

THE WEEK

MAY 30, 2021

Plus

WAR TO

WIN

COVID-19

Coronavirus Disease 2019

WITH INDIA'S BEST MEDICAL MINDS



CRITICAL ILLNESS DUE TO COVID-19: EXPANDING TREATMENT LANDSCAPE

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MEDICAL MINDSPEAK

Overcoming Covid-19: Global inclusiveness, sharing best practices are the need of the hour



The second wave of COVID-19 is more severe and a greater number of cases are coming to the hospital with critical-illness; most of them are having the need to have more oxygen and intensive therapy is required. In such a situation, modern medical practitioners have to work hard. Inclusive approach is the need of the hour. Most importantly COVID pandemic need is to address the healthcare manpower augmentation because in the intensive care management or the severe cases management, we need trained manpower along with the therapeutic inputs. Let us all work with a common mission that the patients with severe COVID should be protected, should be able to return back to the family. I take this opportunity to thank all the committed, dedicated doctors working day and night in the ICUs and all the learned scientists who are working out ways to bring out the best of clinical and therapeutic options to save lives of critically-ill COVID patients as much as possible.

**Prof. Dr. J. A. Jayalal, National President
Indian Medical Association (IMA)**

Time factor is crucial: Standard evidence protocols need to be revisited



This COVID-19 pandemic has had devastating consequences all over the world. Intensive care units are full of ventilated patients due to coronavirus caused acute respiratory failure and the mortality is high, in some countries – very high. The ICU capacities had been expanded – but still not enough. Resources have also become exhausted including human, disposables and drugs alike. As there was no time to perform high quality randomized trials – although after one year some results are trickling in. Physicians were often left with intuition and pathophysiological rationale-based decisions. As some patients showed typical signs of dysregulated immune response, which can result in cytokine storm and multiple organ failure as a consequence that is accompanied by high risk of mortality, the concept of modulating the immune response became in the focus as one of the potential alternative therapies. One of them is extracorporeal removal of the circulating cytokines which can result in rapid hemodynamic stabilization and reduction the levels of cytokines, hence may improve the outcome. This has led to an increased worldwide interest in this technology. Whether this will be reflected by improved overall outcome – time will tell. The question remains: do we have time to wait for the evidence during these devastating times or not?

**Prof. Dr. Zsolt Molnar
Professor, Centre of Translational Medicine
Medical School, University of Pecs, Hungary**

Organic development of management protocol for COVID-19



COVID-19 caused by a novel Virus SARS-CoV2 has posed unique challenges in its management. In the absence of any definitive therapy, clinicians and policy makers have struggled to formulate management guidelines. Several repurposed drugs have been evaluated and are still being evaluated in the hope of providing optimal management to the COVID-19 patients. This gets reflected in the 'National Guidelines for COVID 19 management' as hosted in the MoHFW website. This is a living document which has incorporated changes as new evidence emerged. For example, there has been a paradigm shift in thinking regarding convalescent plasma therapy. In the beginning of the pandemic, this therapy was being used in severe, critically ill patients whereas, now the majority evidence suggests usefulness of high titer convalescent plasma only in very early period after infection. Similarly, corticosteroid, oral or parenteral have been added to the treatment protocol of moderate-severe COVID-19 in view of the emerging data regarding its usefulness. The development of management protocol for COVID-19 will continue to be a dynamic process until we can stumble upon a definitive cure or prevention.

**Dr. Aparna Mukherjee, MD (Peds) PhD, Scientist E
Clinical Trial & Health Systems Research Unit
Epidemiology and Communicable Diseases Division
ICMR, Department of Health Research, MoHFW,
New Delhi**

Cytokine storm management is crucial for critically-ill Covid-19 patients



Covid 19 has had devastating impact on the whole world and India is still suffering! The covid 19 disease progresses from viraemic early phase to cytokine storm late phase in second week of illness. It is not the virus which directly kills but it is the imbalance of cytokines (pro and anti-inflammatory endogenous chemicals) released by white blood cells activated by virus which lead to multi organ failure and death.

Except steroids, none of the other therapies decrease death rates hence we need to look at adjuvant therapies like CytoSorb device which reduces the cytokine (inflammatory) levels, requirement of vasoconstrictive drugs used for maintaining BP and may reverse organ failure and shock. It has been used in a large no of patients in India also and may help in attenuating effects of cytokine storm.

**Dr. Yatin Mehta
Chairman, Critical Care & ICU
Medanta The Medicity, Gurugram**

**Fear never
builds the future,
but hope does.**
— Joe Biden

"I can't help but notice how desperate, how incompetent, a physician can feel not being able to save the life of their own beloved. Saving lives — something you're trained for, something you do automatically — suddenly seems impossible."

— Lili Naghdi

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THE WEEK
Plus

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Editor: Philip Mathew

THE WEEK PLUS IS A MARKETING INITIATIVE

FOREWORD



In the midst of the COVID-19 storm, firstly, I would like to extend my best wishes to all the readers. Today, the entire humanity is engulfed by this microscopic monster. The health crisis has snowballed into an existential crisis. In these highly uncertain times, as India grapples to overcome the second tide, it is imperative to understand the science behind SARS-CoV-2 which shall be elucidated through prospective articles.

The Indian landscape presents an alarming picture. As per the estimates provided by the Indian Council of Medical Research (ICMR), the total infections in India have surpassed 2 crores and total deaths have crossed 2 lakhs. Recent studies have demonstrated that 14% develop severe disease requiring hospitalization and 5% need intensive care. Further, it has been recorded that, out of the total number of deaths, 70% have been attributed to Acute Respiratory Distress Syndrome (ARDS) and 28% to Cytokine Release Syndrome (CRS) and Sepsis. Some of the therapeutic strategies to address the cytokine storm in India include Corticosteroids, Tocilizumab, Itolizumab, Baricitinib, Ulinastatin, Convalescent plasma therapy and Blood purification systems (CytoSorb). Though the scientific communities are striving to upgrade, innovate and rediscover therapeutic alternatives still, currently our health care system is overwhelmed with limited resources and grappling to meet the daunting task.

I am thankful to "THE WEEK, Indian Medical Association, Indian Council of Medical Research and Biocon Biologics Ltd. for their support in creating this platform and making us part of organic dynamic process. The time is to scale up and revitalize our health systems which can enable India to fight for a better tomorrow.

Dr. Prachee Sathe
Director, ICU

Ruby Hall Clinic, Grant Medical Foundation, Pune

INDIA FIGHTS FOR A BETTER TOMORROW- A CONFERENCE ON CRITICALLY ILL COVID-19 PATIENTS- AN OVERVIEW

Starting the conference, "INDIA FIGHTS FOR A BETTER TOMORROW" organized by THE WEEK in collaboration with Indian Medical Association and supported by Biocon Biologics Ltd Dr. Prachee Sathe, talked about 'Critical Illness Due To Covid-19- Indian & Global Scenario.' She said that we are still in the middle of not only the second wave, but a Tsunami, in which we are all going to get wiped off completely if we are not very careful about picking it up early and preventing the patients from going into critical illness. India is the second worst affected only after the US.

Dr.Prachee added, " I wish we should have learnt from western experience, but probably we felt that we have learnt and contained it all and second wave turned out more fatal, with very high number of asymptomatic patients, hospitalizations and higher mortality. As per ICMR, 41.5% patients had oxygen requirement in first wave compared to 55% in second wave. One cannot fight missiles with a stick in the hand while infrastructure is failing miserably. The shortages of beds and oxygen supplies turning away the patients, never ever any intensivist will say no for a deserving patient which is so painful. The only thankful situation is availability of the vaccines where we should have taken advantage but till date, we have been able to vaccinate hardly 1.7% of our deserving population. About the treatment protocols AIIMS, Ministry of health and ICMR had been kind enough to develop and circulate. Home isolation was a great step forward in Indian scenario with lot of public centers for COVID isolation. People developing respiratory rates > 24 and breathless with oxygen saturation < 93 are advised to come to hospital.

Clinical monitoring during moderate disease is very important including some of the repeat laboratory tests, HRCT thorax or serial chest x-rays as needed, but unfortunately certain number of patients do still go in severe disease because of associated comorbidities. In terms of management Remdesivir-like drugs have really cost havoc in a way because it has come into perception of public as the only and useful and life-saving drug which it is not. Oxygen is perhaps the most effective life-saving drug, Remdesivir only could reduce the stay in the hospital by a few days and it cannot be used in renal or hepatic dysfunction and it is useful only if it is used in early phases of the disease, perhaps this is one of the drugs which is mostly misused. Tocilizumab is another drug initially came as a miracle drug, but it is not useful for each and every

patient and we have to choose a subgroup where it can be useful. Convalescent plasma came and went and it is being administered to certain patients preferably within 7 days of symptom, giving after that is of no use.

Cytokine storm now is a buzzword quoted in reference to the sepsis and septic shock. Ultimately, COVID also is the part of sepsis presenting with high levels of interleukins, TNF and leukotrienes. The symptoms of sepsis and cytokine storm cause death in 28% of fatal COVID-19 cases. ARDS is a single-organ failure may be associated with multiple-organ failure because of dysregulated immune response. This is a new disease completely and treatment is still emerging with most of the drugs being experimental in nature and none is still 100% useful or lifesaving. The cytokine storm in COVID is an eye opener and there are lots of things which we still have to learn."

Dr. Yatin Mehta spoke about 'Expanding the treatment landscape to regain control in critically ill patients in the Indian context'. Dr.Mehta said, "Sepsis definition basically includes only two things, sepsis and septic shock, the Systemic Inflammatory Response Syndrome (SIRS) concept in severe sepsis have been removed and what is it. Well, it is basically a life-threatening organ dysfunction caused by dysregulated host response, so the main points here are "life-threatening", "dysregulated host response" and "organ dysfunction". Host response is not the enemy which kills you, it's your response to the enemy which gives you attacks and leads to failing of every organ eventually. Despite the advances in therapy, the mortality still remains high in septic shock. Resuscitation and conventional therapies are of prime importance. Adjuvant therapies are to help the conventional therapies like steroids, immunoglobulins and hemoadsorption devices. There is one such hemoadsorption device which has got emergency use authorization by USFDA and DCGI that primarily removes the cytokines and hydrophobic substances between 10-55 kDa. It is not really a filter, it's an adsorber. This is compatible with conventional hemodialysis, CRRT and with extracorporeal circuits. It eliminates inflammatory cytokines, both pro and anti-inflammatory cytokines, DAMPs and PAMPs toxins and endotoxins, some toxins may be removed, it removes bilirubin and myoglobin, and it adsorbs free hemoglobin, ammonia and bile salts. It attenuates the capillary leak and helps in refractory hypotension, vasoplegic shock, cardiomyopathy and organ dysfunction by preserving capillary integrity,

reducing markers of circulation and decreasing need of vasopressors.”

Dr. Mehta further added, “It is very simple to use, > 1,20,000 devices have been used worldwide. It doesn't remove immunoglobins and albumin. It doesn't activate the coagulation system or complement system and it's all biocompatible. When do we start it, when patient of sepsis shows signs of deteriorating, organ dysfunction, vasopressors increasing, not responding to the initial resuscitation, then within 4-6 hours ideally one should start it. If you are measuring biomarkers like PCT increasing or interleukin-6 is high then this is the time to use it. Stopping depends on how your patient is responding. If there is no response to the first therapy, there may not be any point in using the second time, but if the patient is responding and after stopping the therapy the patient gets worse, then you can use a second device. Basically, endpoints would be reducing doses of vasopressors, decreasing levels of proinflammatory cytokines, improvement in organ dysfunction, PF ratio and liver functions, so this is the time to stop the CytoSorb therapy.

There are a lot of publications in cardiac surgery, liver failure, certain drug intoxications and snake poisoning most of the time comparing expected mortality versus the patient's mortality. It is a very safe device to use. We have used it in more than 100 patients of septic shock and found significant hemodynamic stabilization with reduction in vasopressor requirement, improvement in the severity scores and lab parameters. We also observed that survival outcomes were better in patients when CytoSorb was used within 48 hours of septic shock and chances of survival decreased with the delay in initiation of the CytoSorb therapy. With current treatment modalities, the extracorporeal therapies like CytoSorb provides window of opportunity to doctors to address immune dysregulation in critically-ill hyperinflammatory patients. CytoSorb use may improve survival, reduce ICU and length of hospital stay.”

Prof. Dr. Zsolt Molnar provided global update on Cytokine Adsorber, a potential treatment option in critically ill Covid 19 patients. The problem with critically ill patients that balance of pro- and anti-inflammatory process goes out of control and the pro-inflammation overwhelms anti-inflammation and patients can die due to multiple system organ failure which is caused by the cytokine storm. The cytokine storm is pivotal to COVID disease and can occur in inflammatory conditions like pancreatitis, major surgeries like cardiac surgery, liver failure etc. A very nice paper by Tay and co-workers which summarizes, The Trinity of COVID-19, the immunity, inflammation and intervention and the ways our body can protect us from the invading virus. In this patient population, we have tested mechanical removal of cytokines with adsorption. Key opinion leaders in intensive care Jean Louis Vincent, Paolo Navalesi and Claudia Ronco have emphasized that in Covid-19 patients' hemoadsorption and hemoperfusion should be considered. Dr Durham from the United States treated very ill patients who required ECMO therapy along with CytoSorb and all three patients were discharged and this case had a media reflection. About the published data, well we don't have much but we have some. A small preliminary analysis coming from Freiburg Germany, COVID-19 pneumonia patients requiring ECMO therapy were randomized into cytokine adsorption and without cytokine adsorption showed rapid removal of IL6

with adsorption device compared to controls. A case report, again a very ill patient, COVID-19 pneumonia on VV-ECMO when started on CytoSorb therapy the cytokines, C-reactive protein, IL6 decreased rapidly which was also followed by a decrease in noradrenaline and this report also recommended its use. A very small study from Italy and patients with the COVID-19 pneumonia who were treated with CytoSorb had pretty good survival rate while everybody in the control group died, of course we are only talking about a few patients here but they observed a rapid decline and reduction in the oxygenation in those patients who did not receive CytoSorb. While it was more or less stable both in survivors and non-survivors, so there was a little bit of a drop in non-survivors but the CytoSorb treated patients did better than those who did not receive CytoSorb therapy and investigators concluded that their experience suggests the potential beneficial role of adjuvant therapy in these patients. The most relevant data that we have so far is coming from Saudi Arabia in adult patients who needed intubation or renal replacement therapy and had life-threatening COVID-19 infection. In this study of 50 patients 35 survived and 15 died, within short treatment period of two days, noradrenaline was stopped in every survivor, lactates normalized and IL6 levels decreased. A paper is being submitted as we speak, about the conditions where CytoSorb therapy could be considered; conditions like refractory vasoplegic shock, severe ARDS patients who require ECMO, patients with COVID-19 infection developing acute kidney failure stage 3 requiring renal replacement therapy and those who have very high H score suggesting a cytokine release syndrome.”

Dr. Aparna Mukherjee from ICMR, talked about organic development of clinical management guidelines for covid-19 patients in India stating the organic development because as it is a living dynamic process because there is nothing set in stone. It's a new virus, a new disease with unprecedented spread across the world. It was always supposed to be a bridging therapy till we could find some kind of a cure because definitely is definitely biological plausibility, plasma of somebody who has recovered from COVID-19 should have antiviral neutralizing antibodies. Apart from that, it has shown to have some other effects like the antibody-dependent cytotoxicity complement activation with plethora of anti-inflammatory cytokines that could help in cytokine storm. With this background whole process of convalescent plasma started. We at ICMR, wanted to generate our own Indian data, which is very important and with the help of number of medical colleges and hospitals across the country who stepped in to participate in this RCT. We were able to complete it within four months of the start of the pandemic and this open label RCT included moderate COVID-19 patients with respiratory rate > 24, SpO2 < 93% or PF ratio of 200-300. We wanted a hard end point so, the composite measure of either progression to severe disease or any cause mortality within 28 days were our primary endpoints. We gave two doses of 200 ml of convalescent plasma 24 hours apart and that was compared with the best standard of care that was available. We had 464 randomized patients and 235 Vs 229. The mortality within 28 days was 14.9 and 13.8, so that's like hardly any difference. We really have to select our patients, give them high titer, only then maybe we can see some effect anecdotally. We had the landmark recovery trial which reported that dexamethasone does work, steroid in any form

basically works and reduces all-cause mortality. But again we have to be careful as to when we are giving it because we may actually do more harm than good if we are giving to patients who are in mild disease with no breathlessness or any need of oxygen therapy as by doing so we are going to increase the viral replication. It should only be given to patients who need oxygen support or require mechanical ventilation then only it will be helpful.

Solidarity trial for Remdesivir could not show any mortality benefit at day 28. The network analysis by WHO also shows no mortality benefit when all five RCTs have been taken in that. Still now Remdesivir remains an investigation therapy and has to be given only in hospitalized patients on oxygen. It needs to be given in the viremia phase, not when the patient is already deteriorating because of the cytokine storm and going into mechanical ventilation and we all have to remember that it's not life-saving. Azithromycin, which seemed to be the wonder drug was being given in all types of severity, while it should only be given in the mild phase. Similarly for Ivermectin we need more evidence. We have a very good well-conducted RCT which is recently being published which used inhaled budesonide, if people are having persisting symptoms beyond five days of onset, inhaled budesonide might be used. It might show recovery and since this is anyhow used so widely and we know there are not much side effects. Tocilizumab again is an expensive drug, severely/ critically-ill patients, it might show some bad effect, but here also there have been changes, developments as we started with a higher dose of 8 mg/kg, but their doses have been reduced and now it is being recommended at 4 to 6 mg/kg for whatever worth it is. There is always a change, a paradigm shift in what we are thinking as treatment today and what we might think as treatment tomorrow.

Dr. J.A. Jayalal, National President, Indian Medical Association talked about overcoming covid-19- a case of global inclusiveness; sharing best practices. The second wave of COVID-19 is more severe and a greater number of cases are coming to the hospital with critical-illness; most of them are having the need for more oxygen and intensive therapy. In such a situation, modern medical practitioners have to work hard. Inclusive approach is the need of the hour. There are three important points we need to address first is the healthcare manpower augmentation because that is going to be a very important thing in the intensive care management or the severe cases, we need trained manpower along with the therapeutic inputs. Second, we need to curtail this chain. The break the chain consult has to be there. Government has to take a decision of enforcing a lockdown, we shall not think of economic burden at this moment, but living alone and sustaining the life is more important than thinking of the economic burden. The third is COVID appropriate behaviors and adhering to that and having a zero tolerance is the most important thing, but more so, open in front of us is the vaccination.

Let us all work with a common mission that the patients with severe COVID should be protected, should be able to return back to the family. I take this opportunity to thank all the committed, dedicated doctors working day and night in the ICUs and all the learned scientists who are working out ways to bring out the best of clinical and therapeutic options to save lives of critically-ill COVID patients as much as possible.

An important panel discussion on "War to Win- Roadmap for a Better Tomorrow" with esteemed panelists including Dr.

S. Rajesh, Dr Aparna Mukherjee, Dr. Abdul Samad Ansari, Dr. Purvesh Umraniya, Dr. Rajib Paul, Dr. Krishna Patil and Dr. Dipanjan Chatterjee was moderated by Dr Prachee Sathe.

Dr S Rajesh talked about preparedness of government and strategies to navigate through this severe grim situation of upsurge and mortality and testing facilities. He stated that more than 19 lakh tests have been done and now we have more than sufficient levels of production capacity in the country with respect to RT PCR and rapid antigen kits.

Dr. Yatin Mehta emphasized that one should be open to newer ideas and the use of accurate therapies like for cytokine storm that leads to organ dysfunction and kills, so anything which we can attenuate the cytokine storm may be helpful, but we need to analyze the data and keep our minds open, that is what I would suggest. He also stated that Transplant patients who are on immunosuppressants should receive the COVID vaccination as there is no contraindication.

Dr. A S Ansari and Dr Purvesh Umraniya shared their experiences of treating critically ill COVID patients from Maharashtra and Gujarat respectively. Nearly 4,000 cases at Nanavati Hospital and as a group, Max Group has treated 26,000 cases over the last one year have been treated. Institutional mortality rate has been fluctuating between 5.5 to 6.4%, but we anticipate that ICU hardcore mortality may go up to 15 to 18%, at times even 20% and sometimes at dismal 50-55% in a bad case scenario. Use of oxygen therapy in an escalated manner, going up to high-flow nasal cannula and trying to defer invasive ventilation as much as possible doing awake proning. Steroids were used in approximately 60% of the patients before and now up to 80-90% of the patients with steroids in the intensive care.

Dr Prachee Sathe highlighted the rising incidences of mucormycosis in relation to irrational use of steroids and recommended judicious use of steroids. Dr Aparna reemphasized the importance of correct dose of steroid i.e., 6 mg per day dose of dexamethasone or equivalent.

Dr. Rajib Paul gave an interesting update that the three pillars of success in management of COVID-19; 1 is ICMR, second is the IMA and third is the Industry and Dr Prachee added forth as ICU. He also said that prioritization of patients in the ICU is of help in identifying patients who need early ventilation.

Dr. Dipanjan Chatterjee shared his experiences with ECMO in COVID-19 patients and receiving the referrals." He shared that patients who have had cytokine storm on ECMO, use of CytoSorb has given results. The mortality rate in first COVID phase was almost 60%, so 40% of patients who were not getting oxygenated even on ventilation, they went home with ECMO support.

Dr. Prachee Sathe concluded with take home message that it is important that instead of wasting initial time of 3-4 days after the symptoms have started, testing should be done immediately and isolation should start immediately. We may start using masks even at home for reverse isolation of elderly people at home so that we are not spreading the disease for them. "We must pick up the patients who have got the potential of going into the severe disease and probably the adjunctive therapies would be useful for them at an early stage of progression."

Dr. Niranjana Panigrahi
Consultant, Critical Care Medicine
Apollo Health City, Hyderabad

FIGHTING THE COVID-19 BATTLE – A GLIMPSE INTO THE FRONTIER



The financial capital of India is struggling to overcome the second viral wave. Maharashtra and especially, Mumbai, has remained in the eye of the COVID-19 storm since the time it has landed and inflicted devastating consequences. In spite of this, the city

has shown a gritty resolve and has kept outmanoeuvre the vengeful virus so far.

According to the preliminary estimates, only 3-10% of the infected cases may need intensive care and the case fatality rate varies as per the comorbidity and the presentation of the infected population. As compared to the first, the second wave has seemingly higher infective potential though there are no consistent report of higher mortality. The timely triage and an appropriate initial intervention plays the crucial role in defining the outcome of the sickest patients. Mild to moderate cases can be comfortably managed with home-isolation and supportive care. Several studies highlight the relationship between early identification and improved outcomes. Seamless transition from Covid Care centre to dedicated Covid hospitals is critical for ensuring continuity of care and provision of timely organ support for worsening clinical trajectory. Some of the important parameters which needs attention are resting oxygen saturation (SpO₂), Respiratory rate and exertional desaturation (a drop in saturation of >2% after 6 min walk test) and other biochemical parameters like D-Dimer, IL-6, LDH, CRP and serum ferritin. Extreme fatigue and incessant cause despite supportive care may herald the onset of clinical worsening. Gentle mobility, good hydration, breathing exercise and frequent position changes (awake prone position) can help in recovery along with the supportive care.

At Nanavati COVID Care Centre, the treatment strategy has been adopted in consonance with the ICMR clinical guidance and global best practices. Most of the patients admitted in our ICU are suffering from either severe acute respiratory distress syndrome (ARDS), cardio vascular syndrome (ACovCS), Cytokine Release Syndrome (CRS) and/or Sepsis with multi-organ dysfunction. Most of this patients need close monitoring of vital parameters and suitable organ support (ventilatory, circulatory, renal support and blood purification etc).

Sepsis is the major contributor for poor outcome which re-

sults from life-threatening multi-organ dysfunction in addition to dysregulated host response. If there is an undue delay in the diagnosis or inappropriate treatment regime, the outcomes can be devastating and mortality rate goes up to 50%.

The appropriate treatment regimen is based on surviving sepsis guidelines (bundle of care as defined by international society of physicians and intensivists). The standard treatment includes timely fluid resuscitation, appropriate oxygen support (high flow nasal oxygen, non-invasive ventilatory support and invasive ventilatory support in carefully selected patients), blood thinners, anti-viral and immunomodulatory therapies (to address excess immune response).

In patients with overwhelming inflammatory response also known as Cytokine Storm, the first line of treatment remains corticosteroids, immunomodulatory agents like tocilizumab, Most of the patients respond, however, some need more intensive care in terms of extracorporeal life support and extracorporeal Hemoadsorption therapies (CytoSorb) which has been given emergency use authorisation by governing bodies.

These therapies help by eliminating excessive cytokines and other harmful toxins to provide stabilization of respiratory and circulatory system. Multidisciplinary consultation and shared decision making for optimal timing of this device can be very useful in mitigating the deadly cytokine storm. The current evidence for all this adjuvant measures is still evolving and being repeatedly examined in multi centric trials across the globe.

All said and done, COVID has been the touchstone for health care delivery and resilience of front line workers. A synchronized approach to break the transmission with COVID appropriate behaviour in the society would be crucial to offload pressure of already strained healthcare machinery. Meaningful public and private partnership to provide care to the most needy, neglected, sickest strata of our population would be essential to contain the ongoing damage.

Together we can subdue this virus with a meticulous attention to personnel hygiene, social distancing and participating whole heartedly in the vaccination program.

**Dr. Abdul Samad Ansari, Director Critical Care
Nanavati Super Speciality Hospital
Mumbai, Maharashtra**

FRIENDLY FIRE DUE TO COVID-19 VIRUS



As India braces for the third wave, predicted by the several national and international experts, there has to be mass awareness on ground regarding management of severe COVID patients. As per the recent estimates, 5% of the infected

patients land up in the intensive care units necessitating state of the art therapies and support systems. Majority of the patients progress towards a condition called as sepsis which is manifested by dysregulated host response to infection. This condition is alarming and has a mortality risk of 30-40%. The crux of the matter is our immune system which acts as a dual edged sword. As part of the normal defence, immune system acts like a friendly fire which helps us to destroy the pathogens whereas like anything else, if left uncontrolled can destroy

our body as well. The "Friendly fire" is what helps in killing the coronavirus, which is normal inflammatory immune response to any infection. But when our immune system unleashes a so-called "cytokine storm" into the blood, it overwhelms the body with infection-fighting proteins (cytokines) that can trigger multiple-organ failure and death in Critically ill Covid Patients.

This brings us to the management of the immune response. As per the standard protocol, immunomodulators viz. corticosteroids and biological drugs are predominantly used to contain the cytokine storm. However, due to non-specific action of available drugs and specific timing of use, the use remains restricted. Thus, there emerges the need to eliminate excessive cytokines without compromising safety of the patients. I have experienced & examined the critical covid

patients with hyperinflammation & cytokine storm due to overwhelming immune Response. The new edge technology like the extracorporeal therapy such as CytoSorb (Cytokines Adsorber) which removes excessive cytokines (Majorly IL 6) & other mediators from blood. As a clinicians & intensivist, I have used this therapy to modulate the Immune response (i.e. turning unfriendly fire into the friendly fire). This therapy

helps & supports conventional treatment & improves overall hemodynamic parameters of covid patients. This extracorporeal therapy is safe & efficacious but must be used under supervision of medical practitioner & Intensivist only.

Dr. Purvesh Umrana
Consultant Intensivist

Bhailal Amin Hospital, Vadodara

THE ART OF MANAGING SEVERE COVID-19 PATIENTS



It is as much an art as it is a science when it comes to treating severe COVID-19 patients.

The coronavirus continues to multiply in geometric progression with little signs of abatement. The sequential waves are eroding our well-being, leaving scanty air to breathe.

India today, is in the eye of the storm, with limited resources at hand, it is an Achilles heel to manage critically ill patients.

The pathophysiology of severe COVID-19 patients points out the role of the “cytokine storm” in pulling the condition southwards, where the mortality risk can range from 30-40%, which is exceptionally high. Cytokine storm is considered a dual-edged sword. While an adequate immune response is desired to eliminate the virus, excess of it, due to the inability to tame down the response, can have debilitating effects on our body. It is well established that, the cytokine surge, which in this case, induced by the SARS-CoV-2 virus, is responsible for hemodynamic instability, circulatory shocks (Disseminated Intravascular Coagulation-DIC), sequential organ failure viz. Acute Respiratory Distress Syndrome, Cardiovascular shock, Acute Kidney Injury and Acute Liver Injury.

In India, the Indian Council of Medical Research has laid down the treatment protocol for critically ill patients which is considered to be the standard of care and remains indispensable. It is all about setting the basics right. Besides providing basic treatment, continuous monitoring and proactive interventions are necessary. COVID-19 presents an uncertain situation where the treatment outcomes vary across patients. Thus, documenting subtle nuances is critical at this juncture. This is also the time where, a physician can use his innovative skills to utilize various treatment regimens to improve the outcomes, keeping safety primary.

Furthermore, we at Apollo hospitals believe in the science of art where the treatments are human-centric, infused with values like empathy and care. These soft aspects are usually side-lined and this is precisely what is required. I would like to share one of my cases, where we were able to improve the

patient's outcome using innovative but licenced therapeutic strategies.

A 61-year elderly male, having a history of Renal transplant, Chronic Liver Disease, Diabetes and Hypertension was infected with COVID-19 and was admitted to our ICU. He had a high-grade fever, with escalated heart and respiratory rate. Moreover, his blood investigations revealed very low oxygen, high blood acid levels and high inflammatory markers besides poor renal and pulmonary functions, thus necessitating organ support (Ventilation for lungs and dialysis for kidneys).

As per the protocol standard of care was ensured. However, even after few days, improvements were not visible. At this moment, the team decided to initiate a Hemoadsorption device - CytoSorb (which was granted the Emergency Use Authorization by the US FDA and DCGI), which is designed to remove excess cytokines (inflammatory molecules) and improve hemodynamic functions. After its use for over 24 hours, we were able to find a noticeable improvement in the medicines required to maintain blood pressure (indication of hemodynamic improvement). Gradually, the circulatory and metabolic indicators started showing positive movement. The standard of care started showing its effects. After few days, organ support was weaned and the patient was discharged from the ICU without any adverse event being reported. We were delighted to have used this novel therapeutic, acting as an adjuvant to the standard of care, which helped us to save a life.

Nonetheless, the evidence suggests a low case fatality rate for COVID-19, yet, and such type of therapy is reserved for the very sick and under experienced hands. .

Despite all this it is the utmost responsibility of every human being to contribute to the end of the pandemic by following COVID appropriate behaviour. As the age-old adage says, “An ounce of prevention is worth a pound of cure”, everybody must take maximum precaution and stay alert.

Dr. Rajib Paul
Sr. Consultant Physician & Intensivist
Apollo Hospital, Hyderabad

UTILITY OF ECMO IN COVID 19



The second wave of COVID-19 continues to rage, with more than 4 lakh new patients and more than 4000 people losing their lives daily. The commonest cause of death is inadequate oxygen in the blood, as the virus severely affects the lungs. Although various

modes of supplemental oxygen are used such as oxygen mask, high flow nasal oxygen, BiPAP and invasive mechanical ventilation, all of them depend on the lungs to transfer oxygen to the blood. With increasing lung involvement, there is a state of severe Acute Respiratory Distress Syndrome (ARDS), where the lungs become stiff and blood oxygen levels drop below permissible limits, despite ventilatory support. If untreated, lack of oxygen (hypoxia) affects the function of

other organs, eventually leading to irreversible multiorgan dysfunction and death. Extra Corporeal Membrane Oxygenation (ECMO) is utilized in such situations. This acts as an artificial lung where patient's blood is passed through an artificial membrane lung, through which exchange of oxygen and carbon dioxide takes place, and this oxygenated blood is returned to the patient. Blood flow through the circuit is 4-5 L/min, maintained by a centrifugal pump. Heparin anticoagulation is essential to prevent blood from getting clotted within the circuit. With the initiation of ECMO, the patient's ventilatory support is reduced, to give lungs rest.

This enables the recovery of the diseased lungs. ECMO is continued till the lung function improves, pneumonia is cleared and blood gas parameters are satisfactory. Thereaf-

ter, the ECMO support is gradually weaned off. Patients usually need ventilatory support for few more days till complete lung recovery.

The duration of ECMO support in COVID-19 is prolonged, approximately 2-4 weeks, sometimes even more. They need critical care and nutritional support, to maintain Hemodynamics and prevent secondary infections. Various parameters are continuously monitored by the specialized ECMO team comprising of doctors, nurses, perfusionists and assistants. They need blood product transfusions to maintain haemoglobin level and balance anticoagulation and thrombosis. Some patients develop cytokine storm while on ECMO support, where the outcome is bleak. We have used CytoSorb, a cytokine adsorber, in these patients, some of whom respond favourably without any adverse events. CytoSorb is easy to integrate in ECMO setup and helps to regain control in the patient critical condition. Physiotherapy and mobilization are important in the rehabilitation of patients once they are stable on ECMO and more so after ECMO removal. ECMO in COVID-19 is initiated as rescue therapy, to prevent impending death due to hypoxia. It provides oxygen to maintain vital organ function and life of the patient, till the patient's lungs recover. Approximately 40-60% of patients recover to go home, depending upon

the age, other comorbidities and other organ involvement. In some patients where lungs develop significant fibrosis and don't recover despite prolonged lung rest on ECMO, there is an option to go for lung transplantation. ECMO is a scarce resource, hence a meticulous selection of patients is needed. During a pandemic, the demand for ECMO has increased exponentially. We are running the largest ECMO centre in Asia, with 30 ECMO systems running simultaneously. More than 100 COVID-19 patients have been treated on ECMO, yet the demand remains unfulfilled. Patients in remote locations, who are too sick to be transferred on ventilation, have been retrieved on ECMO and shifted safely to our unit, by both, road and air ambulance. Not all hospitals can have such large setups. Hence, we need to develop a referral system for the sickest patients to enable a smooth transition. The present pandemic has forced us to rethink, innovate and increase our capacity to deliver quality care. In these trying times, it is the smiling face of patients, which inspires us to continue to strive for excellence and perfection.

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ROLE OF EXTRACORPOREAL CYTOKINE HEMOADSORPTION ADJUVANT THERAPY IN SEVERE COVID-19 PATIENTS WITH ACUTE KIDNEY INJURY



The recent studies published in the American Journal of Nephrology highlights the magnitude of acute kidney injury (AKI) that develops in 40% to 60% of COVID-19 ICU patients, including 20% to 30% who require renal replacement therapy (RRT). AKI in COVID-19 patients is frequently severe – 31-66% of AKI patients have Stage-3 AKI, and 14-55% of cases require RRT. Moreover, the COVID-19 patients with AKI have high mortality ranging from 35 to 71%. In comparison, the mortality rates in COVID-19 hospitalized patients without AKI are in most cases much lower, around 6%. Therefore, early recognition of kidney involvement in COVID-19 and the use of suitable therapeutic measures are crucial to reduce morbidity and mortality.

AKI is a clinical syndrome that is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function).

There are multiple challenges in dealing with AKI. First, it rarely has sole and distinct pathophysiology. Many patients with AKI have a mixed aetiology where the presence of sepsis, ischaemia and nephrotoxicity often co-exist and complicate recognition and treatment. Second, the syndrome is quite common among patients without critical illness, thus difficult to diagnose early. Third, the current diagnostic approach of AKI is based on an acute decrease of Glomerular Filtration Rate, as reflected by the rise in serum Creatinine levels and/or a decline in Urine output over a given time interval. However, their significance as an independent determinant is under serious investigation. Fourth, the availability of Renal Replacement Therapies is under stress due to overburdening of health systems. Nonetheless, AKI is manageable with standard of care and novel adjuvant treatments.

In severe COVID-19 patients, the underlying cause of AKI is the Cytokine Release Syndrome (CRS). Despite the standard of care and immunomodulatory medications in place, it is extremely difficult to tame the cytokine storm. Although some medications are available, they are non-specific and can have unintended effects. Hence, there is a need to adopt novel therapeutics which can help us to eliminate the excess cytokines and other toxins. One such device is worthy of mention-CytoSorb.

It is an extracorporeal Hemoadsorption device, based on adsorption technology, which removes excess cytokines from the blood. It is generally integrated with Dialysis machines (HD/SLED/CRRT), Extracorporeal membrane oxygenation (ECMO) or Heart-Lung machine-CPB. The entire circuit is primed with an anticoagulant to prevent blood clots and the time duration of the single-use operation is 24 hours. It is important to note that, the therapy is used as an adjuvant therapy along with the standard of care. At the onset of the pandemic, where the cytokine storm became the new buzz word, the regulatory authorities across the world felt the need for such therapy. Hence, US-FDA and DCGI-India granted the Emergency Use Authorization (EUA) with immediate effect. Several studies were carried out and are currently ongoing, based on which some key recommendations were released. Some of the notable ones are- The recommendations by Brescia Renal COVID Task Force and published by the Italian Society of Nephrology and The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), to specifically use CytoSorb in severe COVID-19 patients with Stage-3 AKI receiving Continuous Renal Replacement Therapy (CRRT). Moreover, the recent National Guidelines on adult COVID-19 patients from Panama recommend CytoSorb therapy. In addition, the recent Handbook of COVID-19

Prevention and Treatment from Zhejiang University School of Medicine, China, as well as the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th Edition) are also recommending blood purification to treat cytokine storm in critical cases of COVID-19 infection.

In light of all this, CytoSorb therapy appears to be a promising and important therapeutic option to help manage the serious complications caused by cytokine storm and hyper

inflammation in critically ill COVID-19 infected patients. We expect to have more data and evidence on the use of CytoSorb as an adjuvant therapy in selected cases as our experience is very limited and we are only 15 months into the pandemic.

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SUCCESSFUL USE OF CYTOSORB THERAPY IN AN ELDERLY, CRITICALLY ILL COVID 19 PATIENT WITH COMORBIDITIES



In these tough times of COVID-19 pandemic, when we all are engulfed by negative news around us regarding increasing number of patients, deaths, shortage of beds, oxygen, medicines and medical supplies. Therefore, we thought of sharing some positive news from Medicover Hospitals, Aurangabad. A team of doctors have recently used CytoSorb therapy successfully in an elderly critically ill patient with comorbidities. Following is the case summary for your reference.

An 82-year-old male with multiple co-morbidities like Diabetes, Hypertension and Kidney disease was admitted with breathlessness, reduced appetite and reduced urine output. He had been treated for COVID-19 infection a couple of weeks before. In view of hypoxia, kidney disease and blood pressure he was admitted in the intensive care unit under the care of kidney specialist Dr. Sachin Soni.

Further investigations showed features of worsened pneumonia, sepsis and kidney failure. He was started on antibiotics, haemodialysis, non-invasive ventilator and medicines to improve hemodynamic parameters. He was also found to be in the phase of post COVID Cytokine Storm. As he was not responding to the ongoing therapy, Dr

Soni discussed the option of the CytoSorb therapy with the relatives. After their consent, the procedure was performed for 12 hours without any complications. The patient showed significant clinical and laboratory improvements. Gradually his condition improved, dialysis was stopped and he was discharged.

CytoSorb is an extracorporeal cytokine adsorber which removes excessive harmful cytokines from the blood circulation. This type of treatment is in vogue since several years and has largely been used in patients with sepsis and septic shock. However, due to emergence of COVID-19 pandemic and associated cytokine storm, this type of therapy may find its rightful place. Western countries are using this type of therapy in COVID-19 related cytokine storm. Importantly, Drug Controller General of India (DCGI) alongside US FDA, have approved this therapy under the Emergency Use Authorization (EUA) category.

Such adjunctive therapy can be more useful and patient friendly, opines, Dr Sachin Soni.

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IMPACT OF SARS-COV-2 BEYOND LUNGS



Emerging evidence shows AKI prevalence of 23% among the COVID-19 critically ill patients. When the kidneys stop working suddenly, over a very short period (usually two days or less), it is called acute kidney injury (AKI). It is very serious and requires immediate treatment. Unlike kidney failure that results from kidney damage that gets worse slowly (Chronic Kidney Disease), AKI is often reversible if it is picked up and treated quickly. Excessive immune response (as measured by CRP and IL-6) in COVID activates certain coagulation factors leading to hypercoagulability (excessive clot formations). These further triggers our immune response, creating a vicious cycle. This mechanism not only impacts the lungs but severely impact kidneys leading to multi-organ dysfunction syndrome (MODS).

Therefore, to break this cycle organ support becomes important. Patients with AKI are treated with dialysis along with novel hemoadsorption technologies, wherein the kidney functions are transferred to a machine for a short period until the body regains control.

We, at Sunshine hospital, Hyderabad, have come across many COVID-19 patients with AKI. Here, I would like to

share a noteworthy case report of a 37-year male COVID-19 patient, a known case of hypertension admitted in stable condition. However, on Day-7, his clinical and laboratory parameters started worsening. It was an indication of the cytokine storm (elevated levels of leukocytes, CRP and IL-6 associated with poor lung performance with deranged kidney function tests). Along with the standard of care, we initiated a novel Hemoadsorption device, CytoSorb placed along the hemoperfusion (dialysis). After 12 hours of use, inflammatory markers reduced, vasopressor requirement tapered and lung performance improved. Similarly, the second device was used. We observed steep reduction in IL-6: 92% after 1st device and 58% after 2nd along with noticeable improvements in major clinical and laboratory parameters. Right therapy at right timing is the key that led to hemodynamic stability, reduced stay in ICU and hospital.

However, due to the limited availability of data, extensive studies elucidating the relationship between COVID-19 and AKI are warranted. At the same time, the role of novel therapeutics needs extensive and rigorous examination.

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CYTOSORB THERAPY FOR CRITICALLY-ILL COVID-19 PATIENTS: THE RATIONALE

CytoSorb is a European Union-approved extracorporeal cytokine adsorber, designed to broadly reduce cytokine storm and other inflammatory mediators in the blood that could otherwise lead to uncontrolled systemic inflammation, organ failure, and death in many life-threatening illnesses. CytoSorb is broadly indicated for use in situations where cytokines are elevated, which includes the treatment of COVID-19 complications. CytoSorb has been used safely worldwide, primarily in the treatment of systemic hyperinflammation in a wide variety of life-threatening conditions such as septic shock, influenza, ARDS, secondary HLH, trauma, liver failure, pancreatitis and many others. In the majority of reported cases, CytoSorb therapy has been used safely to treat many of the complications of organ dysfunction and failure in bacterial and viral sepsis, seen also in patients with COVID-19 infection, including ARDS, shock, and other complications. For example, CytoSorb therapy is associated with hemodynamic stabilization and a reversal of shock, as indicated by a reduction in vasopressor need and improvement in lactate clearance in many studies. CytoSorb has also been used safely with positive clinical outcomes in the treatment of ARDS with both CRRT and ECMO. Animal and cell culture studies support a potential role of CytoSorb in protecting endothelial tight junctions against hyper-inflamed serum, which may translate into reduced capillary leak syndrome, as well as a modulation of pulmonary metabolism, edema formation, and cell mediated infiltration and injury to the lungs. CytoSorb therapy has also been used successfully in documented cases of secondary HLH. Recent recommendations on the management of HLH patients mention cytokine adsorption, which may aid in rescuing critically-ill patients from a deleterious cytokine storm.

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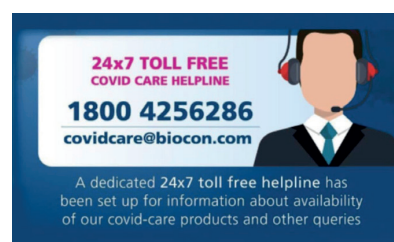
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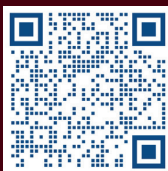
CRITICAL ILLNESS DUE TO COVID-19

EXPANDING TREATMENT LANDSCAPE

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