declared for any of the participants) produced recommendations following standards for trustworthy guideline development using the GRADE approach. We considered an individual patient perspective and contextual factors (i.e. resources, feasibility, acceptability, equity) for countries and health care systems.

The evidence: The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19. The panel discussions were also informed by two other meta-analyses, which were already published and pooled data about the safety of systemic corticosteroids in distinct but relevant patient populations. The resulting evidence summary suggested that systemic corticosteroids probably reduce 28-day mortality in patients with critical COVID-19 (moderate certainty evidence; seven studies,1703 patients; relative risk [RR] 0.80, 95% CI 0.70–0.91; absolute effect estimate 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer), and also in those with severe disease (moderate certainty evidence; one study, 3883 patients; RR 0.80, 95% CI 0.70–0.92; absolute effect estimate 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). In contrast, systemic corticosteroids may increase the risk of death when administered to patients with non-severe COVID-19 (low certainty evidence; one study, 1535 patients; RR 1.22, 95% CI 0.93–1.61; absolute effect estimate 39 more per 1000 patients, 95% CI 12 fewer to 107 more). In addition, systemic corticosteroids probably reduce the need for invasive mechanical ventilation (moderate certainty of evidence; two studies, 5481 patients; RR 0.74, 95% CI 0.59–0.93). In contrast, harms, in the context of the mortality reduction in severe disease, are minor.

Recommendations: The panel made two recommendations: a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.

Understanding the recommendation: Given the moderate certainty evidence of an important reduction in the risk of death, the panel concluded that all or almost all fully informed patients with severe or critical COVID-19 would choose treatment with systemic corticosteroids. Moreover, the panel believed that other perspectives (i.e. costs, equity, feasibility of implementation), and patient values and preferences would not alter decisions. In contrast, the panel concluded that fully informed patients with non-severe COVID-19 would mostly not choose to receive this treatment given that current data indicated they would not likely derive benefit and may derive harm. Moreover, taking both a public health and a patient perspective, the panel warned that indiscriminate use of any therapy for COVID-19 would potentially rapidly deplete global resources and deprive patients who may benefit from it most as potentially life-saving therapy.

Background

As of 1 September2020, 25 327 098people worldwide have been diagnosed with COVID-19, according to the international World Health Organization (WHO) dashboard *(3)*. The pandemic has claimed 848 255 lives, and a resurgence in the number of new cases and continued growth is some countries has threatened high- and low-resource countries alike. Although recent evidence suggested that remdesivir may be effective in reducing the time to clinical improvement in patients with severe COVID-19 *(4)*, the magnitude of reduction in time to clinical improvement and the impact of this antiviral agent on mortality and other important outcomes remains uncertain *(5)*. Where the host immune response may drive the pathophysiology of disease, there has been substantial uncertainty regarding the role of corticosteroids in improving clinical outcomes and reducing mortality in patients with COVID-19.

This clinical practice guideline was triggered by the dissemination of the preliminary report of the RECOVERY trial on 22 June 2020, which suggested that dexamethasone 6 mg given once daily for up to 10 days versus usual care reduced 28-day mortality (482/2104 [22.9%] of patients allocated dexamethasone versus 1110/4321 [25.7%] of patients allocated to usual care; age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.75–0.93; $P < 0.001$) *(1)*.

Methods

This guideline reflects an innovation from the WHO, driven by an urgent need for global collaboration to provide trustworthy and living COVID-19 guidance informing policy and practice worldwide rapidly during an outbreak of an emerging infectious disease, such as this pandemic. For this purpose, WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) to provide methodologic support in the development and dissemination of living guidance for COVID-19 drug treatments.