



Management of severe covid-19: progress and promise

We have learnt so much but there is lots more to learn

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Management of SARS-CoV-2 infection continues to evolve. For patients requiring hospital treatment, mortality can be high (up to 20%) but has decreased over the course of the pandemic. Death rates depend on many factors, including age, gender, ethnicity, comorbidities, region, and the community prevalence of covid-19.¹⁻⁴

Current therapeutic approaches are largely focused on one of the two phases of SARS-CoV-2 infection. The initial phase is marked by viral replication followed by a second phase associated with immune dysregulation, worsening respiratory symptoms, sepsis, organ dysfunction, and higher mortality.

Evidence does not support the use of many proposed therapies, including vitamins C and D, zinc, lopinavir-ritonavir, colchicine, interferons, fluvoxamine, ivermectin, and convalescent plasma.⁵⁻⁹ Monoclonal antibodies against the SARS-CoV-2 spike protein are a promising therapy for mild-to-moderate illness in patients outside hospital.¹⁰

Glucocorticoids are the only medication known to decrease mortality in patients admitted to hospital with covid-19. The Recovery study found that dexamethasone 6 mg daily for 10 days (or until discharge if earlier) decreased mortality in patients with hypoxaemia, especially those requiring mechanical ventilation.¹¹ There was no difference in mortality—and a suggestion of increased mortality—in patients without hypoxaemia. Subsequent meta-analyses confirmed glucocorticoids' benefits in critically ill patients.¹²⁻¹³

Beyond glucocorticoids

Remdesivir, an intravenously administered nucleoside analogue, shortened time to recovery by five days among hospital patients in the ACTT-1 trial.¹⁴ The largest effects were seen in patients treated within 10 days of first symptoms and those needing supplemental oxygen but not advanced support such as high flow nasal cannula or mechanical ventilation. The Solidarity trial, however, reported no mortality benefit over placebo in hospital patients,¹⁵ and recommendations vary. The US National Institutes of Health and Infectious Diseases Society of America, for example, conditionally recommend remdesivir for hypoxaemic patients whereas the World Health Organization recommends against, particularly when costs and feasibility of use globally are considered.¹⁶⁻¹⁸

Other promising treatments include the interleukin-6 receptor antagonist tocilizumab and the Janus kinase inhibitor baricitinib. Evidence from randomised controlled trials of IL-6 receptor antagonists is conflicting. In Remap-Cap, patients receiving

tocilizumab required less organ support and had improved survival, but other trials failed to replicate these findings.¹⁹ In the Recovery trial, tocilizumab increased survival only when given with a corticosteroid, so the observed benefit may be due to steroids alone.²⁰ Further evidence on IL-6 receptor antagonists is required, and likely to follow.

In a trial of baricitinib plus remdesivir, a subset of patients requiring non-invasive ventilation or high flow oxygen recovered eight days quicker than those given remdesivir alone.²¹ However, this advantage disappeared in those also given glucocorticoids. An ongoing trial is comparing baricitinib with dexamethasone in patients given remdesivir. Trials of other immunomodulators are also underway.

Antibiotic overuse remains a problem in the treatment of covid-19. Early in the pandemic, half of all admitted patients received antibiotics.²² However, less than 5% of patients have bacterial co-infection at presentation, although the incidence of secondary bacterial infection is somewhat higher at 14%.²³ Guidelines recommend against empirical antibiotics for hospital patients with covid-19 unless there is strong evidence of bacterial infection.²⁴ For those who are critically ill, however, it is reasonable to prescribe antibiotics until bacterial infection can be ruled out. Biomarkers such as procalcitonin can be raised in patients with covid-19 and should not be used in isolation to guide use of antibiotics.²⁵

Covid-19 is associated with increased risk of thrombosis, both large thrombi and microthrombi in various organs.²⁶ Thromboprophylaxis is recommended within 24 hours of admission (in the absence of contraindications), as one retrospective study suggested a survival benefit.²⁷ In critically ill patients, evidence supports prophylactic doses of anticoagulants for adults without frank thromboembolism, but trials of intermediate or therapeutic intensity treatment have been halted because of lack of benefit.²⁸ Similarly, no high quality evidence supports therapeutic dose anticoagulation in hospital patients who are not critically ill.

Non-drug management

The importance of intensive nursing and supportive care cannot be overstated. Hospital mortality in the United States fell from 22% in March 2020 to 12% in May, before widespread use of drugs such as dexamethasone.²⁹ Conservative fluid management, adequate supplemental oxygen, proning, and lung protective ventilation have been essential in improving outcomes. Early intubation for those requiring more than 6 L/min of oxygen is no longer recommended, as patients can be supported more

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effectively and safely with high flow nasal cannulas and non-invasive ventilation.³⁰

Effective communication is also critical. Patients with covid-19 are managed by a variety of health professionals, including nurses, physiotherapists, and physician specialists in hospital medicine, infectious diseases, pulmonary medicine, critical care, and palliative care. Each team member should aim for honest, straightforward conversations with patients, families, and caregivers to establish shared decision making and help identify expectations and goals of care.

Progress in our understanding SARS-CoV-2 and the development of therapeutics and practices to treat moderate-to-severe covid-19 have been impressive, driven by unprecedented collaboration, dedication, and hard work by patients, healthcare professionals, and clinician scientists around the globe. Developing treatments while sharing knowledge, data, and tools provides the promise of ending the current pandemic and preparing for the next global threat.

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