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Evidence based management of acute COVID-19

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Abstract

SARS-CoV-2, the causative agent of COVID-19, was sequenced in early January 2020 and the WHO declared a pandemic in early March 2020.The original virus which caused the first outbreak in Wuhan has mutated significantly, with the delta variant giving rise to a major wave globally with much morbidity and mortality. By the last week of December 2021, nearly 280 million cases were reported with well over 5 million deaths. With the emergence of the new omicron variant which is said to be more transmissible, there is a risk of another major wave with the potential for health facilities around the world being overwhelmed.

In such a background, health systems must be better prepared to face the challenge, and that should include refining treatment protocols. Preventing hospitalizations with early use of oral antiviral drugs and optimising treatment of severe COVID-19 are equally important. This review aims to outline a management plan based on the stage and severity of the disease by examining the current clinical evidence that has emerged through a multitude of trials. There is general consensus regarding the use of steroids, immunosuppressive therapy and anticoagulation in COVID-19 although there are slight differences in the respective national guidelines.

New research is being carried out with oral antiviral drugs for use in early disease and some of the early results are promising. They could play a decisive role in mitigating the effects of the pandemic in addition to vaccination. As many clinical trials are ongoing it is likely that guidelines will need periodic revision.

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Introduction

COVID-19 is caused by SARS-CoV-2 which is an RNA virus. Its genomic sequence was first revealed to the world by China in early January following an outbreak in the city of Wuhan (1). Many variants of the virus have emerged with the delta variant becoming dominant globally by the last quarter of 2021(2). However, a new variant of concern named omicron is showing early potential of being widespread in future, with it becoming the main cause of new infection in South Africa, the UK and the US (3). As of 25th December 2021, over 279 million cases of COVID-19 were reported globally with over 5.4 million deaths (4). Management of COVID-19 has evolved over time with the continued emergence of new trial evidence. The vaccination drive is inequitable around the globe with some parts having a vaccination rate of under 10 percent, leaving a large populace at risk of developing severe COVID-19. Hence, refining treatment protocols for COVID-19 is of paramount importance.

The asymptomatic and mild to moderately symptomatic patient

Approximately 30-40% of patients with SARS-CoV-2 infection are asymptomatic while another 40% of patients are mild to moderately symptomatic. These percentages could vary depending on the prevalent variant and rates of vaccination in a locality. Generally, less than 20% of patients need hospitalisation with about 5% needing intensive care (5). Asymptomatic and mildly symptomatic patients can be isolated at home with remote monitoring by a medical team. These patients do not need specific treatment other than medications to relieve common symptoms. Paracetamol and antihistamines are used when appropriate. Adequate rest, appropriate hydration and good nutrition are vital components of home management. Regular medications taken by patients for other comorbidities should be continued with appropriate monitoring of parameters such as blood sugar and blood pressure. Patients at extremes of age and those with poorly controlled multiple comorbidities are best isolated in designated treatment centres under the direct supervision of medical teams (6). A mechanism should be in place to urgently transfer patients in home care to hospital when they become acutely ill. Pulse oximetry is a vital tool in home care management systems.

Antibiotics are not necessary as COVID-19 is a viral infection. Several antivirals are currently being evaluated in clinical trials with monlupiravir showing promise in phase 3 trials (7). A paper published in the NEJM showed that early treatment with monlupiravir cutdown risk of hospitalisation and death by 30% (7). The oral antiviral drug paxlovid, which is a combination of a low dose of ritonavir and the experimental drug nirmatrelvir, is reported to have reduced hospitalisation risk by over 80% (8). It was recently granted FDA approval for use in patients isolated at home provided it is started within the first 5 days of onset of symptoms. It will be a while before the drug is widely available for use in this category of patients. The repurposed anti-parasitic drug ivermectin has been evaluated in several clinical trials but it has not shown statistically significant benefit to date (9). There is no proof so far that aspirin has beneficial outcomes in COVID-19 although SARS-CoV-2 is known to cause thrombotic complications (10). However, aspirin should be continued in patients who were already on aspirin as part of their treatment regimens. It is also rational to initiate aspirin in those with high 10-year cardio-vascular risk with the aim of preventing cardiovascular complications, irrespective of the clinical severity of COVID-19.

Treatment with convalescent plasma was evaluated in many trials, without significant benefit (11). However, monoclonal antibodies to SARS-CoV-2 have shown benefit when used early in the disease. Currently, the combination of casirivimab and imdevimab is used in the United States and United Kingdom (12). However, in the United Kingdom it is recommended to be used only in patients who are sero-negative for COVID-19 as per trial evidence from the monoclonal Ab arm of the Recovery Trial (13). In the United States it is given to patients who are at high risk of developing severe disease within 3 days of symptom onset. Other monoclonal antibodies authorised include sotrovimab, and the combination of bamlanivimab and etesevimab. Although monoclonal antibodies were shown to be effective against the delta variant, it is not clear whether it would have the same efficacy against the omicron variant in view of the multiple mutations in the spike protein which the latter possesses. It may take time to develop a newer monoclonal antibody that is more specific towards the omicron variant.

The hospitalised patient

Anticoagulation to prevent venous thromboembolism is warranted in all patients requiring hospitalisation unless contraindicated (14, 15). A prophylactic dose of subcutaneous enoxaparin, 40 mg daily is used widely for this purpose although some advocate an intermediate dose. However, the evidence for the intermediate dose is limited, and there is an increased risk of bleeding in patients who are critically ill. A dose adjustment is needed in renal impairment and unfractionated heparin should be used in patients with end stage renal failure.

Detection of early hypoxia in those with moderate

to severe illness is crucial to prevent morbidity and mortality. Due to the reported phenomenon of happy hypoxia, regular pulse oximetry monitoring is essential. As soon as SpO_2 goes down to 94% or below, specific treatment should be initiated as per many international guidelines. Oxygen supplementation should be commenced and flow rate should be increased in a stepwise manner to keep SpO_2 of 92-96% (88-92% in COPD patients). Low flow oxygen devices, face masks, venturi masks and non-rebreathing masks (NRBMs), which are capable of delivering oxygen flow rates up to 15L/min, should be used to achieve that target. Oxygen concentrators can deliver an oxygen flow requirement of 5L/min. Self-proning strategies are advised to improve oxygenation by recruitment of more alveoli to the diffusion process.

The most important therapeutic management step when the SpO_2 is 94% or less is to initiate steroids. Intravenous or oral dexamethasone 6 mg daily is initiated and continued for 10 days or until discharge, whichever comes first (16). Alternatives to dexamethasone would be prednisolone 40 mg, methylprednisolone 32 mg and intravenous hydrocortisone 50 mg 8 hourly. Currently, there is no evidence for the use of higher doses of steroids although several trials are ongoing to determine the optimal steroid type and dose. A significant concern here is that high dose steroids could raise the 28-day mortality due to sepsis, although there may be initial benefit in suppressing inflammation.

All patients with a SpO_2 of 94% or below should remain anticoagulated for venous thrombo-embolism (VTE) prophylaxis (15). Daily dose of enoxaparin 40 mg subcutaneously is commonly used with a dose reduction to 20 mg when eGFR is less than 30. Alternatively, heparin 5000 units twice daily can be used when eGFR is less than 30. When eGFR falls to 10, only heparin can be used. If there is a high-degree of clinical suspicion of VTE, CTPA/venous doppler evidence of VTE or a high D dimer over 1500ng/ml, the anticoagulant dose should be increased to a treatment dose (enoxaparin 1mg/kg twice daily or 1.5 mg/kg once daily). If eGFR is less than 30, enoxaparin 1mg/kg once daily could be used.

Critical disease

This is diagnosed when SpO_2 falls below 90% with maximum oxygen supplementation, or if the Sp02 is below 94% with evidence of tachypnoea (respiratory rate over 30), haemodynamic instability (heart rate over 120/ min, SBP less than 90 mmHg, lactate over 2mmol/L), over 50% multilobar infiltrates on radiography, and partial pressure of oxygen/fraction of oxygen (P/F) ratio of less than 300. The patient ideally needs transfer to a High Dependency Unit or ICU if available.

Respiratory support could be given through high flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV)-BiLevel. Various proning strategies could be adopted judiciously to enhance oxygenation.

If the patient's response to non-invasive ventilatory support is inadequate (if clinical deterioration is seen and SpO_2 cannot be maintained over 92% with FiO_2 of 0.7), invasive mechanical ventilation should be instituted early. The aim of invasive mechanical ventilation is to reduce or prevent self-inflicted lung injury. Safe intubation should be practised with the most experienced member of the team performing the procedure. Veno-venous extracorporeal membrane oxygenation (ECMO) may also be required if hypoxia does not improve with invasive mechanical ventilation.

The IL-6 blocker tocilizumab is used under strict criteria if there is clinical and biochemical evidence of continued severe inflammation even after initiation of steroids (17, 18). For tocilizumab to be used, the patient should already be on steroids, there should be rapidly rising oxygen demands, the CRP should be over 75 mg/L and bacterial sepsis should be excluded. A dose of 8 mg/kg as a single intravenous infusion can be used up to a maximum dose of 800 mg. A typical dose would be 400 mg as an intravenous infusion. Tocilizumab should only be used in patients who are already established on dexamethasone (or another glucocorticoid). Under special circumstances the dose could be repeated after 12 hours if there is no improvement. Bacterial sepsis could be excluded clinically and with the aid of procalcitonin. There are other contraindications

to the use of tocilizumab. They include severe neutropaenia, thrombocytopaenia (less than 50000/ mm³), active TB, herpes zoster infection and an ALT level five times the normal.

Fluid therapy should be guided by the clinical condition of the patient. Although generally a conservative fluid management strategy is advocated, hypovolaemia should be avoided. Pulse rate, blood pressure, urine output and serum lactate would guide fluid management. If the patient remains hypotensive despite adequate fluid replacement, an intravenous noradrenaline infusion will have to be commenced.

Complications

Secondary bacterial sepsis is a recognized complication of COVID-19. Treatment would be according to blood/urine cultures. A standard antibiotic regimen would be cefotaxime 1g, 8 hourly or ceftriaxone 1g, 12 hourly. Second line antibiotics could be given after careful consideration, and with microbiology advice.

Fungal infections (e.g., aspergillosis, mucormycosis) could occur in the third week of illness. Viral co-infections could also occur (Cytomegalovirus, Herpes Simplex virus and Varicella Zoster virus). Appropriate anti-microbial therapy is indicated.

Acute kidney injury (AKI) is common in these patients (19). Dehydration, sepsis and viral induced kidney damage could be the reasons for AKI. In severe cases renal replacement therapy may be required. Continuous renal replacement therapy (CRRT) is advocated for patients with hemodynamic instability (20). Liver involvement is usually limited except for raised liver transaminases.

Myocarditis could occur due to direct virus induced cardiac muscle damage (21). Arrhythmias could occur, and QTc prolongation should be actively looked for with ECG monitoring. Troponin I should be done periodically to exclude myocardial injury. Emphasis should be placed on maintaining optimal magnesium, potassium and calcium levels. Acute myocardial infarction could occur as a thrombotic complication. Similarly, acute stroke could occur as a result of thrombosis or thrombo-embolism (22). Seizures and meningo-encephalitis are known complications.

Severe derangement of blood sugar control is known to occur especially with severe COVID-19. Insulin therapy may be required in some cases. Maintaining an appropriate level of hydration and good nutrition are essential.

Discharge and follow up

Anticoagulation on discharge should be individualised. The potential risk of bleeding and thrombosis should be considered before consideration of anticoagulant therapy at home (15). The patient may need a follow up course of antibiotics, and symptomatic treatment with decongestants and inhalers where indicated. Follow up clinic visits may be needed in patients with severe pneumonia to detect fibrotic complications, to treat accordingly. Assessment of psycho-social issues could be relevant in selected patients. A long COVID syndrome has been described in patients who report persistent symptoms (respiratory and others) for over 3 months, but details are not clear at present (23).

Other therapeutic interventions used globally

Many therapeutic agents have been used to treat COVID-19 since the pandemic began. Hydroxychloroquine looked promising initially but subsequent randomised clinical trials did not show a statistical benefit. Intravenous remdesivir is used in the United State on the basis of a trial conducted by the National Institute of Health, which showed a reduction of hospital stay by 4 days (24). But a major limitation was that mortality was not assessed in the trial. The WHO Solidarity trial which had many treatment arms including remdesivir, hydroxychloroquine, lopinavir- ritonavir and interferon, concluded that there was no mortality benefit with any of those drugs (25). Therefore, the WHO has given a conditional recommendation against the use of remdesivir outside of a clinical trial. However, it is recommended to be commenced in hospitalised patients with early hypoxia in the guidelines of the

US National Institute of Health.

Although used widely, there is currently no good evidence to support the use of vitamin D and zinc either as treatment or prophylaxis (26). However, known vitamin D deficient individuals in the community should be given the appropriate dose of vitamin D to maintain good bone health. Colchicine has been studied for treatment of COVID-19 due to its anti-inflammatory effects, but no statistically significant beneficial effect has been demonstrated as yet (27). Inhaled budesonide was shown to be of benefit in a small study but larger studies have failed to substantiate efficacy. The antidepressant fluvoxamine has shown some efficacy in trials but findings of larger studies are pending (28).

Research is ongoing with newer molecules (inhaled nitric oxide and several oral antiviral drugs) as potential therapeutic interventions in COVID-19 of varying severity. Therefore, it is likely that guidelines will need revision periodically.

Conclusions

Management of COVID-19 has evolved over the last two years based on research findings and the experience gained by clinicians. The morbidity and mortality of COVID-19 patients have decreased significantly as a result of specific drug treatment and optimised supportive care. However, there is scope for further improvement in the management of mechanically ventilated patients who still carry a high rate of mortality.

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