



## Role of Corticosteroids in COVID-19 infection

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### Abstract

*In December 2019, an outbreak of novel coronavirus threatened the health of mankind. There is no clinically proven vaccine apart from few antiviral treatments claiming efficacy. Although, corticosteroids have been widely used during outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome, there was significant controversy regarding their efficacy in treating coronavirus – 19. In infected Coronavirus disease- 2019 (COVID-19) patients, there is massive cytokine release called as 'cytokine storm' hyper inflammation and immune suppression with reduce helper CD4 cell response. Corticosteroids have a good inhibitory effect on inflammatory mediators and are often used as an additional treatment choice for viral pneumonia. The use of corticosteroids has been largely discouraged because of their immunosuppression effect & fear of worsening of viral propagation. Interest in corticosteroid therapy in COVID-19 has been studied after the results from Randomized Evaluation of COVID-19 therapy (RECOVERY) Trial. However, the World Health Organization has not recommended corticosteroid in the treatment of COVID-19. Many controversies have emerged about the use of corticosteroid in COVID 19. This review summarises the pathophysiology, role of corticosteroid in management, controversies about use of corticosteroid in COVID 19 disease. Various studies & literature review suggests that patients with severe conditions were more likely to require corticosteroids in treatment protocol. Corticosteroids should be used with caution in the treatment of COVID-19 patients & more multicentre clinical trials are further needed to support their use in management of covid-19.*

### Introductions

Coronavirus 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infections. In December 2019, several cases of pneumonia spurted out in Wuhan, China. Unbiased sequencing of samples from patients with pneumonia reveals that it is caused by SARS-CoV-2, a variant of coronavirus which is similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV)<sup>(1)</sup>

The causative agent was later named as severe acute respiratory syndrome coronavirus 2 (SARSCoV- 2) by Coronavirus Study Group, and the disease it caused was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic. In April 2020, over 1,500,000 confirmed cases have been diagnosed in more than 130 countries and areas, resulting in more than 93,000 fatalities so far<sup>(2)</sup>. Globally, as of 10:23am CEST, 13 August 2020, there have been 20,405,695 confirmed cases of

COVID-19, including 743,487 deaths, reported to WHO as per WHO Coronavirus Disease (COVID-19) Dashboard.

SARS-CoV-2 is a new type of highly diverse enveloped positive single stranded RNA virus<sup>(3)</sup>. It can cause a broad range of symptoms including self-reported fever, fatigue, dry cough, and myalgia, diarrhoea, with or without the subsequent development of dyspnoea. There is evidence that the transmission pattern of SARS-CoV-2 is

human-to-human which is spread by respiratory droplets caused by coughing or sneezing<sup>(4)</sup>. Though majority of patients undergo an uneventful recovery, in around 19% there is a progressive worsening leading to severe pneumonia in 14% and critical pneumonia in 5% of patients. Severe cases include respiratory distress, sepsis, and septic shock have been increasingly reported<sup>(5)</sup>.

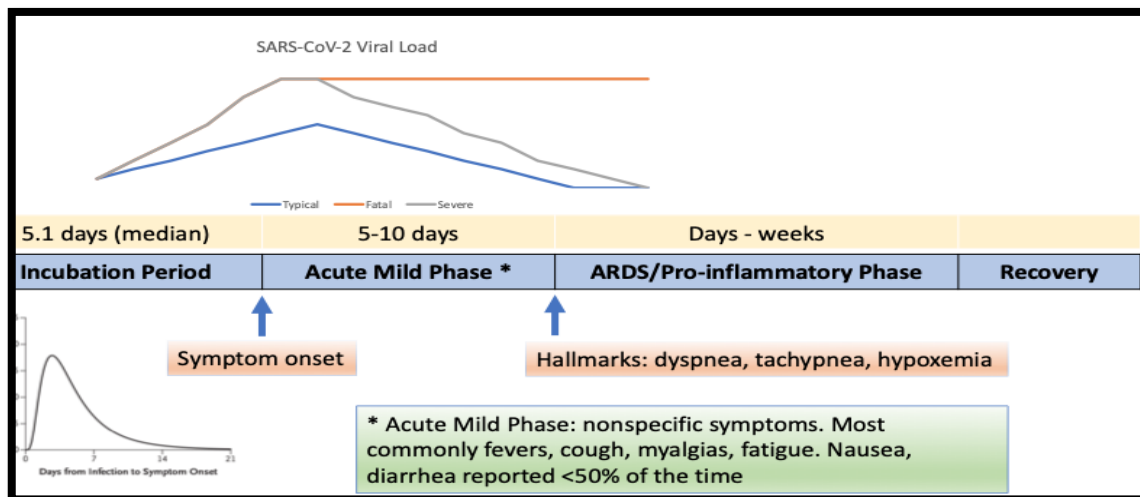


Figure 1: COVID-19 Disease course<sup>(6)</sup>

Global research efforts into potential treatments started in January 2020 and there are now thousands of studies looking at how to treat and manage the disease. While there are no antivirals licensed for use for this indication, data from other infectious coronaviruses, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), as well as *in vitro* studies, demonstrate that there are potential benefits that could be obtained from antiviral therapy. No drugs or biologics have been approved by the FDA for the prevention or treatment of COVID-19<sup>(7)</sup>.

Remdesivir gained emergency use authorization (EUA) from the FDA on May 1, 2020, based on preliminary data showing a faster time to recovery of hospitalized patients with severe disease.<sup>(8)</sup>

On 20 March 2020, the World Health Organization (WHO) announced 'Solidarity', a large global trial that compares local standards of

care with local standards of care plus one of the following treatments: remdesivir; hydroxychloroquine; lopinavir-ritonavir; or an arm that combines ritonavir-lopinavir with interferon-β-1a<sup>(9)</sup>.

Accelerated drug approval is practiced in case of serious medical conditions if the agent is first treatment available and benefits of the new drug are more than that of the currently available agents in the market. The notice has been issued by the Drug Controller General of India On March 30, 2020, to all the stakeholders of India regarding the conduct of clinical trial during an outbreak of COVID-19. Repurposing of already approved agents for a different medical condition is an effective strategy as it saves considerable amount of time, money, and resources. Agents previously used to treat SARS and MERS are potential candidates to treat COVID-19. Following are few drugs repurposed for COVID-19 are reviewed,

Chloroquine and Hydroxychloroquine, antivirals like Lopinavir/Ritonavir, Ribavirin, Selective Investigational Drugs like Remdesivir,

Favipiravir, Anticytokine or Immunomodulatory Agents like Tocilizumab, amonoclonal antibody IL-6 receptor antagonist<sup>(10)</sup>.

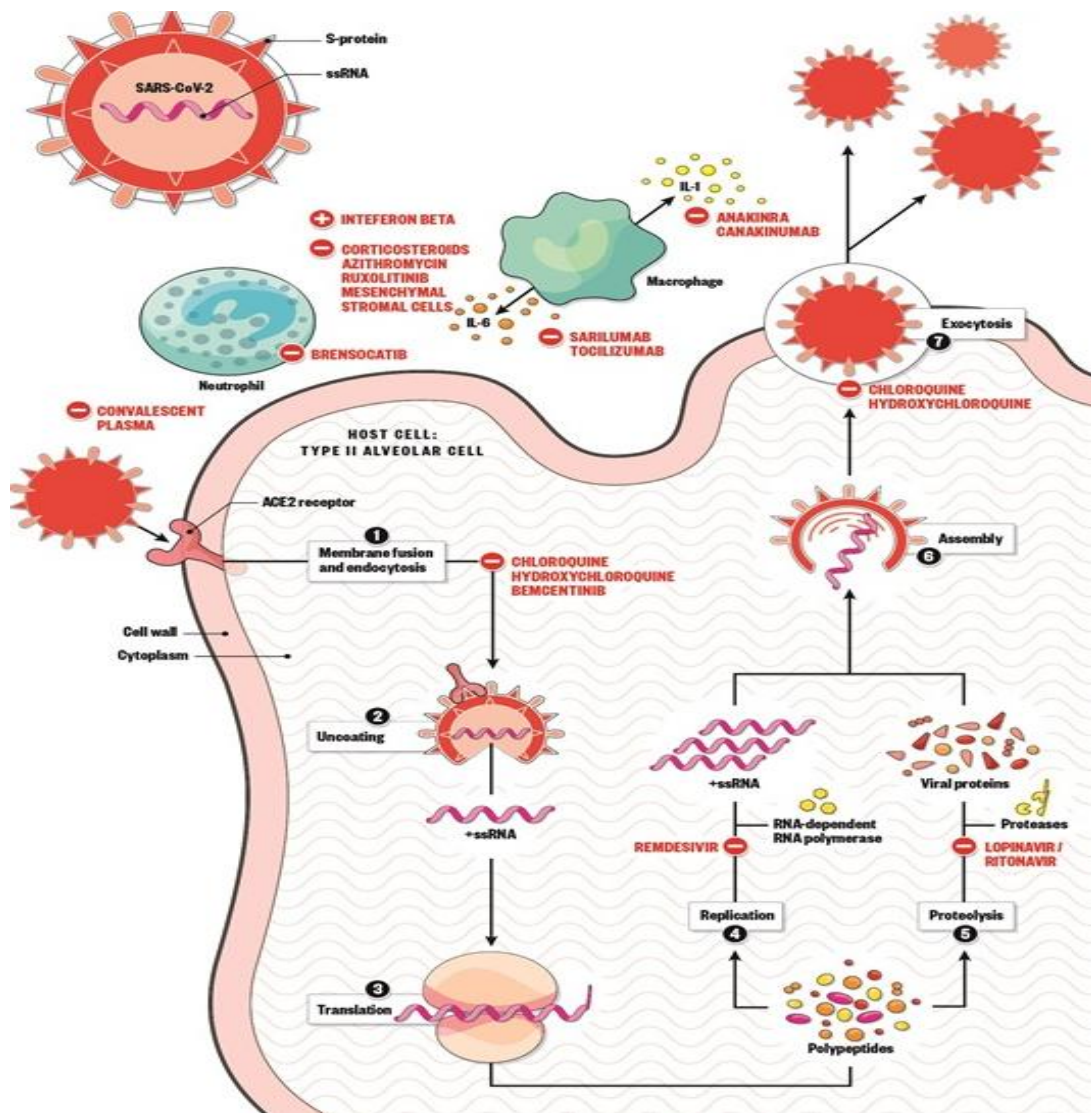


Figure 2: Investigational drugs for COVID 19<sup>(11)</sup>

As of 3 June 2020, around 3,500 patients have been enrolled from 35 countries. In the UK, the ‘Randomised Evaluation of COVID-19 Therapy trial’ (RECOVERY) has recruited more than 11,748 patients from 176 NHS hospitals.<sup>(12)</sup>

The use of corticosteroids in COVID-19 remains a major controversy. Available evidences are inconclusive. According to WHO guidance, corticosteroids are not recommended to be used unless for another reason. Chinese Thoracic Society (CTS) proposes an expert consensus statement that suggests taking a prudent attitude of corticosteroid usage.<sup>(13)</sup>

Corticosteroids have a good inhibitory effect on inflammatory factors and are often used as an auxiliary treatment for viral pneumonia. However, the results of clinical studies on the role of corticosteroids remain controversial. Hence in this article we aim to discuss the role, controversies & clinical trial data for use of corticosteroid in current covid-19 pandemic.

**Pathophysiology of COVID -19**

There is a step wise progression in the course of events after a median incubation period of 4 days.

The adult respiratory distress syndrome (ARDS) usually develops from the second week onwards. The pathogenic mechanism that produces pneumonia seems to be particularly complex. The data so far available seem to indicate that there is uncontrolled viral replication and an excessive immune reaction in

the host. In some cases, a reaction takes place which as a whole is labelled a 'cytokine storm' with hyper inflammation and immune suppression, characterized by decreased memory CD4  $\beta$  T helper cells and increased CD8 cytotoxic activity, patients exhibit lymphopenia with reduced B cells.<sup>(14)</sup>

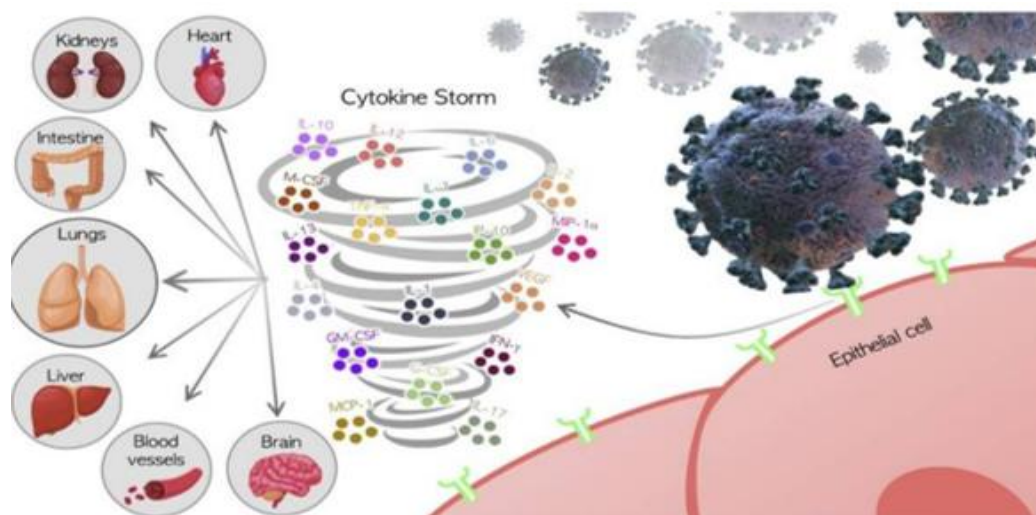


Figure 3: Cytokine storm in COVID 19<sup>(15)</sup>

The effect is extensive tissue damage with dysfunctional coagulation. Underlying the lung viral injury associated with the inflammatory reaction and the microvascular pulmonary thrombosis. Various cytokines involved in the

pathogenesis of ARDS cause by SARS-2 are tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , IL-8, IL-12, interferon-gamma inducible protein (IP10), macrophage inflammatory protein 1A (MIP1A), and monocyte chemo attractant protein 1 (MCP1).

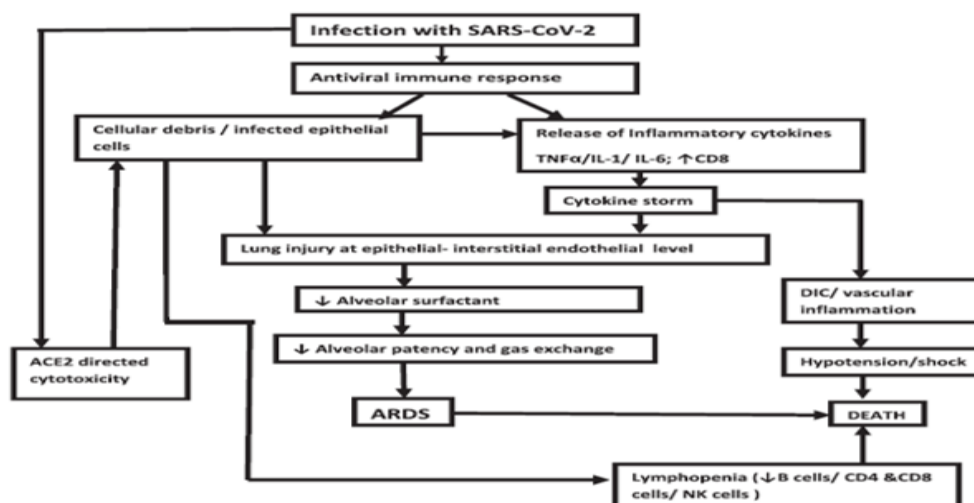


Figure 4 Pathophysiology of ARDS in COVID-19<sup>(16)</sup>

Studies have shown that any intervention which can prevent this cytokine storm can also prevent the lung damage and pulmonary

thromboembolism. It is with this pathophysiology in mind that intervention with corticosteroids has been thought about in COVID-19.<sup>(17)</sup>

### Rationale for Corticosteroids in COVID -19

Corticosteroids have primarily been thought to prevent or reduce ‘cytokine storm’ and its consequences as ARDS, disseminated intravascular coagulation, hypotension, shock and death. Cytokine storm usually happens in the first 5 to 7 days & steroid therapy should be given this period, particularly at the onset of dyspnoea or even earlier to prevent the progression of the ‘cytokine storm’. Corticosteroids reduces the risk of respiratory failure by preventing the further progress of diffuse alveolar damage. Independent risk factors for risk of progression of ARDS to the death are older age, organ dysfunction and coagulopathy. Coagulopathy are manifested by the higher levels of lactate dehydrogenase (LDH) and d dimer.<sup>(18)</sup>

In majority of the studies Methyl prednisolone & Hydrocortisone are the corticosteroids used because of the higher concentration achieved in the lungs. Methylprednisolone has the advantage of parenteral administration, a quicker onset of action and a shorter duration of action compared to the dexamethasone. Also because of lesser mineral corticoid action the long-term side effects like fluid retention, hypokalemia, hypercortisolism and dysglycemia less likely with methyl prednisolone. The studies which have analysed the corticosteroid in COVID 19 pandemic are not uniform in methodology because considerable variation in the timing of initiation of steroid treatment, type of the steroid and dosage of steroid and also the primary aim was not to evaluate the corticosteroid use. The most robust data amongst corticosteroids came with dexamethasone in the RECOVERY trial. This was controlled, open-label trial comparing a treatment in patients who were hospitalized with Covid-19. The treatment was randomly assigned to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Preliminary results are as below.<sup>(19)</sup>

1. There is significant mortality benefit with low dose dexamethasone.

2. 35% mortality reduction among the sickest patients on invasive mechanical ventilation
3. 20% reduction of mortality amongst patients on oxygen therapy (with or without non-invasive ventilation).
4. In addition, patients on dexamethasone had a statistically significant reduction of hospital stay and an earlier likelihood of discharge.
5. Corticosteroid intervention were done in patients with serious or critically unwell patients, particularly those who required high flow nasal oxygen or ventilation.
6. Studies on patients with mild COVID 19 did not show any significant benefit
7. Systemic corticosteroids by its immunosuppressant effect has been hypothesized to aggravate the viral load and prolong the viral excretion.
8. Steroid therapy has also been shown to increase the risk of secondary bacterial infection, for which adequate broad-spectrum antibiotics cover should be given.
9. Personalized strategy should be rational. Judgment of clinical courses, lab findings, radiological appearances, and, if available, pathological examinations should be given priority while taking the decision to initiate the therapy.
10. Repeat chest HRCT at the gap of 1 week to assess the response & to detect the associated complication

### Adverse effect of Corticosteroid therapy in COVID-19

A potential adverse effect of corticosteroid in covid-19 is the worsening /unmasking of latent diabetes. As Corticosteroids produce increased hepatic glucose output reduction in glucose uptake of the skeletal muscle cells, reduction of hepatic glycogenesis. Corticosteroids also produce breakdown of proteins, also have a direct inhibitory action on b cells. This effects are transient and reversible with the stoppage of the

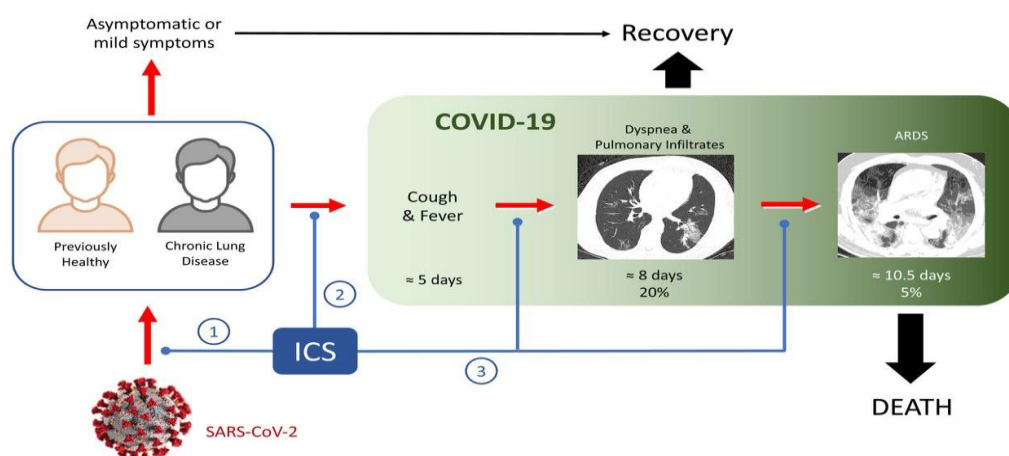
steroids and short course of steroids in most of the COVID-19 trials chances of steroid induced hyperglycaemia is less likely. Still the treating physician need to be aware of this complication and should take all corrective measures to tackle it. Long term side effect of steroid therapy like bone changes like avascular necrosis of the femoral head and suppression of the hypothalamic pituitary-adrenal(HPA) axis is not evaluated as surviving patients of ARDS are followed for short time.

**Inhalational Corticosteroid in COVID-19** <sup>(20)</sup>

There is some important concern about the inhalational corticosteroid use in current COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. What is the effect of COVID 19 pandemic in patients who are taking ICS for conditions like COPD or asthma? Are they more susceptible for infection? what is the course of disease in them if suffered?

Should the ICS be stopped in them who are taking it for Asthma/COPD because of fear of increase vulnerability for COVID-19? Should the ICS be stopped in patient with COVID 19 who are taking it for chronic disease? Clinical trial data suggest the following answers. Surprisingly, the prevalence of chronic respiratory disease among patients with SARS and COVID-19 appears to be lower than among the general population.

Patients with underlying lung disease who develop COVID-19 and are hospitalised have worse outcomes, with a case fatality rate of 6.3% compared to 2.3% overall in China.<sup>(7)</sup> These individuals may have less reserve to cope with the pulmonary effects of severe infection or their immune-pathological abnormalities may make them more susceptible to developing pulmonary inflammation and ARDS. If people with stable asthma stop or reduce their ICS inappropriately in response to concerns about immunosuppression and worries about developing COVID-19, they may be at significant risk of having an exacerbation. A rapid systematic review to evaluate whether pre-morbid use or continued administration of inhaled steroids is a risk factor for adverse outcomes in acute respiratory infections due to COVID-19, SARS or MERS. As per that review at present, there is no evidence as to whether pre-morbid use or continued administration of ICS is a factor for adverse or beneficial outcomes in acute respiratory infections due to coronavirus. At the present time in this COVID-19 pandemic, clinicians should be aware that there is no evidence to support the withdrawal of ICS in patients treated with these drugs, and to do so is likely to be harmful. Those patients of asthma and COPD who are stable on ICS should continue on their treatment.



(ICS): 1: infection with SARS-CoV-2; 2: development of COVID-19 disease; 3: progression of COVID-19.

**Figure 5:** Inhalational corticosteroids (ICS's) in COVID-19<sup>(20)</sup>

Inhaled ciclesonide has is lower immunosuppressive effects when compared to systematic corticosteroids and has benefit of reduce viral replication and pulmonary inflammation. In two in vitro studies, ciclesonide ICS indicated that has anti-viral properties against these respiratory viruses. In the analysis of clinical study with three patients ciclesonide, ICS showed favourable outcomes, however these clinical results should be treated with caution.

### Controversies for use of corticosteroids in COVID-19

Corticosteroids have a good anti-inflammatory effect and are often used for treatment of viral pneumonia. The main anti-inflammatory effect of glucocorticoids is to inhibit a large number of pro-inflammatory genes that encode cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors to address the inflammatory process and restore homeostasis. However, there is controversies about the use of corticosteroids in COVID-19 pandemic depending upon the results of clinical studies.

As per Clark Russell and colleagues<sup>(21)</sup>, corticosteroid treatment should not be used for the treatment of 2019-nCoV-induced lung injury or shock outside of a clinical trial. As per the front-line physicians from a team in China were mostly observational studies selection bias and confounders in observational studies might contribute. As per the conclusion of Russell and colleagues which was taken from the studies were in conclusive. Inconclusive clinical evidence should not be a reason for abandoning corticosteroid use in 2019-nCoV pneumonia. There are studies certain supporting the use of corticosteroids at low-to-moderate dose in patients with coronavirus infection as mentioned below. In one of the retrospective study with SARS proper use of corticosteroids was found to be associated with reduce mortality & shorten the length of stay in hospital for critically ill patients & other complications. Dosage of 25–150 mg/day methylprednisolone or equivalent

(low-to moderate dose of corticosteroids) showed reduce mortality in H1N1 2009 pandemic.

As per Chinese Thoracic Society an expert consensus statement<sup>(22)</sup> on the use of corticosteroids in 2019-nCoV pneumonia. Corticosteroid treatment is a double edged sword. Basic principles should be followed when using corticosteroids:

- (1) Calculate risk Vs benefits before using corticosteroids
- (2) Corticosteroids should be used prudently in critically ill patients with 2019-nCoV Pneumonia
- (3) Cautious use of corticosteroids for patients with hypoxaemia due to underlying diseases / who regularly use corticosteroids for chronic diseases
- (4) Should be used in low to- moderate ( $\leq 0.5-1$  mg/kg per day Methylprednisolone or equivalent) and the duration should be short ( $\leq 7$  days).
- (5) Liberal use of corticosteroids is strictly avoided

There is a need for well-designed randomised controlled trials in the future to promote a more solid foundation for treatment.

In a systematic review & meta-analysis conducted by Zhenwei Yang et al in March 2020<sup>(23)</sup>, total of 5270 patients from 15 studies were included in this meta-analysis and concluded that although Corticosteroids were widely used during outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome, their efficacy remained highly controversial. In COVID 19 pandemic critical patients were more likely to require corticosteroids therapy however, corticosteroid treatment was associated with higher mortality longer length of stay a higher rate of bacterial infection, hypokalaemia.

On 16th June 2020 The World Health Organization (WHO) published initial clinical trial results from the United Kingdom (UK). As per that,

- 1) Dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19.

- 2) Reduce mortality by about one third, in those who are on ventilator
- 3) Reduce mortality by one fifth in patients requiring only oxygen

### Conclusion

From various studies & literature review suggest that patients with severe conditions were more likely to require corticosteroids. Corticosteroid treatment is a double edged sword & could lead to higher mortality, a higher rate of bacterial infection and hypokalaemia. But as per RECOVER trial which has provided a robust data for corticosteroid use in COVID – 19, found that significant reduction in death with dexamethasone in severe case on ventilator or moderate case on supplemental oxygen therapy but no benefit observed in mild to moderate case requiring no oxygen Therefore, corticosteroid should be used with caution in the treatment of COVID-19 patients & moremulticentre clinical trials are needed to further verify this conclusion.

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