International Journal of Health Sciences and Research
Vol.10; Issue: 5; May 2020
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Cytokine Storm Syndrome in COVID-19: Diagnosis and Management Strategies

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ABSTRACT

Coronavirus disease 2019 (COVID-19), is a viral illness caused by novel coronavirus called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was declared as a pandemic by the World Health Organisation (WHO) on March 11, 2020. Initial studies have shown molecular resemblances in the receptor binding domains of SARS-CoV and SARS-CoV-2 which bind angiotensin converting enzyme 2 (ACE 2) receptors, thereby entering the host cells to cause infection. COVID 19 can present as a broad spectrum of illness, from mild common cold to life threatening acute respiratory distress syndrome (ARDS), multiorgan dysfunction and shock. The key step transforming mild disease to severe is immune dysfunction and cytokine dysregulation resulting in what is called as "cytokine storm syndrome". It is prudent to diagnose cytokine storm early in the course of disease to mitigate the subsequent consequences. The use of H score as in secondary haemophagocytic lymphohistiocytosis (sHLH) can be helpful as the inflammatory cytokine profile in sHLH is very similar to that of COVID-19. The article also discusses the past experience and current evidence of use of immunological cytokine specific antibodies, new anti-rheumatic drugs and role of convalescent plasma that may prove instrumental in the fight against COVID 19 as they can precisely target the key steps of the immune response. An approach in this regard is also proposed to screen patients of severe COVID-19 disease for exuberant inflammation by measuring cytokines in an attempt to identify patients who will benefit from this selective immunosuppression.

Keywords: COVID-19; SARS-CoV-2; Cytokine storm syndrome; H score; Hydroxychloroquine; Tocilizumab; Convalescent plasma

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a new but widely prevalent clinical entity is caused by novel coronavirus called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease has affected a substantial proportion of people worldwide in a short span of time and was declared as a pandemic by the World Health Organisation (WHO) on March 11, 2020.[1] As on Apr 12th 2020, around 1,696,588 people were affected by this disease in 203 countries with a death toll of 105,952.[2] The new agent belongs to a large family of coronaviruses known since decades to human mankind. Being first discovered in domestic poultry in 1930, there are now 7 viruses known to cause disease in humans. Coronaviruses are enveloped RNA viruses that cause

respiratory illnesses of varying severity from the common cold to fatal pneumonia. These viruses are zoonotic pathogens, at times infect humans with further spread via human to human transmission. The family has a notorious historical background being responsible for major outbreaks in the past including severe acute respiratory syndrome (SARS-CoV) in 2002 and Middle east respiratory syndrome (MERS-CoV) in 2012.[3]

SARS-CoV-2 was first identified in December 2019 in Wuhan, a city in the Hubei Province of China, rapidly spreading worldwide over next three months. SARS-CoV-2 is an enveloped, positive-sense, single stranded RNA virus with a nucleocapsid, being closely related to SARS-CoV with which it shares around 79% of its genome.[3,4] Also, studies have shown molecular resemblances in the receptor binding domains (spike proteins) of SARS-CoV and SARS-CoV-2 which bind the angiotensin converting enzyme 2 (ACE 2) receptors, thereby entering the host cells to cause infection.[5] [Figure 1] ACE 2 receptors are mainly present on alveolar epithelial type II cells (83% of all ACE 2 expressing cells in body)[6], although expression of these receptors is also noted on heart, kidney, endothelium and gut cells.[7]

Initial studies from China and worldwide demonstrate that COVID 19 can present as a broad spectrum of illness ranging from mild common cold to severe life threatening acute respiratory distress syndrome (ARDS), multiorgan dysfunction and shock.[8] [Table 1] The disease is transmitted from person to person through droplets from an infected person or fomites. With a presumed incubation period of 2-14 days, most cases occur within 5 days of exposure. Importantly, the spread might be possible before symptoms appear, though occurrence of the same is less common.[9,10] Studies have also suggested that the virus may also be present in feces and could contaminate places like toilet bowls and bathroom sinks.[11] However, substantial evidence for the same is lacking at present. The disease mainly infects middle aged (> 30 yrs) and elderly. Symptomatic infections in children are less common and rarely progress to severe disease.[12] The most common clinical features as described in a study conducted in Wuhan enrolling 1099 patients included fever (88%), dry cough (67%), fatigue (38%), dyspnoea (18.7%), myalgias (14.9%). Other symptoms included headache, sore throat, rhinorrhoea and gastrointestinal symptoms. Pneumonia appears to be the most severe manifestation of infection, with ARDS occurring in 3.4% of patients.[13]

SARS-CoV-2, though being less is less fatal than MERS-CoV as per initial data, it does cause a severe disease (especially in geriatric population and in patients with underlying comorbid illness) characterised by interstitial pneumonia with rapid progression to ARDS or septic shock. This is accompanied by multi organ dysfunction including hepatic dysfunction and disseminated intravascular coagulation with high levels of acute-phase reactants and features of the macrophage activation syndrome (MAS) such as increased ferritin levels.[14] The key step transforming mild disease to severe is immune dysfunction and cytokine dysregulation resulting in what is called as cytokine storm syndrome. Current management of COVID 19 is supportive with an ongoing relentless struggle for development of novel therapeutics including antivirals and vaccines. Meanwhile, it is equally important to identify and treat hyperinflammation with existing, approved therapies, thereby curtailing rates of mortality from COVID 19.

CYTOKINE DYSREGULATION IN COVID-19

Special interest is derived in analysing cytokine dysregulation in patients of COVID 19 from the very fact that initial studies validate the upregulation of certain specific cytokines which are associated with more severe disease profile. A study from Huang et al. found that IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α

levels correlated with disease severity with higher levels being found in intensive care unit (ICU) patients,[14] and another study from Diao et al. confirmed that disease severity correlated with TNF-α, IL-6 and IL-10 levels. The study also established increased production of TNF-α in the serum of COVID-19 patients. Also, patients with severe disease in ICU had lower CD4+ and CD8+ T cell counts with a negative correlation with TNF-α and IL-6 concentrations.[15] Another study by WAN S et al measured IL-6 levels in patients of COVID 19. The study demonstrated that only one-third patients with mild disease had raised IL-6 levels as against 76% patients with severe disease.[16] Similar to infection with SARS, as was noted in the beginning of this century, IL-6 is proven to cause suppression of normal T cell activation, probably explaining the initial presence of lymphopenia in this subset of patients.[17] The immune mediated tissue damage is caused by highly cytotoxic CD8+ T cells. Moreover, the immune response in COVID 19 patients is abnormally skewed towards immunosuppressive Th-2, a reciprocation to increased expression of inhibitory factors such as PD-1 by the functionally exhausted T cells, thereby resulting in immune dysfunction.[14-17]

The role of cytokine dysregulation in causing severe COVID disease is well established and specific immunotherapy can be considered an important modality of treatment of these diseases. However, there is still an academic black hole as to what causes this burst release of inflammatory cytokines. Multiple hypothesis, yet to be tested, though offer some explanation. One hypothesis is that the rapid viral replication leading to cell apoptosis may in turn cause the massive release of inflammatory mediators. This phenomenon is called as "cell pyroptosis", a pro-inflammatory form of cell apoptosis.[18] Another hypothesis for this cytokine storm implicates the role of antibodies against spike protein (anti-S-IgG), which promote the accumulation of pro-inflammatory monocytes and macrophages in the lungs.[19] Also, as against the general predisposition of females to development of autoimmune diseases due to their enhanced immune response, occurrence of cytokine storm in COVID 19 disease on the other hand, is more common in males,[20] thereby emphasizing the fact that other factors also may play a role.

Table 1: Spectrum of illness severity: COVID 19.[8]

Illness severity	Percentage (%)
Mild (fever, sore throat, dry cough)	81
Severe illness (dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours)	14
Critical Disease (Respiratory failure, shock, multi-organ dysfunction syndrome)	5

DIAGNOSIS OF CYTOKINE STORM SYNDROME IN COVID 19

As illustrated above, cytokine syndrome in COVID 19 is characterized by by increased IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ, inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α. A retrospective, multi-centre study conducted in Wuhan, China enrolling 150 confirmed cases of COVID 19 concluded that elevated ferritin (mean 1297·6 ng/ml in non-survivors vs 614·0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001), are predictors of fatality and severe disease, thereby suggesting a portentous role of virally driven hyperinflammation.[21] This cytokine profile is very similar to secondary haemophagocytic lymphohistiocytosis (sHLH), a less recognised entity, most commonly triggered by viral infections.[22] sHLH is hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with multiorgan failure. Occuring in around 3.7-4.3% of sepsis,[23] it is clinically suspected in sepsis cases presenting with unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.[24]

As sHLH and cytokine storm syndrome have a similar clinical and

pathobiological profile of hyper-inflammation, these may be considered a similar spectrum of disease. It is utmost important to identify this subset of patients, as they are potential candidates of immunosuppression, thereby reducing mortality and improving the chances of survival. Apart from various isolated biochemical markers of hyper-inflammation including elevated ferritin levels, cytopenias or raised acute phase reactants, cumulative scores like H-score[25] have been designed to aid the clinicians in decision making and predicting the probability of sHLH. The same may be applied to cytokine storm syndrome of COVID 19 with substantial reliability. [Table 2]

TREATMENT MODALITIES FOR CYTOKINE STORM SYNDROME IN COVID-19

The challenge as on date is to identify a specific treatment modality for COVID-19. Though various novel molecules and vaccine trials are ongoing, it is equally essential to explore the existing armamentarium of therapeutics against SARS-CoV-2 to cater to the immediate needs of controlling this pandemic. The drugs which have shown efficacy against COVID 19 in initial trials are listed below.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are one of the veteran class of drugs, used in treatment of malaria and as an immunomodulator in various rheumatological diseases. Studies in the past have demonstrated that the drug also possesses significant antiviral activity as demonstrated against SARS and avian influenza A H5N1.[26] In vitro studies have established that both chloroquine and hydroxychloroquine inhibit SARS-CoV-2, although the later seems to be more potent.[27] The proposed mechanism of action is that the drug acts by increasing the endosomal pH thereby inhibiting the fusion of host cell with the virus. Also, it interferes with glycosylation of ACE-2 receptors, impeding the viral entry into target cells.[28]

A multi-centre study conducted in China concluded that administration of chloroquine leads to better clinical outcomes and reduced hospitalisation without any significant increase in adverse effects.[29] The published clinical data on both these agents, however are limited. In an open-label study of 36 patients with COVID-19, use of hydroxychloroquine (200 mg three times per day for 10 days) was associated with a higher rate of undetectable SARS-CoV-2 RNA on nasopharyngeal specimens at day 6 compared with no specific treatment (70 versus 12.5 percent).[30] However, another randomized trial of 30 adults with COVID-19 in Shanghai, did not corroborate with earlier results showing no significant difference in the proportion of patients with nasopharyngeal viral clearance at day 7 with hydroxychloroquine (400 mg daily for five days) compared with standard of care. However, interferon and other antiviral agents were used in both arms, possibly acting as confounding factors.[31]

Table 2: H Score for secondary HLH, by clinical parameter [25]

Parameter	Number of points
Temperature	
< 38.4 degree Celsius	0
38.4 – 39.4 degree Celsius	33
> 39.4 degree Celsius	49
Organomegaly	
None	0
Hepatomegaly or Splenomegaly	23
Hepatomegaly and Splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
< 1.5 mmol/L	0
1.5 – 4.0 mmol/L	44
> 4.0 mmol/L	64
Fibrinogen (g/L)	
> 2.5 g/L	0
≤ 2.5 g/L	30
Ferritin (ng/ml)	
< 2000 ng/ml	0
2000 – 6000 ng/ml	35
> 6000 ng/ml	50
Serum aspartate aminotransferase (IU/L)	
< 30 IU/L	0
≥ 30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The H Score[25] generates a probability for the presence of secondary HLH. H Scores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. H Scores can be calculated using an online H Score calculator. HLH=haemophagocytic lymphohistiocytosis.

*Defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined.

†HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

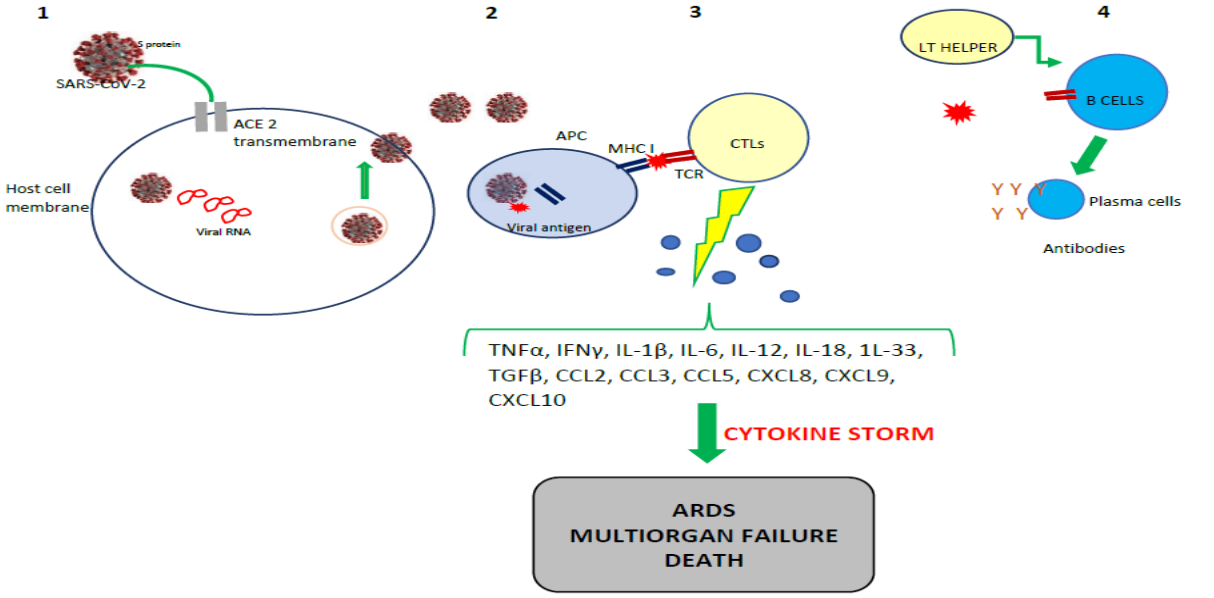

Fig. 1. Pathogenesis of COVID-19: 1. SARS-COV2 entry, replication and release. The virus binds to its ACE2 cell receptor by means of its spike glycoprotein (S protein) and then enters the cell cytoplasm where it releases its RNA genome, begins to replicate, and forms and releases new viral particles. 2. Antigen presentation. The viral antigen is presented to antigen-presenting cells (APCs) that present the antigenic peptides by means of the major histocompatibility complex (MHC). Antigen presentation stimulates both (3) cellular and (4) humoral immunity. 3. Immune effector cells release large amounts of cytokines and chemokines (a cytokine storm) that may rapidly provoke acute respiratory distress syndrome (ARDS), single or multiple organ failure, and eventually death.

Nevertheless, the drug has been recommended in guidelines of few countries (China, Italy, India) for the treatment and prophylaxis of COVID disease. Optimum dosing is indeterminate and vary in all guidelines at present. As per the China's National Health Commission, the recommended adult treatment dose is 400 mg PO Q12h x 1 day followed by 200 mg PO Q12h x 4 days. Indian council of medical research has also recommended chemoprophylaxis for high risk population including healthcare workers with dosage schedule of 400 mg twice a day on day 1 followed by 400 mg once weekly for next 7 weeks. However, the drug needs to be taken with caution with a high possibility of drug toxicity (including QTc prolongation, cardiomyopathy and retinal toxicity) and drug interactions.[32]

IL-6 pathway inhibitors

As mentioned above, coronaviruses including SARS, MERS and now SARS-CoV-2 induce a dysregulated chemokine response commonly termed as a "cytokine storm". The over-activation of effector T cells results in burst release of pro-inflammatory cytokines, thereby forming the pathobiological basis of clinical features like plasma leakage, increased vascular permeability, disseminated intravascular coagulation, acute lung injury and ARDS.[33] Numerous studies have shown that IL-6 is one of the major culprit cytokines in this uncontrolled inflammatory response. Similar to other viruses of this family, COVID 19 disease caused by

SARS-CoV-2 also shows a direct correlation of disease severity with plasma levels of IL-6. Initial studies in China have shown that drugs against IL-6 receptors like Tocilizumab (humanized monoclonal antibody against IL-6 receptors) have the potential to reverse cytokine storm and reduce morbidity. A Chinese retrospective study including 21 critically ill covid patients demonstrated that tocilizumab improved clinical profile (fever, hypoxemia) along with fall in inflammatory markers like CRP. The study also reported resolution of radiological changes in lungs with no significant adverse effects.[34] Treatment guidelines from China's National Health Commission include the IL-6 receptor inhibitor tocilizumab for patients with severe COVID-19 and elevated IL-6 levels. This agent, as well as sarilumab and siltuximab, which also target the IL-6 pathway, are being evaluated in clinical trials.[35]

Janus kinase (JAK) inhibitors

JAK inhibitors are a class of drugs that function by inhibiting the activity of one or more of the Janus kinase family of enzymes, thereby interfering with the JAK-STAT signalling pathway. Disease model studies predict that certain JAK inhibitors may block entry of virus into pneumocytes as they target members of the numb-associated kinase (NAK) family, including adaptor associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), both being involved in viral endocytosis.[36] Baricitinib, currently used for treatment of rheumatoid arthtritis by specifically blocking JAK 1 and JAK 2 subtypes has shown initial promise in management of cytokine dysregulation caused by COVID 19 as it mitigates the host inflammatory response and viral entry into cells. However, further human studies are warranted to establish efficacy and safety in COVID 19.[36]

Antivirals

A number of antivirals are undergoing clinical trials to analyse their possible therapeutic role in severe COVID 19. *Remdesivir*, a novel nucleotide analogue has shown efficacy against SARS-CoV-2 as well as SARS and MERS-CoV in vitro studies.[37,38] However, randomized human trials are ongoing to substantiate its possible use.[39] The drug is given via intravenous route and has potential concern for toxicity (nausea, vomiting, transaminitis and renal dysfunction). *Favipiravir*, a RNA polymerase inhibitor, currently being used for treatment of influenza is also under evaluation in clinical trials for treatment of COVID-19. In a study of patients with non-severe disease (including oxygen saturation >93 percent), use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days) and more frequent radiographic improvement (in 91 versus 62 percent by day 14) compared with lopinavir-ritonavir.[40]

Lopinavir-ritonavir, combined protease inhibitor, primarily in use for HIV infection, initially was reported to have beneficial effects in COVID 19. However, subsequent studies did not corroborate with the same. A randomized trial of 199 patients with severe COVID 19 established that there was no difference in time to clinical improvement or mortality at 28 days amongst patients given lopinavir-ritonavir (400/100 mg) twice daily for 14 days in addition to standard care versus those who received standard of care alone.[41]

Convalescent plasma

Convalescent plasma or passive antibody therapy is based on the principle of administering antibodies against a given agent to a susceptible individual for the purpose of preventing or treating an infectious disease due to that agent. It has the benefit of providing immediate immunity to susceptible persons as against active immunization which involves inducing the immune system of susceptible host and is time consuming. As a general rule of immunology, passive antibody therapy is more operative when used for prophylaxis or when administered shortly after the onset of symptoms. A possible

explanation for this temporal variation is that passive antibody works by neutralizing the initial viral inoculum, which is expected to be much smaller than that of severe disease.[42]

In the case of COVID 19 caused by SARS-CoV-2, the proposed mechanism of action by which convalescent plasma would offer protection is primarily viral neutralization. The sources of antibody for SARS-CoV-2 are human convalescent sera from individuals who have recovered from COVID-19, monoclonal antibodies, or those genetically engineered in certain animal hosts.[43] However, given the need to immediately curb this treacherous pandemic, the only antibody type that is currently available for instant use is that found in human convalescent sera. The number of potential donors are likely to increase as more individuals contract COVID-19 and subsequently recover.

There are reports that convalescent serum was used for therapy of patients with COVID-19 in China during the current outbreak.[44] Although the published data involves small numbers of patients treated, the results suggests that convalescent serum administration reduced viral load and was safe. The available historical evidence from the use of convalescent sera in patients with SARS and MERS, and anecdotal evidence from its use in 245 patients with COVID-19,[44] suggest it is safe. Nevertheless, the risks of administration of convalescent sera needs to be borne in mind which includes inadvertent infection with another infectious disease agent and reactions to serum constituents, including immunological reactions such as serum sickness. Also, the convalescent plasma is likely to be used in severe COVID patients with pulmonary disease, increasing the likelihood of transfusion related acute lung injury (TRALI) and the phenomenon of antibody-dependent enhancement of infection (ADE).[45]

IL-1 receptor antagonist (Anakinra)

Anakinra is a recombinant human IL-1 receptor antagonist. Studies in the past have shown that administration of drug leads to improved survival rates in patients of sepsis with macrophage activation syndrome (MAS) without causing any significant adverse reactions. Given, that IL-1 has a major role to play in cytokine storm with studies supporting elevated levels of IL-1β in patients with severe infection by SARS-CoV-2,[46] Anakinra seems to be theoretically beneficial in mitigating disease severity.

Anti TNF-α agents

Tumour necrosis factor alpha (TNF-α) is a cell signalling protein involved in systemic inflammation, being one of the major cytokines responsible for acute phase reaction. High levels of TNF-α have been observed in patients of COVID 19 with direct correlation with disease severity. It has proposed that Anti TNF-α agents may act as a potential treatment modality in managing COVID 19 disease and a randomized trial of Adalimumab (ChiCTR2000030089) is ongoing to elicit its efficacy.[47]

Corticosteroids

Systemic corticosteroids have been extensively used in the past during the epidemics caused by SARS and MERS and also were tried initially in the current ongoing pandemic of COVID 19. However, till date there is no substantial clinical evidence to support that corticosteroids are beneficial in the treatment of respiratory infection due to SARS-CoV, or MERS-CoV. Infact, studies have shown that early use of steroids during the SARS-CoV infection was associated with a higher plasma viral load with delayed viral clearance.[48] Theoretically, these drugs seem to suppress the systemic inflammatory response associated with ARDS. However, the available observational data suggest increased mortality and secondary infection rates in with corticosteroid therapy in such patients.[49] The current interim guidance from WHO on clinical management of severe acute respiratory infection occurring due to SARS-CoV-2 strongly advises against the use of corticosteroids unless

indicated for another reason.[50]

CONCLUSION

SARS-CoV-2, a new member of coronavirus family has hit the world with an unsolicited surprise causing COVID-19, a highly transmissible disease with varied clinical profile. The outcome of infection depends chiefly on host immune system response. The initial primary immune response is a protective reciprocation by the human body to facilitate viral clearance. However, the same immune response in certain cases overshoots, leading to a burst of cytokines thereby threatening host tissue integrity leading to a cytokine storm syndrome manifested as ARDS and multiple organ failure. In this uncertain and rapidly unfolding situation, we do not have the luxury of formal medical trials with long term follow up results. All that we can bank upon right now is an exchange of medical information and experiences of those countries that have had a head start on having had to grapple with the disease. Also, till the time definitive targeted therapies are discovered against this novel virus, the need of the hour is to utilize judiciously the drugs already available in the armoury of modern-day medicine. The immunological cytokine specific antibodies and new anti-rheumatic drugs may prove instrumental in the fight against COVID 19 as they can precisely target the key steps of the immune response that became dysregulated during the course of the disease. An approach in this regard may be to screen patients of severe COVID 19 disease for exuberant inflammation by measuring cytokines in an attempt to identify patients who will benefit from this selective immunosuppression. In this epoch of pandemic, while the major focus should be to control disease transmission by preventive strategies like social distancing and hand hygiene, parallel attempts are required to explore the available therapeutics to tackle with severe form of disease. This shall not only reduce morbidity and help in optimum utilization of limited health resources but will also buy some time for our fellow researchers to formulate a definitive treatment.

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How to cite this article: Maggo S, Dhull P, Dubey AP et.al. Cytokine storm syndrome in COVID-19: diagnosis and management strategies. Int J Health Sci Res. 2020; 10(5):140-149.

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