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Contents

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EDITORIAL

- 61 New Year's greeting and overview of *World Journal of Critical Care Medicine* in 2021
Wang LL

REVIEW

- 66 Sepsis: Evidence-based pathogenesis and treatment
Pravda J
- 81 What we learned in the past year in managing our COVID-19 patients in intensive care units?
Nitesh J, Kashyap R, Surani SR

MINIREVIEWS

- 102 Glucocorticoid and mineralocorticoid receptor expression in critical illness: A narrative review
Vassiliou AG, Athanasiou N, Vassiliadi DA, Jahaj E, Keskinidou C, Kotanidou A, Dimopoulou I
- 112 Predictive modeling in neurocritical care using causal artificial intelligence
Dang J, Lal A, Flurin L, James A, Gajic O, Rabinstein AA

ORIGINAL ARTICLE**Retrospective Study**

- 120 Emergency service results of central venous catheters: Single center, 1042 patients, 10-year experience
Coskun A, Hincal SÖ, Eren SH

SYSTEMATIC REVIEWS

- 132 SARS-CoV-2 (COVID-19), viral load and clinical outcomes; lessons learned one year into the pandemic: A systematic review
Shenoy S

META-ANALYSIS

- 151 COVID-19 and resuscitation: La tournée of traditional Chinese medicine?
Inchauspe AA

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What we learned in the past year in managing our COVID-19 patients in intensive care units?

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Abstract

Coronavirus disease 2019 is a pandemic, was first recognized at Wuhan province, China in December 2019. The disease spread quickly across the globe, spreading stealthily from human to human through both symptomatic and asymptomatic individuals. A multisystem disease which appears to primarily spread *via* bio aerosols, it has exhibited a wide clinical spectrum involving multiple organ systems with the respiratory system pathology being the prime cause of morbidity and mortality. Initially unleashing a huge destructive trail at Wuhan China, Lombardy Italy and New York City, it has now spread to all parts of the globe and has actively thrived and mutated into new forms. Health care systems and Governments responded initially with panic, with containment measures giving way to mitigation strategies. The global medical and scientific community has come together and responded to this huge challenge. Professional medical societies quickly laid out "expert" guidelines which were conservative in their approach. Many drugs were re formulated and tested quickly with the help of national and international collaborative groups, helping carve out effective treatment strategies and help build a good scientific foundation for evidence-based medicine. Out of the darkness of chaos, we now have an orderly approach to manage this disease both from a public health preventive and therapeutic standpoint. With preventive measures such as masking and social distancing to the development of highly effective and potent vaccines, the public health success of such measures has been tempered by behavioral responses and resource mobilization. From a therapy standpoint, we now have drugs that were promising but now proven ineffective, and those that are effective when given early during viral pathogenesis or later when immune dysregulation has established, and the goal is to help reign in the destructive cascade. It has been a fascinating journey

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for mankind and our work here recapitulates the evolution of various aspects of critical care and other inpatient practices which continue to evolve.

Key Words: COVID-19; Respiratory support; Renal replacement therapy; Extracorporeal membrane oxygenator; Medications; Therapeutics

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Core Tip: Severe acute respiratory syndrome coronavirus 2 transmission and the inpatient therapeutic management of coronavirus disease 2019 has been subject of immense research in the past one year. Our knowledge and understanding of the virus and the treatment of the disease continue to evolve. We attempt to summarize the progress made in a concise but comprehensive manner along with our insights into future directions.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported and widely believed to have originated at Wuhan in the Hubei province, China in late December 2019[1]. It started as a Zoonotic disease and gained a foothold in human population by person-to-person transmission, having evolved into a destructive pandemic infecting more than 100 million people and has caused more than 2.2 Million deaths till date[1,2].

A member of Beta coronaviruses, which includes SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) which have caused localized epidemics in the Asian continent, the SARS-CoV-2 rapidly spread across the globe and has now survived and evolved with mutants due to its ability to stealthily spread by airborne transmission, ability to survive in varying environmental conditions, causing asymptomatic or mild infection in humans with transmission characterized by the ability to infect early on during the prodromal phase of illness, aided generously by "super spreaders"[1,3,4].

The management of the disease has evolved with early conservative guidelines from experts to evidence-based recommendations which continue to evolve every day touching all aspects of care from the use of respiratory assist devices, medication including repurposed drugs, novel and controversial therapies as well as delivery of our critical care services. Here we attempt to capture some of these changes and present the current state of evidence of some of these therapies and services used in the management of COVID-19[5].

INFECTIVITY AND TRANSMISSION CHARACTERISTICS

Since the beginning of the pandemic SARS-CoV-2 duration of shedding, infectivity, and mechanism of transmission of infection have been very keenly studied as they have practical implications. We now have better knowledge and understanding of these characteristics. The viral RNA has been detected by reverse transcriptase-polymerase chain reaction testing from the upper respiratory tract for a mean of 17 d with a maximal duration of 83 d. Likewise, from the lower respiratory tract, the viral RNA has been detected for a mean duration of 17.2 d with a maximal duration of only 35 d. However more importantly the live virus has not been cultured beyond the 9th day of symptom in any study to date. Hence the maximal infectivity is likely in the first week from symptom onset and tapers off subsequently[6].

Respiratory transmission is now considered the predominant mode of infection. Droplets are large particles typically more than 5 microns which are heavier and drop within 6 feet, whereas aerosols are smaller than 5 microns and post evaporation remain suspended like pollens in the air having the ability to travel longer distances [7]. Our current understanding is that the virus is shed as particles across a wide range of sizes [8,9]. A longer duration, closer proximity, forced exhalation of air from a patient with high viral load is now considered necessary for cross-infection to occur with SARS-CoV-2 [8]. Logically a “full high-level barrier protection” with Personal Protective Equipment (PPE), N95 mask & Negative pressure room may therefore be necessary when managing a highly symptomatic patient who is excessively coughing, is on high flow oxygen, noninvasive ventilation (NIV), Mechanical ventilator, is undergoing Bronchoscopy or has a Tracheostomy. In all these situations, a large amount of air is being mobilized across the mucosa covered with the virus, enhancing the possibility of viral aerosolization & infection [8]. In fact if the combination of “full barrier precautions” and adherence to clinical practice guidelines are strict, then the likelihood of infection with SARS-CoV-2 in clinical care areas for staff is substantially reduced or insignificant [10].

The role of respiratory assist devices and maneuvers in the pandemic

COVID-19 is a disease that affects multiple organ systems but primarily and disproportionately affects the Respiratory system. Early in the pandemic stemming from the Chinese experience, COVID-19 patients were intubated early when needing more than 5-6 L/min oxygen to avoid aerosolization of SARS-CoV-2 infection to staff and due to the anticipation, that these patients would deteriorate rapidly with the attendant risk of substantial hypoxia during intubation. However it is now apparent that such aggressive measures are not warranted as it places substantial burden on the need for critical care resources [11]. Although not proven to be causative, the early surge of COVID-19 cases in New York city and Italy in early 2020 was notable for very high mortality noted in intubated patients [12,13].

Adult respiratory distress syndrome (ARDS) is the dominant respiratory clinical syndrome seen in COVID-19 patients [13,14] with histopathology primarily characterized by diffuse alveolar damage very similar to SARS-CoV-1 and MERS-CoV infections [15]. ARDS related lung injury and Respiratory mechanics in COVID-19 appear to be similar to non-COVID-19 ARDS; nevertheless substantial controversy exists regarding management in literature which is intriguing and is addressed in our discussion [11,13,14].

Oxygen supplementation and NIV

It is generally accepted that low flow oxygen with a simple face mask or Cannula is used for supplemental oxygen as the first line of support when SaO₂ is less than 88%. The next line of oxygen supplementation is through high flow nasal cannula (HFNC). It provides oxygen at a very high flow rates (40-80 L/min). This oxygen also is heated and humidified to simulate physiological conditions in the airway promoting patient comfort and tolerance [16]. HFNC is essentially a flow generator helping with mucociliary clearance in the airway and improves the Ventilatory function of the lung by providing low levels of functional “Positive end expiratory Pressure (PEEP)” in the respiratory tract [17]. A type 1 surgical mask can substantially reduce particulate aerosol contamination from nasal devices when placed over them [18]. The dispersion of aerosolized particles is higher than a simple mask for HFNC but much less when compared to NIV in simulated experiments [19,20].

NIV such as continuous positive airway pressure (CPAP) and Bi-level alveolar positive airway pressure (BiPAP) are the next line which provides pressure targeted ventilation. CPAP has traditionally been used in acute cardiogenic pulmonary edema by increasing functional residual capacity and therefore oxygenation and compliance. BiPAP in addition to the latter has also been used in acute exacerbation of the chronic obstructive pulmonary disease for counterbalancing inner PEEP with external PEEP and decreasing work of breathing by acting as an inhalation assist device [17]. Both modes of NIV have been traditionally used in obstructive sleep apnea and obesity hypoventilation syndrome [21]. CPAP and BiPAP must be used with a full-face mask to decrease the risk of aerosolization. BiPAP can also be used with a helmet mask (mostly available in Europe). They have been shown to have an acceptable level of aerosolization which can be further attenuated with the help of a well-fitting helmet mask [22].

In general, HFNC is preferred over NIV. HFNC is much more comfortable for the patient as it allows for speech, eating/drinking as well as comfort [17]. But NIV may be preferred in patients who have acute chronic obstructive pulmonary disease (COPD)

exacerbation with hypercarbia, acute pulmonary edema and those who have sleep disordered breathing.

Evidence from non-COVID-19 literature for HFNC and NIV

In the FLORAL trial involving hypercapnic patients with acute hypoxemic respiratory failure, HFNC was shown to decrease intubation rate which was statistically significant in a sub-group of patients with $Pao_2/Fio_2 < 200$ when compared to non-rebreather mask (≥ 10 L/min) or NIV. Mortality also favored the HFNC group at 90 d when compared to the other two groups in this study[23].

In another study, HFNC was non-inferior to NIV for preventing reintubation and post-extubation respiratory failure in high-risk adults[24].

In another randomised controlled trial involving high-risk adults, the combined use of HFNC and NIV prevented more extubation failures than HFNC alone[25] suggesting that the two modalities can complement each other.

In the LUNG SAFE study, about 15% of ARDS patients were treated with NIV. Failure of NIV was increasingly common with increasing severity of ARDS but mortality was especially higher in patients who had Pao_2/Fio_2 lower than 150 mmHg [26] and hence should be avoided in this subgroup of Moderate to Severe ARDS Patients.

In a systematic review and meta-analysis involving 25 studies and 3804 patients, the use of both helmet and face mask NIV was associated with decreased mortality and endotracheal intubation compared to standard oxygen therapy[27]. However, in sensitivity analysis excluding studies which included COPD exacerbation and congestive heart failure exacerbation, the observed benefit on mortality was not noted. The beneficial effect on mortality was also less certain with patients who had severe ARDS.

Evidence from COVID-19 literature for HFNC and NIV

Good quality data is lacking but some moderate sized retrospective observational studies have been published.

In Lombardy Italy, about 350 of 3988 patients with COVID-19 Pneumonia were treated with NIV, of which 50 percent required intubation. The mortality of the latter group was similar to patients who were intubated on admission to the intensive care units (ICU)[28].

In one published Italian retrospective observational study of 670 patients, the rate of intubation and adjusted mortality did not vary in patients who were treated with High flow oxygen, CPAP and BIPAP[29].

In a study of 110 patients who received non-invasive ventilation *via* helmet for two days, followed by the high flow nasal oxygen therapy or high flow oxygen alone, there was no difference in the ventilator free days at 28 d between NIV and high flow, but patient in the helmet NIV group had decrease in intubation and mechanical ventilation free days, with the *P* value of 0.03[30].

In a systematic review and meta-analysis of non-randomized cohort studies involving about 1897 critically ill patients, there was no statistically detectable difference on all-cause mortality between patients undergoing intubation without *vs* with a prior trial of HFNC/NIV [eight studies, 1128 deaths; 48.9% *vs* 42.5%; risk ratio (RR) 1.11, 95% confidence interval (CI): 0.99-1.25, *P* = 0.08][31].

Monitoring of patients on HFNC and NIV

Patients need to be carefully monitored when on supplemental oxygen devices like high flow or NIV. Intubation should not be withheld when appropriate criteria are met. It is estimated that about 20%-25% of patients can avoid intubation and help preserve Critical resources during the pandemic[17]. Further evidence is needed.

Early vs late intubation

The concept of early *vs* late intubation in COVID-19 pneumonia is controversial which has elicited a fascinating Pros-Con debate[32,33].

Early on, some professional organizations like the Royal College of Anesthetists & Intensive Care Society recommended early intubation to prevent the risk of high environmental contamination with other oxygenation and ventilatory adjuncts like NIV/HFNC[32]. Others like the Society of Critical Care Medicine recommended careful monitoring with NIV/HFNC and intubation when the latter failed[34].

A failed NIV followed by intubation can be associated with an increased risk of complications during intubation like hypotension, desaturation, and aspiration with associated increased risk of mortality[35]. While some studies in non-COVID-19

hypoxemic respiratory failure show increased mortality with delayed intubation[35, 36] others in COVID-19 hypoxemic respiratory failure showed no such increased mortality[13].

Proponents of early mechanical ventilation emphasize the possibility of “Patient self-inflicted Lung injury (P-SILI) “in the non-intubated critically ill patient with acute hypoxemic respiratory failure which is a collective term for the high minute ventilation, a high respiratory drive of the ARDS patient worsening the preexisting lung injury with increased vascular permeability along with local and global lung over distension[37]. P-SILI in a spontaneously breathing patient is akin to ventilator-induced lung injury in a mechanically ventilated patient[33] and is caused by high pleural pressures and trans pulmonary pressure swings. Lung protective ventilatory strategies using mechanical ventilation along with deep sedation and/or neuromuscular paralysis can prevent P-SILI[37,38]. The endotracheal tube helps gain good control over an unstable airway and regulate oxygen, pressure, and volume[39].

Opponents of early and liberal Mechanical ventilation offer many valid reasons. The concept of P-SILI is relatively new and the evidence supporting it is not very robust [33]. Mechanical ventilation brings along with it a host of complications like delirium secondary to sedation, hemodynamic instability secondary to decreased sympathetic drive and positive pressure ventilation, increased risk of infection, immobilization with increased risk of thromboembolism, neuromuscular paralysis, post-intensive care syndrome with its attendant physical and neurocognitive dysfunction[32]. Intubation and mechanical ventilation are associated with one of the highest risks of aerosolization[40] and for the patient, there is risk of procedure related hypotension, hypoxemia, cardiac arrest, and other complications[41]. During a pandemic conserving critical resources and their judicious use is important and intubating every patient with hypoxemic respiratory failure is going to be unethical[42,43].

No randomized control studies have been published on this topic. The definition of early *vs* late intubation is variable across studies. A few small single-center retrospective studies have reported variable outcomes for delayed *vs* early endotracheal intubation[44-47] with one study reporting worser mortality outcomes for delayed intubation and other three being equivocal.

In a systematic review and meta-analysis of non-randomized cohort studies involving about 9000 critically ill patients compared early (less than 24 h after ICU admission) *vs* late (more than 24 h after ICU admission) intubation found no difference in all-cause mortality(3981 deaths; 45.4% *vs* 39.1%; RR 1.07, 95% CI: 0.99-1.15, $P = 0.08$), duration of mechanical ventilation (1892 patients; MD - 0.58 d, 95% CI: 3.06-1.89 d, $P = 0.65$), ICU length of stay and renal replacement therapy (RRT)[31].

Due to limited data, the question apart from some lively, elegant and animated discussions between experts is probably unsettled[33,48].

Nebulization

SARS-CoV-2 virus transmission occurs predominantly through close contact, poor ventilated environment in a susceptible host *via* droplets/aerosols and less likely through fomites[6,7,9]. Transmission *via* bio aerosols from medical procedures like Nebulization and Tracheostomy has been a very valid concern as discussed earlier[49].

As *per* the Global initiative for asthma & The Australian National Asthma Council, the recommendation is to use nebulization therapy only if unavoidable[50,51]. On the contrary, the British National Institute of Health Care and Excellence recommends that patients with COVID-19 can continue using nebulization therapy[52]. Such contrary guidelines and recommendations have sowed doubts in the minds of patients and professional health care practitioners. It is indicative of the fact that the evidence base for these contrary recommendations is not very strong.

Although a continuation of inhalational treatment for chronic respiratory diseases has been universally recommended[51], the optimal mode is less certain. Inhalers have been recommended as they seem to generate fewer aerosols, the drug is contained in the container and less likely to be contaminated by infectious particles, and they also have a low emitted dose[49]. However, either *via* normal exhalation or cough (determined by drug formulation characteristics) induced by the inhaled medication, inhalers can produce exhaled bio aerosols and hence they do not seem to be superior to nebulizer therapy[49].

Theoretically, nebulizer therapy produces an aerosol of the medication in the nebulizer container and hence should not produce infected aerosols unless the container or medication gets contaminated[49]. An aerosol droplet coming in contact with an infected mucous membrane, like in the lung stops being airborne and hence is no longer an aerosol[53]. Hence good hygiene precautions undertaken while using the nebulizer and while loading the medication should prevent the spread of infection by

aerosolization[49,53]. Besides, other precautions to prevent bio aerosolization have been proposed such as the use of viral filters in the circuit of nebulizers/ventilators, use of vibratory mesh nebulizers which separate medication from patient interface including circuits, and good provider/patient hygiene and using mouthpiece with handheld devices[53]. Universally full barrier precautions as discussed earlier should be practiced to limit infection.

Bronchoscopy

At the beginning of the pandemic, many Pulmonary/Bronchology societies made recommendations for COVID-19, but were limited by generalizations, lack of exhaustiveness, and clear guidance was not available due to the novelty of the disease; extrapolation from previous coronavirus pandemics was required[54]. Almost all societies recommended deferring bronchoscopy in non-urgent cases, observing full barrier precautions when performing bronchoscopies, restricting the number of personnel who could be participating in the procedure, limit aerosol producing procedures like nebulization, use of atomizers and jet ventilation[55]. Peri procedurally recommendations included using sedation (or even paralytics when feasible) to avoid coughing, avoiding high flow and high shearing maneuvers, all intended to limit aerosolization. Flexible bronchoscopy is encouraged and rigid bronchoscopy is discouraged with post-procedure recommendations lacking consensus[54]. To avoid cross-contamination or accidental transmission, single-use flexible bronchoscopes are encouraged[54]. The patient can wear a mask and a slot can be made for introducing the bronchoscope[54,55].

Certain acceptable indications for bronchoscopy in COVID-19 times include but not exhaustively, symptomatic airway stenosis, symptomatic hemoptysis, migrated stent, therapeutic aspiration of obstructive symptomatic secretions or masses, diagnosis of secondary infections in intubated COVID-19 patients, diagnosis of cancer, and diagnosis of infection in immunocompromised patients[55].

In a single-center, where 241 bronchoscopies were performed on 107 COVID-19 patients, 54 patients (50.5%) had Broncho Alveolar Lavage (BAL) with 35 patients (65%) demonstrating a positive culture. About 1/3rd of intubated patients required bronchoscopy presumably due to thickened white gelatinous secretions (likely due to heated air with less humidification as was recommended by guidelines) or bloody secretions due to high use of anticoagulants. BAL cultures were more likely to be positive (65%) compared to tracheal cultures (45%). 6% of BAL cultures also grew a second organism. The study showed a high rate of secondary infection in COVID-19 patients above and beyond that was diagnosed with tracheal cultures, indicating that under treatment may be driving higher mortality[56].

In another single-center series of 93 intubated patients, 101 bronchoscopies were performed which did not show increased secondary infection when compared to non-covid ventilator associated pneumonia[57].

In general, bronchoscopy has not shown any definitive increase in transmission when proper precautions have been observed[56,57].

Tracheostomy

Tracheostomy has been widely used across the globe for COVID-19 management. Initially, expert guidelines were made available which were very conservative in their recommendations but now we have better evidence to guide our decisions[58]. Certain pertinent issues concerned with Tracheostomy are addressed here.

The Indications for tracheostomy have traditionally not been well defined, dependent on multiple factors and individual circumstances[59]. In the current COVID-19 times, tracheostomies have been performed early (less than 7 to 10 d after intubation) and for very liberal indications with critical care resource utilization as a goal commensurate with principles of "Disaster management" [60-62]. However, guidelines based on several critical considerations including virology of transmission and infectiousness of the patient recommended the timing to be past 10 d and when patients show clinical improvement[59]. This is because it is difficult to predict the clinical trajectory of ARDS patients with COVID-19. After the patient has navigated the first few days of Critical illness and shown clinical improvement, but anticipate prolonged mechanical ventilation, with reasonable pulmonary reserves, the FiO₂ less than 40% and PEEP less than 8, then tracheostomy can be considered[59,60,63,64]. Given that there are advantages and disadvantages to both early and late tracheostomy, and with relatively proven non-inferiority, the timing of tracheostomy like in non-COVID-19 patients has to be individualized[61,63]. In practice, a systematic review and meta-analysis encompassing 462 COVID-19 patients revealed that 250 patients (71.5%) received tracheostomy 14 d after intubation, which is consistent with

conventional practice[65].

Tracheostomy can be performed by the “open or surgical” method in the operating room or by “Percutaneous dilatation” at the patient bedside. Initially, the recommendation was to use the “Open or Surgical” method to minimize exposure to bio aerosol which is potentially more with the percutaneous method[59,64]. However, with diligent and appropriate use of “Full barrier” precautions including PPE with or without a negative pressure room, the increased risk to healthcare personnel has not materialized and the emphasis is now to optimally use available resources as both methods have been proven to be safe[59,62,64,65]. In a pooled analysis of 3060 tracheostomies, 55.7% were created by the open method and 43.4% were created by the percutaneous method[65].

Post-procedural management guidelines suggest to limit staff exposure to bio aerosols have been published and it has been demonstrated that this can be implemented successfully by training new staff members unfamiliar with tracheostomy care, thereby helping free critical ICU resources when necessary[59,62,64].

Post tracheostomy outcome data in COVID-19 patients are now available. In a pooled analysis, of 2890 mechanically ventilated patients 54.9% were reported to have been successfully weaned, of 2628 patients 34.9% were successfully decannulated, and of 2980 patients 513 patients (13.1%) had died[65].

Overall tracheostomy in COVID-19 patients has evolved from the early time of guidelines recommending “abundant caution” to now practice and outcomes which seem to be more consistent with “regular order”.

Convalescent plasma and monoclonal antibody

Convalescent plasma has been used to treat many infectious diseases in the past like Influenza, MERS-CoV, Ebola Virus, Influenza, *etc.*, but efficacy and evidence are not firmly established[66,67]. The goal of such passive immunization is to neutralize the infectious organism with the help of naturally formed and passively transferred antibodies[66]. Novel neutralizing monoclonal antibodies (nabs) and nano antibodies have also come into play during the coronavirus pandemic[68].

SARS-CoV-2 virus enters the cell *via* the angiotensin-converting enzyme 2 (ACE2) receptors on the respiratory and gastrointestinal tract epithelium. The SARS-CoV-2 virus has an outer “S” glycoprotein, with S1 and S2 subunits. The S1 subunit has a receptor binding domain along with receptor binding motif, the latter attaches to the ACE2 receptor in the host, and there is a conformational change in the S protein leading to S2 fusing with the host cell wall membrane followed by internalization of the virus into the host cell. The SARS-CoV-2 antibody in the convalescent plasma/nabs can halt the virus from multiplying and establishing a foothold in the host by interfering with receptor attachment, inhibiting wall fusion after attachment, and preventing uncoating of the virus once inside the cytoplasm[68,69].

With COVID-19, convalescent plasma has been widely used from the early days of the pandemic on a compassionate basis with regulatory approval[70]. However; results from various studies have been inconsistent.

Analysis of large observational data and different Randomized control studies show that when plasma with low SARS-CoV-2 antibody titer or when used later in the disease trajectory or both results in lack of survival benefit, does not halt the progression of the disease or help with stabilization of symptoms[70-72]. COVID-19 patients with moderate to severe ARDS, especially intubated patients do not derive any benefit from convalescent plasma[70-73].

On the contrary, when the plasma has high antibody titer, and patients receive early on at symptom onset in the community or even during early hospitalization when patients have mild to moderate disease, it results in better survival, disease stabilization and halts the progression of the disease[70,73,74].

As *per* Food and Drug Administration (FDA), high titer convalescent plasma corresponds to a neutralizing antibody titer of ≥ 250 in the Broad Institute's neutralizing antibody assay, a signal-to-cutoff of ≥ 12 in the Ortho VITROS immunoglobulin G (IgG) assay, or a level of $\geq 1:2880$ in the Mount Sinai COVID-19 ELISA IgG Antibody Test[75].

The role of passive immunization with convalescent plasma or Neutralizing antibodies is to inhibit viral replication early in the disease when the host does not have sufficient antibodies of its own. Once the infection is established, native antibodies are formed and inflammatory processes are at work, at which point the passively transfused antibodies are not helpful[76].

Similarly neutralizing Monoclonal antibodies like Bamlanivimab were found to help reduce viral load, and hospitalization in recently diagnosed mild to moderate COVID-19 disease as outpatient especially in patients with co-morbidities across age groups,

especially in elderly, but not useful in hospitalized severely ill COVID-19 patients[77]. In the yet to be published Blaze-2 trial, Bamlanivimab used as a prophylaxis in nursing home and assisted care home residents were found to decrease symptoms and even have a survival advantage when compared to placebo[78]. And although peer review is pending, this appears to be a promising therapy when used in high-risk patients either as prophylaxis or early disease complementing the huge anticipated benefit of vaccine administration on a large scale.

The FDA has updated its Emergency use authorization on February 4, 2021 and now limits the use of high titer COVID-19 convalescent plasma only for the treatment of hospitalized patients with COVID-19 early in the disease course and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response[79].

The recovery trial has reported its findings in a preprint article on the use of high titer convalescent plasma in hospitalized patients which is yet to be peer reviewed [80]. 5795 patients were randomly allocated to receive convalescent plasma and 5763 to usual care alone. There was no significant difference in 28-d mortality between the two groups: 1398 (24%) of 5795 patients allocated convalescent plasma and 1408 (24%) of 5763 patients allocated usual care died within 28 d (RR 1.00; 95%CI: 0.93-1.07; $P = 0.93$). Similarly there was no change in the proportion of patients discharged from hospital, progression of patients not on mechanical ventilation towards intubation, successful cessation from mechanical ventilation or need for RRT. However, the mean number of days from symptom onset was 9, and therefore likely the plasma was not used early enough in the disease course.

Glucocorticoids

Glucocorticoids are one of the oldest, well known, inexpensive, immunomodulatory agents with wide ranging immunosuppressive, anti-inflammatory and anti-allergic effect. They also have a multitude of adverse effects as well[81]. It was therefore natural to test their effectiveness as a therapeutic agent for COVID-19, and although some of the earlier studies did not show any benefit, the “RECOVERY Trial” was the earliest well conducted randomized controlled trial that showed survival benefit in severely ill patients needing supplemental oxygen and ventilation[82]. The latter study showed that there was mortality benefit with use of dexamethasone.

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care[77].

Overall 17 percent relative reduction in mortality (22.9 *vs* 25.7 percent, RR 0.83, 95%CI: 0.75-0.93),

Patients on invasive mechanical ventilation or (ECMO) at baseline–36 percent relative reduction (29.3 *vs* 41.4 percent, RR 0.64, 95%CI: 0.51-0.81). Age-adjusted analysis suggested a 12.3 percent absolute mortality reduction.

Patients on noninvasive oxygen therapy (including NIV) at baseline–18 percent relative reduction (23.3 *vs* 26.2 percent, RR 0.82, 95%CI: 0.72-0.94). Age-adjusted analysis suggested a 4.1 percent absolute mortality reduction.

Currently as *per* a pooled meta-analysis, the use of glucocorticoids is estimated to cause 31 fewer deaths *per* 1000 [odds ratio (OR) 0.87, 95%CI: 0.77 to 0.98; risk difference 31 fewer *per* 1000, 95%CI: 55 fewer to 5 fewer], risk of mechanical ventilation is reduced by 28 *per* 1000 (OR 0.73, 0.58 to 0.92; risk difference 28 fewer *per* 1000, 45 fewer to 9 fewer), and duration of hospital stay is reduced by almost 1 d (mean difference -0.99 d, -1.36 to -0.64), all results estimated to be of moderate certainty[83].

With this the use of glucocorticoids became well established as standard of care for the treatment of severely ill COVID-19 patients needing supplemental oxygen and or ventilation. This has been followed by the question whether the standard 6 milligram Dexamethasone *per* day therapy which was used in the RECOVERY TRIAL is sufficient a dose or if there is an incremental benefit by dose increase? Also, another pertinent question is whether there is any benefit of targeting any other specific immune pathways.

While Randomized control data involving the inhibition of complement C5 inhibitor, raviluzumab has not been shown to be of benefit as *per* preliminary unpublished data[84], the role of Interleukin-6 inhibitor, tocilizumab has been quite intriguing.

Tocilizumab

Tocilizumab is an interleukin 6 receptor antagonist monoclonal antibody that has been used to treat patients with COVID-19 respiratory and organ failure targeting a key step in inflammatory mediated damage[68]. Early treatment data in observational and randomized control studies, not involving many critically ill patients and without

Glucocorticoid use showed that Tocilizumab was safe but did not have any significant Clinical outcomes[85-87]. There were six small trials which did not show any significant benefit from Tocilizumab[88]. However, data from “STOP COVID”-a large observational study and “REMAP CAP”-A well designed open label international randomized control study consisting of 803 patients, suggest that “the early use of Tocilizumab on entry to ICU” may have important survival and other outcome benefits in the short term which was not seen in less sick patients studied in randomized control trials outside the ICU[85-87,89]. This was especially noted in patients who had ICU admission within 3 d of symptom onset[89] or had evidence of organ failure on admission to ICU[87]. Participants in the Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) study also had a relatively larger proportion of patients on glucocorticoids (more than 80%) compared to other studies[86,87]. In “REMAP-CAP” Tocilizumab ($n = 353$) and Sarilumab ($n = 48$) each reduced in-hospital mortality compared with standard of care (28 and 22 *vs* 36 percent; OR for hospital survival 1.64, 95%CI: 1.14-2.35 for Tocilizumab and 2.01, 95%CI: 1.18-4.1 for Sarilumab).

The Tocilizumab arm of RECOVERY TRIAL reported preliminary results which are undergoing peer review[88]. This was an open label randomized placebo-controlled trial in which 82% patients took glucocorticoids like dexamethasone. 2022 patients received tocilizumab and 2094 received standard of care. To be eligible for randomization, patients with COVID-19 were to have hypoxia ($SpO_2 < 92\%$) and C-reactive protein more than 75 mg/dL.

Of 596 (29%) patients in the Tocilizumab group and 694 (33%) patients in the usual care group died (RR 0.86; 95%CI: 0.77-0.96; $P = 0.007$) at 28 d, an absolute difference of 4%. This translates into Numbers Needed to Treat for saving one life of 25.

Tocilizumab also increased the probability of being discharged alive within 28 d from 47% to 54% (RR 1.23, 95%CI: 1.12-1.34, $P < 0.0001$).

Among patients not on invasive mechanical ventilation when entered into the trial, Tocilizumab significantly reduced the chance of progressing to invasive mechanical ventilation or death from 38% to 33% (RR 0.85, 95%CI: 0.78-0.93, $P = 0.0005$).

Allocation to Tocilizumab reduced the use of all forms of dialysis (5% *vs* 7%, RR 0.75, 95%CI: 0.59-0.96, $P = 0.02$).

Tocilizumab did not have any effect on the chance of successful cessation of invasive mechanical ventilation.

These benefits were seen in all patient subgroups, including those requiring oxygen *via* a simple face mask through to those requiring mechanical ventilators in an intensive care unit.

Tocilizumab is estimated to reduce the relative risk of death by 14% and reduced the time spent in hospital by 5 d when used for patients on oxygen and in addition to the corticosteroid dexamethasone[90].

Taken together data from all 8 trials, use of tocilizumab was associated with 13% proportional reduction in 28-d mortality (death RR 0.87, 95%CI: 0.79-0.96, $P = 0.005$). It is noteworthy that these mortality benefits were noted in the RECOVERY TRIAL only in patients receiving concomitant steroids.

In summary, it appears that in severely ill COVID-19 patients with hypoxia accompanied by hyper inflammatory state, the early concomitant use of glucocorticoids and Tocilizumab improves outcomes including survival, organ support and progression of disease, suggesting additive or synergistic effect with these two agents.

This beneficial data appears to be quite specific for Tocilizumab, as the numbers of patients with Sarilumab in REMAP-CAP study were few. Trials involving Sarilumab are in progress and results are expected in the future[88].

The United Kingdom government and Center for disease control have expeditiously approved the use of Tocilizumab based on data from REMAP-CAP and RECOVERY TRIALS[90,91]. Other government and Professional societies are expected to update their guidelines soon as well.

Remdesivir

Remdesivir is an inhibitor of “viral RNA dependent RNA polymerase” which inhibits SARS-COV-2 *in vitro*[92] but has not been shown to decrease viral load when compared to placebo[93]. It has been studied extensively in clinical trials and the findings are summarized below.

The outcome data has been measured using the multipoint ordinal scale with each number denoting a particular “clinical status” and the changes are measured and reported accordingly[92-94].

In the international, multicentric auditory consonant trigram test-1 study conducted by the National Institute of Allergy and Infectious Diseases and others, 541 patients were assigned to Remdesivir and 521 to placebo in a double-blind placebo-controlled trial; the study drug was given intravenously for 10 d. A significant number of patients had severe disease with SpO₂ less than 94% by definition and requiring supplemental oxygen. It reported a primary outcome of improved median recovery time of 10 d compared to 15 d with placebo. There was a trend to improvement in mortality which was not statistically significant, 11.4% and 15.2% in two groups, respectively [hazard ratio (HR) 0.73; 95% CI: 0.52-1.03] by day 29. In sub-group analysis, there was mortality benefit noted in patients who were on simple low flow oxygen, (HR 0.30; 95% CI: 0.14-0.64). Remdesivir also showed shorter hospital length of stay, reduced disease progression, and lesser utilization of respiratory assist devices like oxygen, invasive mechanical ventilation, and ECMO[92].

In the World health organization led SOLIDARITY trial[95], which was conducted at multiple sites in 30 countries, 11330 adults underwent randomization. Death occurred in 301 of 2743 patients receiving Remdesivir and in 303 of 2708 receiving its control (RR 0.95; 95% CI: 0.81-1.11; *P* = 0.50) showing no survival benefit. In this study which had good adherence, Remdesivir was given intravenously for 10 d. Remdesivir did not reduce the incidence of new ventilation.

In another randomized control trial, for patients with moderate clinical disease (Pulmonary infiltrates with SpO₂ more than 94% by definition); Remdesivir did not demonstrate any difference in clinical status when compared to placebo after a 10-d course. Interestingly, the same study showed improvement in clinical status after a 5-d course. The study was confounded by open-label design and imbalances with co-therapy and therefore the significance is unknown[96].

Other randomized control trials did not show any difference in clinical status outcome between a 5 and a 10-d course of Remdesivir[33,34] and the drug is generally safe with no significant adverse effects[92,94,96,97].

Baricitinib, an oral selective Janus kinase inhibitor 1 and 2 inhibitors impair cell entry of the SARS-CoV-2 virus and inhibits cellular signaling pathway. It has been tested in RCT in combination with Remdesivir and compared to placebo it has improved median time to recovery by 1 d (RR for recovery, 1.16; 95% CI: 1.01-1.32; *P* = 0.03). At 15 d, time to recovery favors the drug combination. In sicker patients who are on NIV or high flow oxygen the time to recovery was 10 d compared to 18 d. (RR for recovery, 1.51; 95% CI: 1.10-2.08). However, given the lack of efficacy for survival, in practice, it can be used with Remdesivir, when steroids are contraindicated[98].

In summary in patients with severe disease (SpO₂ less than 94% with pulmonary infiltrates) and risk of the hyper inflammatory response, Remdesivir may help improve time to clinical recovery and reduce duration of hospitalization, but does not improve survival[92-94,99-101]. It is likely not very helpful or may have very modest benefits in patients who have mild to moderate disease (Pulmonary infiltrates with SpO₂ more than 94%)[34,96,100]. As *per* a meta-analysis, it may help to reduce the need for ventilation but the effect may not be large. It may help to reduce serious adverse events and may aid with some recovery. For non-ventilated patients, a 5 d course compared to 10 d course results in reduced costs, more benefits and less harm[101].

With lack of improvement in survival, the soft benefit of improvement in clinical status, the need to be given by intravenous infusion often as an inpatient over 5 d, lack of cost effectiveness and an endless number of patients with this pandemic, remdesivir is not an optimal answer where the treatment needs to be inexpensive, scalable and equitable[99,101,102]. However since it does reduce time to clinical recovery and reduces duration of hospitalization among survivors, it can help free up inpatient resources in a pandemic and hence gets approval from FDA and Infectious disease society of America[101,103].

Hydroxychloroquine

It is an immunomodulatory drug that has been used extensively in rheumatological disorders. It was repurposed for use in COVID-19 patients and many governments around the world including the United States allowed emergency authorization for its use. Its mechanism of action appears to be by inhibiting glycosylation of ACE2 receptors and increasing the pH of endosomes, in effect preventing virus entry into the cells[104,105].

Many studies have been performed with or without concomitant use of azithromycin compared to placebo after initial case reports and non-randomized studies showed efficacy for the drug against SARS-CoV-2[104]. However, none of the randomized control trials, systematic reviews, and meta-analyses, with or without Azithromycin has shown any benefit for Hydroxychloroquine with regards to survival

[92,104,105]. Likewise, there is no benefit with regards to the length of hospitalization, virological cure rate, clinical status score based on a multipoint ordinal scale, need for mechanical ventilation, and radiological improvement[92,104,105]. There was concern over QT prolongation due to both hydroxychloroquine and azithromycin having those properties as well as concern for the possibility of other side effects without much proven benefit as noted before[104,106]. Currently, both these drugs are not used for COVID-19.

ECMO and COVID-19

ECMO is a resource-intensive therapy that has been used when conventional critical care management has failed to help the patient[107]. It has been used in previous pandemics like pandemic influenza A with variable success[108].

It is recommended by experts that ECMO be offered only at experienced centers that have adequate manpower and material resources as well as expertise in managing them, as every aspect of its care from patient selection, maintenance and liberation is highly specialized and nuanced[107]. In fact when regions are under crises level of care amid a surge of cases, then it may be difficult to offer highly resource-intensive therapies like ECMO[107].

The indications, contraindications, and general principles of ECMO care in COVID-19 remain the same[107] with some finer changes to approach and management. It is preferred that aerosolization of the virus is limited and hence transportation is restricted. Cannulation is best performed at the bedside in the ICU. Tracheostomy which is often performed to help lighten sedation and facilitate decannulation needs to be restricted. All personnel need to observe full barrier precautions[107]. Nevertheless, there is evidence that tracheostomy can be safely managed with standard full barrier precautions as mentioned elsewhere in this article and likely guidelines may change. The patient may not be able to be prone due to cannula and likewise, mobilization may be restricted[107].

Patients with COVID-19 often require deep sedation due to various factors and hence post ECMO delirium may need more supportive ICU care or discharge to specialized rehabilitation centers[107,109]. Veno venous ECMO is the most commonly used ECMO for respiratory failure and outcomes are better with this modality compared to veno arterial ECMO which is used only when concomitant circulatory support is necessary[107,109]. Given the high incidence of thrombosis in COVID-19, therapeutic anticoagulation keeping activated partial thromboplastin time 1.5 to 2.5 times normal is recommended often bordering on the higher side[107] to prevent clot formation in the oxygenator and other parts of the circuit.

Initially reports suggested poor outcomes with ECMO[110] with mortality in the range of 80%-100% but subsequently, a report from the Extracorporeal Life Support Organization registry which included only experienced centers suggested that the 90-d mortality in more than 1000 carefully selected patients was about 40% and this compares reasonably well with non-COVID-19 patients, indicating that when patient selection is optimal and with the application of best principles of standardized care, the outcomes can be optimal in COVID-19[109].

RRT

RRT is a term that denotes a process of replacing the non-endocrine function of the kidney in acute or chronic kidney injury/disease encompassing filtration across the permeable membrane, exchange of solute and electrolytes along with the removal of fluid[111]. There are different modalities which include standard intermittent hemodialysis (IHD), continuous RRT (CRRT), prolonged intermittent RRT (PIRRT), and peritoneal dialysis[112]. CRRT or its variates are preferred in critically ill patients due to their superior ability for fluid removal, causing less hemodynamic instability and consistent metabolic control[112]. It also provides for predictable dosing of medication in renal failure. However, CRRT is not superior to IHD when it comes to survival or Renal recovery[112].

CRRT functions by way of three different mechanisms namely convection, diffusion, and adsorption by the filtering membrane[113]. Different modalities or techniques which employ one of these machines are used such as simple diffusion (continuous venovenous hemodialysis), convection (continuous venovenous hemofiltration), or a combination of both (continuous venovenous hemodiafiltration)[114]. No one technique is superior to the other overall and employing any of them is a matter of availability, patient characteristics, and clinician judgment or preference[114]. Timing of RRT, whether early or late after diagnosis of acute kidney injury (AKI) and establishing indication for RRT has been an important question for many well-conducted clinical trials, largely demonstrating equivocal outcomes[113].

There is a paucity of COVID-19 data for RRT. Recommendations from guidelines have essentially been an extension from the non-COVID-19 population with emphasis on limiting staff exposure and optimal utilization of resources during the pandemic [114]. Full standard barrier precautions for staff taking care of ICU patients are recommended [114]. CRRT is ideal for ICU patients which can be managed by ICU nurses but if limited PIRRT can be used which will optimize resource utilization [114]. IHD consumes more specialized resources and equipment along with a dedicated dialysis nurse in full attendance for the duration of the session and is, therefore, less preferred [112]. Access to CRRT is essential with the right internal jugular vein being preferred especially if proning followed by femoral access, left internal jugular vein, and subclavian veins [112].

COVID-19 has been recognized as a prothrombotic disease having consequences for filter life, and as such regional citrate anticoagulation can be used if already in use in the institution. The latter should not be started if such practices are not already in vogue [113,115]. Systemic anticoagulation with low molecular weight heparin or Ultra fractionated heparin or other agents may be necessary to prolong the life of the circuit but specific evidence-based anticoagulation protocols are lacking in the literature [116]. Extracorporeal blood purification with RRT has been proposed as a therapeutic strategy to remove cytokines and other biological immune mediators to improve clinical outcomes. However, evidence for such therapies is currently lacking and is recommended only in the context of clinical trials [116,117].

In a systematic review of COVID-19 patients with AKI, involving 51 studies and 21531 patients, the incidence of AKI was found to be 12.3%. Patients with transplants had a higher rate of AKI at 38.9% (290 patients) and 39% in ICU patients (565 patients). Patients who did not survive had higher rates of AKI at 42% (1745 patients) [118].

RRT use was reported in 39 studies involving 17,664 patients. With overall use of 5.4% with higher rates noted in 16.3% in ICU patients (776 patients), and 15.6% in transplant patients (117 patients) [118]. AKI was more common in studies from North America, followed by Europe, and was least noted in China [118]. There is increasing evidence that both AKI and the need for RRT are important factors influencing survival in COVID-19 patients [112].

CONCLUSION

It was Sir William Osler who inspired by Thomas Carlisle said, "It is not our goal to see what lies dimly in the distance but to do what lies at hand".

The COVID-19 pandemic has continued to teach us many important medical, social, political, economic, and humane lessons at a huge cost. Early on with a limited understanding of the virus, its transmission, spread in the community and the medical management of the disease, our response as a global community was reactive, guided by abundant caution. Medical practices and literature consisted of non-peer-reviewed articles, case reports, and case series consisting of incomplete and non-standardized data resulting in approaches and clinical management which were not scientifically sound, exposing patients to potentially nonbeneficial or even harmful treatment strategies [119,120].

Organized efforts to develop sound epidemiological, demographic, and evidence-based data resulted in governmental organizations (*e.g.*, United Kingdom based Recovery trial), international trial networks (*e.g.*, REMAP-CAP), The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study COVID-19 Registry and others who were well-positioned to rapidly deploy pragmatic trials, design data collection networks to meet data analytic needs in response to the COVID-19 pandemic [119,120].

As evident from our review, the application of sound scientific evidence-based management principles distilled from decades of research in the past, with some accommodations in practices specific to the SARS-CoV-2, mitigation strategies, along with the careful implementation of disaster management principles in times of surge have resulted in better and superior outcomes. This is borne out by the fact that although outcomes have varied highly between centers [121], they have generally improved with time [122], especially when health care delivery systems are not stressed due to surge [123]. This is evident by one organization's meticulous and highly diligent efforts to manage the pandemic by way of standardized, protocolized management principles accommodating new information as well as providing room for research opportunities [124]. This along with rapid large-scale effective immunization provides us hope to get back our lives and business back to normal

soon.

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