Inaugural Issue, Volume - I
(September - December 2020)

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Current Issues in Patient Care

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FROM THE DESK OF THE EDITOR-IN-CHIEF

"Journey of a thousand miles
begins with the first step"

Healthcare e-Compendium is the initiative of DPSRU (Delhi Pharmaceutical Sciences and Research University) and DRSC (Doctors' Scientific Resource for Continuous Education). *Healthcare e-Compendium* is an open-access online source of latest medical articles, case studies, food & nutrition updates, topics on manufacturing excellence and global brands. Eminent doctors from India and abroad have contributed these articles.

In current situation, Digital technology in healthcare has a positive impact in terms of speed of giving information and a non-contact interaction in healthcare. Almost all the information is exchanged digitally. Telemedicine, artificial intelligence (AI) - enabled medical devices for health check-ups, robotic surgery, health records are just a few examples of digital transformation in healthcare. With this online medical journal our effort is to provide a platform for practising physicians to share their clinical knowledge with their peers both in India and globally.

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I sincerely appreciate the efforts and contribution of all the doctors, DPSRU faculty members and DRSC team who helped in bringing out this inaugural issue of *Healthcare e-Compendium* and give my best wishes for its success.

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Obeticholic Acid: An Advanced Treatment for Primary Biliary Cholangitis (PBC)

Abstract

Primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis is an immune mediated cholestatic disease, It's an increasing prevalence worldwide. It occurs more commonly in women than men at a ratio of 10:1, Large case series have reported prevalence rates of PBC ranging between 19 and 402 cases per million. However, serological studies of huge, presumably healthy cohorts demonstrate that AMA prevalence are often as high as 0.5%. PBC is a rare and progressive cholestatic liver disease. Several options are available for treatment of associated symptoms. But for management of PBC, UDCA remains first-line therapy. While OCA is being approved by FDA as a combination therapy in patients with inadequate response to UDCA, is the proven and effective second-line therapy.

Dr. Shemin Shah A
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Introduction

Primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis, is an immune mediated cholestatic disease characterized by destruction of the tiny intrahepatic bile ducts; if left untreated, persistent inflammation and cholestasis cause biliary cirrhosis and end-stage liver disease [1]. It's an increasing prevalence worldwide. It occurs more commonly in women than men at a ratio of 10:1 [2]. Large case series have reported prevalence rates of PBC ranging between 19 and 402 cases per million. However, serological studies of huge, presumably healthy cohorts show that AMA prevalence are often as high as 0.5%. Differences in estimates of PBC incidence and prevalence could also be thanks to the true difference in prevalence rates between populations or secondary to variable diagnostic criteria, case-finding methods, and physician awareness [3]. Anti-mitochondrial antibodies (AMAs) directed against the lipoyl domain of the E2 subunit of pyruvate dehydrogenase (PDC-E2) are detected in 95% of patients with primary biliary cirrhosis (PBC) and are present before the onset of clinical disease [4]. Many primary biliary cholangitis (PBC) patients are on ursodeoxycholic acid (UDCA) for months to even years have an inadequate response (Defined as a lack of normalization of alkaline phosphatase (ALP). Large longitudinal studies have shown that such a response is related to greater degrees of histologic progression. Within the Global PBC Study, approximately 40% of patients had an elevated risk of disease progression because of insufficient response of their ALP to UDCA therapy [5]. The identification of UDCA as PBC treatment was a monumental breakthrough in life science, but unfortunately approximately one-third of PBC patients lack an adequate biochemical response defined as a discount within the surrogate biomarker ALP to but 40% of baseline or but 1.67–2 times the upper limit of normal. OCA became the second approved treatment for PBC in 2016. Given the urgent need for extra treatments, it had been given a fast-track approval through a pathway for orphan drugs [6]. Obeticholic acid (OCA) may be a semi-synthetic hydrophobic steroid (BA) analogue that's highly selective agonist of

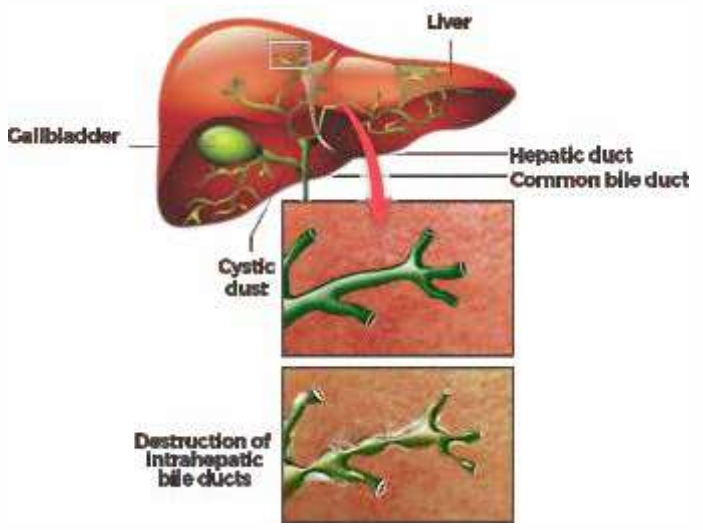

Figure 1: Destruction of intrahepatic bile ducts in Primary Biliary Cholangitis

farnesoid X receptor (FXR), a key nuclear BA receptor, which induces expression of gut-derived hormones, especially fibroblast protein 19. The resulting beneficial effects of OCA on glucose and lipid metabolism and particularly hepatic inflammation make it a candidate for the treatment of a spread of conditions including primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH) [7].

Diagnosis of PBC

Diagnosis of primary biliary cirrhosis (PBC) is based on established criteria that include cholestatic liver tests, a positive anti-mitochondrial antibody (AMA) test, and diagnostic or compatible liver biopsy findings. Up to 40% of patients with PBC are asymptomatic at the time of diagnosis and are identified after abnormal laboratory studies are found at the time of a routine health examination or during evaluation of unrelated complaints [8].

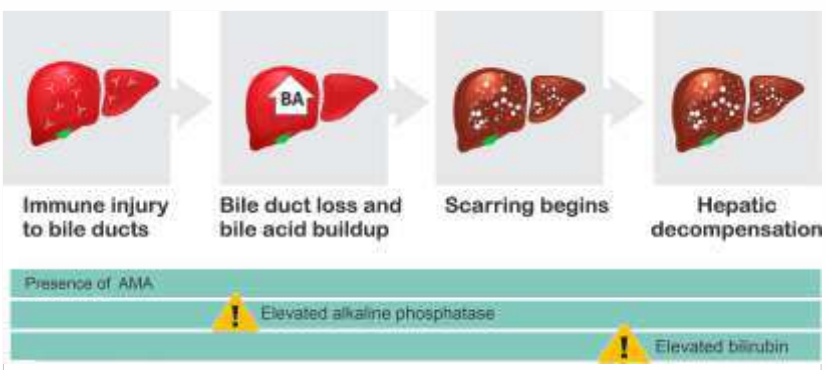

Figure 2: Progression of Primary Biliary Cholangitis in different stages

Liver Biochemical Tests

Most patients with PBC have abnormal liver tests including elevations of ALP, mild elevations of aminotransferase (alanine aminotransferase or aspartate aminotransferase) activity, and increased levels of immunoglobulins (mainly IgM). Some patients with PBC may have high alanine aminotransferase or aspartate aminotransferase activities associated with hyper-γ-globulinemia (elevated IgG). The magnitude of biochemical test elevations is loosely related to the severity of the disease [9]. In patients without cirrhosis, the degree of ALP elevation is related to the severity of ductopenia and inflammation on liver histology. The increase in aminotransferase and IgG levels reflects the degree of periportal and lobular neuroinflammation. The level of serum bilirubin reflects the severity of ductopenia and biliary piecemeal necrosis. Hyperbilirubinemia, hypergammaglobulinemia, hypoalbuminemia, and thrombocytopenia are indicators of the development of liver cirrhosis and portal hypertension. As in other chronic cholestatic disease, Serum cholesterol levels often elevated. As in other cholestatic diseases, serum cholesterol levels are often elevated [10].

Autoantibodies

AMA is found in 95% of PBC patients. Antinuclear antibody and anti-smooth muscle antibody are found in nearly half. In approximately 5% to 10% of the patients, AMA is absent or present only in low titer (≤1/80), when immunofluorescent techniques are used. The presence or absence of AMA, rather than the magnitude of antibody level, is most important in diagnosis. In some patients, antinuclear antibodies, particularly anti-glycoprotein 210 (anti-gp210) and/or anti-sp100, are present and may correlate with prognosis [11]; in some other AMA negative patients, antibodies against the major M2 components (PDC-E2 and 2-oxoglutaric acid dehydrogenase complex), are present using enzyme-linked immunosorbent assay or Western blotting techniques. There are five common strategies for detecting AMA in clinical practice, including indirect immunofluorescence, immunoblotting, enzyme immunoassay, Luminex beads, assay, and enzyme inhibition assay. The indirect immunofluorescence method has the lowest sensitivity, with over 15% of AMA-negative sera by indirect immunofluorescence showing reactivity to MIT3, a combination of three mitochondrial antigens [12].

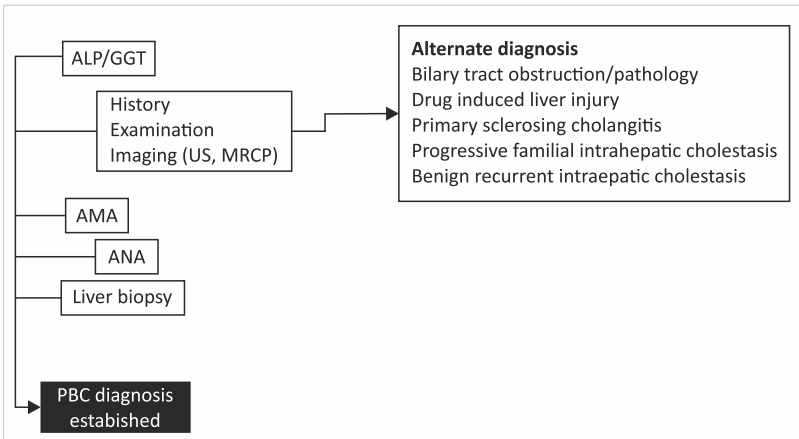

Figure 3: Algorithm for the diagnosis of PBC. US, Ultrasound; MRCP, Magnetic Resonance Cholangiopancreatography; ALP, Alkaline Phosphatase; GGT, Gamma-glutamyl transferase; AMA, Anti-Mitochondrial Antibodies; ANA, Anti-Nuclear Antibodies [13]

Need of Additional Therapy

Historically, ursodeoxycholic acid (UDCA), a naturally occurring bile salt, was the only approved therapy for PBC. However, 40% of PBC patients do not respond to UDCA. Therefore, a large percentage of patients have disease progression to end-stage liver disease [14]. Many other agents have been trialed in treating this puzzling disease, including colchicine, fibrate, and methotrexate. However, these other therapies have not proven to be effective. Thus, there was a critical

need for new pharmacotherapies to treat PBC and prolong survival from this disease. Obeticholic acid (OCA) is a new treatment for PBC that was recently approved by the Food and Drug Administration (FDA) [15].

Many novel therapeutic approaches are proposed to target patients with no or incomplete biochemical response to UDCA. Among them, Peroxisome proliferator-activated receptor α agonists, farnesoid X receptor agonists, and biotherapies such as anti-cluster of differentiation-20, glucagon-like peptide-1 receptor agonists, and estrogen-α receptor agonists could be promising [16].

After UDCA, Obeticholic acid (OCA) was the second drug to successfully meet the primary endpoint of a large placebo-controlled phase III trial in PBC.

This goal was achieved both in patients with incomplete response or intolerance to UDCA and in UDCA-naive patients. OCA is a synthetic bile acid derivative with a high affinity for FXR, a nuclear receptor that closely regulates bile acid synthesis and secretion, and has been shown to mediate anti-inflammatory and anti-fibrotic effects [17].

Currently Available Treatment Options

Primary biliary cholangitis, being in nature an autoimmune disease, cannot be treated. Although the associated complications can be prevented and progression of disease can be slowed down by various available options. These include –

Ursodeoxycholic Acid (UDCA)

UDCA is been used widely after being approved by USFDA. Its use has changed the course of disease by decreasing the progression of disease to liver transplant.

UDCA is a hydrophilic, synthetic bile acid which has been shown to protect cholangiocytes from inflammatory cholestatic injury induced by toxic hydrophobic bile acids such as chenodeoxycholic acid (CDCA) [18]. Prior to widespread use of UDCA, approximately 49% of patients with PBC progressed to cirrhosis, compared to 13% on long-term UDCA treatment [19]. Multiple studies have demonstrated that when UDCA is started in early stages of PBC, patient survival is comparable to the general population [20].

Standard of care for PBC includes treatment with 13–15 mg/kg/day of UDCA in divided doses was found to have significantly welled improvements in ALP level and Mayo risk score compared to the lower dose [21]. Biochemical response is typically determined after 6–12 months of continued treatment. Unfortunately, up to 40% of patients have an inadequate response to therapy [22]. Risk factors associated with decreased response rates are male gender and female younger than 45 years at the time of diagnosis [23]. Inadequate or absent response to UDCA is the strongest predictor of poor outcomes in PBC patients [24]

Obeticholic Acid (OCA)

OCA, a farnesoid X receptor (FXR) agonist, is a more potent analogue of CDCA. OCA helps in maintaining the bile acid homeostasis by decreasing bile acid synthesis and increasing bile acid flow (choleresis). In the liver, FXR agonists downregulate CYP7A1 resulting in decreased conversion of cholesterol to bile acids. In the ileum, FXR up-regulates fibroblast growth factor-19 (FGF-19) which then acts on the liver to further decrease bile acid synthesis [25].

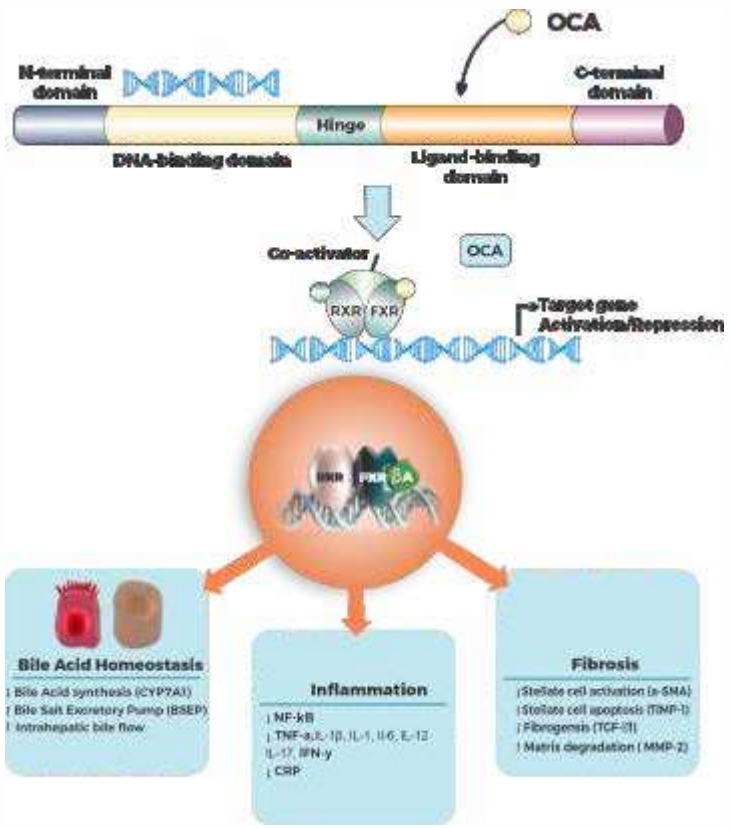

Figure 4: Mechanism of action of obeticholic acid involving FXR activation

In 2016, OCA was approved by the FDA as an additional therapy for patients with inadequate response to UDCA alone, and as a second-line agent for monotherapy in PBC patients intolerant to UDCA.

The drug was granted fast track designation and accelerated approval after two phase 2 trials and a phase 3 trial, the POISE study, demonstrated statistically significant outcomes with improvement in ALP levels [26]. The POISE study was a 12-month trial which assessed the efficacy of OCA, with the primary

endpoints were ALP less than 1.67 times the upper limit of normal with a reduction of at least 15% from baseline, and a normal bilirubin [27]. Currently, the phase 4 COBALT trial (NCT02308111) is underway to confirm clinical benefit of OCA in PBC after prolonged use.

Approved dosing of OCA is dependent on the presence or absence of cirrhosis and is dosed at 5 mg daily initially in non-cirrhotic patients or in Child-Pugh class-A cirrhotic patients. The dose can be titrated up to a maximum of 10 mg daily in this patient group. On the other hand, Child-Pugh class-B or -C cirrhotic patients are dosed at a max of 5 mg weekly.

Approved PBC Therapies

Medication	Dose	
Ursodeoxycholic Acid (UDCA)	13-15 mg/kg/day in divided doses	
Obeticholic Acid (OCA)	In non-cirrhotic patients and Child-Pugh class A cirrhotic patients: start with 5 mg daily.	In Child-Pugh class B and C cirrhotic patients: 5 mg weekly
	If inadequate response after 3 months if therapy, can titrate up to maximum dose of 10 mg daily.	

Treating the Symptoms

Besides, FDA approved medications for PBC, UDCA and OCA, have no impact on management of the associated symptoms. Therefore, the available treatments are also coupled with treating of the symptoms independently. The most common symptoms observed with PBC are pruritus and chronic fatigue, both of them can be debilitating and lead to decreased quality of life. And also, metabolic bone disease, fat soluble vitamin deficiency, hyperlipidemia, sicca complex and liver transplant being the others. Unfortunately, treatment options are limited and liver transplantation may be the only cure for many.

Fatigue

Chronic fatigue is the most common symptom of PBC. Many studies are being carried out investigating the medications, such as modafinil, rituximab and others for treating the fatigue associated with PBC were unable to prove their efficacy [28]. Further research is required in this area.

Pruritus

Pruritus is another common symptom of PBC, reported by up to 80% of patients. Currently, multiple medication options for PBC associated pruritus includes, Bile Acid Resins, rifampicin; and opioid antagonists, such as Naltrexone [29, 30]. But are associated with mild side effects.

Conclusion

PBC is a rare and progressive cholestatic liver disease. Several options are available for treatment of associated symptoms. But for management of PBC UDCA remains first-line therapy. While OCA is being approved by FDA as a combination therapy in patients with inadequate response to UDCA, is the proven and effective second-line therapy.

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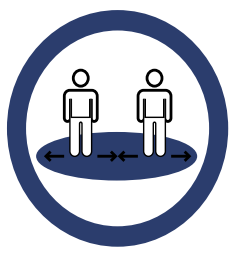

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Emerging Therapies and Recommendations to Handle Covid-19 Pandemic

Abstract

The World Health Organization (WHO) was informed of cases of pneumonia of unknown microbial etiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients. Since then, the epidemic has escalated and rapidly spread around the world, Coronaviruses are large group of viruses that cause illness in humans and animals. Rarely, animal coronaviruses can evolve and infect people and then spread between people such as have been seen with MERS and SARS. The situation is still evolving and hence there is yet no definitive therapy but to conclude the use of repurposed medications can be a boon till a definitive therapy and vaccines are developed.

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Epidemiology

Current available evidence for COVID-19 suggests that the causative virus (SARS-CoV-2) has a zoonotic source that is related to bat-origin SARS-like coronavirus. It is an envelope RNA beta coronavirus related to the Severe Acute Respiratory Syndrome (SARS) virus; the persons infected by the novel coronavirus are the main source of infection. [1] Direct person-to-person transmission occurs through close contact, mainly through respiratory droplets that are released when the infected person coughs, sneezes. These droplets may also land on surfaces, Infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. Experts suggest the amount of infections may be much higher than India's testing rates are among the bottom within the world. The infection rate of COVID-19 in India is reported to be 1.7, significantly less than within the worst affected countries. [2]

Etiology

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019. [3] Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS].

Transmission Dynamics

An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before this confirms that person-to-person spread occurred among close contacts since the middle of December 2019, including infections in healthcare workers. [4] However, these reports relate to indoor crowded spaces with poor ventilation and a detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports. Further research is required. [5] The virus has been found to be more stable on plastic and stainless steel (up to 72 hours) compared with copper (up to 4 hours) and cardboard (up to 24 hours). [6] In healthcare the virus is widely distributed in the air and on object surfaces in both general wards and intensive care units, with a greater risk of contamination in the intensive care unit. [7] While viral RNA has been detected on surfaces and air samples across a range of acute healthcare settings, no virus has been cultured from these samples indicating that the deposition may reflect nonviable viral RNA. [8]

Symptomatic Transmission

Transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by direct contact with infected people, or by contact

with contaminated objects and surfaces.

Pre-symptomatic Transmission

The incubation period is estimated to be between 1 and 14 days, with a median of 5 to 6 days. Some patients may be contagious during the incubation period, usually 1 to 3 days before symptom onset. Pre-symptomatic transmission still requires the virus to be spread by infectious droplets or by direct or indirect contact with bodily fluids from an infected person.

Asymptomatic Transmission

An asymptomatic case is a laboratory-confirmed case that does not develop symptoms. There is some evidence that spread from asymptomatic carriers is possible, although it is thought that transmission is greatest when people are symptomatic.

Clinical Features

COVID-19 patients reporting to various COVID treatment facilities have reported the following signs and symptoms:

- Fever
- Cough
- Shortness of breath
- Fatigue
- Expectoration
- Myalgia
- Rhinorrhea, sore throat, diarrhea

Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms have also been reported. Older people and immune-suppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, and absence of fever. Children might not have reported fever or cough as frequently as adults.
(As per WHO surveillance guidelines)

Severity of Symptomatic Infection

World Health Organization: COVID-19 disease severity [9]

Mild Illness

Symptomatic patients meeting the case definition for COVID-19 without evidence of hypoxia or pneumonia. Common symptoms include fever, cough, fatigue, anorexia, dyspnea, and myalgia. Other nonspecific symptoms include sore throat, nasal congestion, headache, diarrhea, nausea/vomiting, and loss of smell/taste. Older people and immunosuppressed people may present with atypical symptoms.

Moderate Disease

Adolescent or adult: clinical signs of pneumonia but no signs of severe pneumonia, including blood oxygen saturation levels (SpO_2) ≥90% on room air.
Children: Clinical signs of non-severe pneumonia (i.e., cough or difficulty breathing plus fast breathing and/or chest in drawing) and no signs of severe pneumonia. Fast breathing is defined as:

- <2 months of age: ≥60 breaths/minute
- 2-11 months of age: ≥50 breaths/minute
- 1-5 years of age: ≥40 breaths/minute

Severe Disease

Children: Clinical signs of pneumonia (i.e., cough or difficulty in breathing) plus at least one of the following:

- Central cyanosis or SpO_2 <90%
- Severe respiratory distress (e.g., fast breathing, grunting, very severe chest in drawing)
- General danger sign
- Inability to breastfeed or drink, lethargy or unconsciousness, or convulsions

While the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications.

Risk factors for Severe Illness

People who have any of various signs and symptoms without shortness of breath, dyspnea, or abnormal imaging. People who have respiratory frequency >30 breaths per minute, SpO_2 ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50%. People who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Impact of Age

Risk factors for developing severe disease are as follows: age greater than 60 years, active cigarette smoking, immune-suppressing medications or conditions, chronic pulmonary disease, and heart disease.

Pharmacological Treatments With Potential Clinical Benefit

Identify Effective Drugs for Prevention and Treatment and its Outcomes

Several clinical trials are ongoing to help establish the efficacy of various treatments, including antiviral therapies, re-purposed medications, and anti-inflammatory medications. However, a subset of patients will develop severe pulmonary disease or critical illness. For this subset of patients and patients with risk factors for developing severe disease, antiviral medications may be considered.

Virology and Drug Targets

Origin of Virus

A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or "wet" market, suggesting a zoonotic origin of the virus. While the potential animal reservoir and intermediary host (s) are unknown at this point, studies suggest they may derive from a recombinant virus between the bat coronavirus and an origin-unknown coronavirus; however, this is yet to be confirmed. Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses. Over 5 months after the initial outbreak, the virus is yet to be identified in an animal host.

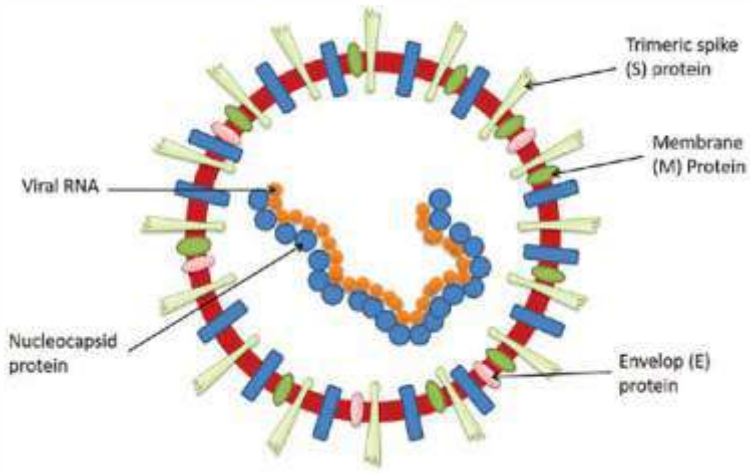

Figure 1: Structural details of Coronavirus

Representing the structure of novel corona virus, which is like other RNA viruses containing various glycoproteins on the envelope and the RNA genome in the core. As shown in Figure 1, the viral cycle is like other viruses consisting of attachment, integration, uncoating, use of host cell machinery for replication, assembly and finally release of virions. Steps in coronavirus replication are potential targets for antiviral drugs and vaccines. [10]

Review of Selected Repurposed Drugs

Chloroquine and Hydroxychloroquine have a long-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. A recent open-label non-randomized French study of 36 patients (20 in the hydroxychloroquine group and 16 in the control group) reported improved virologic clearance with hydroxychloroquine, 200 mg, by mouth every 8 hours compared with control patients receiving standard supportive care.

Management Guidelines

Management of Mild Cases

In the containment phase, patients with suspected or confirmed mild COVID-19 are being isolated to break the chain of transmission. Patients with mild disease may present to primary care/outpatient department, or detected during community outreach activities. Patients with risk factors for severe illness should be monitored closely, given the possible risk of deterioration. Mild COVID-19 cases may be given symptomatic treatment such as antipyretic (Paracetamol) for fever and pain, adequate nutrition and appropriate rehydration. Tab Hydroxychloroquine (HCQ) may be considered for any of those having high risk features for severe disease (such as age> 60; Hypertension, diabetes, chronic lung/kidney/ liver disease, Cerebrovascular disease and obesity) that will be at high risk under strict medical supervision.

Management of Moderate Cases

The patient will undergo detailed clinical history including co-morbid conditions, measurement of vital signs, Oxygen saturation (SpO2) and radiological examination of Chest X-ray, Complete Blood Count and other investigations as indicated. Antibiotics should not be prescribed routinely unless there is clinical suspicion of a bacterial infection. Patients with suspected or confirmed moderate COVID-19 (pneumonia) is to be isolated to contain virus transmission. Patients with moderate disease may present to an emergency unit or primary care/outpatient department, or be encountered during community surveillance activities, the defining clinical assessment parameters are Respiratory Rate of more than or equal to 24 and oxygen saturation (SpO2) of less than 94% on room air (range 90-94%). Such patients will be isolated in Dedicated COVID Health Centre (DCHC) or District hospital or Medical College hospitals.

Early Supportive Therapy and Monitoring

Give supplemental oxygen therapy immediately to patients with Severe COVID and respiratory distress, hypoxaemia, or shock: Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO2 ≥ 90% in non-pregnant adults and SpO2 ≥ 92-96% in pregnant patients. Children with emergency signs should receive oxygen therapy during resuscitation to target SpO2≥94%. All areas where patients with Severe COVID are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single- use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag). Use conservative fluid management in patients with Severe

COVID when there is no evidence of shock.

Pathophysiology of COVID19

SARS-CoV-2 virus is primarily known to effect respiratory tract, by entry through mouth, nose and eyes. While symptoms of the disease accounts similar to mild pneumonia of unknown origin, but are extremely heterogeneous, ranging from minimal to significant hypoxia to acute respiratory distress syndrome (ARDS). The disease progress rapidly and is known to effect other organs as well and can ultimately be fatal, if not kept under check. [11]

After inhalation of SARS-CoV-2 virus, it enters the alveoli of lungs, where it replicates and multiplies causing infection, increasing the viral load. This increased viral load when exhaled out during respiration with cough and sneezing enters outside environment from where it infects to other host organisms.

The infection of alveoli of lungs by viral or bacterial cells is termed as pneumonia. This infection causes the disruption of alveolar cells leading to release of pro-inflammatory chemicals, that is cytokines. The resulting cytokine storm thickens the walls of alveoli and increases the fluid built up in lungs, decreasing the gaseous exchange of oxygen and carbon dioxide which causes ARDS. ARDS causes the shortness of breath in infected patients and need for ventilation.

While all this process going on immune system tries to fight the infection; further, adding to thickening of alveolar wall, making it harder for gaseous exchange and building up of more fluid inside the alveoli which finally leads to collapse of alveoli. Our body then tries to repair the collapsing alveoli leading to fibrosis formation, which eventually forms the scar tissue hardening the lungs and further limiting gaseous exchange.

Moreover, the pro-inflammatory chemical goes to hypothalamus in brain causing the rise in set body temperature, that is fever. Pro-inflammatory chemicals can also spread to other body organs via blood stream, causing systemic inflammation resulting into septic syndrome. In addition to this, lack of oxygen inside body leads to multi-organ dysfunction.
If kept unchecked, all these symptoms of cough, pneumonia, fever, acute respiratory distress syndrome, systemic inflammation and organ failure, finally can be fatal to a host organism.

Pre-clinical and Clinical Evidence of Potential Therapeutic Targets

Researches to find the cure, treatment and vaccines are going on all across the globe. For this various potential therapeutic target are being considered. Many preclinical and clinical trials are being carried out using these potential therapeutic options, showing promising evidence for treatment.

Emerging therapies for COVID-19 treatment		
Antiviral	**Anti-inflammatory**	**Convalescent Plasma**
• Remdesivir • Favipiravir • Lopinavir - Ritonavir	• Glucocorticoids • Tocilizumab • Siltuximab	• Serum-containing neutralizing antibodies

Antiviral Therapy

The treatment done using drugs which directly keeps the check on virus multiplication and decreases the viral load falls under this section of antiviral therapy.

Remdesivir

Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses and coronaviruses; and has shown prophylactic and therapeutic efficacy in non-clinical models of these coronaviruses.
In order to evaluate the efficacy and safety of the drug in patients with COVID-19, a randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial was done in China. Patients in the experimental group received an initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days via intravenous infusion in addition to routine treatment. [12]
One study showed 68% of clinical improvement in the category of oxygen support, 100% in improvement in patients breathing ambient air or low flow supplemental oxygen and 71% on non-invasive oxygen support. [13] Another study showed that the group of patients treated using remdesivir had shorter recovery time as compared to placebo group. [14]
In May 2020, the US FDA issued emergency use authorization (EUA) of remdesivir to allow severe COVID-19 (confirmed or suspected) in hospitalized adults and children. [15]

Lopinavir – Ritonavir

Lopinavir a peptidomimetic molecule is a protease inhibitor. Lopinavir is administered exclusively in combination with ritonavir.
Due to lopinavir's poor oral bioavailability and extensive biotransformation, it is co-formulated with ritonavir to enhance its exposure. Ritonavir is a potent inhibitor of the enzymes that is responsible for lopinavir metabolism, and its co-administration "boosts" lopinavir exposure and improves antiviral activity. [16]

This combination was investigated in an open-label, individually randomized, controlled trial, where patients received lopinavir-ritonavir 400 mg/100 mg, orally twice daily plus standard of care. No significant effect on the primary outcome measure of time to clinical improvement and no evidence of reduction in viral RNA titres compared to control were found. However, peer-protocol analyses suggested possible reductions in time to clinical improvement, particularly in those treated within 12 days of symptom onset. Further studies of lopinavir–ritonavir are ongoing. [17]

Favipiravir

Favipiravir is a guanine analogue with pyrazine-carboxamide structure. The antiviral activity is exhibited through selectively targeting conservative catalytic domain of RNA-dependent RNA polymerase (RdRp), interrupting the nucleotide incorporation process during viral RNA replication. [18] Favipiravir has been used in the treatment of infectious diseases caused by RNA viruses such as influenza, Ebola, norovirus and recently SARS-CoV-2.

Clinical trials testing favipiravir against COVID-19 have been carried out vigorously in various countries. A randomized control trial (ChiCTR200030254) has shown that COVID-19 patients treated with favipiravir have superior recovery rate (71.43%); and the duration of fever and cough relief time are significantly shorter than in umifenovir group. [19]

An RCT enrolling patients within 12 days of symptom onset found that favipiravir was superior to arbidol in terms of the clinical recovery rate at day 7 in patients with mild illness, but not in those with critical illness. [20]

Anti-inflammatory Medications

The novel coronavirus SARS-CoV-2 that causes COVID-19 invokes a hyper-inflammatory state driven by multiple cells and mediators. This condition can be managed using various anti-inflammatory medications.

Glucocorticoids (Corticosteroid)

During the SARS-CoV epidemic of 2003, therapeutic systemic corticosteroids were administered in patients who were infected and developed severe respiratory disease. [21]

Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects. It was tested in hospitalized patients with COVID-19 in the U.K. national clinical trial RECOVERY and was found to have benefits for critically ill patients.

According to preliminary findings shared with WHO, for patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth. Dexamethasone was administered as an oral (liquid or tablets) or intravenous preparation, at a dose of 6 mg once daily for ten days.

Tocilizumab and Siltuximab

Considering the proven role of cytokine dysregulation in causing this hyperinflammation in the lungs with IL-6 being a key driver, particularly in seriously ill COVID-19 patients, it is crucial to further explore selective cytokine blockade with drugs like the IL-6 inhibitors. Several randomized controlled trials (RCT) of tocilizumab and siltuximab, alone or in combination, are now proposed in patients with severe COVID-19. [22]

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody and is antagonists of the IL-6 receptors. In Italian Phase II open-label trial (NCT04315480) with tocilizumab 8 mg/kg single dose is being conducted in patients with severe multifocal interstitial pneumonia due to COVID-19 to evaluate its role in the virus-induced cytokine storm. [23]

Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R, inhibiting IL-6 signaling. A Phase II, randomized, open-label study to compare the efficacy and safety of siltuximab versus methylprednisolone in hospitalized patients with COVID 19 pneumonia has begun recruiting patients in Spain (NCT04329650). An another retrospective observational case–control study evaluating the use of siltuximab in patients diagnosed with COVID-19 infection who have developed serious respiratory complications is also registered in Italy (NCT04322188). [24]

Convalescent Plasma

Convalescent plasma is obtained from the individual who was suffering from SARS-CoV-2 infection and now is been recovered from the disease. During infection, the patient's immune system tries to fight infection, in response to which particular antibodies are generated. By the time infection ceases these antibodies are present in the circulating blood, which can be separated from blood as plasma. These extracted plasma containing particular antibodies can be administered to the other infected person as a treatment therapy. [25]

The use of convalescent plasma was earlier used for treatment during outbreaks of Ebola virus (2014), and MERS (2015). This approach with other viral infections

such as SARS-CoV, also suggested that transfusion of convalescent plasma was effective. In severe illness, one uncontrolled study of five patients given convalescent plasma suggested a possible benefit. [26]

However, Casadevall and Pirofski highlighted few risks related to passive administration of convalescent sera, which falls into two categories, serum disease and antibody-dependent enhancement of infection. Serum disease is associated with the transmission of other blood infections, whereas the antibody-dependent enhancement is the concern that antibodies to one form of coronavirus could enhance infection to another viral strain. [27]

Complications and Prognosis of COVID 19

SARS-CoV-2 initially effect respiratory system causing COVID19. These accounts for the mild-to-moderate symptoms causing distress; but if accompanied by other ailments or not kept under check, its course of progression becomes serious, causing severe symptoms. This may account for may complication requiring a need for ventilation, IV therapies and a longer hospital stay.

Complications arising are associated with infection due to invasive mechanical ventilation, increased chances of ventilated related pneumonia and catheter-related bloodstream infection. Apart from these taking lots of drug medication required for treatment cause ulcer formation and may lead to GI tract bleeding. During longer hospital stay patient is bedridden and develops bedsores and ICU-related weakness. All these complications accounts for additional measures to be taken to prognoses the correct course of recovery.

Conclusion

SARS-CoV-2 has infected a large number of population all across the globe. While researches are going on to find cure and treatment still not available calls for symptomatic management. This has recommended to testing and trials using various proposed medication showing promising results to treat COVID19. Based on preclinical and clinical trials of potential therapeutic targets such as antivirals remdesivir and favipiravir, a high dose of anti-inflammatory medications and convalescent plasma therapy can be safe for the treatment of the disease. Additionally, various other measures should be accompanied to reduce the incidences of associated complications as well.

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Handling ICU Patient with Symptoms of Acute Respiratory Distress Syndrome (ARDS) and Low Immunity

ABSTRACT

Coronavirus pandemic due to SARS-CoV-2 infection has created a chaos across the globe causing many causalities. Severe conditions of COVID-19 infection lead to acute respiratory distress syndrome (ARDS) and pneumonia, which can prove to be fatal for the infected individual. Initial alveolar damage is linked to viral infection and damage due to cytokine storm, and which later leads to multi organ dysfunction. The main treatment strategy for pulmonary distress and acute respiratory distress syndrome is to provide oxygenation therapy and ventilation support. Further research is required to identify more specific therapies for COVID-19 related ARDS.

Keywords: *SARS-CoV-2, COVID-19, ARDS, Cytokine storm, Oxygen therapy, Ventilation support*

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Introduction

The outbreak of novel coronavirus was detected in Wuhan in December 2019 resulted in a worldwide pandemic. On February 11, 2020, the World Health Organization (WHO) formally named it as coronavirus disease 2019 (COVID-19). [1] Globally, more than 15,654,428 confirmed individuals and over 636,475 deaths, across more than 200 countries, territories or areas have been reported. [2] As the virus continues to spread at an alarming rate, healthcare workers are seeking effective and actionable management program for affected patients. Most of the people who came in contact with Coronavirus presented with mild symptoms (80.9%), then severe (13.8%), and finally critical (4.7%). Patients with underlying diseases had much higher fatality rates than patients with no underlying diseases (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, 5.6% for cancer, and 0.9% for none). [3]

A recent single-center study found that most critically ill patients developed organ dysfunction, where 67% were found to have acute respiratory distress syndrome (ARDS), 29% with acute kidney injury (AKI), 23% with cardiac injury, 29% with liver dysfunction, and 2% with pneumothorax. [4] According to the opinion of experts', the patients should also be considered as critical cases if they are suffering from high respiratory frequency (RR ≥ 30 bpm) and low oxygen index (arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤ 200 mmHg) under high-flow nasal cannula oxygen therapy (HFNC). The experts drew up sections on the management of COVID-19 disease, mostly based on their experience in Wuhan.

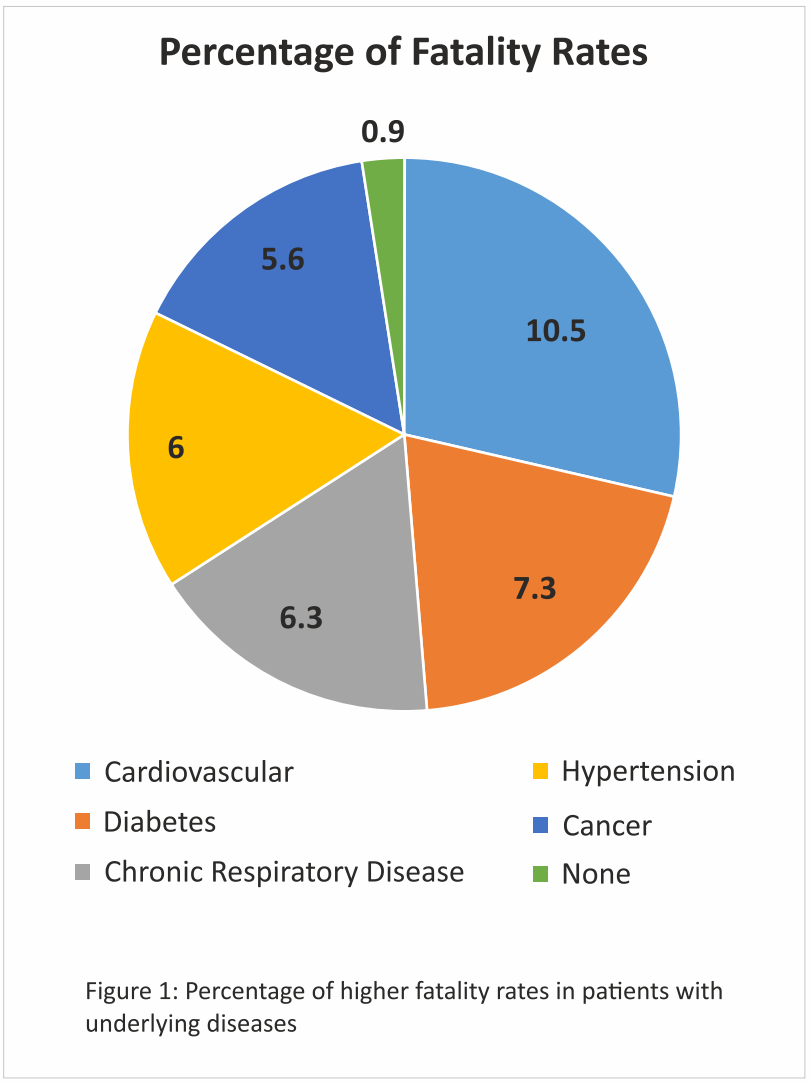

Figure 1: Percentage of higher fatality rates in patients with underlying diseases

COVID-19: A Newly Emerged Respiratory Disease

As late in the year 2019, when most people were diagnosed with pneumonia kind of symptoms due to unknown reason, it led to the rigorous findings for cause of such situation. This lead to the discovery of newly emerged SARS-CoV-2 causing COVID-19. The disease spreads from person to person through airborne droplets carrying SARS-CoV-2 viruses, or via coming into contact with any kind of surfaces contaminated with the strains of this coronavirus. [5]

After the individual host comes into contact with SARS-CoV-2, the virus enters inside the body through mouth, nose or eyes into lungs, and starts multiplying there causing infection. Majority of infected individuals are asymptomatic or show mild symptoms. Other infected patients start observing symptoms related to respiratory distress, shortness of breath, fever, fatigue, muscle pain, dry cough, sore throat, loss of smell or taste, nausea, vomiting and diarrhea. The patients with other kind of comorbidities like pulmonary and cardiovascular issues, obesity, diabetes, asthma, hypertension, lung fibrosis, COPD and interstitial lung diseases develops severe kind of disease characteristics. [6] If not treated properly, the symptoms worsen and after this the disease progresses leading to acute respiratory distress syndrome (ARDS) preceded by acute lung injury (ALI), or maybe even death. Patients with ARDS require oxygen therapy and ventilation support along with ongoing treatment, based on their condition and progress of recovery.

Cytokine Storm: Overreaction of Body's Immune System

SARS-CoV-2 is a positive sense single stranded RNA virus. It encodes spike S protein which binds to the ACE2 receptor on cell surface of host cell and promotes fusion by endocytosis. Upon entering the host cell like any other virus, SARS-CoV-2 uses host cells machinery to synthesize viral proteins and replicates viral genome. [7]

After entering the human body, viruses trigger the series of immune responses such as, apoptosis, autophagy, activating innate immunity and various other stress responses. Initially if the person has strong immunity, then bodies innate immune system comes into play by activating antiviral defense mechanism such as antiviral T cells and natural killer (NK) cells, and releasing of interferons (IFN) by infected cell. [8]

In earlier study on SARS and MERS, it was observed that these viruses have evolved a method to delay interferon production by virus infected cell. This resulted in severe lung injury and enhanced inflammatory responses, leading to the production of outburst of inflammatory cytokines, known as cytokine storm. This correlates with the disease severity and poor prognosis of COVID-19 patients. [9]

Transcriptomic RNA-sequence analysis of COVID-19 patients has revealed that several immune pathways and pro-inflammatory cytokines CXCL, CCL2, CXCL2, CCL8, IL33, and CCL3L1 in bronchoalveolar lavage fluid (BALF) and TNFSF10, CXCL10, IL10, TIMP1, C5, IL18, AREG, and NRG1 in peripheral blood mononuclear cells (PBMC) were induced by SARS-CoV-2 infection, suggesting a sustained inflammation and cytokine storm. Importantly, SARS-CoV-2 infection–induced excessive cytokine release correlates with lung tissue injury and COVID-19 pathogenesis. [10]

The patients who develop severe disease condition are linked most likely due to genetics, epigenetics or other factors. COVID-19 is well known to effect respiratory system, but other organ system also including organs like heart and brain. Many neurological symptoms have been reported in patients and infection due to SARS-CoV-2 has been found in brainstem of infected humans as well as experimental animals. [11]

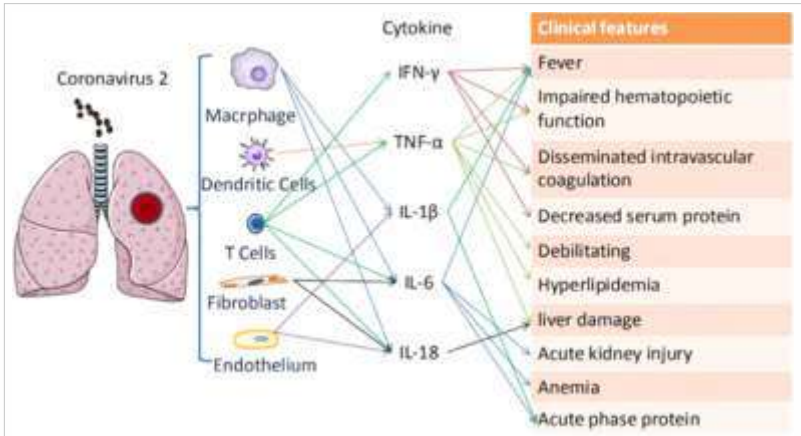

Figure 2 : Schematic representation of clinical features versus pathogenic inflammatory cytokine response in SARS-CoV-2 infections

Method

The statements regarding the evidences on how to cope with current pandemic situation were drawn up by a group of 16 front-line intensive care experts in China who fought against the COVID-19 in Wuhan. The quality of evidence was assessed using the methodology described in grades of recommendation, assessment, development, and evaluation (GRADE). [12]

Summary of Guidelines for Handling Critically Ill Patients

According to the GRADE method and summary of the results, experts drew up 46 statements. Of these

guidelines, 5 had a high level of evidence (GRADE 1±), 21 had a low level of evidence (GRADE 2±), and 20 were expert opinions.

As the front-liners of the COVID-19 outbreak response, health care workers are exposed to a high risk of infection. Therefore, health care workers must follow the standard precautionary principles and try their best to ensure the personal protection, hand hygiene, ward management, environmental ventilation, and sanitization of the object surface, in order to prevent nosocomial cross-infection.

1. Convalescent Plasma Therapy Should Probably be Used for Severe and Critically Ill Patients With COVID-19

Plasma treatment tends to lower the upper respiratory tract virus load and decreases serum cytokines levels in patients with severe virus infection. A study performed in 10 severe COVID-19 patients found that convalescent plasma treatment could improve clinical outcomes, improve immune function, and promote absorption of lung lesions. [12]

2. Oxygen and Respiratory Support

Respiratory failure is the primary organ dysfunction, which worsens the prognosis of COVID-19 patients. Oxygen therapy and respiratory support are the major treatments for COVID-19-induced ARDS. Due to inflammatory and necrosis-induced small airway occlusion, which was confirmed by autopsy of COVID-19-induced ARDS, positive pressure ventilation is important to restore the collapsed airway and to improve the gas exchanges. However, high end-inspiratory pressure increases stress and strain to normal alveoli and increases the risk of lung injury. Oxygen therapy and respiratory support for COVID-19-induced ARDS should balance airway recruitment and risk of lung injury.

Noninvasive ventilation support (NIV) and high-flow nasal cannula oxygen therapy (HFNC) are important treatment options for COVID-19-induced mild and moderate ARDS. The mechanisms of the two treatments are positive end-expiratory pressure, decreased respiratory workload, decreased incidence of intubation, ease of use, and higher comfort. In a randomized trial of adult patients admitted to the ICU for acute hypoxemic, non-hypercapnic respiratory insufficiency, continuous positive airway pressure (CPAP) delivered by face mask was associated with an early improvement in oxygenation. [13]

3. Using Prophylactic Antibiotics for COVID-19 Patients

Due to the nature of virus infection, it is not logical to use prophylactic antibiotics, and there is no evidence that this treatment option could reduce the incidence of the secondary infection. On the other hand, according to the management guidelines of COVID-19 from WHO and China empiric antibiotic treatment should only be given to the patient based on the clinical diagnosis (community-acquired pneumonia, healthcare-associated pneumonia or sepsis), local epidemiology and susceptibility data, and treatment guidelines. [12]

4. Immunity Therapy

There is some evidence that immunotherapy may be effective against novel coronavirus infection. An article published on the MedRixv website stated that the mortality of COVID-19 patients might be negatively related to the number of lymphocytes in patients. Both helper T cells and suppressor T cells in COVID-19 patients tend to be below normal levels and lower level of helper T cells in the severe group. The percentage of naive helper T cells increased, and memory helper T cells decreased in severe cases. Thus, enhancing the immunity of the patient might strengthen the fight against novel coronavirus. [14]

Vitamin C (ascorbic acid) is a water-soluble vitamin that has beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity. Humans require more vitamin C in states of oxidative stress, vitamin C supplementation has been evaluated in numerous disease states, including serious infections and sepsis. Because serious COVID-19 may cause sepsis and acute respiratory distress syndrome (ARDS), the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied.

5. Antiviral Therapy

Antiviral drugs are proven effective and should probably be considered for SARS-CoV-2 treatment.

Favipiravir is an antiviral medication that was initially developed to treat influenza in Japan. In February 2020, post the outbreak of Novel Coronavirus (COVID-19), Favipiravir was studied in China and several other countries as an experimental treatment of COVID-19.

Favipiravir is a broad-spectrum oral antiviral drug that selectively inhibits RNA-dependent RNA polymerase (RdRp) and the viral replication phase of SARS-CoV-2. "The drug has demonstrated positive outcomes, including a reduction in the duration of COVID-19 and improved lung conditions for the patients". [15]

6. Anti-inflammatory agent

Ulinastatin (UTI), is a serine protease inhibitor with anti-inflammatory properties. It inhibits cytokine storm, which is a severe immune reaction wherein the body releases too many cytokines into the blood too quickly.

Results from trials have shown that Ulinastatin improved oxygenation index, shortened duration of mechanical ventilation and decreased mortality and ICU stay compared to standard therapies in Covid-19 patients.

Conclusion

As the pathogenesis of COVID-19 is not yet well understood and associations between clinical status and viral clearance, radiological or immunological evaluations are unclear, the use of clinical outcomes should be encouraged. Rapid identification of such therapies is thus essential, but challenging. Repurposing of existing antiviral and immunomodulating drugs is an important strategy, because the safety profile of these drugs is well known. We may expect that in the next few weeks carefully performed trials will be reported that will guide doctors around the world to give the best care (both in terms of reducing viral replication and mitigating hyper-inflammation) to COVID-19 patients.

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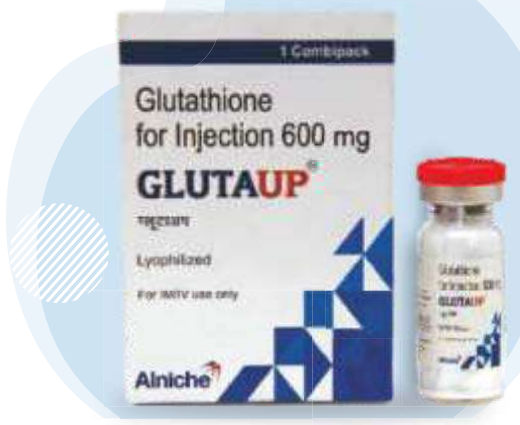

GLUTAUP
Glutathione 600 mg I.V.

(Glutathione 600mg i.v)

- Reduces oxidative stress
- Protect host immune cells
- Prevents massive release of "cytokine storm"
- Inhibits replication of various viruses

Dose: 600mg to 2.4 gm

ASCORJET 1.5 3
Ascorbic acid 250 mg/ml Injection

(Ascorbic acid 250mg)

- Reduces Oxidative stress
- Enhances Immunity
- Exhibits anti-inflammatory properties
- Inhibits expression of pro-inflammatory cytokines

Dose : 100 to 200 mg / kg per day

Glutabest
L-Alanyl-L-Glutamine 20% Infusion

(L-Alanyl-L-Glutamine 20% infusion)

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- Reduces pro-inflammatory cytokine release

Dose: 0.3-0.5 grams per kilogram

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Mental Health and Importance of Staying Healthy during COVID-19 Pandemic

Introduction: *Covid-19 pandemic has created a panic and rapidly changing situation that has caused negative emotions and has altered the daily routine of the people.*
The pandemic has caused fear, tension and stress across the globe. In such crisis, once emotional and mental health is of outmost importance.

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De-addiction Specialist

What is mental health?
Mental or emotional health refers to your overall psychological wellbeing. It can include the way you feel about yourself, the quality of your relationships and your ability to manage your feelings and deal with difficulties.

Mental health and physical health are very closely connected. Mental health plays a major role in your ability to maintain good physical health. Mental illness such as depression and anxiety, affect your ability to carry out day to day activities.

If one is not emotionally sound, it can eventually lead to catastrophic decisions and events.

According to the world health organization (WHO):"Mental health is a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community."

WHO also states that, "mental health is more than just the absence of mental disorders or disabilities."

So rather than being about **'what's the problem?'** it's really about **'what's going well?'** It's not around the illness but regarding the wellness.

Mental health is an integral part of physical health. The health of the mind is just as important as the health of the body's.

A report by the World Health Organization (WHO) revealed that 7.5 per cent of the Indian population suffers from some form of mental disorder. Mental illnesses constitute one-sixth of all health-related disorders and India accounted for nearly 15% of the global mental, neurological and substance abuse disorder burden. [1]

The treatment gap, which is defined as the prevalence of mental illnesses and the proportion of patients that get treatment, is over 70 per cent. WHO also predicts that by 2020, roughly 20 per cent of India will suffer from mental illnesses. And to cater to this demographic, we have less than 4,000 mental health professionals. [1]

How a mental health condition affects quality of life?
Mental health doesn't always remain the same. It can change as situations changes and as you move through different stages of your life. When someone has a mental health condition, it can effect on how they think, feel and behave.

A low quality life, is frequently aftereffect of extreme psychological wellness conditions, which is portrayed by sentiments of misery; absence of control, decision and self-governance; low confidence and certainty; a feeling of not being a part of society; lessened action; and a feeling of sadness and dampening.

Balance between life activities and responsibilities for becoming mentally strong
It's very important to maintain a healthy balance between life activities and responsibilities

forenhancing mental strength. Mental strength is the capacity of a person to deal with stress, pressure, challenges and perform to the best of ability irrespective of the circumstances. If we want to be mentally healthy, then we need to build our mental strength and it developed over time by practicing gratitude. [2]

We can maintain a balance between life activities and responsibilities and become mentally strong by practicing these techniques [2]:
1. Positive Thinking
2. Anxiety Control
3. Visualization
4. Goal Setting
5. Attentional Control

Risk factors for mental health and well-being

Irrespective of age, gender, income or ethnicity everyone has some risk of developing a mental health disorder.

Individual attributes and behaviors, social and economic circumstances and environmental factors in together can affect a person's mental health and well-being.

The following factors may contribute to mental health conditions [3]:

1. Individual attributes and behaviors: These relate to a person's innate as well as learned ability to deal with thoughts and feelings and to manage him/herself in daily life ('emotional intelligence'), as well as the capacity to deal with the social world around by partaking in social activities, taking responsibilities or respecting the views of others ('social intelligence'). An individual's mental health state can also be influenced by genetic and biological factors; that is, determinants that persons are born or endowed with, including chromosomal abnormalities (e.g. Down's syndrome) and intellectual disability caused by prenatal exposure to alcohol or oxygen deprivation at birth.

Example:
- Self-esteem, confidence,
- Ability to solve problems and manage stress or adversity,
- Communication skills,
- Physical health and fitness.

2. Social and economic circumstances: The capacity for an individual to develop and flourish is deeply influenced by their immediate social surroundings – including their opportunity to engage positively with family members, friends or colleagues, and earn a living for themselves and their families – and also by the socio-economic circumstances in which they find themselves. Restricted or lost opportunities to gain an education and income are especially pertinent socio-economic factors.

Example:
- Social support of family & friends
- Good parenting / family interaction
- Physical security and safety
- Economic security
- Scholastic achievement
- Satisfaction and success at work

3. Environmental factors: The wider sociocultural and geopolitical environment in which people live can also affect an individual's, household's or community's mental health status, including levels of access to basic commodities and services (water, essential health services, the rule of law), exposure to predominating cultural beliefs, attitudes or practices, as well as by social and economic policies formed at the national level; for example, the on-going global covid-19 pandemic is expected to have significant mental health consequences, including increased rates of suicide and harmful alcohol use. Discrimination, social or gender inequality and conflict are examples of adverse structural determinants of mental well-being.

Example:
- Equality of access to basic services
- Social justice, tolerance, integration
- Social and gender equality
- Physical security and safety

What are the common mental health disorders?

The most common types of mental illness are as follows:

• **Depression** [4]

Depression refers to a wide range of mental health problems characterized by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioral symptoms. Distinguishing the mood changes between clinically significant degrees of depression (for example, major depression) and those occurring 'normally' remains problematic and it is best to consider the symptoms of depression as occurring on a continuum of severity.

Symptoms of Depression Include [5]

- Trouble in concentrating, remembering details, and decisions making
- Fatigue
- Guilt feeling, worthlessness, helplessness and hopelessness
- Insomnia, early-morning wakefulness, or sleeping too much
- Irritability, Restlessness
- Loss of interest in things once pleasurable, including sex
- Overeating, or appetite loss
- Aches, pains, headaches, or cramps that won't go away
- Digestive problems that don't get better, even with treatment
- Persistent sad, anxious, or "empty" feelings
- Suicidal thoughts or attempts

Generalized anxiety disorder [4]

The essential feature of GAD is excessive anxiety and worry, occurring on more days than not for a period of at least 6 months, about a number of events or activities. The person with GAD finds it difficult to control the anxiety and worry, which is often accompanied by restlessness, being easily fatigued, having difficulty concentrating, irritability, muscle tension and disturbed sleep (Brown et al., 2001). GAD is mostly comorbid with depression.

Physical symptoms of GAD may include [6]

- Restlessness
- Fatigue
- Tense muscles
- Interrupted sleep

Panic Disorder [4]

People with panic disorder suffer from regular panic attacks involving attacks of sudden short-lived anxiety with or without any visible cause. They frequently take action to avoid being in particular situations in order to prevent those feelings, which may develop into agoraphobia, a fear of places from which the individual considers to be dangerous, or difficult to escape from.

Agoraphobia may lead to a common avoidance of situations like: being alone outside the home or being home alone; being in a crowd of people; travelling by car or bus; being in a particular place, such as on a bridge or in a lift.

Obsessive-compulsive disorder [4]

A person with OCD either has obsessions or compulsions, but mostly both.

An obsession is an unwanted distracting thought, image or urge that repeatedly enters the person's mind.

Common obsessions include contamination from dirt, germs, viruses, body fluids and so on, fear of harm, obsessions with the body or physical symptoms, unwanted sexual thoughts, including homosexuality, religious obsessions, including concerns about offending God.

Compulsions are form of repetitive behaviors that the person is obsessive to perform.

Common compulsions include washing and cleaning (including constant hand-washing), checking (including checking body parts or checking that nothing terrible happened), repeating (including rereading and repeating routine activities like getting up from a chair), mental compulsions (including praying to prevent harm and mentally reviewing events).

Post-traumatic Stress Disorder [4]

PTSD develops when a person has gone through some extremely stressful and traumatic events such as deliberate acts of interpersonal violence, severe accidents, disasters, loss of a loved one or abuse of some form like sexual abuse.

Symptoms Include

The core symptoms are:

- Recalling the acts or feelings as if the event is recurring;
- Nightmares; and repetitive and distressing intrusive images,
- Irritability,
- Difficulty in concentrating,
- Sleep problems and
- Avoidance of trauma reminders

Social anxiety disorder [4]

Social anxiety disorder is also known as social phobia, is an intense fear of being judge, negatively assessed or refused in social situations. This results in intolerable suffering and impacts a person's ability to perform effectively their daily life routine.

Common symptoms of social anxiety disorder

- Excessive blushing,
- Sweating,
- Trembling,
- Palpitations,
- Nausea and
- Panic attacks are the most common symptoms

SAD is often comorbid with other disorders such as depression and anxiety.

Specific Phobias [4]

A specific phobia is an unjustified, strong and continuous fear of a specific object or situation that is not in proper relation to the actual risk, danger or threat. The fear and anxiety occur immediately after coming in contact with the feared object or situation and lead to avoidance or extreme discomfort. Specific phobias are long lasting, causes intense physical and psychological reactions, and can affects one's ability to function normally at work, at school or in social gathering.

There are many types of specific phobias which can also occur along with different types of anxiety disorders. Some of the common types of specific phobias are fear of:

- **Situational Type:** such as airplanes, enclosed spaces or going to school
- **Natural Environmental Type:** such as thunderstorms, heights or water
- **Animals Type:** such as dogs, snakes or spiders
- **Blood-injection-injury Type:** such as needles, blood, accidents or medical procedures
- **Other Type:** such as situations that may lead to choking, vomiting, avoidance of loud noises or clowns

How Coronavirus Pandemic Affect Mental Health?

After the outbreak of Corona virus pandemic in December 2019, it has affected the world as a whole, creating turmoil in the society as well as in the mental

state of all humans. Maintaining the mental health in such a calamity is of prime importance. Various studies and surveys on psychological impact of pandemic has shown increased negative mental health outcomes, such as sleeplessness, panic, anxiety, depression, paranoia, obsessive behaviour, post-traumatic stress disorder and even suicidal attempts. The general mass fear of COVID19, termed as 'Coronaphobia', has generated plethora of psychiatric manifestation across the different strata of the society. [7]

According to a study from China reports in total, 53.8% of respondents rated the psychological impact of the outbreak as moderate or severe; 16.5% reported moderate to severe depressive symptoms; 28.8% reported moderate to severe anxiety symptoms; and 8.1% reported moderate to severe stress levels. [8]

According to Indian survey, sleep difficulties, paranoia about acquiring COVID-19 infection and distress related social media were reported in 12.5 %, 37.8 %, and 36.4 % participants respectively. The perceived mental healthcare need was seen in more than 80 % of participants. [9]

As a human we all are socially dependent on each other for not only our regular day to day basic necessities but also for creating a sense of social wellbeing. This helps us human keeping mentally healthy and a wisdom that we all are together in adversities keeps us going on.
In today's scenario of COVID-19, it is a must for all to keep social distancing to stop the disease from spreading and creating a catastrophe. This has not only led us from decreasing a social intellect, but as well has led us in confinement. The fear of contacting the disease, seeing our dear ones in distress or losing them has created the anxiety and stress. This has steered us in affecting our mental health as an individual and our families.

In response to COVID19 crisis, most governments have closed the non-essential business and schools; prohibited large social gatherings and quarantined the travellers in addition to social distancing. This has created the feeling of loneliness and isolation; that to for unknown duration. This lack of uncertainty about future, unemployment and disturbances in financial management has increased risk of mental and physical illness. The universal psychological impact has caused mass hysteria, economic burden and financial losses.

Ways to Manage Mental Health during Coronavirus Pandemic

COVID19 pandemic may have caused fear, anxiety and panic due to isolation and loneliness; but maintaining our mental wellbeing, caring and helping for the people around us is the approach how we can emerge victorious as humanity from this calamity.

Following are the various methods which can be employed to relive the stress and manage mental health during these times [10]:

- Connecting with family and friends via calls can beat the isolation and boredom.
- Talking about our feelings and ways to cope can help us, but also our near and dear ones from easing worries and fears, as well as reducing stress and anxiety.
- Helping and supporting the people around us in a way possible, can help others from overcoming their problems and also giving us the sense of satisfaction as a person.
- Keep your physical fitness by exercising regularly; eating a well-balanced healthy diet and drinking lots of water can release the toxins from body.
- Maintain a timely sleep pattern avoiding caffeine and screen time before bed, keeping the overall relaxing environment.
- Try to manage negative thoughts and focus on things which can be controlled like actions which can be taken to feel better.
- Check on right information and facts to keep precautions, or correct method to manage if a person gets infected.
- Think about new routines and hobbies to try, so that one can engage themselves and do not feel secluded like reading, writing, painting, playing, crafting, etc.
- Set your daily goals and achieve them to get the sense of control and purpose.
- Try to meditated, this helps in relaxing the feeling of anxiety and conserving the overall mental health.

Besides all these, eating a well-balanced healthy diet can keep you fit physically as well as mentally. This also helps in enhancing immunity to fight infections and reducing the chances of getting sick. The goal can be achieved by taking nutritional supplements also.

Manage Mental Health during COVID-19 Pandemic

Do's	Don'ts
• Positive thinking	• Substance use
• Eating balanced diet	• Negative thoughts
• Regular exercise	• Eating too much fast food
• Connecting each other via call	• Lethargic activities
• Social distancing	• Watching too much news
• Meditation	• Travelling and partying
• Developing interesting hobbies	• Stress and anxiety
• Maintain regular sleep pattern	• Social gatherings

Role and Importance of Nutritional Supplements in Boosting Immune Health

Corona viruses impact our overall physical and mental health. While maintaining our mental health, it is also important to maintain the physical health as well. Coronaviruses primarily infect our respiratory tract, and eventually having an effect on our other systems also. Therefore, it is of prime importance to fight the infections and cure the symptoms. To do so one must have a strong immune system and/or should take measures to boost immunity.

Eating a balanced diet, regular exercise, drinking water and maintaining healthy lifestyle is a way for enhanced immunity. Although times like these of pandemics calls to take an enhanced measure; hence taking an additional supplement to boost immunity are essential.

Coronavirus attacks respiratory tract causing a burst in cytokine storm which causes symptoms similar to like that of flu, cough and cold. It leads to an excessive oxidative stress, inflammatory responses and demands energy to fight infections. In this case supplement which can support to reduce infection, have antioxidant and anti-inflammatory response should be added to diet.

Healthy immune system leads to healthy body and healthy mind. There are various nutritional supplements to help in boosting immune system and fight infections:

Ubiquinol:

Easily absorbed form of Coenzyme Q10, plays a vital role in boosting the immune system. It helps to power cells to provide ample energy for immune cells. It also acts as an antioxidant scavenging free radicals and oxidants. Studies show it cleans up oxidants causing cellular damage and allows body to repair and restore health. [11]

Methylcobalamin:

Form of vitamin B12, active in human metabolism helps in immunomodulation. It is required for proper red blood cell formation, neurological function, and DNA synthesis. Studies have shown it to be associated with neuronal health and cellular immunity. [12, 13]

Benfotiamine:

Derivative of thiamine (vitamin B1) has an antioxidant effect and exhibits a potential anti-inflammatory response. As well has a beneficial effect on cognitive impairments associated to mental disorders. [14, 15]

Alpha-lipoic acid:

Naturally occurring dithiol compound in human body is a powerful antioxidant which can directly scavenge reactive oxygen species (ROS). It might have immunomodulatory effects on both adaptive and innate immune systems. It is also considered to have a role in neurodegenerative diseases and associated cognitive impairments. [16, 17]

Pre-probiotic:

Live micro-organisms that confer health benefit to the host. There are several genes and specific compounds derived from probiotics which mediate immunoregulatory effects. Also recent studies have demonstrated the connection between central nervous system and enteric nervous system. Studies have shown variety of mechanism by which gut microbiota can signal the brain and influence several processes in relation to neurotransmission, neurogenesis, and behaviour. As the proverb says health gut leads to healthy mind. [18, 19]

Conclusion

During the current COVID pandemic era the on-going confusion, fear and anxiety has created various mental issues among the individuals in society. In times like these it is important to stay healthy and mentally sound till this calamity subsides and also subsequently. For this one needs to keep calm, meditate, help others, engage in hobbies, exercise regularly, maintain proper lifestyle, etc.

For viral diseases like COVID19 when no cure is presently available, and therapies are done treating the symptoms, it is important to maintain a healthy immune system. Eating healthy has a positive impact on physical health and mental health as well. This can also be achieved by adding nutritional supplements to diet. Therefore, staying physically healthy and maintaining mental health is how we can beat the COVID pandemic all together.

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Phytosomal Curcumin: A Novel Technology Ensuring Higher Bioavailability of Curcumin to Deliver the Benefits of Anti-Inflammatory, Immunity Enhancing and Antiviral Properties to Immunocompromised Patients

Abstract

Curcumin is a natural spice that has been traditionally used as a medicinal herb for many decades, it shows antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties. Curcumin is effective in treating chronic conditions like cancer, diabetes, arthritis, Alzheimer's, and many others. Although it has several benefits curcumin has a few shortcomings in terms of bioavailability. This is a review article written with the objective to systematically analyze the information regarding the benefits, properties and immunomodulatory effects of curcumin, and to understand the existent gaps which have prevented its widespread application in the medical community and the new technological modifications that are coming up to improve its role in clinical applications.

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Introduction

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) a polyphenol, also called diferuloylmethane, is the main natural polyphenol found in the rhizome of Curcuma longa (turmeric) and others Curcuma spp. Turmeric has been traditionally used in Asian countries as a medicinal herb as it has antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties. It has also been shown to benefit inflammatory conditions, metabolic syndrome, pain, it has been also shown to benefit the kidneys [1].

Properties of Curcumin

- Curcumin has shown impressive antioxidant and anti-inflammatory properties and is found to be a natural product in treating a wide array of diseases. It shows antioxidant property as there are different functional groups like methoxy, phenoxy, and carbon-carbon double bonds in its structure. It has a remarkable anti-inflammatory property and over the decade it is used to treat inflammatory-mediated diseases including cancer, atherosclerosis, diabetes, rheumatoid arthritis, and so forth. Several preclinical and clinical data showed the effectiveness of curcumin in the prevention and treatment of various human diseases including cancer, cardiovascular, inflammatory, metabolic, neurological, and skin [2].

- Curcumin reduces chronic inflammation occurring in several medical conditions such as arthritis, bowel disease, heart disease, cancer, and diabetes, etc.
- Accelerates the healing of the wounds and collagen deposition in the skin.
- Effectively helps in treating Diabetes associated symptoms such as impaired wound healing, increased thirst, vision loss, nerve damage, weight loss, etc by increasing insulin secretion to reduce high glucose levels in the blood.
- Shows anti-cancerous effect on the growth of cancerous and tumor cells. It inhibits the function of cancer-inducing growth factors and enzymes and blocks the signaling pathway that is involved in the development of cancer.

- Aids in the treatment of depression and anxiety by reducing its associated symptoms.
- Increases the levels of omega-3 a fatty acid that promotes the development of the brain.
- Relieves rheumatoid arthritis-related symptoms like stiffness, pain, swelling, etc.
- Boosts cardiac health by lowering high cholesterol levels in the blood.
- Stimulates detoxification to protect the liver from diseases, allowing removal of toxins and cancer-causing substances from the body.
- Maintains cognitive function and prevents the risks of neurodegenerative diseases such as Parkinson's and Alzheimer's.
- Elevates the amount of brain-derived neurotrophic factors which are involved in enhancing brain function, improving memory, and reduces oxidative damage [3].

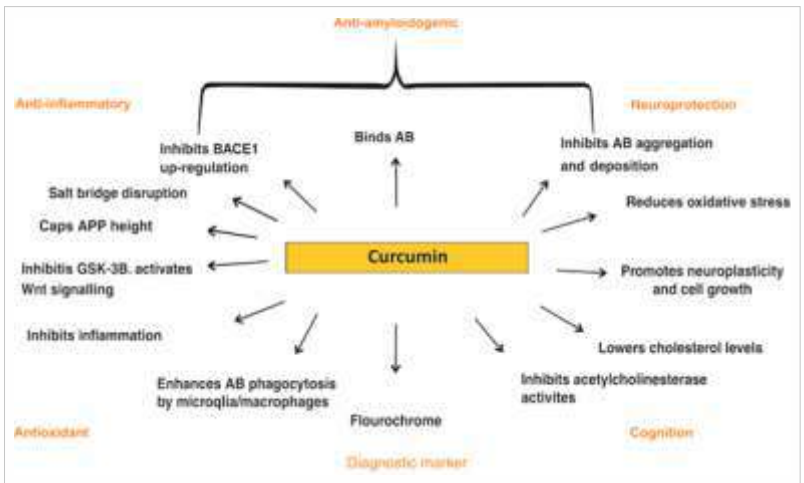

Figure 1: Curcumin properties and proposed mechanism of action [4]

Curcumin as Immune Modulator

Curcumin has immunomodulatory abilities that arise from its interaction with various immunomodulators, including cellular components as, dendritic cells, macrophages, and both B and T lymphocytes, and also molecular components, such as cytokines and various transcription factors [5]. Curcumin inhibits the immunostimulatory function of dendritic cells (DCs). These effects have been related to the suppression of CD80 and CD86 expression, two membrane proteins that are necessary for T cell activation, Curcumin increases serum levels of IgG and IgM, thus improving immune function. Curcumin induces apoptosis and inhibit proliferation of a number of NK/T-cell lymphoma cell. Curcumin is also involved in mediating NK cells function by increasing nitric oxide (NO) generation in NK cells following prolonged treatment and enhancing their cytotoxicity [6,7,8]. Curcumin is further involved in eliminating cancer by reducing the T-regulatory cell population, maintaining reactive oxygen and nitrogen production by macrophages, and NK cell cytotoxic activity [9,10,11].

Limitations of Conventional Curcumin

Despite all the positive benefits, a major criticism that curcumin faces are its poor bioavailability [12]. Curcumin has been shown to exhibit poor bioavailability, many studies showed very low, or even undetectable, concentrations in blood, tissues, and urine. Possible reasons are due to its poor absorption, rapid metabolism, chemical instability, and rapid systemic elimination [13]. The majority of oral curcumin is excreted in the feces (≤90%) [14]. Many limitations have been recognized for the therapeutic use of curcumin: its poor pharmacokinetic/ pharmacodynamic properties, its chemical instability, it's low efficacy in different disease models, its toxic profile under certain experimental settings [15] hence, technology-based delivery systems might help to overcome the limitations that are linked to conventional curcumin and therefore improve its therapeutic efficacy and improve its role in clinical application [16].

Phytosome – A Novel Technology

Phytosomes are the spherical cell like structure, containing a phospholipid in combination with standardized polyphenolic herbal extract. They are non-polar in nature which makes them better in absorption, utilization and as an outcome produce better results than conventional herbal extracts [17].

Phospholipids are the major component of cellular membranes. They act as a carrier for both polar and non-polar active substance [18]. Many phospholipids have nutritional importance, like phosphatidylserine provide nutrition to brain cells, phosphatidylcholine helps in liver cell regeneration, etc. [19]

There are many standardized extracts and phytochemical constituents which shows excellent biological activities in vitro, but do not express any activity or lesser response in vivo. This may be due to intrinsic property of drug molecule like poor solubility, molecular size, or destruction in gut, etc. [20] These inherent properties of drug lead to decreased absorption and inadequate drug availability inside the body.

The problem of low absorption can be alleviated by using phytosome technology. The phytosomal formulations enhances the absorption of the active phytochemical compounds. They now complexed with phospholipids are permeable across the lipid rich gut lining, and are also protected from destruction due to secretions inside the gut environment. This not only increases the bioavailability of the drug constituent, but also decreases the quantity of active drug molecule to be taken to achieve the desired therapeutic activity [21].

Features of Phytosome

Phytosomes as novel herbal vesicular drug delivery systems assure to deliver the drug through the pathway channelizing the active phytoentity to the desired site of action. Beside their actions phytosome possess the following properties [22]:

a Show better stability as complexed chemical bonds are formed between phytochemical and phospholipids.
b Enhances the permeability across the biological membranes.
c Reduced dosage due to better bioavailability.
d Protected from the destruction in gastric secretions and resist the action of gut microbiota.
e Duration of action is increased.
f Higher therapeutic effect due to better absorption through different routes.
g Phosphatidylcholine part of the formulation not only act as a carrier but also possess several therapeutic properties, such as hepato-protective effect; may have a synergistic effect with the particular phytochemical.
h Phytosome complex is biodegradable, so drug entrapment does not occur.

Phytosome Curcumin

Phytosomes have been successfully used for the enhancement formulations of several types of herbal extracts. One of them being curcumin, an active constituent of turmeric standardized extract. Traditional curcumin extract has the limitation of bioavailability, hence, this led to the attempts for designing of new formulation and drug delivery systems. Phytosome technology helps in overcoming this limitation of traditional delivery system and shows an increased absorption and enhanced bioavailability of curcumin [23].

Production Methodology of Phytosomal Curcumin Preparation

Phytosomal curcumin is prepared by the addition of phospholipids to the ethanol solution of the hydroalcoholic extract of turmeric rhizomes. This is done under continuous reflux and stirring. The resulting suspension is concentrated by reduced pressure to a thick residue. Phytosomes can be isolated by precipitation with non-solvent, lyophilization, spray drying or vacuum drying [24]. This can be ground to form a fine powdered and then cast into the desired product form.

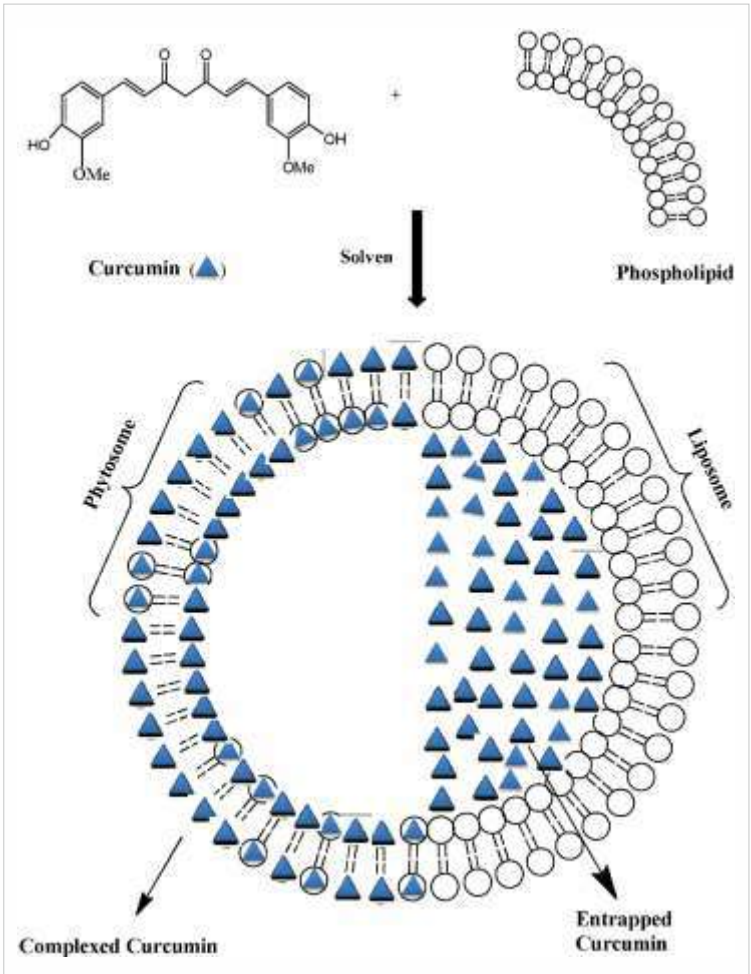

Figure 2: A schematic representation of the structure and preparation of phytosomal curcumin

Phosphatidylcholine (or phosphatidylserine) is a bifunctional compound. The phosphatidyl moiety is lipophilic and the choline (serine) moiety is hydrophilic in nature. This dual solubility of the phospholipid makes it an effective emulsifier. Thus, the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then surrounds the choline bound material. Hence, the phytoconstituents produce a lipid compatible molecular complex with phospholipids (also called as phytophospholipid complex) [24]

Complexation of curcumin with phosphatidylcholine has been reported to result in enhanced bioavailability, improved pharmacokinetics and increased hepato-protective activity compared with uncomplexed curcumin [25].

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Complexation of curcumin with phosphatidylcholine has been reported to result in enhanced bioavailability, improved pharmacokinetics and increased hepato-protective activity compared with uncomplexed curcumin [26].

Properties and Benefits Over Traditional Curcumin

Curcumin as an active constituent of turmeric has many therapeutic value, but its traditional delivery system leads to poor bioavailability. Conventional curcumin's innate nature does not allow it to dissolve in gut environment and is also not absorbed across the intestinal cells. Moreover, studies have shown that the non-complexed curcumin is rapidly metabolized, conjugated in liver, and finally gets excreted in faeces. Therefore, has limited systemic bioavailability [27].

The phytosome curcumin, that is phosphatidylcholine-curcumin complex (Meriva®) is more readily incorporated into lipophilic cell membranes, making it significantly more bioavailable than unbound curcumin. The in vivo study has peak plasma concentration and AUC were five times higher for phytosome curcumin than for unbound curcumin [28]. In another study, researcher investigated the comparative absorption of a standardized curcuminoid mixture and phytosomal curcumin (Meriva®). Their result showed that total curcuminoid absorption from phytosomal curcumin was 29 folds higher compared with the non-phytosomal curcuminoid mixture [29]. Upon administration of phytosomal curcumin, plasma concentrations of curcumin sulfate and curcumin glucuronide were found to be 3 to 20 folds higher than those traced after the administration of uncomplexed curcumin.

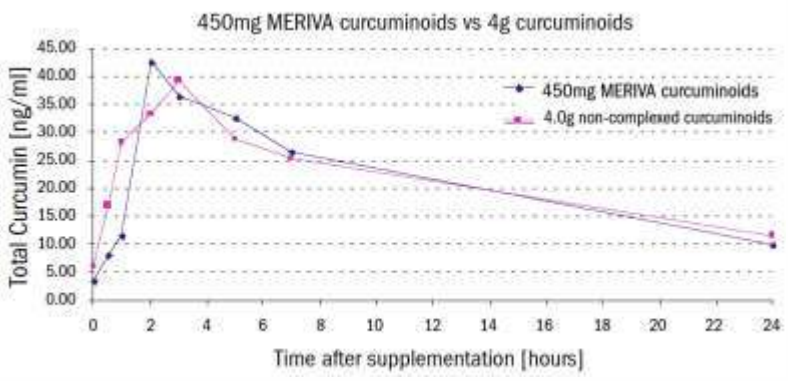

Figure 3: Absorption of Curcumin Phytosome (Meriva®) Compared to Non-complex Curcumin in Humans

Henceforth, it is found that phytosomal curcumin has following benefits over traditional curcumin:

a Has stability and do not get affected by gut environment
b Gets readily absorbed across the intestinal gut membrane
c Has better bioavailability
d Does not get conjugated in liver
e Does not get rapidly metabolised

Various Studies with Phytosomal Curcumin

There have been several studies investigating the safety and efficacy of phytosomal curcumin in the treatment of various human diseases such as cancer, osteoarthritis, diabetes and inflammatory diseases. The data suggest the phytosomal formulation of curcumin has good properties for clinical use.

Cancer

Curcumin can modulate several pathways and molecular targets involved in different stages of cancer pathogenesis [30]. In vivo and in vitro studies have shown that phytosomal curcumin can exert cytotoxic and apoptotic effects in cancer cell lines and animal models [31].

Ibrahim et al. evaluated the efficacy of curcumin conjugated with phosphatidylcholine as a treatment against mammary gland tumor. Mammary gland tumor cell line (ENU1564) was inoculated into the mammary fat pad of athymic nude mice. The mice were treated orally with either pure curcumin or phytosomal curcumin (Meriva®). The tumor and its lung metastasis were evaluated grossly, microscopically, and immunohistochemically. The results revealed that phytosomal curcumin significantly increases the expression of MMP-9 and inhibits the lung metastasis of ENU1564 cells [32].

In a GL261-implanted glioblastoma mouse model, intraperitoneal administration of phytosomal curcumin was shown to shift the polarization of tumor-associated macrophages towards the tumoricidal M1 phenotype [33].

In a clinical study, Belcaro et al. used curcumin phytosomes to control the adverse effects of chemotherapy and radiotherapy in 160 patients. The results showed that supplementation with phytosomal curcumin could alleviate the adverse effects of chemotherapy and radiotherapy [34].

Panahi et al. investigated the efficacy of phytosomal curcumin as an adjunct to chemotherapy in patients with solid tumors. In the mentioned study, patients took phytosomal curcumin (1500 mg/day in 3 divided doses; n = 19) for 6 weeks. The result indicated a significant enhancement of quality of life (QoL) and suppression of systemic inflammation following supplementation with phytosomal curcumin [35].

Diabetes

Curcumin targets several molecular species and biochemical pathways involved in insulin resistance, diabetes and its complications such as PKC-a, b 2-MAPK, PPAR-g, MCP-1, TNF-a and nitric oxide [36]. In one study, improvement of diabetic microangiopathy and retinopathy was examined in 38 diabetic patients treated with Meriva®. The results showed an enhancement of microangiopathy in the Meriva® group at 4 weeks post-treatment. In addition, there was a significant improvement in the venoarteriolar response and a decline in the score of peripheral edema following treatment with phytosomal curcumin. At the retinal level, high-resolution and duplex scanning techniques were utilized to measure retinal flow and results indicated an enhancement in the Meriva®-treated patients. These results suggested that curcumin, when administered in the phytosomal form, is quite helpful in the management of diabetic treatment [37].

In a pilot study, Appendino et al. investigated the effects of 4-week treatment with phytosomal curcumin, administered at a daily dose of 1 g, in controlling the development of microangiopathy in diabetic subjects [38]. The results showed that in the patients group, there was a significant decrease in skin flux at the surface of the foot. Moreover, a significant decline in the edema score and a corresponding improvement in the venoarteriolar response were also observed. Finally, the PO2 was improved after four weeks of treatment, leading to a better oxygen diffusion into the skin due to decreased edema.

Inflammatory diseases

Several studies have investigated the role of curcumin in modulating inflammatory response in different diseases [39].

The anti-inflammatory properties of curcumin are mediated via its capability to suppress key regulators of the inflammatory response such as 5-lipoxygenase (5-LOX), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [40]. Phytosomal curcumin was used to evaluate curcumin's effects on the ileum and colon in a mouse colitis model. The results showed that curcumin has direct and indirect myorelaxant effects on mouse ileum and colon. The indirect effect was reversible and noncompetitive with the cholinergic agent [41].

Allegri et al. assessed the efficacy of phytosomal curcumin in treating recurrent anterior uveitis of different etiologies. The studied population included 106 patients who completed a 12-month therapeutic period. The patients group was divided into three subgroup of various uveitis origins: group 1 (autoimmune uveitis), group 2 (herpetic uveitis), and group 3 (other etiologies of uveitis). The investigators evaluated relapse frequency, relapse severity and the overall quality of life in all treated subjects. The results revealed that there were significantly reduced ocular discomfort symptoms following treatment with phytosomal curcumin in most patients and the medication was well tolerated. Based on this result, phytosomal curcumin was suggested as a potential therapeutic agent for the eye relapsing diseases such as anterior uveitis and in conditions like glaucoma, maculopathy and dry eye [42].

Osteoarthritis (OA) is a known and leading cause of physical disability, and is responsible for impairment to the life quality particularly in the elderly population. Non-steroidal anti-inflammatory drugs (NSAIDs) are the main treatment option for this disease. Various reports have shown that long-term use of these drugs is associated with several adverse effects. Same for other medical complications, finding new treatment options is actively pursued. Various studies have indicated that Meriva1with specific properties can be used as a new option in the treatment of OA [43].

Belcaro et al. investigated the efficacy and safety of Meriva1 during extended administration in OA patients. Their results indicated significant enhancements of both clinical and biochemical indices in the phytosomal curcumin versus control group. [43].

In another study, the efficacy of Meriva® in 50 subjects with OA at a dosage corresponding to 200 mg/day curcumin was investigated. The results showed that global Western Ontario and McMaster Universities (WOMAC) score significantly decreased after three months of treatment. In addition, walking distance in the treadmill test was prolonged from 76 m to 332 m, and there was a significant decrease in C-reactive protein (CRP) levels from 168 to 11.3 mg/L in the subpopulation with high CRP. In this latter study, the control group experienced only a modest improvement in the efficacy measures (WOMAC score, the CRP plasma concentration and treadmill test), while the treatment costs (use of anti-inflammatory drugs, hospitalization and treatment) were significantly reduced in the treatment group [43].

Conclusion

Curcumin has a potent antioxidant and balanced anti-inflammatory properties. It possesses diverse therapeutic activities for the treatment of various diseases. But the poor absorption and low bioavailability of conventional curcumin possess an

obstacle in harvesting the full potential benefit of curcumin. Phytosome technology being a novel drug delivery system has emerged as a promising strategy for enhancing the bioavailability of curcumin. Moreover, several studies have shown the beneficial, effective and safe use of phytosome curcumin in treatment of various diseases.

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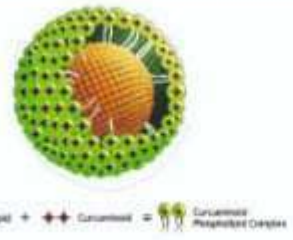

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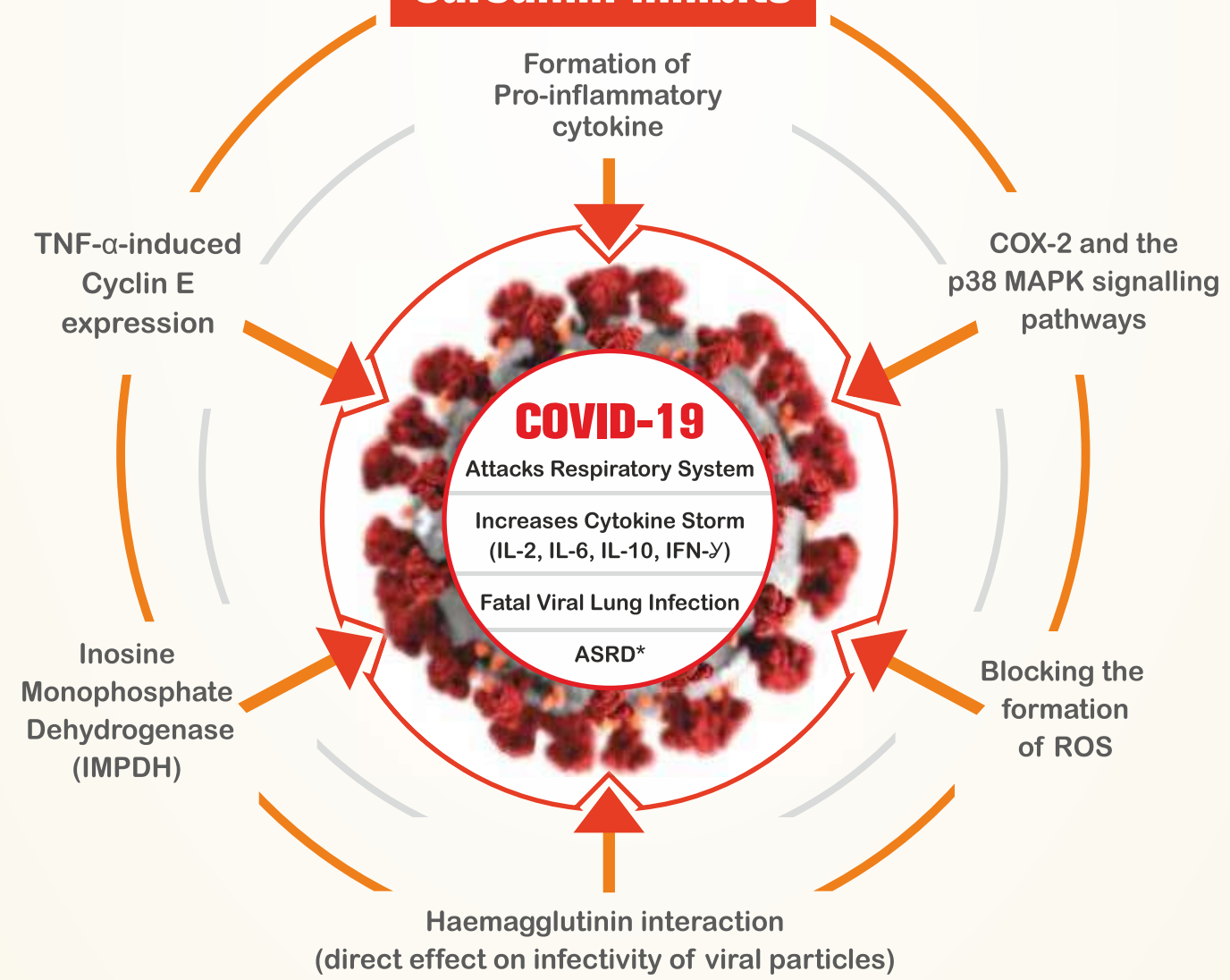

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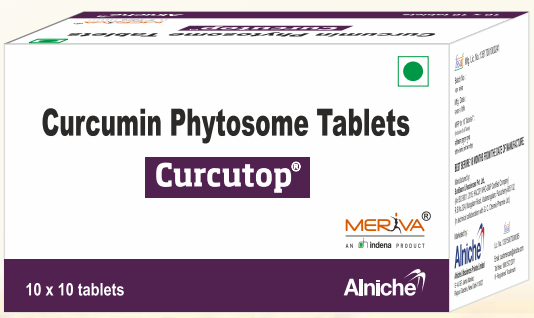

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Role of Total Parenteral Nutrition (TPN) in Critically Ill ICU Patients with COVID-19 Infections

Abstract

COVID-19 pandemic is affecting the whole world with unpredicted challenges and risk to patients as well as healthcare system globally. The disease primarily affects respiratory system posing the threat of spreading over different organs, deteriorating to multi-organ failure and can be fatal. It is a danger to malnourished elderly people, persons with the low immunity, patients with underlying ailments and chronic diseases. Such patients require special attention under continuous observation in intensive care units. The prolonged ICU stay leads to the demanding nutritional need under such conditions, calling for proper treatment with total parenteral nutrition (TPN).

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DNB (Medicine), DNB (Neurology)
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Introduction

Total Parenteral Nutrition (TPN), also known as intravenous or IV nutrition feeding, is a method of administering nutrition into the body through the veins. It provides nutrients for patients who do not have a functional GI tract, and enteral feeding is not possible. It provides patients with all or most calories and nutrients through solutions that contain a mixture of protein, carbohydrates, glucose, fat vitamins and minerals.

TPN is a standard tool in the armamentarium of the physicians in their quest for delivery of comprehensive health care to patients. It is sterile liquid chemical formula administered into a vein, generally through a PICC (peripherally inserted central catheter) line, but can also be administered through a central line or port-a-cath.

TPN is used when the intestinal tractis obstructed, or when absorption of nutrients is not carried out properly by small intestine, or when gastrointestinal fistula (abnormal connection) is present. It is used when the bowels need to rest and not have any food passing through them.

TPN is used in malnourished individuals to prepare them for major surgery, chemotherapy, or radiation treatment. It is also recommended for critically ill patients such as, with serious bowel issues, severe burns, multiple fractures, and conditions of demanding nutrition requirement, such as COVID-19.

COVID-19 Patients in ICU Hospital Stay

COVID-19 pandemic is affecting the whole world with unpredicted challenges and risk to patients as well as healthcare system globally. The disease primarily affects respiratory system posing the threat of spreading over different organs, deteriorating to multi-organ failure and can be fatal. This calls for the treatment under continuous observation of the patients in intensive care units (ICU). [1]

COVID-19 is affecting the people of all ages, but mainly posing a risk to malnourished elderly people, persons with the low immunity, patients with underlying ailments and chronic diseases. The individual falling under these categories has a worse prognosis and higher mortality rates. Therefore, these groups of people requires special attention and prolonged ICU stay. [2]

The COVID-19 infection itself and the longer duration ICU admission is associated with cause of malnutrition, loss of skeletal muscle mass and altered function which are associated with poor quality of life, disabilities and morbidities even after ICU discharge.[3]

In addition to it, development of sepsis, inflammation and generation of oxidative stress, further contribute to exacerbation of symptoms and deteriorating condition of patients. This necessitates proper nutritional assessment and treatment to effectively decrease the complications and improve clinical results of the condition. Therefore, giving a special attention to the nutritional needs of COVID-19 patients is of prime importance to reduce the overall casualties. [4]

Nutritional Requirement of COVID-19 ICU Patients Achieved by TPN

COVID-19 patient with severe symptoms needs ICU admission and also for intensified conditions by extended stay during hospitalization; consequently, leads to the demand of nutritional therapy based on their state of health. Following recommendation based on international guidelines for COVID-19 treatment must be considered: [3, 5]

Nutritional Requirement		Recommended Value
Energy		• 84-126 kj/kg/day • 10% increase for every 1°C increase in body temperature
Protein		• 1.3 g/kg/day • With a high supply of branched chain amino acids upto 50%
Carbohydrate		• 2 g/kg/day • Should not exceed 150 g/day
Fat		• 1.5 g/kg/day • Medium and long chain fatty acid should be given priority
Fluid volume		• 30 mL/kg/day (adult) • 28 mL/kg/day (elderly) • Approx 4 mL/kg for every 1°C increase in body temperature
Micronutrients	Vitamin C	• High dose of 3-5 g/day
	Vitamin D	• 100.000 IU within a week • 500.000 IU within a week (if insufficient value of) <12.5 ng/mL)
Non-protein energy supply ratio	Sugar / Lipid ratio	• Approx upto (50-70)/(50-30)
	Non-protein calorie / Nitrogen ratio	• Approx upto (100-150)/(11)

Energy:

As virus primarily attacks lungs; so, COVID-19 patients have higher energy requirement than normal. The recommended requirement is 84-126 kJ/kg/day (1 kcal = 4.184 kJ). If there is fever; for every 1°C increase in body temperature, the body's energy consumption increases by 10%. It is critical for COVID-19 patients to maintain the energy balance. However, considering the increased metabolic load with severe infection, moderately low calories can reduce the metabolic load.

Protein:

Increased inflammation leads to high catabolic events; and to reduce this, it is of top priority to increase the protein supply. The recommended requirement is 1.3 g/kg/day with a high supply of branched chain amino acids upto 50%. This not only prevents muscle loss but also augment the strength of respiratory muscles.

Carbohydrates:

The recommended requirement is 2 g/kg/day and should not exceed 150 g/day. The administration of carbohydrate should be restricted in critically ill COVID-19 patients with respiratory failure. As oxidation of carbohydrates rises from the production of carbon dioxide, it must be avoided in such patients to drop the respiratory quotients.

Fat:

The recommended lipid requirement of the critically ill patient is 1.5 g/kg/day. Of these the use of medium and long chain fatty acid should be given priority, with a high proportion of ω-3 fatty acids and ω-9 fatty acids. Essential fatty acids play a major role in immune responses by altering the composition of cell membranes and modulating cell signaling. Arachidonic acid, a ω-6 fatty acid, is arguably the most important eicosanoid precursor to prostaglandins and leukotrienes. On the other hand, ω-3 fatty acids dampen inflammatory responses through their effects on eicosanoid production and specific cytokines.

Fluid volume:

The recommended requirement for stable patients is 30 mL/kg/day of fluid for adult and 28 mL/kg/day for elderly. It is of utmost importance to maintain neutral fluid balance in critically ill COVID-19 patients with specific consideration to renal and prerenal failure. It is

recommended to control the amount of intravenous fluids in elderly patients and for large areas of pulmonary consolidation. If there is fever; for every 1°C increase in body temperature, supplement approx. 4 mL/kg fluid.

Non-protein energy supply ratio:

It is recommended to maintain sugar/lipid approximately upto 50-70/50-30 and non-protein calorie/nitrogen approximately upto (100-150)/11.

Micronutrients:

The requirement of micronutrients in ICU patients depends on the nutritional therapy used. For routine administration supplements of multivitamins and minerals are considered (as complex of vitamin B, zinc, and selenium). The administration of other micronutrients in doses higher than the recommendations should only be carried out if a specific deficiency is present. High-dose vitamin C (3-5 g/d) is recommended as it is effective for ARDS and significantly reduces mortality rate. Administration of vitamin Dis also recommended (100.000 IU to a maximum of 500.000 IU within a week); if the level is <12.5 ng/mL (insufficiency). As it improves the adverse clinical outcomes including higher mortality and infection rates, longer mechanical ventilation and hospital stays.

Immuno-nutrients:

They influence immune system and improve metabolic and nutritional indices, such as nitrogen balance and serum proteins. There are several types of immunonutrients, such as arginine, nucleotides, glutamine, ω-3 fatty acids, etc. Their functions and mechanisms are different from each other. They can inhibit inflammatory responses and regulate immune function, which helps in promoting patient recovery.

Administration of Nutrition

Proper quality and quantity of nutrition not only provided body with immunity to fight disease but also guarantees faster recovery from disease condition, such as COVID-19. In the critical patient admitted to ICU with respiratory insufficiency, if stay last longer than 48 hours as expected, the medical nutritional therapy must be started with the following priority: [5]

- Early enteral nutrition (EN) must be started within 48 hours, if no contraindications are present.
- Total Parenteral nutrition (TPN) must be started within 3 to 7 days and must be considered when all strategies for EN have failed to avoid severe malnutrition. For already malnourished patients, it can be started slowly on day 3 and the infusion rate gradually increased up to the 7th day. For patients at risk of malnutrition, with stable clinical conditions, TPN can be started on day 7, by changing the fluid therapy.
- Both EN and TPN must be prescribed at increasing speeds to avoid overfeeding, and the target speed must be reached in about 3-4 days.
- TPN is preferred if the necessary requirements are not met with EN.

Total Parental Nutrition Indicated for Critically Ill ICU Patients

The primary reason for TPN in chronically ill patients where enteral feeding is not possible. TPN is useful to boost inadequate oral intake. The successful administration of TPN requires careful assessment of patient, appropriate medical knowledge & experience of its complications. Below is a list of some more relevant indications of TPN: [6]

- Newborns with gastrointestinal anomalies such as tracheoesophageal fistula, massive intestinal atresia, complicated meconium ileus, massive diaphragmatic hernia, gastroschisis, omphalocele or cloacal exostrophy, and neglected pyloric stenosis.
- Failure to thrive in infants with short bowel syndrome, malabsorption, inflammatory bowel disease, enzyme deficiencies and chronic idiopathic diarrhea.
- Other paediatric indications include necrotizing enterocolitis, intestinal fistulae, severe trauma, burns, postoperative infections and malignancies.
- Adults with short bowel syndrome secondary to massive small-bowel resection or internal or external enteric fistulae.
- Malnutrition secondary to high intestinal obstruction for example achalasia, oesophageal strictures and neoplasms, pyloric obstruction and gastric neoplasms.
- Prolonged ileus due to medical or surgical causes (for example post-operative, following abdominal trauma or polytrauma).
- Malabsorption secondary to sprue, enzyme & pancreatic deficiencies, regional enteritis, ulcerative colitis, granulomatous colitis, and tuberculous enteritis.
- Functional gastrointestinal disorders like idiopathic diarrhoea, psychogenic vomiting, anorexia nervosa.
- Patients with depressed sensorium (for example, following head injury or intracranial surgery) in whom tube feeding is not possible
- .Hypercatabolic states secondary to severe sepsis, extensive full - thickness burns, major fractures, polytrauma, major abdominal operations etc.
- Patients with malignancies in whom malnutrition may jeopardize successful delivery of a therapeutic option (surgery, chemo- or radiotherapy).

- Paraplegics/quadriplegics with pressure sores in pelvic or perineal regions where fecal soiling is a problem.

Contraindications of Total Parental Nutrition

Treating a patient with TPN when it is not indicated is not only frustrating for the doctor as well as the patient, but is also an unnecessary drain on scarce resources. Definite contraindications to TPN include the following:

1 Where gastrointestinal feeding is possible. Almost always, this is the best route to provide nutrition to the patient. [7]
2 Patients with good nutritional status in whom only short term TPN support is anticipated.
3 Irreversibly decerebrate patients.
4 Lack of specific therapeutic goal: TPN should NOT be used to prolong life if death is inevitable. [8]
5 Severe cardiovascular instability or metabolic derangements. These should be corrected before attempting intravenous hyper-alimentation.
6 Infants with less than 8 cm of small bowel as it has been, conclusively proved that they cannot adapt to enteral feeding despite prolonged periods of TPN.

Monitoring of Artificial Feeding and TPN

When an oral diet does not fulfill the energy goal, oral nutritional supplements should be considered first and then EN medication. If there are limitations on the enteral path, it may be recommended to prescribe peripheral PN for the population that does not meet the target energy protein through oral or enteral feeding. Regular monitoring is essential to detect and minimize complications and determine response to nutritional support.

Patients receiving TPN should have their nutritional requirements reviewed regularly, taking into account clinical condition, treatments (e.g. dialysis), drug therapy, nutritional status, response to TPN and supporting laboratory data.

Clinical assessment of the patient can reveal ascites, oedema, impaired wound healing or loss of muscle mass that may not be evident from monitoring weight and biochemical indices see the table below: [9]

When an oral diet does not fulfill the energy goal, oral nutritional supplements should be considered first and then EN medication. If there are limitations on the enteral path, it may be recommended to prescribe peripheral PN for the population that does not meet the target energy protein through oral or enteral feeding.
During the initial step of re-nutrition, most problems can be avoided by close monitoring and sufficient intakes. Infusion rate, body temperature, cardiac and respiratory function, urinary volume, twice daily weight and digestive production must be constantly tracked.

Complication of Total Parental Nutrition

Complications can be classified in four groups: central venous catheter (CVC) associated PN solution stability and drug reactions, metabolic or nutritional and other organ systems.

CVC related complications include infection, occlusion, central venous thrombosis, pulmonary embolism and accidental removal or damage. Metabolic or nutritional complications include deficiency or excess of individual PN components including electrolytes, minerals, glucose, essential fatty acids, vitamins, trace elements and the presence of contaminants.

Infection is one of the commonest complications of CVC's and is potentially fatal. The occlusion of the CVC that occur inside the CVC. Lumen (blood, substance or PN precipitate) in the vein (a clot or a fibrin sheath) external to the CVC due to the tip

Resting against the surface of the vein or due to external compression Clavicle, for example, or patient positioning.

Monitoring Patients Receiving TPN

Fluid balance	**Monitor daily**
Glucose tolerance	Initially levels checked every 4-6 hours, daily when stable
Weight	Daily weight can show fluid changes Long term trends determine changes in tissue mass
Venous access	Venous access site regularly checked for signs of infection, phlebitis
Routine biochemistry	Serum Na, K, urea and creatinine checked dailyinitially Ca, Mg and P checked at least twice a week initially Trace elements zinc, copper, selenium checked monthly Vitamins B12, Folate, Vitamin A, Vitamin E checked monthly
Urinalysis	Urinary levels of electrolytes useful when determining clinica| significance of plasma levels

The target of hormonal and metabolic changes in starvation facilitate survival by reducing basal metabolism price, protein conservation and organ prolongation act, given the preferential skeletal catabolism muscular tissue and depletion of visceral cell mass. PN-related metabolic bone disease (MBD) with decreased bone mineral density (BMD) osteoporosis, pain and fractures has been identified in adults with long-term parenteral nutrition. Careful monitoring of hepatic function during PN is highly important in order to mitigate or correct factors responsible for liver disease.,

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Management of Coronavirus Disease (COVID-19) in ICU: Challenges and Recommendations

Abstract

COVID-19 pandemic spread globally has created a challenge for the health care fraternity. The deployment of various measures for smooth management of infected patients is crucially required. The improved infection prevention methods, rapid diagnosis, functional isolation wards and skilled professionals are also critically important, not only for patients but also for healthcare workers and other patient who are at risk of contracting nosocomial transmission. Along with these the hospital administration, governments and policy makers also are important for handling of infrastructure, staff management and critical supplies adequately on time. Collaboration of agencies at different local, national and international levels offer improved outcome from this chaotic scenario.

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Introduction

COVID-19 is coronavirus pandemic which has spread globally, causing mass infection and creating a surge in critically ill patients. [1] Therefore, it is necessary for the ICU, medical facility, hospital management and researchers to be ready for this chaotic scenario. Hence it is must to focus on the cumulative experiences gained up till now on the management of COVID-19 patients and associated conditions. This provides us with the overview of upcoming challenges and the recommendations to deal with them.

Epidemiology and Clinical Features of Critically Ill Patients

The cases diagnosed positive for COVID-19 crossed a million mark in April 2020, all across 204 countries, causing fatality rate of 5.2%. [2] These rates vary across different regions, do not account for patients having mild symptoms or are not diagnosed.

As per the status on July 31, 2020 the total number of registered cases globally reaches 17,303,253 causing 673,284 deaths leading to 3.89% fatality rate. In India, the total cases reached to 1,638,321 causing 35,743 deaths leading to a fatality rate of 2.18%. [3]

Most of the cases diagnosed as critical include the clinical features of respiratory failure, shock and multiple organ dysfunction or failure. Whereas, clinical features of severe cases include dyspnoea, respiratory rate ≥30 breaths per min, oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen [PaO2/FiO2] ratio <300 mm Hg, and increase in lung infiltrates >50% within 24–48 h. [4] All the critical and severe cases require ICU admission, but the actual scenario depends on the capacity and availability of beds. The most critically ill patients diagnosed with COVID-19 infection were older and had other comorbidities, such as diabetes, hypertension, cardio-vascular disease, chronic lung disease, cancer and others.

The most common symptoms affecting COVID-19 patients are dry cough, fever, difficulty breathing and fatigue. [5] The approximate time for development of pneumonia from the onset of symptoms is 5 days, whereas to development of severe hypoxemia and ICU admission is approximately 7-12 days. [6] The most common complication is acute hypoxemic respiratory failure (sometimes with severe hypercapnia) from acute respiratory distress syndrome (ARDS), followed by shock, myocardial dysfunction and acute kidney injury. [7] older patients are associated with a number of fatal cases and the median time of death accounted from the onset of symptoms is approximately 2-8 weeks

Diagnosis

The initial approach by ICU practitioners towards COVID-19 patients should be taken with caution, as some of the non-clinical feature of covid-19 is not easily distinguishable from other respiratory symptoms. [9] Besides the presence of symptoms, diagnosis for clinical presentation as suggested by WHO are [10]-

a Patient suffering from acute respiratory illness and fever
b If patient has travelled to or resides in area where community transmission is reported
c Patient has come in contact with a confirmed or probable COVID-19 case in 14 days before symptom onset
d Patient with severe acute respiratory symptom who requires hospitalization without an alternative diagnosis

Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP). [11] The samples are collected through swab from upper and lower respiratory tract. Upper respiratory tract samples at times give false-negative results, therefore, WHO recommends testing lower respiratory tract sample such as sputum and endotracheal aspirates. [12] The sample collection procedure generates aerosol, and should be carried out under strict precautionary measures. [13]

The sensitivity for detection of COVID-19 sample RT-PCR is low, therefore repeated samples must be tested besides the negative results of initial sample, if affirmative clinical features are observed. [14]

Management of Acute Respiratory Failure

The data for supportive ICU care is based on the existing available evidences from other types of respiratory viral infections and general intensive care management. Generally, it is suggestive to use non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) for critically ill COVID-19 patients. [6] There are controversies related to nosocomial transmission of infection associated with use of NIV, as epidemiological data suggests its transmission, whereas human laboratory data disapproves this. [15] Moreover, NIV is known to reduce intubation and mortality in mild cases of ARDS, but are associated with high mortality in moderate-to-severe cases of ARDS. Therefore, the patients need close monitoring with airborne precautions and use of single rooms is to be taken into account. [16]

The intubation of patients with COVID-19 infection possess the risk to health care workers also, therefore, a full PPE should be worn up by the skilled professionals prior to procedure. While using the equipment which may generate aerosol, a viral filter can be placed between exhalation valve and mask as a precautionary measure; [17] and also use of muscle relaxant can reduce coughing.

Prone positioning is related to the reduced mortality rate and must be applied during early phases. The SARS-CoV-2 has a tendency to affect peripheral and dorsal regions of lungs, this provides ideal conditions for a positive oxygenation response to prone positioning. Veno-venous extracorporeal membrane oxygenation (ECMO) in some cases, is known to improve survival rate in severe ARDS patients, therefore must be reserved for emergency. However, decision to provide very advanced care for some patients should be based on number and severity of cases. [18]

Other Intensive Care Management

The condition of hypervolemia due to vomiting, anorexia and diarrhea is known to occur in COVID-19 patients, therefore administration of fluids should be done cautiously. SARS-CoV-2 spike protein has high affinity to human angiotensin converting enzyme 2 (ACE2), which is crucial to virus for host cell entry. This membrane-bound receptor is expressed in lung, heart and other organs, therefore might be responsible for high incidence of myocardial dysfunction in COVID-19. [6] Hence a conservative fluid strategy must be deployed and also early use of vasopressors and inotropes are recommended (figure 1).

As the laboratory diagnosis of COVID-19 takes time, and the symptoms are hard to be differentiated from the other bacterial and viral pneumonia, so early administration of empirical broad-spectrum antibiotics are common. [6] but the therapy should be de-escalated with the conformation of positive results.

The retrieving from invasive mechanical ventilation must be considered to reduce the chances of ventilator-associated pneumonia, but must be balanced with the risk of premature extubation and subsequent increased chances of re-intubation. As per the reports, the average ICU stay of COVID-19 patients are approximately 8 days. [8] However, WHO recommends the discharge of patients requires clinical recovery and negative result of the two tests done 24 hours apart. [19]

COVID-19 is known to be associated with cytokine storm, as also observed with other kinds of viral infection. Therefore, it is proposed that immunosuppression as an approach might be beneficial to patients with hyper-inflammation. [20]

Few reports show the use of systemic corticosteroid for the severe or critical COVID-19 patients. [6] But this role is not clearly to be beneficial in these cases. Moreover, a systemic review of an observational study of corticosteroid for SARS is associated with possible harm, such as avascular necrosis, psychosis, diabetes, and delayed viral clearance. [21] Therefore it is not recommended to use corticosteroid in viral severe acute respiratory infections, including COVID-19, until further confirmation supporting research is available.

Cytokine storm not only overwhelms the immune system, but also contribute to significant systemic inflammatory reaction which is destructive to kidney and other vital organs. Patients admitted to ICU with COVID-19 infections are also observed to suffers from other ailment such as, ARDS, trauma, kidney failure, acute heart damage, and secondary bacterial infection. [8, 22] The common complications in these ailments are usually cytokine storm, further deteriorating the condition of patients. Cytokine filtration may be a proposed way to mitigate such situation. These filters do not destroy or remove virus, but act like a sponge to absorb and capture cytokines; along with uremic toxins filtered by kidneys and endotoxins released by bacteria which induces cytokine gush. The use of cytokine filters helps in reverse the shock, control severe inflammation, proper function of heart and improve breathing; mitigating few of the primary reasons patients suffer during COVID-19 infection. [23]

Repurposed and Experimental Therapies

Still the cure or proven therapy is not available for COVID-19, however, some therapy used for earlier kinds of coronavirus infections are been used empirically and are under investigation. [19] Of them the more prominent ones are – remdesivir, faviparavir, lopinavir–ritonavir, chloroquine, hydroxychloroquine, tocilizumab, convalescent plasma, IV immunoglobulin and other traditional herbal medicines. [24].

There are other therapies as well, whose results are not proven, but are being administered in the hope of improved outcomes. However, trying of new therapies must be balanced by ethical consent and scientifically supporting data for safe conduct. During the Ebola outbreak, WHO experts concluded that due to "exceptional circumstances", it was "ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention". [25] However still the expert guidance is required, and the patient treated must be enrolled in clinical studies as per the rules and guidelines.

Infection Prevention

With the rapid transmission, every case seeding more than two secondary cases. [26] As many as healthcare workers including MBBS student, resident doctors, nurses and mess workers, have tested positive for

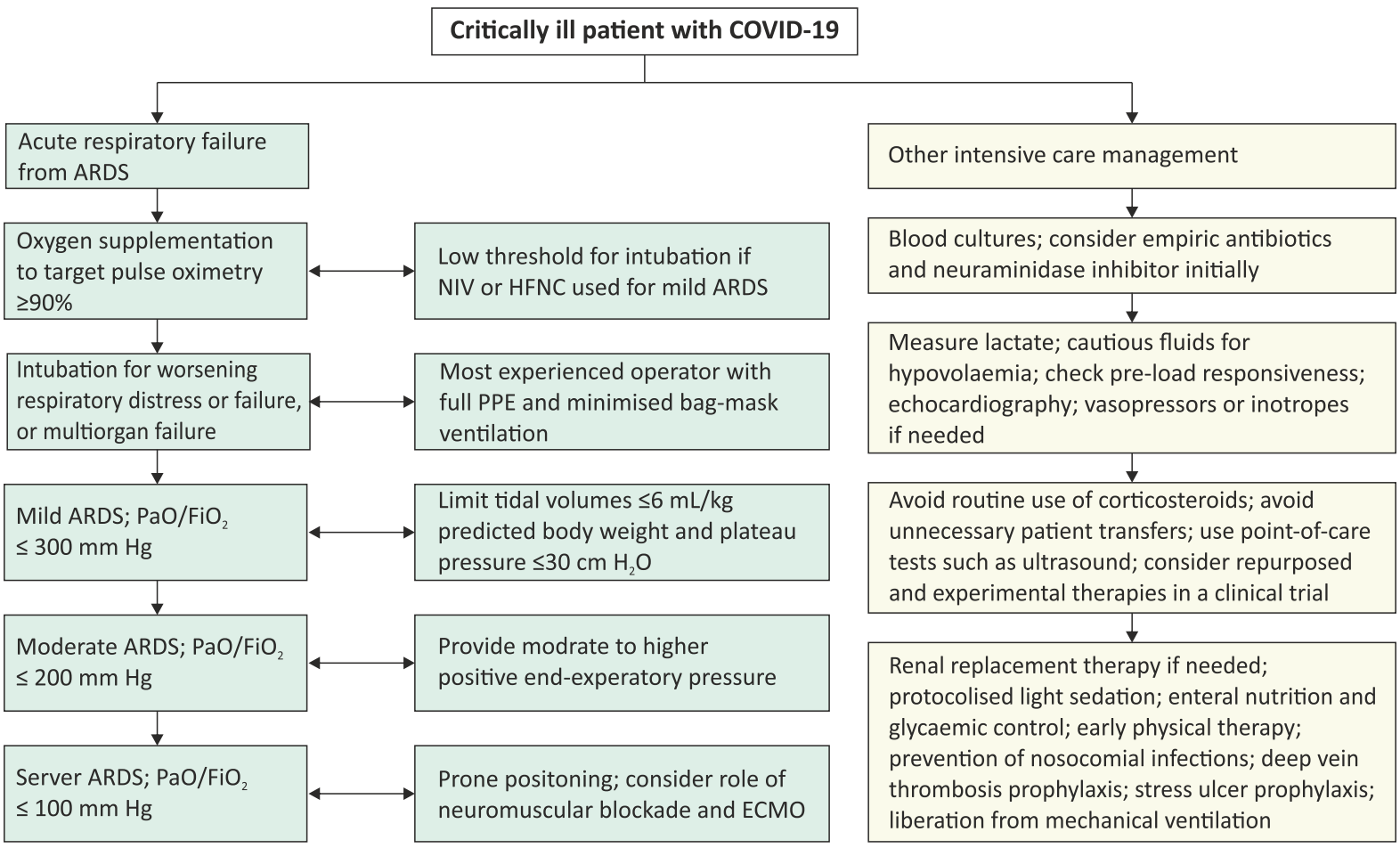

Figure 1: Clinical management of critically ill patients with COVID-19. [24] [ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; ECMO: extracorporeal membrane oxygenation; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; PaO2/FiO2: partial pressure of arterial oxygen to fraction of inspired oxygen; PPE: personal protective equipment]

COVID-19. WHO recommends that use of Personal Protective Equipment (PPE) should be made compulsory by hospitals for every health worker to wear it while treating patients. PPE should include medical masks, gowns, gloves, and eye protection with goggles or face shields. [27] For aerosol-generating procedures, masks should be N95 or FFP2-equivalent respirators, and gowns or aprons should be fluid resistant.

Health-care workers often focus on donning PPE, however data suggests, there is a significant risk of self-contamination when doffing PPE. [28] Specific steps of wearing and removing PPE, together with hand cleansing, is crucial to be followed. [29] Encouraging staff to build a safety culture and point out protocol errors are useful to reduce nosocomial SARS transmission. [30]

For infection prevention, surface decontamination plays an important role as viable SARS-CoV-2 persists up to 72 h on inanimate surfaces such as plastic and stainless steel. [13] Health-care workers should clean their mobile phones regularly or wrapped with specimen bags that are discarded after contact with patients as they might be contaminated with common viral pathogens. [31] In Singapore, Environmental contamination by SARS-CoV-2 was detected on furniture and equipment within a patient's room and toilet. [31] Viable Coronavirus was detected on doorknobs, bed guardrails, air exhaust dampers, and elevators during the MERS outbreak in South Korea. [32] SARS-CoV-2 might be transmitted faecally, proper disposal of soiled objects is also permitted. [31, 33]

To prevent further transmission, visits to the ICU should be restricted, [34] and interfaces likewise video conferencing via mobile phones can be used for communication between family members and patients or health-care workers where feasible.

ICU Infrastructure

Suspected or confirmed COVID-19 should ideally be admitted to an airborne infection isolation room (AIIR) that is at negative pressure relative to surrounding areas, with accessible sinks and alcohol hand gel dispensers (figure 2), especially if aerosol-generating procedures are done. [35] This protocol protects other patients and health-care workers. In case, If AIIRs are not available, critically ill patients can be placed in adequately ventilated single rooms with the doors closed, as recommended by WHO. [36]

One of the Asian survey depicts that only 37% of ICU rooms were single rooms, and 13% of ICUs had no single rooms. [37] Generally the number of single rooms and AIIRs were lowest in low-income countries. In case if single ICU rooms are not available, cohorting of cases in shared rooms with dedicated staff is an alternative, with beds spaced apart. [36]

PPE should be considered for patients in shared rooms as there remains a concern of nosocomial transmission, especially when aerosol-generating procedures are performed. For non-intubated patients, oxygen masks with HEPA filters might provide some protection. [38]

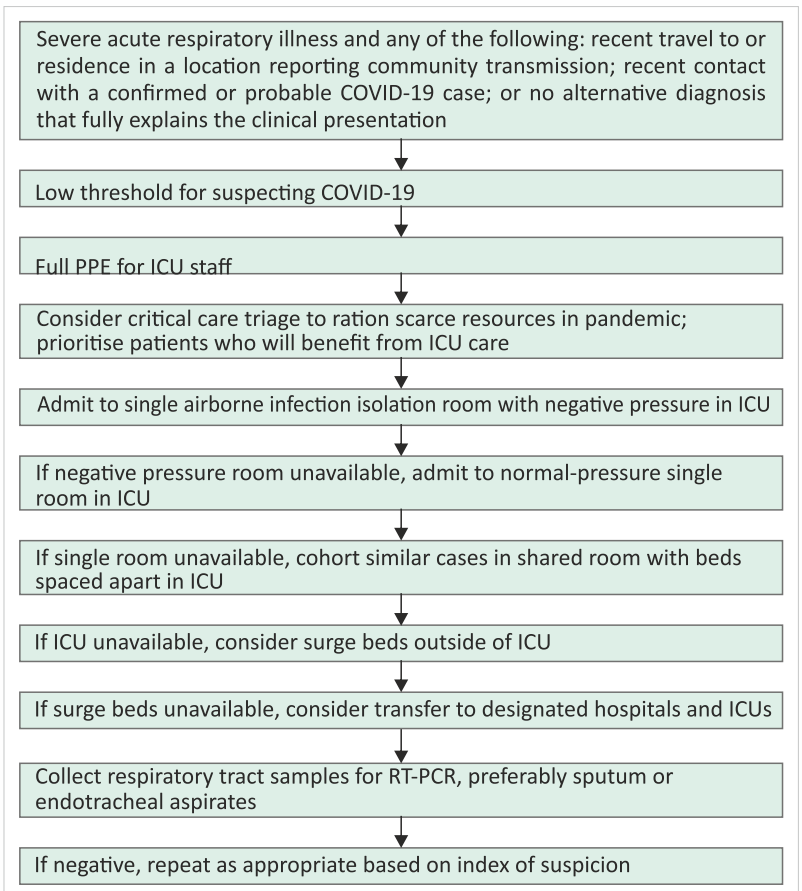

Figure 2: Initial approach to critically ill patients with suspected COVID-19. [24] [COVID-19: coronavirus disease 2019; ICU: intensive care unit; PPE: personal protective equipment]

ICU Capacity

Though controlling the community spread of COVID-19 is difficult but possible, [39] and is crucial for the preservation of ICU capacity. Modelling of needs for intensive care is crucial at national and regional level. [26]

There might be a shortage of ICU beds in many countries at the first place, let alone isolation or single rooms. The median number of critical care beds per 100,000 population was 2.3 in ten low-income and lower-middle-income countries, 4.6 in five upper middle-income countries, and 12.3 in eight high-income countries in Asia in one analysis, [40] and 9.6 in 28 high-income countries in Europe in a 2012 report. [41] China, an upper-middle-income country, has 3.6 critical care beds per 100,000 population, [40] and Wuhan was initially overwhelmed by COVID-19. Italy, a high-income country with 12.5 critical care beds per 100,000 population, [41] continues to struggle with the

outbreak. By contrast, a low-income country such as Uganda has only 0.1 critical care bed per 100,000 population. [40, 42] This raises serious concerns about the ability of resource-limited settings to manage critically ill patients with COVID-19.

Surges in the number of critically ill patients with COVID-19 can occur rapidly. [39] Thus, governments, hospital administrators, ICU practitioners, and policymakers must plan in advance for a substantial increase in critical care bed capacity. [26,43] In pre-existing ICU, beds can be added, but space constraints and nosocomial transmission from crowding limit this option. Other options are the provision of intensive care outside ICUs, which are in high-dependency units, remodeled general wards, post-anesthesia care units, emergency departments, or deployable field units (Figure 2). [43]

ICU capacity involves not only in bed numbers but also in equipment (eg, ventilators), consumables, pharmaceuticals, and staffing. [26,43] To avoid the short supply of equipment's, there should be focus on availability of necessary equipment, not only on bed numbers. To reduce strain on ICUs, elective surgeries should be postponed, and lower-acuity patients discharged to other areas.

ICU Staffing

Increase in patient mortality is associated with high ICU workload-to-staffing ratios. [44] Acquisition of staff with colleagues from other ICUs or even non-ICU areas might be required. Likewise, in Wuhan, more than 40 000 health-care workers were deployed from other parts of China to Wuhan. [4] Training and Basic course for external staff, such as mobile app for access to course material while caring for patients, on general intensive care management and specific COVID-19 protocols is crucial. [43]

Staffing of ICUs must take into account the risk that health-care workers might become infected with SARS-CoV-2. To minimize the risk of infection, rostering of staff should consider segregation of teams to limit unprotected exposure of all team members to infected patients or colleagues, and the resultant loss of staff to illness, medical leave, or quarantine. Physical distancing of staff, including having meals separately, is also important.

The constant fear of being infected and the demanding workload have added stress on Health-care workers. They are vulnerable to mental health problems, including depression and anxiety. [45] Staff who worked in high-risk SARS units continued to suffer from post-traumatic stress disorder years later. Necessary measures need to be taken to prevent such problems which includes a focus on infection prevention to reassure staff, clear communication from hospital and ICU leadership, limitation of shift hours and provision of rest areas where feasible, and mental health support through multidisciplinary teams, including counsellors, psychiatry and psychologists. [45]

ICU Triage

Critical care triage should ideally be coordinated at a regional or national health-care systems level, and by following the guidelines for COVID-19. [46] Prioritize patient care and allocate resources in accordance with generally accepted ethical principles is required.

For Inclusion criteria, identify patients who may benefit from admission to critical care and primarily focus on respiratory failure, since the provision of ventilator support is what fundamentally differentiates the ICU from other acute care areas. For exclusion criteria identify patients who are not candidates for ICU admission including patients such as with a poor prognosis despite care in an ICU, requiring resources that cannot be provided, whose underlying illness has a poor prognosis with a high likelihood of death and who are too well. [47]

A triage policy, complemented by clinical decision support systems, implemented by clinicians might identify patients with such a low probability of survival that they are unlikely to benefit from ICU care. [48] However generic physiological outcome prediction scores might not accurately predict the course of illness, older adults with comorbidities, higher d-dimer and C-reactive protein concentrations and lower lymphocyte counts do worse. [4,49] Apportioning of resources likewise involves the retention and withdrawal of life-supporting medicines for existing ICU patients.

Conclusion

World must get ready for the likelihood that containment and mitigation measures may come up short, all nations should increase efforts to prevent the spread of COVID-19. Regardless of whether SARS-CoV-2 infects a little extent of the 7•8 billion people on earth, a large number will become critically ill and require ICU care. The ICU practitioners must prepare itself for this possibly surge of patients and streamline workflow, ahead of time, for rapid diagnosis and isolation, clinical administration, and infection prevention. All essential bodies such as hospital administrators, governments, and policy makers must join hands with ICU practitioners to get ready for a significant increment in basic consideration bed limit protect of health-care workers from nosocomial transmission, physical

fatigue, and mental well-being issues. Some questions need to be addressed by researchers concerning what remains an inadequately understood disease. To this end, pandemics provide a great opportunity for collaboration at the local, regional, national, and international level. Platforms such as the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the International Forum for Acute Care Trialists (InFACT)—formed during the 2009 H1N1 pandemic—enable large research networks to share common goals and standardize data collection globally will be key to the success of these efforts.

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SurgiSeal – An USFDA Approved Topical Skin Adhesive with Patented OctylFlex Technology

Abstract

Traditionally, most incision were closed by sutures but in recent times topical skin adhesive are being used frequently. SurgiSeal, a topical skin adhesive offers many characteristics of a ideal wound closure device that is easy to use,a rapid wound healer, painless, results in excellent cosmesis, not require device removal, and is cost-effective. Surgiseal (2-octylcyanoacrylate)provides the optimal balance between strength and flexibility with patented OctylFlex Technology. Surgiseal can replace suture that are 5-0 or smaller in diameter for incision or laceration repair and is designed to save time during wound repair.The formulation leads to the scarless surgery with desired cosmetic results.

Keywords: *Skin Adhesive, SurgiSeal, scarless, painless, rapid wound healer, 2- Octyl cyanoacrylate*

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Introduction

Every year there are over 7 million traumatic lacerations [1] and between 26 to 90 million surgical incisions which require closure by surgeons, emergency physicians, and primary care practitioners [2] Conventionally, these wounds and incisions were closed with sutures, staples, or surgical tapes, but in recent times tissue adhesives are being used frequently. Ideally, a wound closure device should be easy to use, provide rapid wound healing, painless, result in excellent cosmesis, not require device removal, and be cost-effective. Although none of the presently available closure devices meet all of these needs, topical cyanoacrylate tissue adhesives offer many of the characteristics of this ideal wound closure device [3].

Cyanoacrylates were first manufactured in 1949. The first adhesives were found to have an extreme inflammatory effects on tissues. N-butyl-2-cyanoacrylate, which was developed in the 1970s, became the first adhesive to have negligible tissue toxicity and good bonding strength, as well as acceptable wound cosmesis [4].

2-octylcyanoacrylate, the latest in cyanoacrylate technology, has comparatively less toxicity and almost four times the strength of N-butyl-2-cyanoacrylate [5]. It provides the optimal balance between strength and flexibility. SurgiSeal can replace sutures that are 5-0 or smaller in diameter for incision or laceration repair and is designed to save time during wound repair.

Structure and Mechanical Properties

Generally, the strength and other physical properties of the cyanoacrylate adhesives are directly linked to the length and complexity of their alkyl side chain. Short, straight-chain derivatives (ethyl or butyl cyanoacrylate) form tight and stronger bonds compared with complex or long-chain derivatives (propoxypropyl cyanoacrylate and octylcyanoacrylate) [6].

Cyanoacrylate when applied topically degrade slowly, forms few toxic degradation products before the polymers slough off. In theory, the longer the chain (e.g., octyl), the slower the polymer degrades and thus less probability of cytotoxicity or histotoxicity as the chain length increases.

The heat released during the polymerization of OCA is less as compared to that of BCA because of OCA's slower rate of polymerization. While a polymer film of OCA is stronger and more flexible, OCA's setting time is longer than BCA's in general [7].

SurgiSeal was developed with the goal to improve and enhance 2-OCA's characteristics as a tissue adhesive. Even though the active ingredient of both SurgiSeal and the leading competitor is 2-OCA, SurgiSeal integrates many innovations in formulation, manufacturing process and applicator design which makes the product stand out in terms of benefits and convenience.

SurgiSeal consists of more than 98% 2-OCA with a trace amount of polymerization accelerator. The 2-OCA is stabilized with a free radical inhibitor and an anionic inhibitor. For visual detection, a trace quantity of the colorant is also included. SurgiSeal is packaged in a user-friendly and single use plastic applicator containing 0.35mL of adhesive. SurgiSeal is sterilized inside the final packaging by a certified sterilization method. The plastic applicator seal is connected to a piece of sponge, allowing the adhesive to be easily dispensed onto the sponge once the sponge connection is folded. A uniform sealing film is formed by applying the adhesive-saturated sponge tip on the wound.

In addition to the chemical, physical and mechanical properties, another practical aspect of cyanoacrylate adhesive is ease of use, which is often related to the applicator design of the adhesive [8].

Medical Application Performances

Adhesive Strength and Flexibility

SurgiSeal has been evaluated for key adhesive properties, such as tensile strength, overlap shear strength, peel adhesive strength and impact strength. The leading competitor also has been evaluated for the same. All the tests were conducted according to the standard methods of ASTM (American Society for Testing and Materials).

SurgiSeal demonstrated strong adhesive strength in all testing. SurgiSeal is significantly stronger in the test of T-Peel loading and is comparable in the tests of Tensile loading, Lap shear tensile loading and Wound closure strength.

Table 1 : Testing Results of Adhesive Properties

Properties	*Surgiseal*	*Leading Competitors*	*ASTM Method*
Tensile loading (lbs/in^2)	14.16±1.39	10.88±1.41	F2255-05
Lap-Shear tensile loading (lbs/in^2)	14.58±1.63	15.68±1.93	F2258-08
T-Peel loading (peak lbs)	39.64±4.73	27.14±2.97	F2256-05
Wound closure strength (peak lbs)	2.67±0.93	2.36±0.87	F2458-05

Flexibility was also tested using the mandrel bend technique according to ASTM D4338-97. Both SurgiSeal and the leading competitor passed the test and showed no signs of cracks, blistering, blushing, fractures or flaking.

To assess the efficacy of SurgiSeal for the application of incision wound closure, in vivo biomechanical evaluation was performed using the rat linear incision wound model. The average ultimate pressures applied at the wound site for SurgiSeal and the leading competitor were the same, indicating that SurgiSeal possesses bonding strength comparable to the leading competitor's.[9]

Setting Time

Setting time is also positively correlated to polymerization rate. In general, as per earlier discussion, OCA has a slower polymerization rate as compared to BCA and thus has a longer setting time. To achieve a shorter setting time, a trace amount of an accelerator is added in the formulation of SurgiSeal is slightly shorter than that of the leading competitor.

Surface Coverage

Applicator dispensing width is defined as the dispensed adhesive width of an individual stroke of an applicator, and the surface coverage area is measured by the applicator dispensing width and length. Both SurgiSeal and the leading competitor were tested on pig skin. The average dispensing width of SurgiSeal was 17.6mm, compared to the 7.7mm average dispensing width of the leading competitor. The average surface coverages of SurgiSeal and the leading competitor were 27.9 and 11.5 inch2, respectively. The tests demonstrate that SurgiSeal can provide much larger and wider coverage per applicator compared to the leading competitor [8].

Permeability

Adhesives with a high Moisture Vapor Transmission Rate (MVTR) improve wound care [11]. For these tests, MVTR was determined using a Mocon Permatran-W101 Water Vapor Permeability Instrument in accordance with ASTM D-6701. SurgiSeal and the leading competitor were applied and cured on a 2" square collagen film. MVTRs for SurgiSeal and the leading competitor were 2180 and 918 g/m2/day, respectively. SurgiSeal film is more vapor permeable than the leading competitor's film, which should contribute to better and rapid wound healing.

Ease of Use

The leading competitor's product is stored in a glass vial that is crushed prior to application. The vial is then squeezed to apply the adhesive smoothly while avoiding dripping of the adhesive. A SurgiSeal applicator can be opened by simply folding the sponge connection thus it is more convenient to use [8].

Faster Wound Sealing

According to the Instruction for Use, the leading competitor requires at least two layers of application [12]. SurgiSeal requires at least two layers of applications on a wound incision. The second layer can be applied after the first layer dries, usually after 30 seconds.

SurgiSeal has a shorter setting time, a wider dispensing width and a larger coverage area, giving it faster wound sealing than the leading competitor [8].

Product Unique Feature

1 **OctylFlex Technology:** SurgiSeal is manufactured using patented OctylFlex Technology. This unique formulation and process provides the optimal balance of the properties that matter most to a physician – strength to preserve the integrity of the wound closure and unmatched flexibility for patient comfort and physician control.

2 **Precision Applicator:** SurgiSeal patented applicator is designed to provide greater coverage. The self-contained applicator is designed to increase efficiency or to be used on multiple laceration, and to reduce waste.

3 **High Strength Formulation:** SurgiSeal adhesive is made up of 2-Octyl Cyanoacrylate formulation which features a greater breaking strength and broader use in clinical application

4 **Microbial barrier/Protective Coating:** As a microbial barrier SurgiSeal adhesive can be used as an auxiliary sealant in conjunction with conventional suture, which can reduce post-operative infection rate

5 **High Moisture Vapor Transmission Rate:** The formulation is designed to provide optimal permeability, increasing moisture and oxygen content transmission to the wound in order to gain rapid wound healing [10].

Figure 1: Unique Product Features

Cyanoacrylate Adhesives as Topical Wound Dressing

Cyanoacrylate tissue adhesives have been studied extensively compared with sutures and other wound closure agents for topical wound closure and have consistently been shown to produce cosmetic results while improving the speed of closure and being overall less painful [13].

SurgiSeal being a topical skin adhesive has awide application on various types of surface laceration. It can be effectively used for repairing laceration wound and superficial incision closures.

Lacerations are the wounds seen as a cut on the skin with a blunt, linear or irregular edges. These can be minor or can run into deep dermal layers. The tension lines across the wound site makes the edges to spread and difficult to heal. Therefore, for proper healing the edges need to come together for succsessful wound clousre.

SurgiSeal being tissue adhesive in nature helps in keeps the wound edges in place relieving the tension across the wound site. This leads to faster healing, reducing extent of unpleasant scar formation and getting the desired cosmetic outcome. However, the deep dermal wounds require buried suturing to reduce tensile shear forces which may cause premature sloughing. Moreover, SurgiSeal has smooth covering over the wound with wide area coverage forming the waterproof sealing and providing the antimicrobial barrier [14].

Proper Application of Tissue Adhesive for Topical Wound Closure

Proper wound preparation involves evaluating the patient and the wound for factors that may have an impact on wound healing and the eventual cosmetic outcome. The appropriate use of anesthetics, irrigation, and debridement as well as the method of wound repair can be determined from this evaluation [15].

For the superficial incision closures and repairing laceration wound, apply SurgiSeal as follows:

1 Prior to use make sure the laceration or incision site is clean and hemostasis is achieved.

2 For deep dermal wounds, do buried suturing as per the size and depth of wound to reduce the shear tensile forces acting over the wound edges.

3 Make the patient lie-down and ensure wound is on a horizontal plane to avoid adhesive running into unwanted areas.

4 Appose the wound edges with fingers, forceps, or skin hooks. Even Steri-Strips can be used to bring the edges together before applying adhesive. In doing so, they form strong topical bridges over the apposed skin edges of wound, holding them together for 7 to 14 days for normal healing to occur.

5 Paint the adhesive over the approximated wound edges. Do not push the tip into the wound.

6 Apply the adhesive in two to three coatings, allowing each coat to dry slightly before reapplying the next layer. Number of layers to be applied depends on clinical site and tension over the wound.

7 Maintain apposition of the wound for 30 to 60 seconds. Drying of the adhesive usually occurs in 2 to 3 minutes. After polymerization, the wound can be seen under the transparent adhesive.

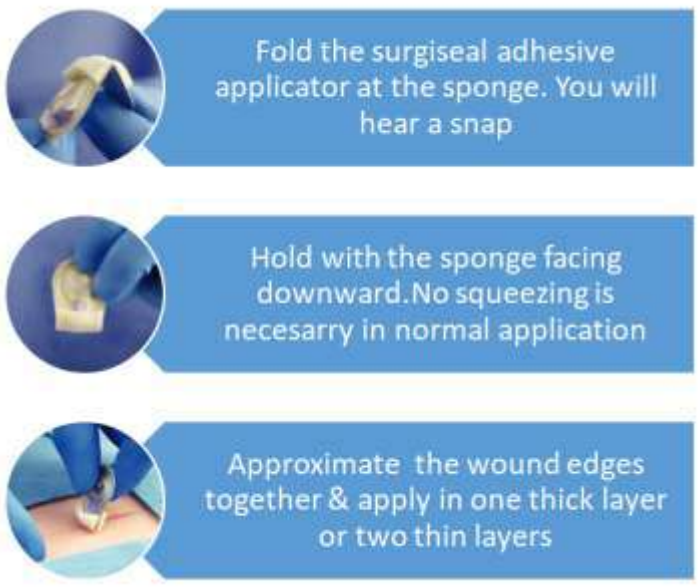

Figure 2: Method of Application

Points to be taken care of during application of topical skin adhesive

Complications and poor outcomes with the use of tissue adhesive can be avoided by selecting the proper wounds for closure with adhesives, using dermal sutures where appropriate, and following the proper application techniques. Beside these there are following points to be noted during application [16]:

1 **Hemostasis:** It is important in providing a neat, secure wound closure. This can be obtained with dermal sutures where appropriate, pressure on the wound, or the use of vasoconstrictor solutions.

2 **Avoid adhesive getting in the wound:** Appose the edges tightly prior to application to ensure that the adhesive do not get inside the wound. If this happens the patient may end up with poor cosmetic results, and it will likely increase the wound infection and dehiscence rate as well.

3 **Avoiding heat:** If one thick layer is applied, the heat from the exothermic polymerization may cause a burning discomfort to the patient and, in some cases, a minor thermal injury. The best way to avoid any discomfort caused by the heat is to apply the adhesive in thin layers with multiple strokes.

4 **Controlling the amount of adhesive and run-off:** Adhesive being low in viscosity has the tendency to run-off and get into the unwanted areas such as eye.

5 **Erroneous application:** If the adhesive gets to an unintended place, Avoid applying adhesive in drop and spread adhesive into a thin layer in case that adhesive is accumulated. It can usually be wiped off before it sets. If it gets into the eye, it can be removed with ophthalmic ointment. On other areas, the adhesive can be removed with acetone; however, care should be taken since acetone should not be used on open wounds because of its histotoxicity.

After Care of the Topical Skin Adhesive

Octyl cyanoacrylate topical skin adhesive has high tensile strength, it holds the wound edges together and provide microbial protection until the wound heals naturally. The adhesive remains in place for 5-10 days before naturally sloughing off the skin. Keep wounds clean because they are prone to infection for the first 24 to 48 hours after repair [17].

While the wound is healing, aftercare of the wound should be taken properly, as follows:

1 Regularly check for the appearance of wound. As wound heals, it is common to experience swelling, redness or itching. Therefore, do not pick, scratch, or rub at the adhesive film. Contact a doctor if the appearance changes or the wound reopen or edges separates. Protect your skin from injury until the skin has had sufficient time to heal.

2 Patient may shower or bath immediately after surgery. However, do not soak or scrub the wound, as this can lead to premature sloughing off of the adhesive, leading to wound dehiscence. Do not swim, and avoid periods of heavy perspiration until the adhesive has naturally fallen off. Pat dry the wound area after bathing with soft towel [18]. If necessary, apply a clean, dry bandage over the wound to protect it.

3 Use of ointments should be avoided because they act as an emollient which can degrade tissue adhesives as well as cause skin maceration, leading to premature sloughing off of the adhesive.

4 Avoid prolonged exposure to sunlight and tanning lamps while the film is in place to prevent hyperpigmentation and/or hypertrophic scar formation.

5 Care should be taken while changing the dressing. Do not place tape over the adhesive film, as when the tape is removed adhesive film gets removed along with it.

Conclusion

Skin and tissue around the wound are sensitive any additional injury in this region leads to more damage. Earlier techniques of wound closure, like suturing and

7 stapling, provides the wound closure but additionally leads the puncturing of the healthy tissues around the wound and also may lead to relocation of microbes on the surface to enter inside the skin. Furthermore, the puncturing of tissues may lead to additional marks and unwanted scar formation. Altogether, these techniques are painful and needs precise expertise to carry out the procedure.

SurgiSeal as a topical skin adhesive holds the wound edges together and helps in natural healing of the wound. It also forms the waterproof layer and microbial barrier keeping the infections at check. Its application is painless, easy to learn and can effortlessly be incorporated into physicians practice. The high tensile strength of octyl-cyanoacrylate provides flexibility and freedom to move around. The formula leads to the minimum scar formation and the desired cosmetic results.

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2-Octyl Cyanoacrylate

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- For O-10 inches incision
- Vol- 0.50ml
- Angeled Tip Applicator

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  (Superior flexibility & Optimal strength)
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- Optimum viscocity
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Multiple Ways to Create Records / Upload Documents

Unique Patient Check-in Module

Easy to use Appointment Module

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HEALTH CARE e-Compendium

Current Issues in Patient Care

We invite papers, review articles and case studies for the next issue of e-compendium. Please submit to Nasharah Siddiquee at editorial.drsc@gmail.com

Last date of submission for next issue - 12th October 2020