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Current Issues in Patient Care

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FROM THE DESK OF THE EDITOR-IN-CHIEF

Emergence of social media has a key impact on global development through easy exchange of information. This provides an opportunity to share the latest information among HCPs. In recent times we have seen its importance in COVID-19 pandemic, wherein latest research on the virus, medication and vaccine is flashed across the world within a matter of minutes. However, there should be a judicious use of social media for the betterment of humanity. To accomplish this, DRSC is now on social media platform reaching new horizons by helping spread scientific knowledge to theknowledge seekers.

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.

DPSRU is the 1st Pharmacy university in India with a vision to be the ultimate destination for education, training and research in pharmaceutical sciences and allied areas and thereby, cater the health needs of the people at large. Our faculty is engaged to shape able leaders, administrators and personnel who can take up responsibilities as pharmaceutical sciences professionals, suitable for community, industries and institutions related to health. DPSRU has always been at forefront in connecting with Clinicians for providing them innovative products as suited for Indian masses.

I sincerely appreciate the efforts and contribution of all the Doctors, DPSRU faculty members and DRSC team who helped in bringing out this third issue of Healthcare e-Compendium. I am sure in near future this will be soon reach at Global platform and libraries of Medical & Pharmacy colleges.

CONTENTS

Recovery Post COVID-19: An Urgent Need to Help Patients Get Back to their Active Life

Abstract

The novel Coronavirus disease 2019 (COVID-19) is a disease caused by severe intense respiratory condition COVID (SARS-CoV-2). The World Health Organization (WHO) has declared this outbreak a global health emergency on April 24, 2020. It has spread to 213 countries, with 109M confirmed cases, and 61.1M cases have been recovered from COVID-19. In the present circumstance, it is imperative to understand the possible outcome of COVID-19 recovered patients and determine if they have any other detrimental illnesses by longitudinal analysis to safeguard their life in the future. It is essential to follow-up these recuperated patients and performs detailed appraisals for discovery and proper administration towards their mental, physical, and social domain. This urges us to suggest that it's essential to provide physical and emotional counselling, mental support, and a couple of recommended guidelines to recover patients and society to restore to normalcy. Epidemiological, clinical, and immunological investigations from COVID-19 recuperated patients are incredibly essential to comprehend the illness and plan better for possible episodes.

Keywords: *COVID-19, SARS-CoV-2, Rehabilitation, COVID Recovery*

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Introduction

The novel coronavirus 2019 (COVID-19), the unprecedented pandemic, has caused severe panic among individuals worldwide. It is a severe illness with a high attack rate on the respiratory system followed by a high fatality rate worldwide. According to a report, active alveolitis that is active during the host immune system response to the SARS-CoV antigen might lead to pulmonary fibrosis in certain patients after recovery [1]. Fifty-five patients who recovered from Middle East Respiratory Syndrome (MERS) were found to have lesions present in the periphery of the lungs. Even with such a high mortality rate, there is hope that the COVID-19 patients will recuperate from this unexpected situation [2]. In this situation, researchers should take responsibility for regular follow-up surveys of COVID-19 recovered patients during the convalescent phase. It would help evaluate any changes in the acquired immune function, blood parameters, psychological factors, biochemical factors, and organ functions. Reports have proposed that the SARS-CoV-2 predominantly influences individuals who have had any past ailments identified with lungs, kidney, heart, and the GI tract [3,4].

Lungs: The virus-mediated cytokine activation in the alveolar macrophages results in lung fibrosis and damage.

Kidney: Activated nucleotide-binding domain (NOD)-like receptor protein-3 (NLRP3) signaling can cause pyroptosis and cell death.

Heart: This viral infection can rupture the necrotic lipid core and form blood clots resulting in myocardial infarction.

Brain: If the neural structure gets infected by SARS-CoV-2, it results in the lack of smell and, in some cases, may additionally trigger neurodegenerative diseases within the COVID-19 recovered patients.

Eyes: The tears act as the route of transmission to other organs of the human system through the nasolacrimal system [4,5].

Also, the COVID-19 recovered patients may have psychological stress due to their infection and may be skeptical about their acceptance in society post-COVID-19. Hence, it is crucial to conduct follow-up studies in recovered patients to determine if they might have any other detrimental illnesses. According to World Health Organization (WHO), the death rate of COVID-19 patients will be around 3 to 5%, and the remaining patients affected by COVID-19 will mostly recover. More research is required on the diagnostic and therapeutic approaches for patients' wellbeing after recovering [5,6].

Hence this review emphasizes focusing the research on various multi-organ damages which could occur because of SARS-CoV-2 infection. Further, we propose the possible complications faced by the COVID-19 recovered patients and suggest handling the aftermath by providing counseling on overcoming psychological stress and ensuring patients' physical and mental wellbeing.

Understanding Post-COVID Long Term Symptoms

While the lungs are the primary organs suffering from COVID-19, there are many organs other than lungs that are affected. This increases the danger of long-term health problems that individuals may still face months after the initial infection. Healthcare providers are reporting long-term impacts which will affect the guts, kidneys, skin, and brain.

Older adults and other people with underlying medical conditions are more likely to possess lingering COVID-19 symptoms. However, even people that weren't hospitalized and who had mild illness can experience persistent or late symptoms long after a few weeks. Most commonly, these longer-term symptoms include:

- Fatigue
- Shortness of breath
- Cough
- Joint pain
- Chest pain

Some individuals may also experience:

- Difficulty thinking and concentrating (brain fog)
- Depression and anxiety
- Muscle pain
- Headaches
- Fast or pounding heartbeat
- Intermittent fever

COVID-19 Repercussions and Challenges

The COVID-19 affected patients have symptoms like fever, mild respiratory symptoms after infection of 5–6 days, and most of them with mild disease will recover.After the recovery, those patients should take care of their health status and follow-up. Additionally, to lungs, other organs, including kidney, heart, liver, gastrointestinal tract, and eye, are possible infection sites (figure 1). A recent study reported that the human kidney might be a specific target for SARS-CoV-2 infection [6]. During follow-up of SARS recovered patients, the infection has been reported in other organs, including the kidney and gut, along with alveolar cells within the lungs [7]. People who have recovered from COVID-19 should focus on maintaining and monitoring their health status. They need to be in regular monitoring for their future complications that might occur after their recovery. Hence, the recovered patients are recommended to finish a master health check-up to check for risks for other diseases.

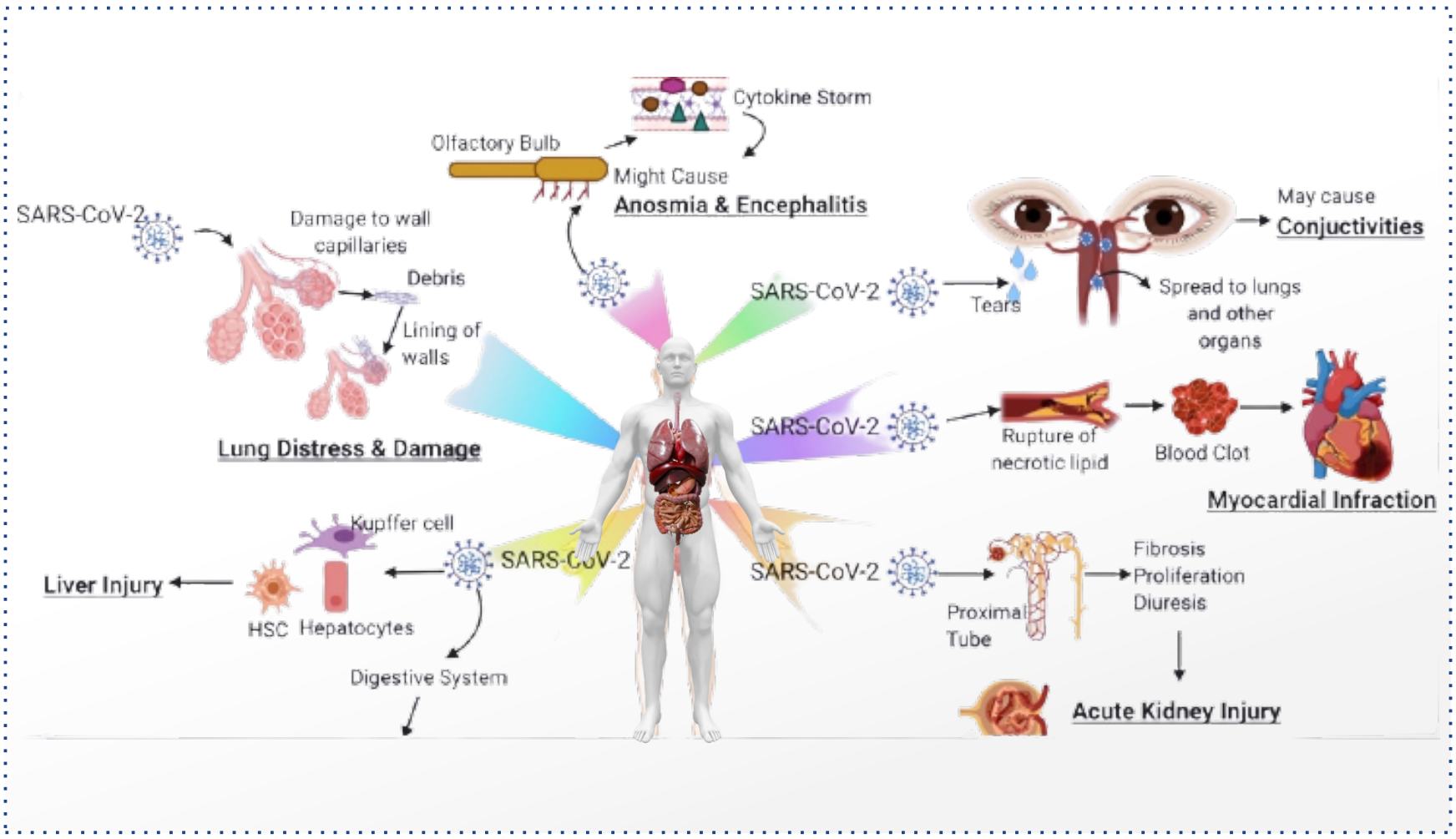

Figure 1: Effect of SARS-CoV-2 infection on organs in different parts of the body. (Clockwise)

Most of the COVID-19 recovered patients experience stress for several weeks, which usually disappears within a brief period. Still, the psychophysical symptoms, including depression, fear, and anxiety, may persist for an extended time. The recovery time depends on an individual's age and pre-existing conditions before the onset of the infection. According to WHO, people of 10–50 years of age are likely to recover from the disease since the death rate for this age category is well below 1%. The COVID-19 patients who were hospitalized resume their everyday lives after spending weeks breathing with mechanical ventilators' assistance. A number of the recovered patients will still have some lingering effects of the virus and the hospital environment. Such situations would make the recovered patients feel paranoid, and therefore the aftermath of the disease would be persistent within the back of their minds. During the quarantine period, the infected, also as few recovered patients, are devoid of human contact, which could increase the probabilities of psychological symptoms. Hence, we propose providing counseling, moral support, also like a couple of recommended guidelines to the COVID-19 recovered patients returning to normalcy [8].

Rehabilitation and Interventions

Patients who were seriously ill with COVID-19 and have passed the critical phase of lung infection and are discharged but have pulmonary dysfunction symptoms should be prescribed a rehabilitation program to restore wellness and reduce anxiety and depression [9, 10].

Rehabilitation is like medical aid to ensure that patients do not deteriorate after discharge and need readmission. It begins with an assessment aiming to discover the patient's primary problems and concerns and understand how they arise and can be alleviated. Effective rehabilitation interventions fall into five categories that are the same across all conditions [11]:

- Everyday exercise to increase cardio-respiratory work
- Performing basic functional activities
- Psychosocial treatments
- Education with an emphasis upon self-management
- Set specific actions custom-made to the patient's priorities, requirements, and goals, cover all domains of the biopsychosocial model of illness, be assessed routinely for their benefits, and decide if they should be continued, changed, or relinquished.

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Physiotherapy and Post-Acute COVID-19 Rehabilitation Phase

Physiotherapists are instrumental in rehabilitating patients as they transition from the acute phase to the post-acute phase [12]. The outcomes of COVID-19 will be narrowed down in each individual, and their rehabilitation needs will be specific to these consequences, such as:

- Long-term ventilation
- Immobilization
- Deconditioning
- Related impairments – respiratory, neurological,
- and musculoskeletal

COVID-19 patients will often present with pre-existing comorbidities, which must be considered within the patient's rehabilitation plan.

Rehabilitation for Patients with Mild and Moderate COVID-19

Most patients with COVID-19 present with mild influenza-like symptoms and may encounter fever, fatigue, cough, muscle pain, and other indications. The principal respiratory rehabilitation interventions include airway clearance, respiratory control, posture management, active work, and exercise [13, 14]. A diagnosis of COVID-19 may build a feeling of fear in patients [15], and psychological counseling is especially significant. Besides, these patients should zero in on making sure to do regular work and rest, have a balanced diet, and stop smoking [13]. For patients with mild and moderate signs and symptoms of COVID-19, Traditional Chinese Medicine (TCM) and adjuvant therapy involving acupuncture, cupping, moxibustion, massage, acupoint application, and aromatherapy are reported [16].

Rehabilitation for Severe and Critically Ill COVID-19 Patients with Underlying Comorbidities or who are Elderly

Severe and critically ill patients with COVID-19 often develop respiratory distress and/or hypoxemia one week after onset, progressing to ARDS, septic shock, metabolic acidosis, and even death [12, 15, 16].

For severe and critically ill patients, specialists from different nations have proposed that respiratory rehabilitation should be undertaken once a patient's condition is steady, but not start too early, to abstain from intensifying respiratory failure or unnecessary spreading of the virus through droplets [12, 16]. Therefore, determining an exact recovery time is significant. Timely rehabilitation can reduce or even eliminate these complications and the adverse effects on patients' everyday life [17,18].

Early rehabilitation should be performed within a patient's resilience level, including posture management, rollover, active/passive joint activity, respiratory muscle training, sputum training, basic exercises for patients confined to their beds, mobility training, stand on support, standing independently, and ADL training [12, 19-22]. For patients with ventilator dependence, progressive resistance training of inspiratory muscles has been observed as a feasible and viable treatment to improve inspiratory muscle strength and improve quality of life (QoL) after weaning [13, 23]. In the early stage of severe illness, aerobic exercise should be avoided as it may cause respiratory failure in some patients [21].

Rehabilitation of Patients with COVID-19 who Encounter Psychological Disorders

Patients diagnosed with COVID-19 may experience outrage, fear, nervousness, depression, insomnia, or hostility during the isolation treatment period, as well as psychological problems such as depression, loneliness, lack of cooperation, or abandonment of treatment due to fear of the disease, which all negatively affect patient treatment and rehabilitation [21, 24]. Patients in ICU have been found to have differing levels of nervousness, depression, and post-traumatic stress disorder (PTSD). These conditions can prompt dyspnea, tachycardia, raised blood glucose levels, hyperlacticacidemia, and low blood pressure, thus influencing treatment adequacy [23, 27].

Prevention or treatment of these clinical symptoms is likely to be of considerable benefit to ADL and patient recovery. Two studies detailed that clinical psychologists may assist patients to recover from their intense and unpleasant encounters. Clinical psychologists provide patients with stress management, interactive communication, and personalized care. The findings of both studies showed that patient's vital signs improved, and pain scores decreased, and that complication rates, anxiety, and sleep patterns all improved. Notwithstanding, barely any examinations have straight forwardly measured the impacts of early mediations by clinical therapists for patients who are severely or critically ill [28, 29]. Each patient's degree of capacity to convey may vary; therefore, they should personalize psychological treatment. Patient education can improve understanding and reduce anxiety levels. This methodology has been shown to improve recuperation times and reduce pain, psychological stress, and length of hospital stay [29].

Relaxation exercises (e.g., progressive muscle relaxation, breathing exercises and meditation) have been reported to improve vital signs and patient mood. Moreover, these exercises have been found to reduce the incidence of complications, fatigue, fear, pain levels, length of hospital stay and use of sedatives, and improve sleep quality [16]. Distraction methods (such as reading, listening to music, and engaging in dialogue) have been found to improve patients' pain symptoms [16]. Similarly, hypnotic interventions can effectively reduce the use of analgesics and relieve pain [29]. One study demonstrated that acupuncture, massage, and other TCM treatments could also reduce patient stress [30]. Music therapy is a widely used non-pharmaceutical intervention, which has been accounted to reduce stress, depression, anxiety, pain, and feelings of isolation for patients [27, 29].

Even though drug therapy is currently the central intervention to alleviate patients' anxiety and psychological distress, non-pharmacological interventions have gradually become widely acknowledged and implemented, benefiting many patients and reducing the risk of drug-related adverse reactions [27, 31].

Mental Health

A topical study published in the Lancet reviewed many previous studies and reported the effect of quarantine on patients' mental health. Many studies reported adverse psychological effects, including post-traumatic stress symptoms, confusion, and anger. Stress factors included longer quarantine duration, fears of infection, helplessness, frustration, boredom, inadequate supplies, inadequate information, and stigma. Long-lasting psychosocial impacts were also reported. Such unprecedented reporting of mental health sufferings during COVID-19 calls for a full mental health policy and program to minimize psychological and emotional issues during the COVID-19 outbreak [32]. The WHO (2020) too has shared strategies to enable the global populace to remain mentally healthy during this unprecedented global health crisis [33]. In summary, it implores people to engage in routine activities, stay calm, indulge in hobbies, stay connected through social

media, talking to friends or counselors in case of unmanaged anxiety or fear, doing physical exercises, and not resorting to alcohol or drug to deal with emotional problems [34].

Recommendations

The COVID-19 symptoms range from various organ dysfunction like the lungs, heart, eyes, brain, and gastrointestinal tract. Although the SARS-CoV-2 infected persons recover from the preliminary effects, there might be some aftermaths that the recovered patients may have to face. Many recovered patients still may need paranoid feelings about the COVID-19 disease. Therefore, through this review, we offer a couple of recommendations to safeguard the COVID-19 recovered patients and their families from the repercussion of this disease. The recommendations are (figure 2) :

- Utmost care should be provided to COVID-19 recovered patients.
- Tighter supervision of workplace safety should be provided to safeguard the security of people's lives, alongside the COVID-19 recovered patients.
- Rapid follow-up tests should be recommended for the recovered patients.
- The signs and symptoms of the recovered patients should be monitored regularly.
- Extensive attempts are to be made to make awareness about the virus to recovered patients.
- The relations of the recovered patients should be trained in empathy skills to relate and communicate with them by encouraging two-way discussions.
- Home monitoring programs for recovered patients can help them to improve their diet and physical activity.
- Recovered patients should drink plenty of water and other fluids to stay well hydrated and to consume nutritious food to improve their immunity.
- Proper counseling and education about the ill-effects of smoking and alcohol consumption must tend to recovered patients.
- Recovered patients should be recommended to cooperate with researchers who are voluntarily involved in conducting and collecting the info for the health status assay.
- Recovered patients should be encouraged to share their feelings about the treatment, quarantine, symptoms of the disease, and their experience on the entire to scale back their psychological burden.
- To beat this psychological stress, it's advised to practice yoga and breathing exercises, which can help combat the psychological stress caused due to this disease.
- The community/society must be educated not to stigmatize or isolate recovered patients.
- Counseling is usually recommended for the recovered patients periodically not to lose courage and keep themselves mentally strong [35].

Figure 2: Recommendations for SARS-CoV-2 recovered patients.

Conclusion

COVID-19 has known to be a deadly disease affecting people worldwide. It has tested all medical services, including rehabilitation, and will continue to do so for the next coming years. It has recently uncovered a multifaceted condition known to affect various other organs and not just our lungs. Rehabilitation intervention (including positioning and respiratory management, physiotherapy, traditional herbal medicine, and psychological support) should be given along with routine treatment, which can decrease hospital length of stay and improve patient status and quality of life. Ideal arrangement and insightful planning can assist with restricting any effect that emerges from this pandemic. Individuals who have recovered from the condition may be stressed, contributing to psychological issues like depression and anxiety. As the world recuperates from COVID-19, it is essential to move forward with all the necessary measures for the physical and mental wellbeing of recovered patients. It is essential to conduct follow-up studies in the COVID-19 recovered patients and provide the appropriate management of this dreadful disease in terms of psychological, physical, and social aspects.

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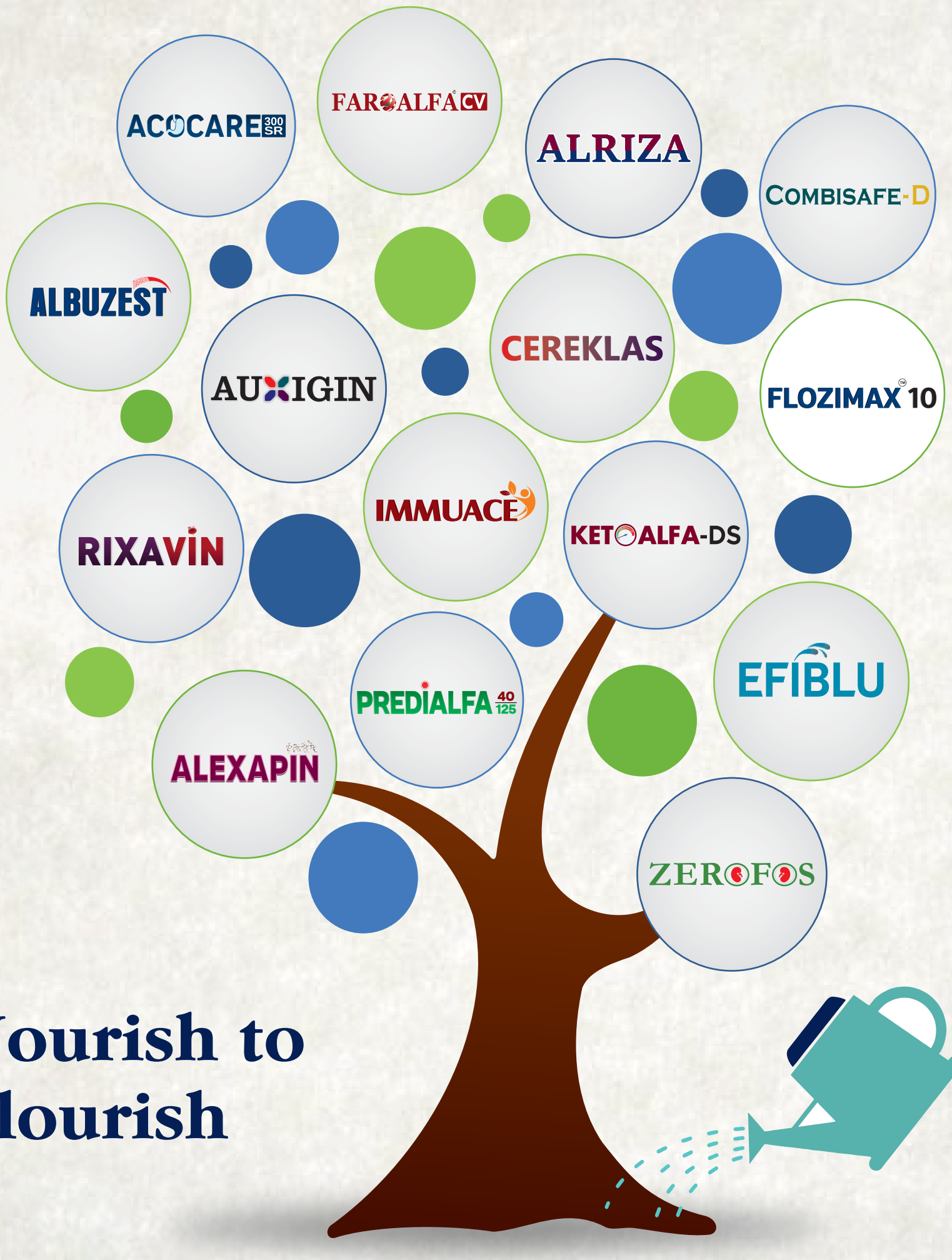

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Building Long-term Immunity - Should it be an Essential Part of Each Prescription

Abstract

The current global pandemic of COVID-19 has emphasized on the need of a strong immunity. Different types of disease-forming organisms activate different parts of the immune system primarily. All vital nutrition and essential vitamins and minerals can achieve a strong immune system, which will help to fight diseases naturally. Besides a healthy diet, daily exercise is also vital for a good immune system. Although, daily intake of nutrition is always not achieved and an intake of immunity booster can help to maintain it.

Keywords: *Innate Immunity, Adaptive Immunity, Active Immunity, Passive Immunity*

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Introduction

The immune system helps to protect the body from harmful substance by detecting and responding to antigens. Antigens are substance (usually proteins) that present on the outside of a pathogen. Non-living substance can also be antigens such as toxins, chemicals, drugs, and foreign particles (such as a splinter) [1].

Two components of immune system are innate and adaptive immunity (Table 1). The innate immunity occurs in all metazoans, while the adaptive immunity is only present in vertebrates [2].

Innate immunity, also known as native immunity, which is widely, distributed form of immunity. It is defined as the first line of defence against pathogens, representing a critical systemic response to stop infection and maintain homeostasis, contributing to the activation of an adaptive immune response [3].

Adaptive or acquired immunity is the active constituent of host immune response, mediated by antigen-specific lymphocytes. It is highly specific to a particular pathogen, including the development of immunological memory. Adaptive immunity is classified as 'active' or 'passive' [4]. Active immunity is acquired through the exposure to a pathogen, which triggers the release of antibodies by the immune system. Passive immunity is acquired through the transfer of activated T-cells derived from an immune host (antibodies) either artificially or through the placenta, requires booster doses for continued immunity as it is short lived.

Table 1: Parameters of Innate and Adaptive Immunity

Parameters	Innate immune system	Adaptive immune system
Specificity	Response is non-specific	Pathogen and antigen specific response
Timing	Exposure leads to immediate maximal response	Lag time between exposure and maximal response
Memory	No immunological memory	Exposure leads to immunological memory
Present in	Found in nearly all forms of life	Found only in jawed vertebrates

The diagram given below shows classification of immunity (figure 1) [5].

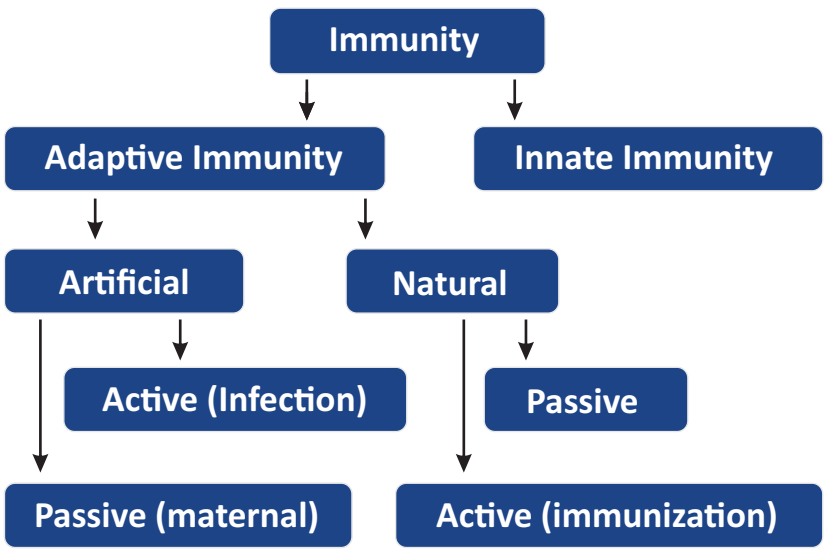

Figure 1: Divisions of Immunity

Role of Immunity in Recovering from Illness

The immune system of human is a complex and powerful defense mechanism; the foremost effective mechanisms of immune system depend upon characteristics of the infectious agents. The initial function of the immunity is to guard the body from pathogens, which are disease causing organisms as virus and bacteria. To achieve this function cell, tissue and protein within the immune system work together [6].

How Immunity Works?

The immune system must be ready to recognize pathogens. Pathogens have molecules, called antigens, on their surface. Antigens provides a sole signature for pathogen that permits immune system to identify pathogens and differentiate pathogens from body's own cells and tissues. The immune system reacts in two ways when a pathogen enters into the body.

a. **Innate immune response**: It identify certain molecules that are present on many pathogens. In response to action of infection, these cells react to signalling molecules which is released by the body. As a result, innate immune cells quickly start fighting an infection. Leading into an inflammation. The cells involved during these reactions not only kill pathogens but will also help activate cells involved in adaptive immunity.

b. **Adaptive immune response**: It is slower than the innate response but is better in targeting specific pathogens. There are two main cell types involved during response: T cells and B cells. There are some T cells which kill pathogens and infected cells; other T cells help to regulate the adaptive immune response. The main function of B cells is to make antibodies against specific antigens. Antibodies (immunoglobulins) are protein that attach themselves to pathogens. This then signals immune cells to devastate the pathogen (figure 2).

When pathogen causes an infection it takes time for T and B cells to respond to these new antigens. These cells then develop memory for the pathogens once exposed to them, so that they are ready for the subsequent infections. Some T and B cells become memory cells due to adaptive immunity. Memory cells usually stay within the lymph nodes and then the spleen and "remember" particular antigens. If an individual is re-infected with the same pathogen again, these cells are now ready to rapidly and aggressively begin fighting the infection [7].

The Immune Response

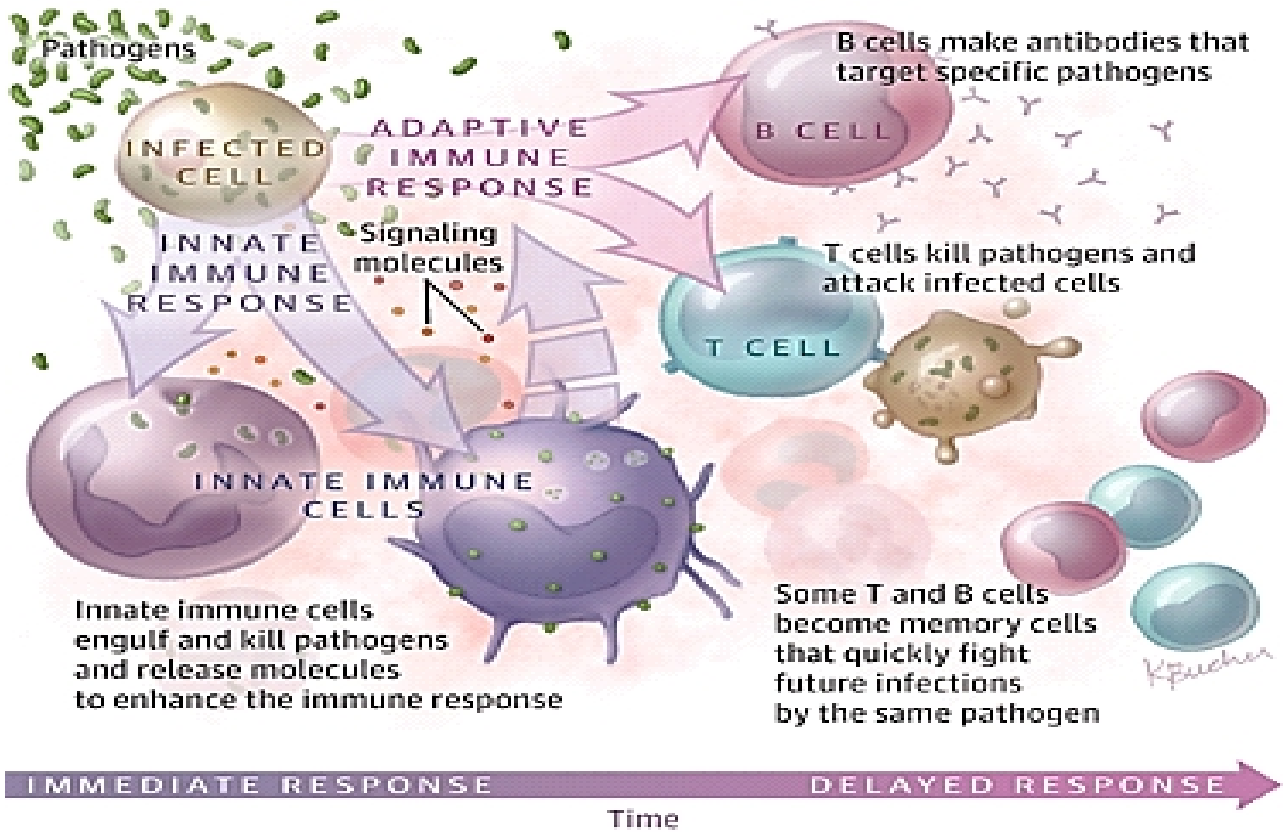

Figure 2: The immune response against invading pathogens

Supportive Care during Recovery

During COVID 19 outbreak, it was observed that people with 'weak' immune system are at higher risk of getting affected by virus. Immune system is responsible for destroying viruses and germs that enter the body and protects from diseases. So it is important to take every measures possible to ensure that the immune system remains healthy and strong. Stronger immune system can be built with few lifestyle amntendmes.

Lifestyle changes to strengthen overall immunity

a. **Diet**: A good nutrition is the key to a healthy and strong immune system that provide protection against seasonal illness and other health problems. Gut and immune system goes hand-in-hand, means keeping gut healthy, to ensure healthy immune system. Therefore, including foods in diets that are gut-friendly, such as probiotics, fermented and cultured foods, and sprouted vegetables. Adding more amount of antioxidant-rich foods in diet that can help fight against cell damage and body invaders. Consuming a balanced diet that contains protein, fiber, vitamins, minerals, and other nutrients that boost the immune system and help support immune response and play a role in healthful eating style.

b. **Workout**: There is powerful link between exercise and the body's defense system. Practicing yoga, daily walk or regular exercise routine can help decrease your chances of developing any health issues. Regular exercise helps in the production and strengthening of white blood cells (WBCs) that helps to fight against disease. Exercise helps WBCs to circulating more rapidly, allowing them to detect harmful organism before they can cause any problem. Physical activity and good nutrition may help to minimise the risk of negative consequences of age-related immune dysfunction. [8]

c. **Sleep**: Insufficient sleep can affect immune system. A protein called cytokines is released by immune system when body is in sleep mode, this protein helps to fight against infection and inflammation therefore its production needs to be increased once you are infected. Production of cytokines may reduce due to lack of sleep. You need at least 7-8hrs of sleep is needed, it will not only keep immune system healthy but also keeps body active throughout the day.

d. **Herbal diet**: There are some herbs that help to boost your immunity.

Moringa- It is a herb that may ward off many health complications and helps to strength immunity. It contains high amount of vitamin C even more than oranges. It also contains some other important nutrients that helps in the strengtheningofcells,muscles,tissues and helps in healing. Consuming moringa helps to increase the levels of calcium, iron, potassium and amino acids.

- Neem- Since time immemorial, it is respected and wildly used to strengthen immunity. It has several properties like anti-viral, anti-bacterial and anti-fungal properties. Apart from that it also helps to keep the body from attacks by harmful pathogens. Neem purifies the blood by flushing away toxin and this helps to strengthen immunity.
- Neem- Since time immemorial, it is respected and wildly used to strengthen immunity. It has several properties like anti-viral, anti-bacterial and anti-fungal properties. Apart from that it also helps to keep the body from attacks by harmful pathogens. Neem purifies the blood by flushing away toxin and this helps to strengthen immunity.
- Tulsi- It is also known as basil which is powerful germicide. Because of its phytochemicals and antioxidant, it can effectively locate germs, virus and bacteria the moment they enter body and destroy them.
- Ashwagandha- It helps to decrease the stress level. Stress lowers immune response and make the body in the risk of viral infection.
- Ginger- It is ancient remedy for common cold and flu. It contains gingerol - an antioxidant that strengthen immunity. It is good in preventing respiratory tract infection.
- Turmeric- It contains curcumin (phytochemical) that helps in the removal of toxin from body and strengthen immunity to fight off germs and

Guidelines to Strengthen Immunity

Enhancing the body's natural defense system (immunity) plays an important and significant role in maintaining optimum health. Importance of immunity gained importance during the outbreak of the global pandemic of COVID-19 in recent times. Various authorities and ministry of AYUSH recommended self-care guidelines for preventive health measures and boosting immunity.

The following measures are recommended by Ministry of AYUSH [9]:

- Daily yoga and meditation in the morning for half an hour is beneficial.
- Indian common spices like turmeric powder, coriander powder and garlic cloves are suggested in cooking.
- Drink homemade herbal tea or decoction prepared using basil, cinnamon, dark pepper, dry ginger and raisins - a few times per day.

Recommended Lifestyle Interventions [10]:

Nutrition	▪ Fiber-rich, nutrient-dense, antioxidant-rich whole food plant foods such as green leafy vegetables (3-5 servings/day), fruits (2-4 servings/day), whole grains, legumes, nuts and seeds. ▪ Food enriched with healthy fatty acids in fish, meat and eggs needs be in daily diet. ▪ Limit salt consumption, soft drinks, or sodas. ▪ Junk foods, processed fast foods and unsaturated fats should be strictly avoided. ▪ Exercise regularly to maintain a healthy body weight.
Physical activity	▪ Engage in moderate-intens ity aerobic physical activity (eg, brisk walk) 30 min-1 hr/day or 150-300 min per week, plus resistance exercise (eg, press-ups, situps, and weights) for 1 h, two to three times/week on non -consecutive days. ▪ Exercise caution with patients in moderate stage of COVID-19 who may be breathless on exertion.
Sleep	▪ Improving sleep hygiene, aiming for 7-8 hours uninterrupted, restorative sleep every night
Harmful substances	▪ Avoid alcohol intake and smoking in a daily basis. This can damage the lungs.
Stress management	▪ Adopt a variety of measures to keep stress levels low, including favourite music, videos, and movies. ▪ Conversation with friends and family about life event should be shared to avoid anxiety, depression and mental health issues. ▪ Use reliable sou rces, such as the World Health Organisation. Minimize anxiety by limiting news, current affairs, and stressful drama. ▪ Consider relaxation techniques such as deep breathing, meditation, Yoga, Tai Chi, and mindfulness, using apps or online resources.
Positive psychology	▪ Do activities and direct your thoughts to enhance well-being and create positive emotions, such as counting blessings, kindness practices, focusing on personal goals/strengths.

Nutritional Care: Integral Part of Rehabilitation

Immunological disorders in critically ill patients is a serious challenge in critical care management, as its incidence increases risk of other secondary infections in ICU patients, eventually which increases their length of stay in hospitals [11]. Patients with persistent critical illness have a high mortality and a high risk of long term morbidity. From this perspective developing a comprehension of the underlying immune response in persistent critical illness in its context is fundamental of improving the management of these patients and avoiding complications.

Proper nutritional value and addition to the diet gives an extra advantage of recovery and protection against diseases which further helps the body to fight against the viral and bacterial infections. The immunological regulation and functioning require nutritional support post illness for recovery with vitamins, micronutrients playing the vital role. The roles of important vitamins and minerals are discussed as follows:

- **Vitamin C**- An essential micronutrient for humans, vitamin C contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. It supports the epithelial skin barrier function against foreign bodies harmful microorganisms and promotes antioxidant activity. Besides the antioxidant properties, it also aggregates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. It is likewise required for apoptosis and clearance of the spent neutrophils from sites of infection by macrophages, thereby decreasing necrosis/NETosis and potential tissue damage [12].
- **Vitamin D**- The vitamin exists in two forms, D2 (ergocalciferol) and D3 (cholecalciferol). The forms of vitamin D has number of effects on every cells of the the immune system. It is known to enhance innate cellular immunity through stimulation of expression of anti-microbial peptides [13]. Besides fighting directly against microbes, monocytes and other innate antigen presenting cells (APC), in particular dendritic

cells (DC), are important targets for the immune modulatory effects of vitamin D. Antigen presenting cells are in charge for the induction of the adaptive immune reaction as they present antigens to T and B cells and are capable of regulating them by either immunogenic signals such as cytokines and expression of co-stimulatory molecules [14].

- **Vitamin B**- The various forms of vitamin B participates in playing a vital role in cell functioning, energy metabolism, and proper immune function [15]. Vitamin B helps in activating the process of the innate and adaptive immune responses, leading to reduction in pro-inflammatory cytokine levels. This results in improving lung functioning, endothelial integrity, prevents hyper coagulation and further helps in reduction of the length of stay in hospital [16]. Vitamin B exhibit in different forms as Vitamin B1 (Thiamine), Vitamin B2 (Riboflavin), Vitamin B3 (Nicotinamide, Niacin), Vitamin B5 (Pantothenic acid), Vitamin B6 (Pyridoxine), Vitamin B9 (folic acid, folate) and Vitamin B12 (cobalamine) with different properties in maintaining the immune system; like, Folate is an essential vitamin for DNA and protein synthesis and in the adaptive immune response. Vitamin B12 or cobalamin is essential for red blood cell synthesis, nervous system health, myelin synthesis, cellular growth and the rapid synthesis of DNA [17].
- **Vitamin E**- A potent lipid-soluble antioxidant, found in higher concentration in immune cells compared to other cells in blood, is one of the most effective nutrients known to modulate immune function. The importance has been observed in studies showing a reduction in inflammatory cytokines and improvement in T cell proliferation with vitamin E supplementation [18]. It prevents lipid peroxidation and the associated cell membrane damage. It may assist in the maintenance of membrane integrity, maintain signal transduction and production of key proteins and other mediators. Also directly affect the function of immune cells [19].
- **Vitamin A**- A popular and important micronutrient that is known for its potential benefits for maintaining vision, promoting growth and development, and protecting epithelium and mucus integrity in the body. It is known as an anti-inflammation vitamin because of its important role in enhancing immune function in the body. Vitamin A exists in the form of retinol, retinal, and retinoic acid, among which retinoic acid shows the most biological activity. Studies have shown that important organs of body need constant dietary intake of the vitamin, and retinoic acid was shown both to promote the proliferation and to regulate the apoptosis of thymocytes [20].
- **Zinc**- An essential mineral that the body doesn't produce on its own. Zinc is needed and crucial for many processes in the body like gene expressions, enzymatic reactions, immune cell functions, DNA and protein synthesis, wound healing and overall growth and development. It is necessary for cell signaling and a deficiency can lead to weakened immune response.
- **Selenium**- A trace mineral, that is having fundamental importance to human health. Selenium is a component of selenoproteins and enzymes which have antioxidant properties that help to dissociate peroxides, preventing inflammation and heart disorders. Supplementation with selenium has shown immunostimulant effects, including an enhancement of proliferation of activated T cells [21].
- **Iron & Copper**- Iron is an essential element for blood production. Its deficiency affects the capacity to have an adequate immune response. Iron is crucial for immune cells proliferation, especially lymphocytes, which is engaged in the generation of response against infection. Zinc and copper both are essential and the deficiency of either of them can increase the chances of bacterial infection. Copper is also responsible for production of red blood cells in association with zinc [22].

Case Study- Importance of Immunity Boosters During COVID-19 Outbreak

Recently, the world has witnessed a global pandemic, Coronavirus outbreak caused by the SARS-CoV-2 virus, which has mutated to allow human-to-human spread. When there was no approved vaccines and medicines for the viral infection, immunity played a vital role to save lives of people. Satisfactory levels of vitamins C, D and E are very important during coronavirus outbreak to diminish symptom burden and reduce the length of duration of respiratory infection. Research also supports a role for minerals such as zinc as they have antiviral effects and may improve immune responses and suppress viral replication [23]. The intake of adequate amounts of vitamins and minerals through diet is essential to ensure the proper functioning of the immune system. Fruits, vegetables, meat, fish, poultry and dairy products are good source of these vitamins and minerals. To support immune function during COVID-19 disease higher dietary intakes of vitamins D, C and E, zinc and omega-3 fatty acids was found to be beneficial.

Apart from the current pandemic, boosting immunity is also necessary for chronic illness like diabetes, bacterial infections, hepatitis etc. Strengthening the immune system is very crucial as it also maintains healthy gut with probiotics and helps in the fight against foreign bodies.

Conclusion

The current pandemic has given a clear message of the importance of immunity and its role in chronic diseases. It was observed that elder people, chronic disease patients and children were at more risk than younger individuals. As, elder people are immunocompromised and prone to infections, whereas the population is affected by malnutrition. Unhealthiness builds grimness, mortality, and causes critical financial effect on the medical services frameworks, while the monetary circumstance of a nation impacts all parts of ideal nourishment care. The expanded danger of dismalness and mortality brought about by hunger is an aftereffect of the expanded pace of contaminations, just as by postponed recuperation. A daily intake of healthy diet is much necessary and need of the hour. In present times, with the fast paced life and fast processed food with limited nutritional values are affecting our nutritional intake, and further affecting our health and immune system, that is causing infections and serious health issues. Recommended nutraceutical and immunity booster supplements in every prescription prescribed to a patient will give an added advantage of making a strong immune system and which will further help in the long run to fight against serious infections and also maintain the daily intake of essential vitamins, minerals and all important nutrients to be a part of daily diet. An immunity booster daily can change the whole scenario of the healthcare system by reducing mortality rate, hospital stay and be prepared in the near future. This initiative will change major concerns like malnutrition, compromised immunity, chronic diseases etc. in the long run.

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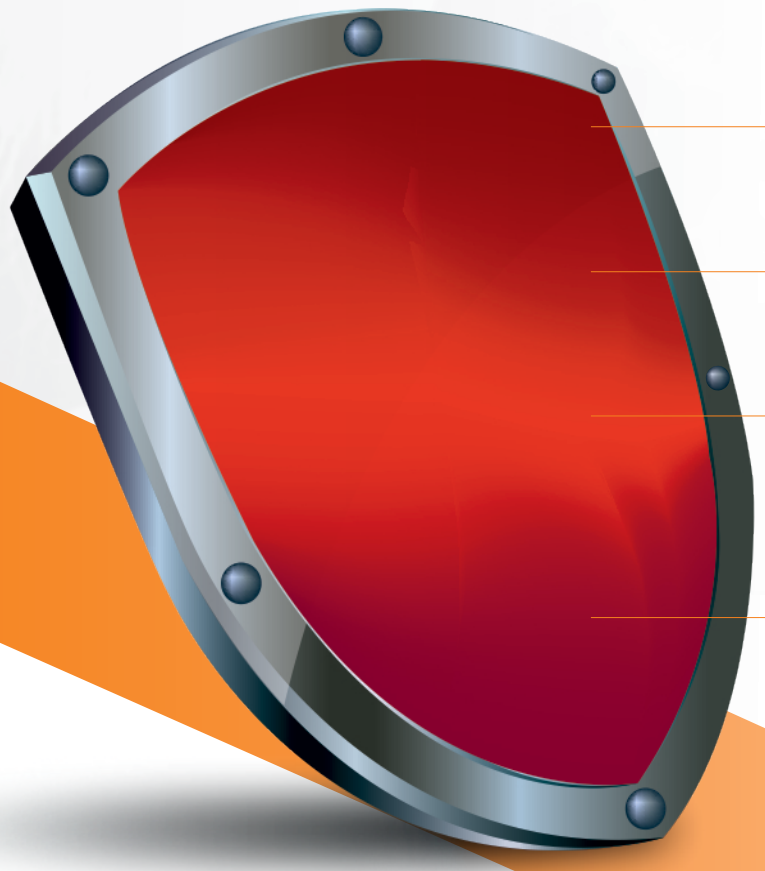
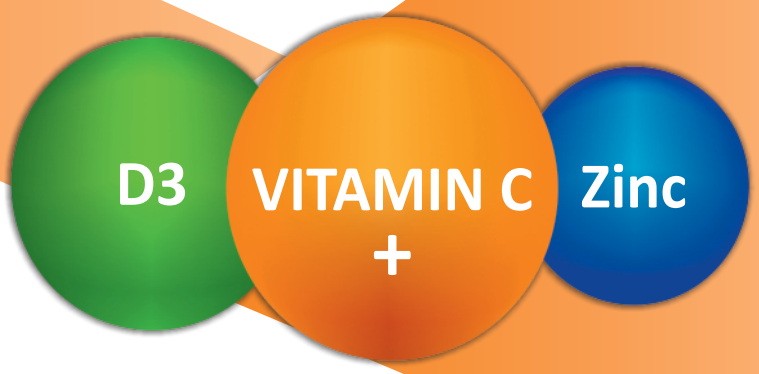
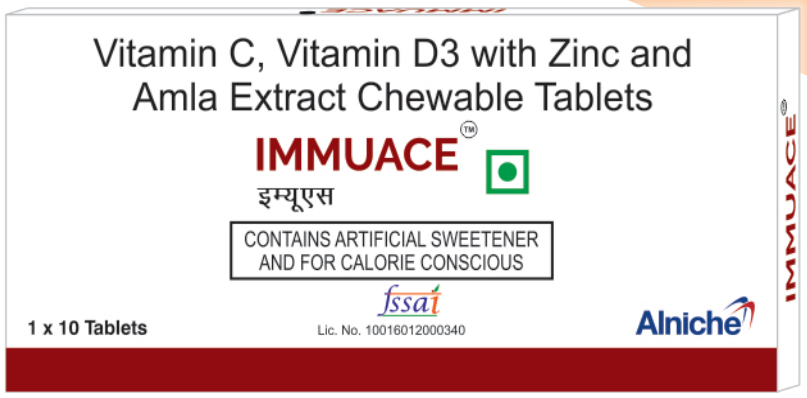


- **Encourages the WBC production[1]**
- **Fights off viral infections, cold & flu[2]**
- **Proper functioning of the immune system**
- **Enhances the absorption of calcium & phosphorus**





Dosage :

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What Does Patient Want Now: Are Their Preference and Requirement Changing?

Abstract

The novel Coronavirus Disease 2019 (COVID-19) has affected the healthcare systems badly and put a massive challenge across the globe. The traditional healthcare system did not imagine the severity and intensity of the COVID-19 pandemic, which dented the economy, personal health, and human lives. The healthcare systems require the massive updates in terms of functionality and management of the pandemic. At the one side, they need to restructure the operations and on the other hand, they are required to win the trust of the patients again while fighting the pandemic simultaneously. The patient preference has changed due to pandemic and they are seeking the ways to interact with their healthcare providers in a safe environment and are avoiding the physical visits. Patients in very urgent situations only prefer the physical visits. The technology-driven and forward-looking digital healthcare system in compliance with government regulations are the need of the hour. The proper and smooth virtual customer interactions, development of the digital platforms for patients, deeper patient-doctor communication through audio-video interaction, machine learning, use of artificial intelligence to drive research, and secure database systems to preserve medical data are the key steps which could lay foundation of the new and improved healthcare system. The requirement is necessary for physical as well as for mental healthcare management. Not only the changes in healthcare systems, the need also implies enhancing the regulatory framework as well as more healthcare services may shifts from hospitals to out-of-hospital care and homecare settings. This improvement will pave the way for rapid crisis management capabilities of the healthcare system..

Keywords: *COVID-19, Healthcare System, Patient Preference, Artificial Intelligence in Healthcare System, Telemedicine*

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Introduction

The first case of novel Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), was reported in Wuhan, China, in December 2019. Till then, a total of 120 million cases were recorded globally, with 2.65 million death so far [1,2,3]. The actual number of deaths due to COVID-19 may be likely to be higher than the number of confirmed deaths, which could be due to limited testing and problems associated with the attribution of the cause of death [3]. The entire world faced the lockdown and disconnected from each other, with merely virtually connected. The common public and the healthcare professional, including doctors, nursing, and paramedical staff, lost their lives, saving the patient's life and fighting against the pandemic.

India was no behind the rest of the world [4]. The virus and virus attack spared no country keeps spreading with new changing strains challenging the healthcare workers worldwide. Healthcare professionals face the unprecedented situation of making difficult decisions and working under extreme pressures to fight against the pandemic. In the beginning, many healthcare systems, unaware of the pandemic and limited information about the intensity of COVID-19, had confusion in efforts to fight against the pandemic that led to controversial decisions about the resources, testing, and treatment [5]. It revealed the deep underlying healthcare problems in systems worldwide and point out the lack of preparedness of healthcare systems in pandemics.

However, the situation is improving somewhat, but it had already made a big dent in terms of the economy, health, and humanity. The COVID-19 pandemic will end eventually, with the availability of vaccines now, but the reason for the end, its timing is not precise yet. It gives rise to the discussion of managing the healthcare services post-pandemic. The present article focuses on the patients' expectations and preferences along with the requirements of healthcare systems after pandemics and how the healthcare system can evolve to match those expectations of the patients.

Attacks on Healthcare System

As per the WHO report, there were different types of attacks on healthcare related to COVID-19 with varied contexts that ranged from heavy weapons targeting health facilities to the stigmatization of health care workers [6]. This has a negative impact on the healthcare industries and the challenges were increased. Either in the form of cyber-attack or as the physical assault, they imposter risks to the patients who need care urgently and challenges to healthcare providers, thus undermining the healthcare system as described in the below infographic (figure 1):

Patients' Expectations from Healthcare Providers

There is a level of trust deficit among patients, which has changed their behavior. They do not trust the media and other information, which they hear from different sources. They want accurate information about the things they want to know from their healthcare providers. The patients expect the environment to feel safe with maintaining social distancing and get the right information for their queries. Mental health, along with physical health, becomes utmost importance to patients. COVID-19 has affected mental health as well due to job losses and emotional strains, and the patients with chronic diseases have been affected badly. Social distancing, virtual visits, and teleconsultations are new normal for the patients. Most of the patients are avoiding visiting hospitals and would like to do that only in emergencies only. Physical appointments and follow-up visits have decreased, and patients prefer virtual visits. Suppose it is necessary to visit the hospital. In that case, they expect social distancing in the waiting room, seeing healthcare providers wearing masks and gloves,

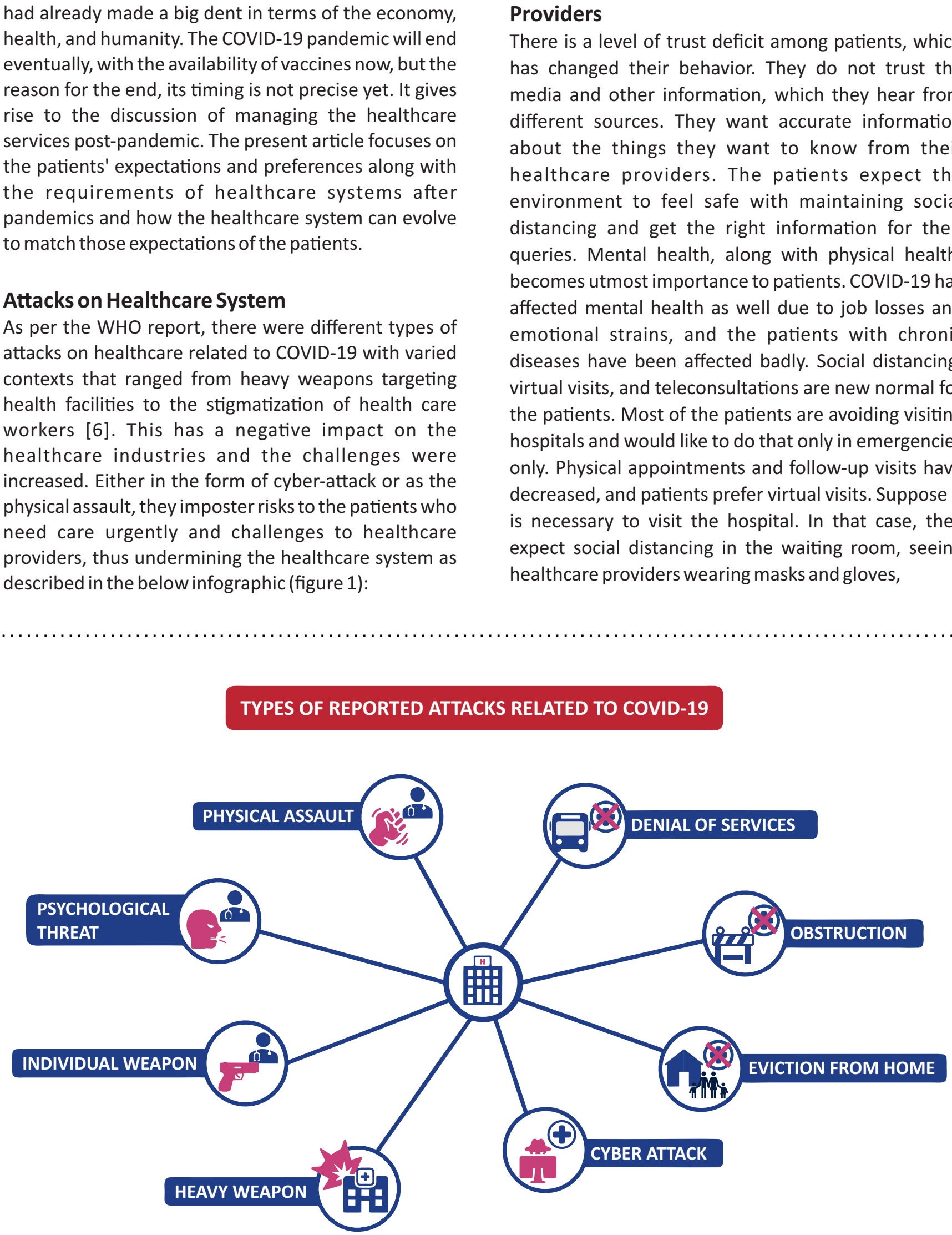

Figure 1 : Attacks on health care in the context of COVID-19 [Source: WHO]

keeping COVID-19 patients in a completely separate area from non-COVID-19 patients, waiting in the car or outside until it's time for the appointment, avoid touching to humans and things in hospitals and to come out from hospital as soon as possible. The patient expects a redesign of their care management and wants a calm and proactive approach from their healthcare providers.

As per one study from Accenture, the majority of patients have shifted to virtual care. Virtual tools are acting as an essential lifeline for continuing care. The patients had a highly positive experience using the video calls, monitoring devices and virtual platforms and wanted to continue that after the pandemic [7]. As per Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey, the key important themes for the patient's included [8]:

- Hospital environment, cleanliness, hospital policies, procedures, and its impact on patients' perceived autonomy
- Complete patient care
- Communication with and between healthcare teams and use of terms in layman language that patients can understand easily
- Responsiveness and attentiveness to needs

The patient expectations and satisfaction was studied in 4 Australian hospitals and concluded that besides the above mentioned factors, a proper and clear communication at arrival and discharge from hospital, environmental factors such as room sharing with other patients, and enhanced follow-up at homecare were most important for patients [9].

Virtual care seems to stay for a long time as an adaptation in patient behavior and can be an integral part of the patient experience. Many virtual platforms have evolved and developed interfaces to provide healthcare services to the patients seeing these patients' altered behavior. Many healthcare prominent names have also started digital outpatient departments to provide care to the patients, which does not require physical presence or visits to the hospitals. The evolving trends can be a game-changer for the healthcare industry in the long run.

Post-COVID Changes in Healthcare Delivery System

Due to the pandemic, the entire healthcare system stretched, and the pandemic's rapid spread globally brings hospitals/healthcare facilities to exhaustion. The healthcare professionals continue to risking their lives and fighting against the pandemic to deliver critical services. Plato said the "necessity is the mother of invention," but the "disruption" is the accelerator of change in the current scenario. Though it is challenging, we need to find some of the positive elements from the severe pandemic and its impact on improving healthcare systems. Due to lockdown, we, the people, adopted new habits of doing social distancing, work from home, tele/video conferencing. The changes were also adopted to how the patients interacted with the healthcare systems and their caregivers.

The healthcare professional working in COVID-19 dedicated wards, even those who belong to other specialties like dentistry, dermatology, ophthalmology, neurology, orthrology, neurology, etc. also facing major challenges to run their private practices. This has already affected the healthcare systems, and the healthcare sector may observe many changes, which could include:

- Less physical visits/no-long queues
- High-rise in insurance
- Importance to the timing of consultation/
- appointment
- New infrastructure and technology implementation in clinics
- Increase in online visibility
- Change in a doctor-patient relationship
- Change in the healthcare process
- Window-shopping

To enhance the preparedness for crisis management in healthcare systems, integrating technology and process will play a significant role. The approach to "think different" is the key. Virtual health offerings are the way to create competitive advantages in healthcare systems.

As per the report from Mckinsey [10] and an article from the JAMA network [11], the key shifts across the healthcare systems may involve the following approach which patient will like and the need of the hour to face the challenges:

- New paradigms for infrastructure, the geographic distribution of providers, and care settings of flexible design, enabling the construction of Greenfield facilities, and customized approach for faster re-purposing of beds
  - Separating the specialty-wise treatment and delivery of elective care in dedicated specialty facilities to relieve the already strained ICUs
  - Acceleration of the online-offline integration (enhanced use of telehealth system) so that non-critical cases could be tackle without a visit to health facilities

- Separation of ancillary functions, such as imaging and lab tests, from core hospital operations to minimize the associated risks
- Accelerated transition to ambulatory care and day surgery to avoid the long stay in hospitals and healthcare facilities

■ Operational excellence, which will be critical in the next normal
- Prolonged revenue growth challenges may remain due to the slow economic recovery
- The new set of costs challenging the margins due to the increased labor costs among the healthcare workers, especially for trained resources and critical care segments

■ Emergence of new growth opportunities and diversification
- New growth opportunities such as telehealth consultations, home healthcare services, primary care that do not require an emergency visit, and proactive health screening
- Innovative arrangements between the private and the public sectors to manage the healthcare needs and crisis management
- Consolidation of smaller providers, which the big players could acquire to cope with the expected financial stress

Apart from the above-mentioned pragmatic shifts, certain parameters should be adjusted until the situation becomes normal. These enablers include "technological advancements" (artificial-intelligence [AI]-based diagnosis, could-based medical records and database storage, digital platforms to enhance remote communication, use of home-based monitoring devices), "flexibility in insurance and reimbursement" (regulations for insurance to involve telehealth and home healthcare services), "patient awareness" (more awareness to patients who expect a seamless technology-driven experience, virtual platforms, medications, homecare, healthcare deliveries at home-setting), and "regulatory changes" (government regulations for healthcare systems, resources, licensing, broader set of skills, specialty versus multi-purpose beds etc.).

Technology is the significant parameter to integrate all the enablers mentioned above and enhance the healthcare systems. The digital development of platforms will provide new kinds of interaction and behavioral changes among the patients, ultimately altering the relationship between patients and doctors. Telemedicine will provide a new way for healthcare systems, and the market is estimated to grow by 2024. The use of AI, remote monitoring, and the development and use of homecare monitoring devices will play a significant role in the new robust systems, which will pave the way for a technology-driven healthcare system.

Along with technology, proper resourcing of the healthcare professionals is a major concern due to exhaustion and long working hours in a high-pressure work environment due to COVID-19, and they are the frontline warriors risking their lives. Apart from the physical health, mental health has also emerged as an important factor, which needs to be taken care of. Due to emotional strains, job losses, low confidence, increased cases of depressions; patients are also seeking mental healthcare providers. The healthcare systems are also adopting the tele psychologist's approach to counsel the patients that need mental support, and tele counseling enables a great virtual platform for the patients. However, the need of the hour is also the appropriately trained staff, especially from mental healthcare management perspectives, as there is a lack of well-trained psychologists.

Conclusion:

We have the opportunity to reform the healthcare system and adopt the new advancements. There is a lot of pressure and stress on the present healthcare system, healthcare workers, and facilities since the last few months, taking a toll on the workers' physical and mental health. It is necessary to look beyond the traditional healthcare system to adopt a technology-driven and forward-looking digital healthcare system in compliance with government regulations. The enhanced customer interactions and improved efficiency through bots, digital platforms for patients, deeper patient-doctor communication through audio-video interaction, machine learning, use of artificial intelligence to drive research, and secure database systems to preserve medical data are the key steps which could lay foundation of the new improved healthcare system this need to be implemented for physical as well as for mental healthcare management. Along with the changes in healthcare systems, the need also implies enhancing the regulatory framework as more healthcare services may shifts from hospitals to out-of-hospital and homecare settings. This improvement will pave the way for rapid crisis management capabilities to face challenges related to COVID 19 and show the path to preparedness for crises.

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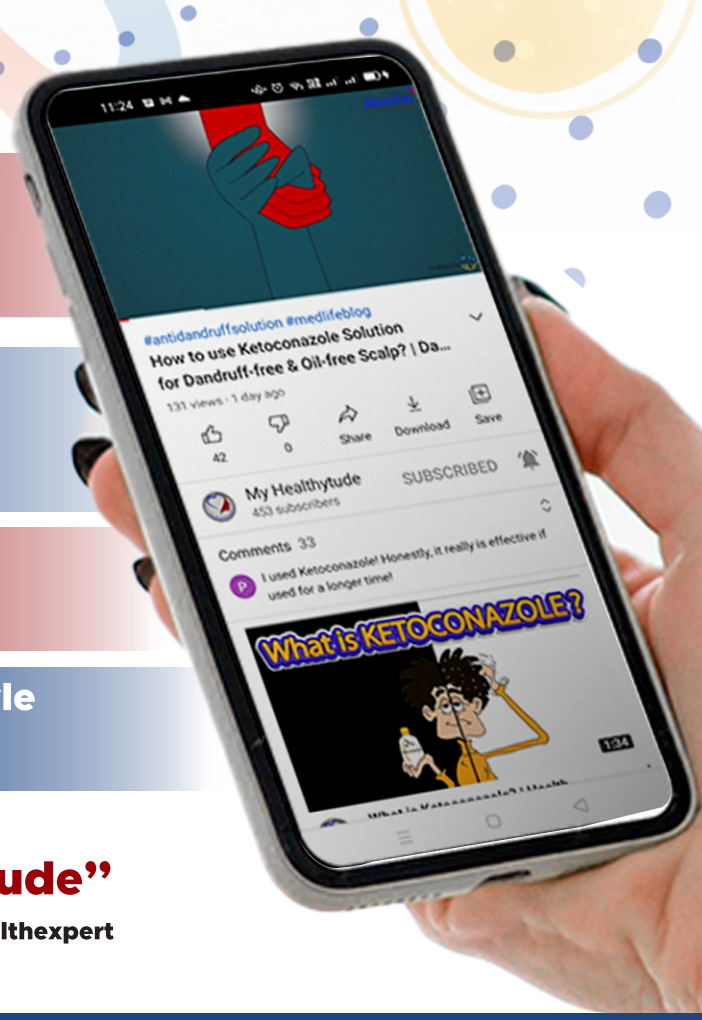

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Zerofos-DS: Reducing the Pill Burden in CKD Patients Suffering from Hyperphosphatemia

Abstract

Hyperphosphatemia is an electrolyte disorder where serum phosphorus levels get elevated caused due to chronic kidney disease, hypoparathyroidism, metabolic or respiratory acidosis, Excessive phosphate load, pseudo hypoparathyroidism or transcellular shifting. The most common cause of hyperphosphatemia is chronic kidney disease (CKD) as it is very prevalent in patients with CKD. CKD patients with hyperphosphatemia have to take multiple number of pills due to multiple associated comorbidities which consequently cause poor adherence to therapy. The high pill burden is associated with the non-adherence to therapy and poor treatment outcomes. In patient with chronic diseases, non-adherence to medications is quite common, and it may be seen in almost over 50% of the patients.

There are different types of phosphate binders available which reduce the serum phosphorus levels but these phosphate binders contribute to the highest number of pills taken by patient among all the therapies. The central problem associated with the phosphate binder treatment is the insufficient patient adherence caused by usually high pill burden and ensuing gastrointestinal adverse events. The measure to reduce pill burden and increase adherence to therapy is to decrease the number of pills. Zerofos-DS (by Alniche Life Sciences) is a double strength medicine 1st time in India which offers effective treatment to hyperphosphatemia in half the number of pills as compared to conventional phosphate binders. In conclusion, Zerofos-DS is an advanced approach to treat hyperphosphatemia as well as to increase the patient adherence to therapy by reducing the pill burden.

Keywords: *Hyperphosphatemia, Chronic Kidney Disease, Phosphate binders, Serum phosphorus, Pill burden, Non-adherence, Zerofos-DS*

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Introduction

Inorganic phosphorus is an intracellular anion that plays an important role in energy production, functioning of cells, signal transduction, and membrane transport.

Hyperphosphatemia - is an electrolyte disorder where there is an elevated level of phosphate in the blood or when there is too much phosphate in your blood[1]. It is a common complication in CKD (Chronic kidney disease) patients, particularly in those patients who requires therapy for renal replacement. Most people have no symptoms while others develop calcium deposits in the soft tissue. Often there is also low calcium levels which can result in muscle spasms.[1]

Causes of Hyperphosphatemia include:

- Chronic kidney disease
- Hypoparathyroidism
- Metabolic or Respiratory acidosis

Chronic Kidney Disease is the major cause for hyperphosphatemia as function of phosphorus homeostasis is lost in this condition in last stages.

The pool size for phosphorus exchange is decreased by the kidney disease by inhibiting the bone formation [2]. With the progression of chronic kidney disease (CKD), bone and mineral metabolism becomes dysregulated and to maintain normal phosphorus and calcium levels increasing levels of parathyroid hormone serve as an adaptive response. This response becomes maladaptive and high level of phosphorus may occur [3]. The consequences of hyperphosphatemia can be numerous, uremic bone disease, development of secondary hyperparathyroidism, and the promotion of vascular and visceral calcifications (figure 1).

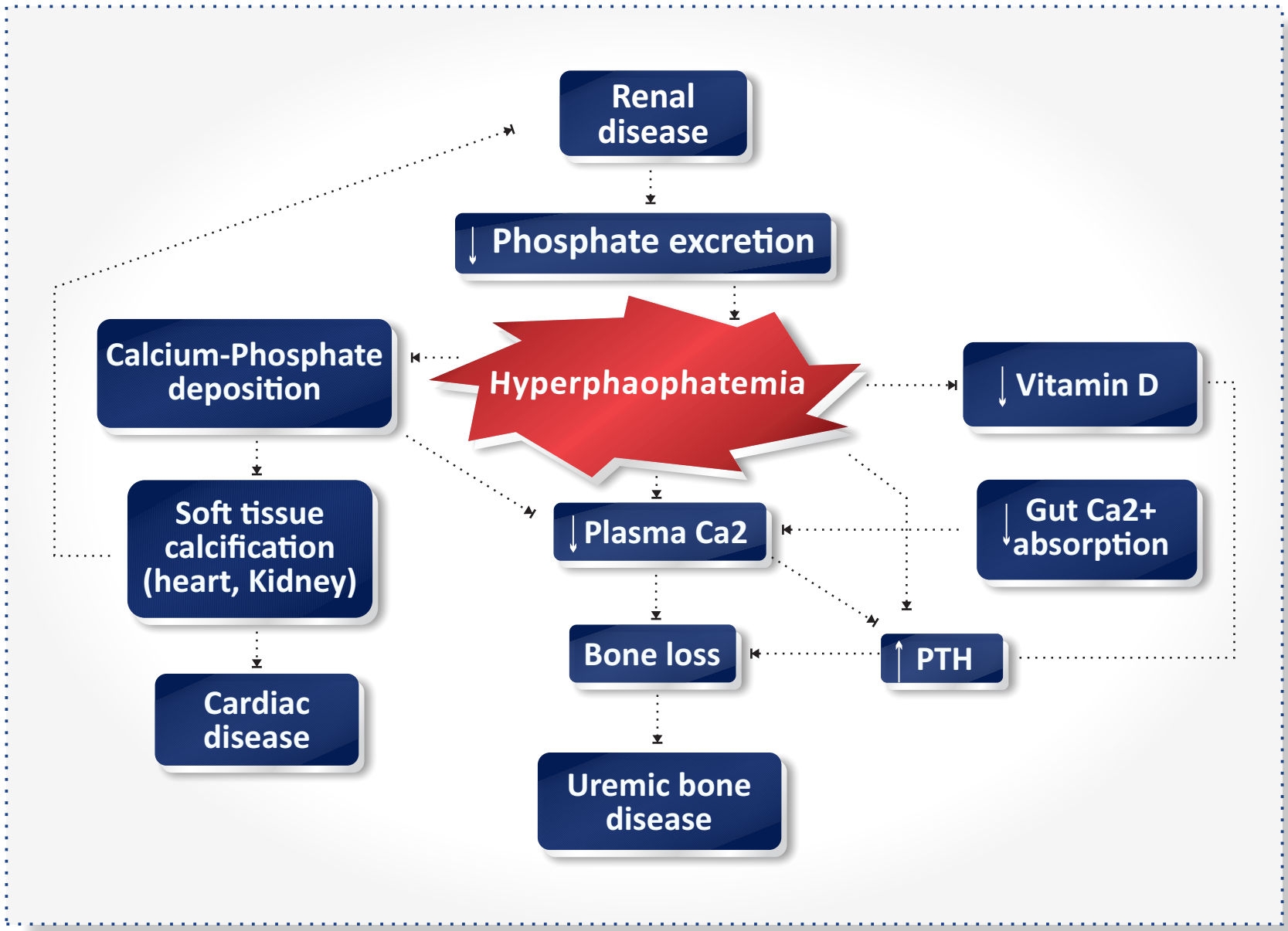

Figure 1: Development and consequences of hyperphosphatemia in Chronic Renal Disease

The association between increased risk of death from cardiovascular disease/vascular calcification and hyperphosphatemia has been well established for a long time

The serum phosphorus has now consistently been shown to be an independent predictor of the risk for death. [4]

Etiology

The most common cause of Hyperphosphatemia is renal failure. The filtration of inorganic phosphate is reduced significantly by glomerular filtration rate of less than 30 mL/min, increasing serum phosphorus levels. Some other less common cause of Hyperphosphatemia includes increased renal reabsorption or high intake of phosphorus.

Excessive use of phosphate-containing laxatives or enemas, and vitamin D intoxication can cause high intake of phosphate. Vitamin D increases intestinal phosphate absorption. Renal phosphate reabsorption is enhanced by hypoparathyroidism, acromegaly and thyrotoxicosis resulting in hyperphosphatemia. Hyperphosphatemia can also be due to genetic causes as several genetic deficiencies can lead to decreased FGF-23 activity, hypoparathyroidism and pseudo hypoparathyroidism.

Epidemiology

Hyperphosphatemia is a prevalent condition in kidney patients and a common laboratory abnormality encountered by nephrologists. The prevalence of hyperphosphatemia is 50 to 74% in patients with end-stage renal disease (ESRD) [5].

After excluding patients with end-stage renal disease (ESRD), with acute kidney injury (AKI) or whose phosphate did not get measured at admission, David E. Leaf and Myles Wolf found that 12% of all patients at admission to a tertiary care hospital, had incidence of hyperphosphatemia [6].

Pathophysiology

Hyperphosphatemia, in general, can be caused due to Decreased renal excretion, Excessive phosphate load, Hypoparathyroidism and pseudo hypoparathyroidism or Transcellular shifting

1. Decreased renal excretion - The 90% of the daily phosphate load in the body gets excreted by kidneys, and when renal function becomes diminished it causes decreased secretion and increased retention of phosphate

2. Excessive phosphate load - As phosphate is the major intracellular anion in human body, the massive tissue breakdown due to any cause can result into the release of intracellular phosphate into extracellular fluid. The cause for massive tissue breakdown can be severe hemolysis, tumor lysis syndrome, or rhabdomyolysis
3. Hypoparathyroidism – Hypoparathyroidism is a rare disease that results in hypocalcemia. The most possible common cause is the injury or dysfunction of the parathyroid gland, removal of the parathyroid gland during anterior neck surgery. Symptoms include muscle cramps, seizures, paresthesia and laryngospasm

   Pseudo hypoparathyroidism – It is a condition which is characterized by a resistance to PTH at its receptor. The indications for pseudo hypoparathyroidism include high serum phosphate, low serum calcium and inappropriately high PTH levels
4. Transcellular shift - Diabetic ketoacidosis and lactic acidosis can rarely cause phosphate massive cellular shifts out of the cells.

Pill Burden in CKD Patients and Quality of life

Due to complex chronic illness and multiple associated comorbidities, kidney patients have a high pill burden. One study found MHD patients had a median PB of 19 pills/day [7]. Phosphate binders accounted for 49 ± 19%, and were the single largest contributor, of the total pill burden (figure 2) [7]. Complex medication regime has been shown to impair adherence in chronic conditions. Impaired and poor adherence are cause of increased healthcare costs, poor quality of life and mortality also. Increasing adherence to medication regimens is important to achieve treatment outcomes [8]. In patient with chronic diseases, non-adherence to medications is quite common, and it may be seen in almost over 50% of the patients [9]. Together with managing the comorbidities and complications, the major goal of treatment in CKD is slowing the rate of progression of disease. Poor adherence or non-adherence to medication is potentially harmful and can result into increased cost of treatment over long term. According to some studies, it is shown that non-adherence in CKD caused increase in expense of medications and hospitalizations, uncontrolled hypertension and more frequent dialysis [10]. Thus, the beneficial effects of drugs is reduced by non-adherence and can eventually lead to CKD progression and occurrence of ESRD (End stage renal disease). Worldwide, the variation of adherence to medication in CKD patients have been reported between 3% to 83% [11]. The major predictors for the poor adherence or non-adherence to medication includes high pill burden, high cost, forgetfulness, not feeling well, complex dosing schedule, poor knowledge of disease/treatment, adverse effects, and taking alternative medicine among others. Therefore, adherence to medications in CKD patients remains a major concern to therapy.

Dialysis patients, are prescribed many medications and poor health-related quality of life (HR-QOL) because of a very high burden of co-existing diseases. It is reported that, in dialysis population the daily pill burden is one of the highest as compared to any other chronic disease like diabetes mellitus and congestive heart failure [12] [13] [14].

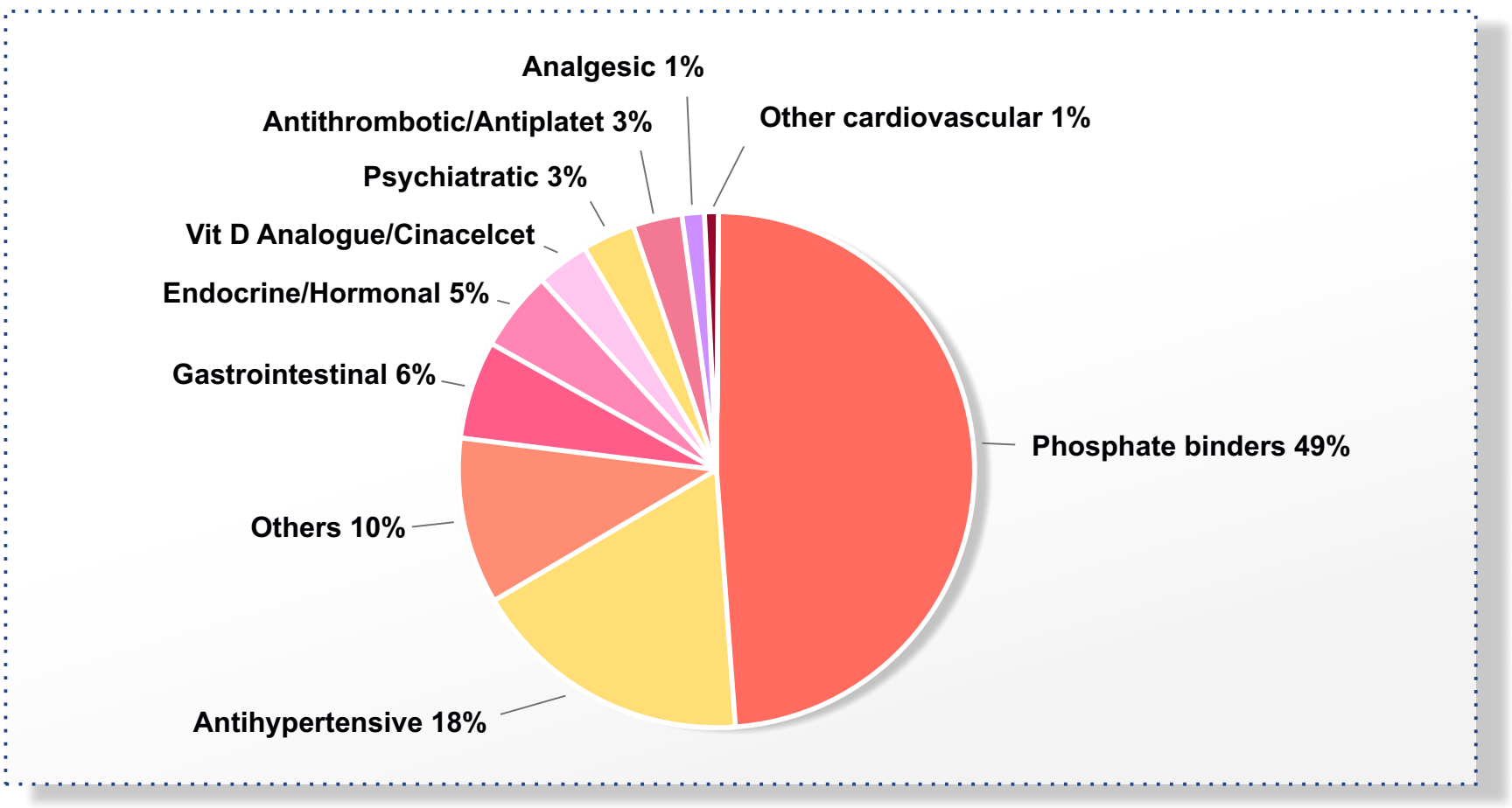

Figure 2: Percentage of pill burden from different classes of medications

For uncontrolled serum phosphorus levels there are many reasons; increasing the number of prescribed pill does not seem to improve control and it may also come at the cost of poorer HR-QOL (Health related – quality of life) [15].

Serum phosphorus control may be complicated by pill burden non-adherence [16, 17]. On an average, over 50% of the dialysis patients are not adherent to their PB regimes, but depending on the patient measurement method and patient population this level ranges from 21 to 74% [18, 19]. Pill burden affects the adherence of patients and often pose a large pill burden which is associated with lower health-related quality of life.

So, there is a direct relation between medication adherence and burden, and health-related quality of life (HRQOL) in predialysis chronic disease (CKD). There was a significant association between the maintenance of polypharmacy over time, the prevalence of polypharmacy and increasing CKD stage, age, BMI, diabetes mellitus, cardiovascular disease and a history of smoking. Comorbid diabetes mellitus was a significant risk factor for the initiation of polypharmacy in CKD patients.

Pill Burden by Current Phosphate Binders and their Limitations

There are different kind of phosphate binders available like Calcium acetate, Sevelamer hydrochloride, Sucroferric oxyhydroxide, lanthanum carbonate, Calcium carbonate and Calcium chloride. The mechanism of action of an effective phosphate binder is that they reduce the absorption of dietary phosphate in the gastrointestinal tract by exchange of the anion phosphate with an active cation (carbonate, acetate, oxyhydroxide, and citrate) to excrete them through feces by converting it into non-absorbable compound. In patients with end-stage renal disease, phosphate binders are widely used to achieve serum phosphorus control. Phosphate binders are probably the single largest contributor to the daily pill burden as suggested by clinical experiences. Also, prediction of risk of death has now also been consistently shown by the serum phosphorus levels independently. According to the current KDIGO clinical practice guideline, it recommends lowering elevated serum phosphorus levels toward the normal range in patients with ESRD on dialysis through restriction of dietary phosphorus intake, increase in clearance by dialysis, and the use of phosphate-binding medications [4]. The high pill burden from phosphate binders may affect patient's ability to maintain serum phosphorus levels and adherence to the therapy [20].

The central problem associated with the phosphate binder treatment is the insufficient patient adherence caused by usually large pill size, high pill burden and ensuing gastrointestinal adverse events [21]. In a study, many patients were found to adhere completely to phosphate binder prescription even under supervised study conditions [22].

The major limitation of the current available phosphate binders is the pill burden they cause to the patient which contributes to the poor treatment outcomes, impaired health related – quality of life in maintenance dialysis patients. Thus, a high pill burden may be one of the factors that limit the ability to optimize serum phosphorus levels as it is likely that high pill burden and hyperphosphatemia is bidirectional. There are various sources through the phosphorus intake becomes high and different types of treatments are available for its cure but every treatment has its own limitation (fig. 3).

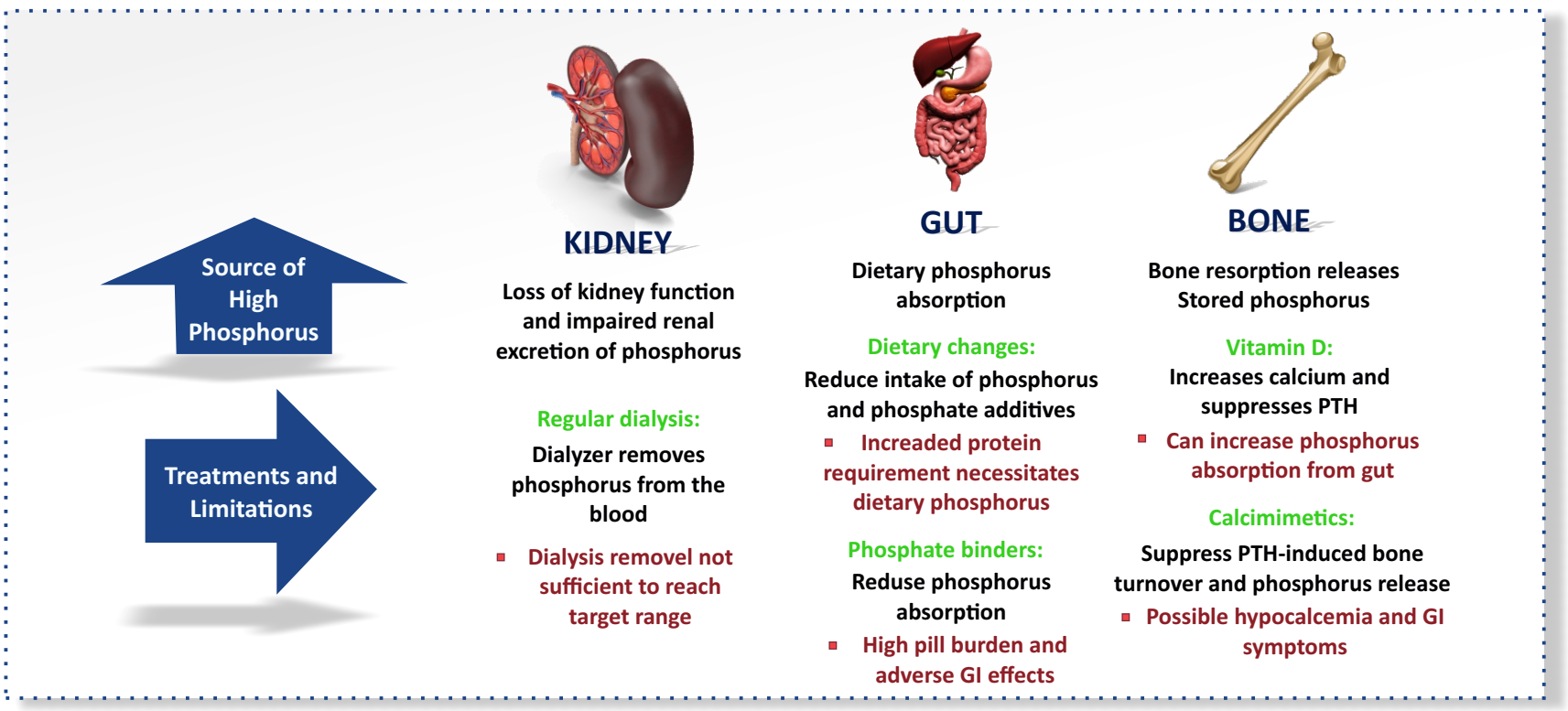

Figure 3: Sources of high phosphorus and their treatments and limitations

Measures to Reduce Pill Burden (Zerofos DS)

The oral phosphate binders are effective in decreasing serum phosphorus levels but when it comes to their pill burden these agents have high pill burden and low adherence rates. As reduced adherence to the prescribed phosphate binder therapy is associated with the increase in concentrations of serum phosphorus.

The double strength medicine can be an option when it comes to decrease the pill burden as if patient is taking 6 tablet per day then he/she will have to take the half tablets of double standard medicine i.e., 3 tablet which will reduce the pill burden of phosphate binders by 50%

Zerofos-DS (composed of Calcium acetate, by Alniche Life Sciences) is a first double strength medication in India, which comes in a form of 1334mg where the conventional Calcium Acetate tablet comes in 667mg. With the composition of two tablet in one.

It belongs to a class of medications called phosphate binders. The phosphate is retained by the people with advanced kidney failure, which leads to too much phosphate in their bodies (hyperphosphatemia). Hyperparathyroidism is caused by high phosphate levels, which leads to calcium deposits in tissue and abnormal bone formation. Zerofos-DS is a natural mineral that works by holding onto phosphate from the diet so that it can pass out of your body. In dialysis some phosphate is removed from blood, but to keep phosphate levels balanced it is difficult to remove enough phosphate. ZEROFOS-DS is used to prevent high blood phosphate levels in patients who are on dialysis due to severe kidney disease.

Calcium acetate is a first line treatment for hyperphosphatemia in patients with ESRD on maintenance dialysis as it more cost-effective when compared to other phosphate binders, has higher binding capacity and can effectively work in high pH.

Zerofos-DS is a very effective measure to reduce the pill burden in CKD patients as the patients normally taking 6 tablets when move to Zerofos-DS will now take 3 tablets reducing the pill burden of phosphate binders by 50%.

Mechanism of Action

ZEROFOS-DS (Calcium Acetate, by Alniche Life Sciences) belongs to a class of medications called phosphate binders. Zerofos-DS is a natural mineral that works by holding onto phosphate from the diet so that it can pass out of your body. Dialysis removes some phosphate from blood, but it is difficult to remove enough to keep phosphate levels balanced.

ZEROFOS-DS is used to prevent high blood phosphate levels in patients who are on dialysis due to severe kidney disease. It works by binding with the phosphate in the food patient eat, so that it is eliminated from the body without being absorbed. Binding phosphate in the intestines reduces absorption of phosphate into the body.

Salient Features

i. Zerofos-DS is used for reducing blood phosphate levels in people with end-stage kidney disease on dialysis who have high phosphate levels by binding with the phosphate in the food patient eat.
ii. Reduces pill burden for better patient compliance taking less number of tablets when compared to other drug class where patient have to take more number of tablets.
iii. Maintains serum phosphorus levels below 6.0mg/dl by binding with the excess amount of phosphate in the serum.
iv. Calcium acetate control mineral metabolism adequately by using half as much elemental calcium compared with calcium carbonate [23].
v. Effective and safe phosphate binder by lowering the incidence of adverse events [24].
vi. When calcium acetate is used, control of hyperphosphatemia can be achieved with a lower risk of hypercalcemia with considerably lower administration of calcium [25].

Conclusion

As we have discussed above, the CKD patients have to take number of pills due to multiple associated comorbidities and due to the high pill burden, they suffer from poor adherence to drug and therapy. Among all the pills CKD patients take, phosphate binders have highest number of pills hence have the higher pill burden. The measures for reducing pill burden is decrease the number of pills the patient is taking and Zerofos-DS (by Alniche Life Sciences) comes in double strength which offers composition of 2 tablets in one thus reduce the pill burden of phosphate binders by 50%. The combination of two conventional tablet of calcium acetate is provided in one tablet of Zerofos-DS. It is concluded that Zerofos-DS is an effective approach to reduce serum phosphorus levels with the benefit of low pill burden and better patient compliance.

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Brivaracetam: A 3rd Generation Anti-Epileptic with Higher Efficacy and Better Safety Profile

Abstract

Epilepsy is the 4th most common and disabling chronic neurological disorder affecting 65 million people globally. Yet we have an incomplete understanding of the detailed pathophysiology and treatment options available for epilepsy. This article provides an overview of seizures and epilepsy, epidemiological consideration, antiepileptic drugs classification, Brivaracetam and its comparative studies with Levetiracetam.

Keywords: *Seizure, Epilepsy, Brivaracetam, Levetiracetam, SV2A Receptor, Efficacy, Focal Seizures, Pharmacokinetics, Tolerability*

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Introduction

A "seizure" is defined as a sudden event causing alteration of neurological functions due to abnormal, excessive, hypersynchronous discharge from a group of CNS neurons in the brain.

"Epilepsy" is a chronic neurological disorder, defined as tendency to have recurrent and unprovoked seizures. However, a person is diagnosed with epilepsy if they have two or more unprovoked seizures, not caused by reversible medical conditions.

Epilepsy has numerous possible causes including an imbalance of neurotransmitters, tumors, strokes, and brain damage due to illness or injury and sometimes combination of these. In most of cases, there may be no cause for epilepsy.

A seizure provoked by a reversible medical condition (e.g., high fever, hypoglycemia, alcohol withdrawal) does not fall under the definition of epilepsy because it is a temporary secondary condition, not a chronic state. Hence, all seizures cannot be considered as epilepsy.

Epidemiological Consideration

Epilepsy is one of the most common neurological disorders, having an incidence of approximately 50 new cases per year per 100,000 populations. About 1% of the population suffers from epilepsy, and about one-third of patients have refractory or drug resistant epilepsy (i.e., seizures are uncontrolled even by two or more appropriately chosen antiepileptic medications).

Various studies estimated that the overall prevalence of epilepsy in India is 5.59-10 per 1000. [1-5]

Males are getting affected in more numbers by epilepsy was reported in a study conducted in India by Bharucha et al. [6] in which prevalence rate of males (5.1 per 1000) was recorded significantly higher than that in females (2.2 per 100).

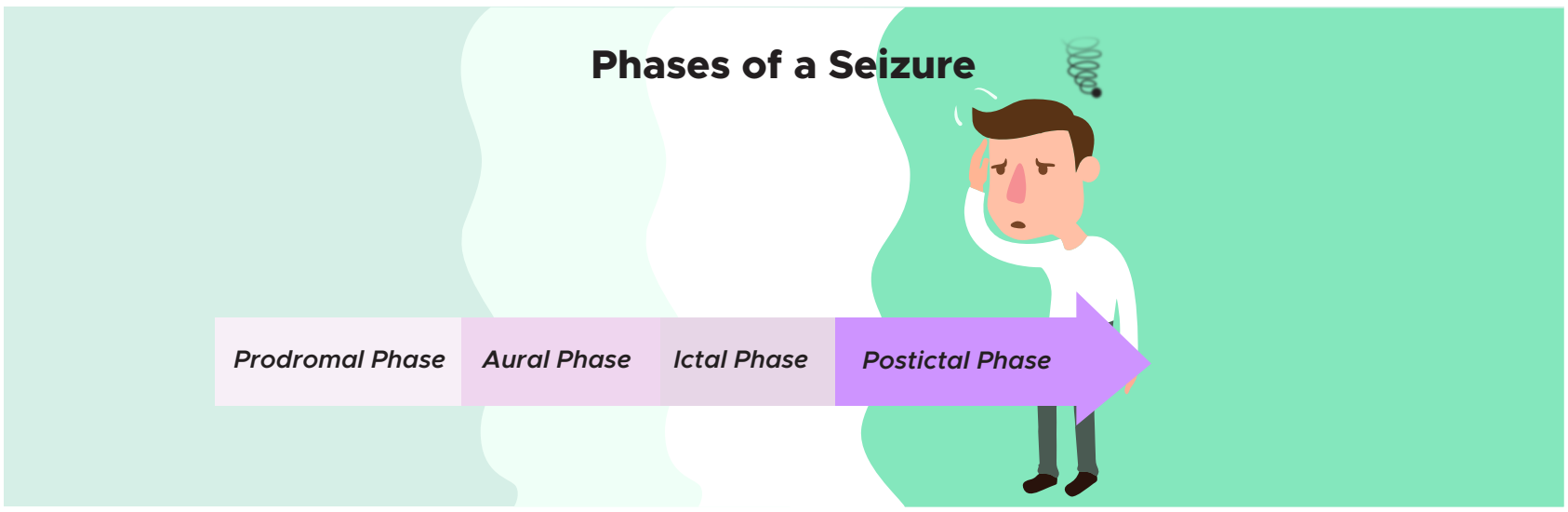

Figure 1: Different Phase of a Seizure

Approximately 75% of epileptic case starts during childhood, indicating the increased susceptibility of the developing brain to seizures.

Phases of Epilepsy

A seizure can be consisting of four different phases (figure 1): prodromal, early ictal (aura), ictal, and post-ictal. [7, 8]

1. **Prodromal:** The prodromal phase serves as a warning sign of seizure, but unlike aura phase prodromal phase is not a part of the seizure.

   About 20% of people with epilepsy experience a prodromal phase –an intuitive feeling or sensation that can occur several hours or even days before the actual seizure attack. Symptoms include confusion, discomfort, anxiety, irritability, headache, tremor, and anger or other mood swings.
2. **Aura:** For most of the epilepsy patients, the earliest sign of seizure activity is an aura. It acts as a warning or earliest sign of an on-coming seizure and the beginning of the ictal phase. The ictal phase includes the time between the starting (aura, if present) and the end of the seizure. Common symptoms include loss of vision or blurring, hallucinations, Deja vu (feeling of familiarity with a person, place, or thing without having experienced it), Jamais vu (feeling of unfamiliarity with a person, place, or thing despite having already experienced it), ringing sounds, strange offensive smells, bitter or acidic taste, nausea, numbness, tingling, dizziness, pain in head, arm & leg, subtle arm or leg jerking, strong feelings of joy, sadness, fear or anger.
3. **Ictal Phase:** The ictal phase express in different ways for different patient with epilepsy. They may experience a variety of symptoms, including but not limited to confusion, memory lapses,

   distractedness, sense of detachment, eye or head twitching movement in one direction, inability to move or speak, micturition or constipation, pale/flushed skin, hearing loss, strange sounds, vision loss, blurring vision, chewing or lip-smacking, unusual physical activity such as

   dressing/undressing, walking/running, pupil dilation, difficulty breathing, sweating, tremors, twitching, arm or leg stiffening, numbness etc.
4. **Post-Ictal Phase:** This is the recovery period after a seizure. Some people recover immediately, while others need sometime from minutes to days to become normal & feel like they're back at their control. Duration depends directly on the seizure type, severity, and region of the brain affected. Symptoms include drowsiness, confusion, memory loss, nausea, body pain, difficulty finding names or words, headaches/migraines, thirst, arm or leg weakness, low BP, feelings of fear, embarrassment, or sadness.

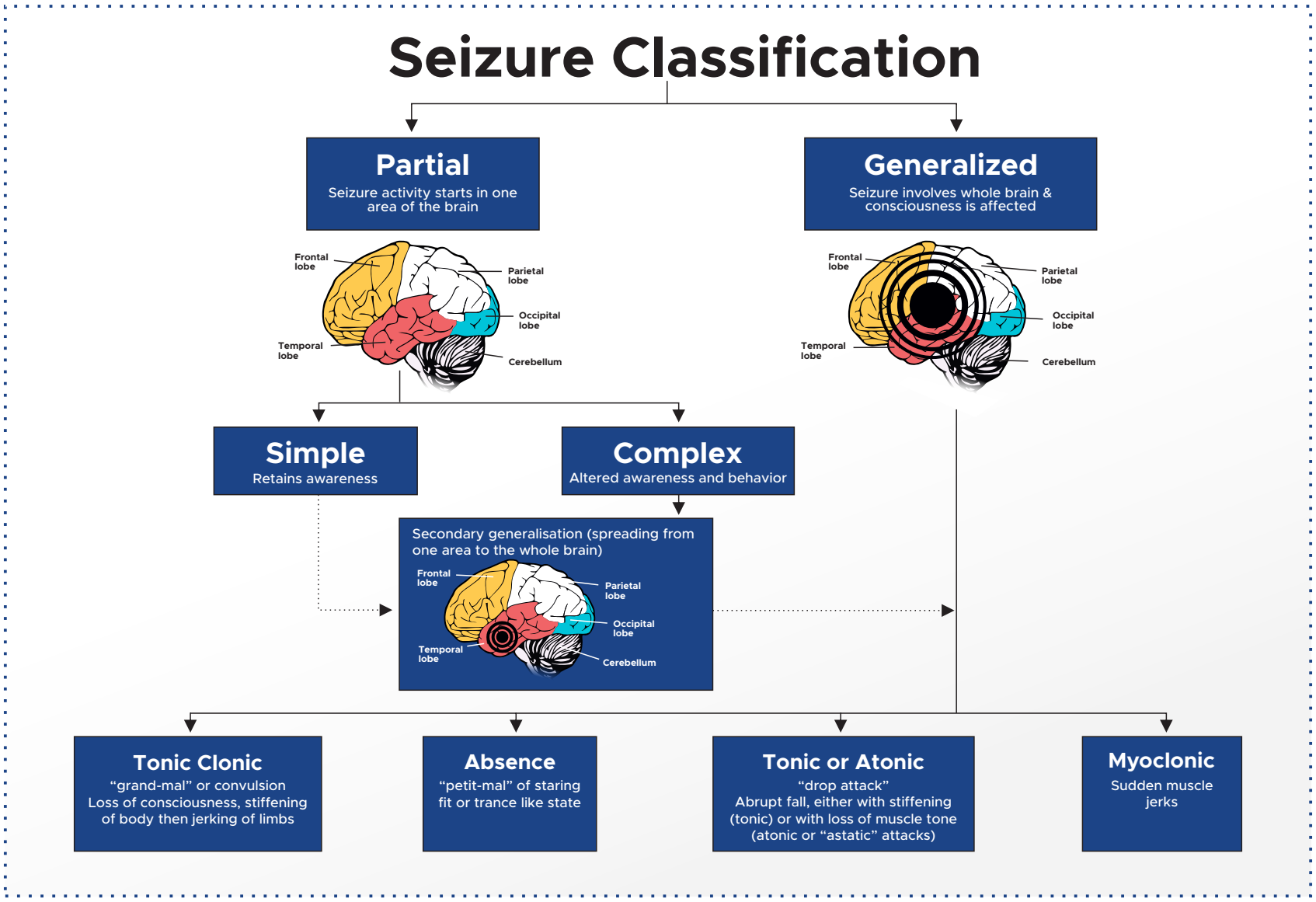

Figure 2: Classification of Seizures

Types of Epilepsy

Seizure type depends on the part of the brain involved and how much of the brain is affected. The two broad classes of epileptic seizures are partial (simple and complex) and generalized seizures. There are several different types of seizures, fall under these categories (figure 2):

1. **Focal or partial seizures:** In focal seizures abnormal electrical brain function occurs in limited area of the brain, particularly with complex focal seizures, patient may experience an aura before the seizure event. Focal seizures are of two types:

a. **Simple focal seizures:** Symptoms depends on the area of the brain involved. If occipital lobe (the back part of the brain that is involved with vision) is the region of the abnormal electrical brain function, sight may be altered, but more commonly affected part is muscles. The seizure is limited to an isolated muscle group, such as the fingers, or to larger muscles in the arms and legs. Patient is fully conscious in focal seizure and may also experience sweating, nausea, or become pale.

b. **Complex focal seizures:** Commonly occurs in the temporal lobe (the area of the brain that controls emotion and memory function) of the brain. Consciousness is usually lost during these seizures. Sometimes the patient stops being aware of the activity around him or her, may look awake, but may have a variety of unusual behaviors. These behaviors may be in the form of gagging, lip smacking, running, screaming, crying, and/or laughing. When the person recovers, he or she may complain of being tired or sleepy after the seizure.

2. **Generalized seizures:** It involves both sides of the brain. Consciousness is lost and experience a postictal state after the seizure occurs. Generalized seizures include the following types:

a. **Absence seizures:** Involve brief, lapses of consciousness and staring episodes. Signs include rapid eye blinking or twitching of mouth or face. Duration of the seizure is no longer than 30 seconds. Once the seizure is over the patient may not remembered what just occurred, acting as though nothing happened. Patient may have 100-200 episodes in a day. Absence seizures almost always start at the age of 4 to 12 years.

b. **Atonic seizures:** With atonic seizures, there is a sudden loss of muscle tone and the patient may fall from a standing position or suddenly drop his or her head. During the seizure, the person feels difficulty in walking and become unresponsive.

c. **Generalized tonic-clonic seizures:** This is the classic form of generalized seizure and is characterized by five distinct phases. The body will blend (contract), extend (straighten out), and tremor (shake), followed by a clonic phase (contraction and relaxation of the muscles) and the postictal period. Not all of these phases may be seen in every patient.

d. **Myoclonic seizures:** Involve quick movements or sudden jerking of a group of body muscles. These seizures may occur several times a day, or for several days in a row.

3. **Infantile spasms:** This is rare type of seizure disorder occurs in infants before six months of age. Mostly occur when the child is awakening, or when trying to go to sleep. The infant has temporary episodes of movement of the neck, trunk, or legs that lasts for a few seconds. Infant may have 100 of episodes a day. This may affect infant growth and development.

4. **Febrile seizures:** This is associated with high fever and is not epilepsy. These seizures are more commonly seen in children between six months and five years of age, and may have a family history. Febrile seizures that last for less than 15 minutes are called simple, and do not have long-term neurological effects. Duration of 15 minutes or more are called complex and there may be long-term neurological changes in the child.

Major Causes of Epilepsy

While the exact cause of the seizure may not be known, the most common are the following:

- In newborns and infants:
  - Birth trauma
  - Congenital problems
  - Fever or infection
  - Metabolic or chemical imbalances in the body
- In children, adolescents, and adults:
  - Alcohol or drugs
  - Head trauma
  - Infection
  - Congenital conditions
  - Genetic factors
  - Progressive brain disease
  - Alzheimer's disease
  - Stroke
  - Unknown reasons

Some other possible causes of seizures may include the following:

- Brain tumor
- Neurological problems
- Drug withdrawal
- Medications
- Use of illicit drugs

Symptoms of Epilepsy

The patient may have different degrees of symptoms depending on the type of seizure. The following are common symptoms of a seizure or warning signs of seizures:

- Jerking movements of the arms and legs
- Stiffening of the body
- Loss of consciousness
- Breathing problems or breathing stops
- Loss of bowel or bladder control
- Falling suddenly for no visible reason, especially when associated with loss of consciousness
- Not responding to surroundings
- Shaking the head rhythmically, when associated with loss of awareness or even loss of consciousness
- Periods of rapid eye blinking and staring
- The person's lips may become bluish and breathing may not be normal. The movements are often followed by a period of sleep or disturbed.

Antiepileptic Drugs

Antiepileptic drugs are classified as **first-generation (conventional), second-generation (newer)** and **third generation (newest) agents** as mentioned in Table 1. The choice of drug depends on the type of seizure.

Antiepileptic drugs inhibit neural activity either by decreasing ↓ neural excitation or increasing ↑ neural inhibition.

Brivaracetam (BRV)

Brivaracetam is a propyl analogue of levetiracetam and a 3rd generation antiepileptic racetam derivative which granted USFDA approval in February 2016 as add-on therapy for treating focal seizures (also known as partial onset seizure) in adults and adolescents 16 years of age or older with epilepsy. [11]

Mode of Action

The exact mode of action of brivaracetam is unknown; it binds to the human SV2A protein in the brain and reduces presynaptic neurotransmitter release. It has 15–30 fold higher and 20 times more selective binding affinity than levetiracetam. So, SV2A binding is believed to be the primary mechanism for brivaracetam anticonvulsant activity. [12]

Pharmacokinetics Profile

Brivaracetam is rapidly absorbed with a median time to maximum concentration (tmax) of approximately 1 hour. High-fat food delays T max (3 hours) and decreases maximum concentration (Cmax), but has no effect on area under the plasma concentration–time curve (AUC), and there is only weak plasma binding of <20%. [13-15]

BRV is extensively metabolized, primarily by hydrolysis of the acetamide group to the carboxylic acid metabolite by an amidase, followed by hydroxylation by cytochrome P450 (CYP)2C9 to form a hydroxy-acid metabolite. [16-17] More than 95% of the brivaracetam dose is eliminated in the urine within 72 hours, 8.6% is eliminated unchanged, and the rest is excreted as metabolites. [15,18] Mean half-life (t½) is ~9 hours and plasma clearance is 3.4 L/ hour following a single BRV 50 mg oral dose in healthy participants. [19]

Adverse Reaction

The following serious adverse reactions are observed with brivaracetam:

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs) including brivaracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs.
- **Neurological Adverse Reactions:** Brivaracetam causes somnolence, fatigue, dizziness, and disturbance in coordination. Patients should be monitored for these signs and symptoms.
- **Psychiatric Adverse Reactions:** Brivaracetam causes psychiatric adverse reactions but offers better tolerability than levetiracetam. [20]
- **Hypersensitivity (Bronchospasm and Angioedema):** Brivaracetam can cause hypersensitivity reactions. Bronchospasm and angioedema have been reported in patients taking brivaracetam.
- **Withdrawal:** Similar to other antiepileptic drugs, brivaracetam should also be withdrawn gradually because of the risk of seizure recurrence. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

Drug-Drug Interactions

Rifampin: Co-administration with rifampin decreases plasma concentrations because of CYP2C19 induction. Brivaracetam dose should be increases up to 100% while receiving concomitant treatment with rifampin.

Carbamazepine: Though available research did not reveal any safety concerns, but if tolerability issues arises carbamazepine dose reduction should be considered.

Phenytoin: Brivaracetam can increase plasma concentrations of phenytoin; hence phenytoin levels should be monitored when co-administered to or discontinued from ongoing phenytoin therapy.

Table 1: Antiepileptic drugs classification with indications and mode of action.

Classification	Agent	Indication	Mechanism of action
First-generation (conventional) antiepileptics	Valproate	• First-line treatment for tonic-clonic seizures • Partial (focal) seizures • Absence epilepsy • Status epilepticus [9] • Myoclonic seizures • Migraine prophylaxis • Bipolar disorder	• Inhibits GABA transaminase → ↑ GABA→ decreased neuronal excitability • Inactivates Na+ channels
	Carbamazepine	• First-line treatment for tonic-clonic generalized and focal seizures • First-line treatment of trigeminal neuralgia	• Inactivates Na+ channels
	Ethosuximide	• First-line for absence seizures	• Inhibition of voltage-gated calcium channels (T-type) in neurons of the thalamus
	Phenytoin, fosphenytoin	• First-line treatment for tonic-clonic seizures • Focal seizures • Status epilepticus [9]	• Inactivation of Na+ channels • Zero-order elimination (i.e., constant rate of drug eliminated)
	Phenobarbital	• First-line treatment in neonates • Tonic-clonic generalized seizures • Focal seizures • Status epilepticus	• GABA agonist → ↑ GABA action
	Benzodiazepine	• First-line for status epilepticus • Second-line treatment for eclampsia	• Indirect GABA agonist → ↑ GABA action
Second-generation (newer) antiepileptic	Lamotrigine	• First-line of focal seizures • Second-line treatment for generalized seizures and absence seizures • Mood stabilizer for treatment of bipolar disorder	• Inhibition of voltage-gated Na+channels → ↓ glutamate release
	Levetiracetam	• First-line treatment of focal seizures • Generalized seizures	• Blockage of SV2A receptor → GABA and/or glutamate release modulation and inhibition of voltage-gated Ca2+ channels
	Gabapentin	• Second-line treatment for focal seizures • Postherpetic neuralgia • Peripheral (poly)neuropathy	• Inhibition of presynaptic P/Q-type Ca2+ channels via action on the α2δ-subunit → ↓ Ca2+ intracellular flow → ↓ glutamate release [10] • Does not bind to GABA receptors despite being a GABA analog

	Vigabatrin	• Refractory focal seizures (adjunctive therapy) • Monotherapy for infantile spasms • West syndrome	• Inhibits GABA transaminase irreversibly → ↑ GABA
	Topiramate	• Focal and tonic-clonic seizures • Migraine prophylaxis • Idiopathic intracranial hypertension	• Blockage of voltage-gated Na+ channels • ↑ GABA
	Tiagabine	• Focal seizures with or without impairment of consciousness (adjunctive therapy)	• Inhibits GABA • reuptake → ↑ GABA
3rd generation (newest) antiepileptic	Eslicarbazapine	• Monotherapy or adjunctive therapy for Partial-onset seizures	• Stabilises the inactive state of voltage-gated sodium channels
	Lacosamide	• Adjunctive treatment of partial-onset seizure • Diabetic neuropathic pain	• Inhibition of sodium channels
	Brivaracetam	• Adjunctive treatment of partial-onset seizures with or without secondary generalisation	• Blockage of SV2A receptor → GABA and/or glutamate release modulation
	Perampanel	• Adjunctive therapy for partial seizures and generalized tonic-clonic seizures	• Selective non-competitive antagonist of AMPA receptors

Brivaracetam versus Levetiracetam

- **Onset of brain activity:** Brivaracetam (BRV) displays a fast and unrestricted passage across the blood-brain barrier. The passive diffusion permeability is superior to levetiracetam (LEV), with no evidence of transporter-mediated extrusion from the brain, leading to faster onset of brain activity. [21]
- **Protection:** BRV demonstrates a more pronounced effect on inhibition of neuronal hyper synchronization than selectracetam (SEL). [21] In contrast with LEV and SEL, BRV shows seizure protection in the maximal electroshock seizure (MES) and the subcutaneous pentylenetetrazol (PTZ) tests, although at high doses; and also has significant protection against the partial seizure phase in animal models of focal epilepsy. [21]
- **Potency:** BRV demonstrated higher potency than LEV in various animal seizure models, which includes MES and PTZ tests in cornea-kindled mice, hippocampus-kindled rats, and the 6 Hz seizure model in mice and also in models of primary generalized epileptogenesis. [22] Furthermore, potent efficacy was evident in a model status epilepticus. [23]
- **Affinity:** Studies observed that BRV has a 15- to 30-fold increased affinity for synaptic vesicle protein 2A (SV2A) compared with LEV. [24] The differential effect of the allosteric SV2A modulator on the binding of LEV and BRV indicates that they influence different conformations of the SV2A protein [21], which determines that LEV and BRV bind to SV2A at closely-related sites but interact with these sites differently. [25]
- **Dosing:** Studies that compare BRV and LEV using high-frequency neuronal stimulation suggest that BRV augments synaptic depression and thereby decreases synaptic transmission at 100-fold lower concentrations than LEV. [26]
- **Selective SV2A ligand and adverse effects:** Studies support the absence of any relevant contribution of conventional anti-epileptic drugs (AED) mechanisms to the anti-epileptic properties of BRV and suggest it represents the first, selective SV2A ligand for epilepsy treatment [21]. The selectivity of BRV may be associated with fewer clinical adverse effects and is even supported by findings obtained from a study showing that epilepsy patients experiencing non-psychotic behavioral adverse events related to LEV had benefited from switching to BRV. [27]

Conclusion

Brivaracetam is a third-generation anti-epileptic drug. It is different from levetiracetam based on the higher affinity, selectivity, and differential interaction with SV2A. Its higher lipophilicity correlates with significant potential and complete seizure suppression and more rapid brain penetration in preclinical models. These properties of brivaracetam propose its favorable potential as an anti-epileptic drug that might provide broad-spectrum efficacy, along with a better tolerability profile and fast onset of action. Brivaracetam represents the first selective SV2A ligand for epilepsy treatment and will significantly contribute to the existing range for anti-epileptics.

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A Novel, Patented, Ready-to-Drink Protein for Early Recovery and Shortened Convalescence – EZEPRO

Abstract

In the context of critical illness, evidence suggests that exogenous protein/amino acid supplementation has the potential to favorably impact whole-body protein balance. It has been suggested that exogenous protein should be supplemented in sufficient amounts to mitigate protein loss. Observational studies have demonstrated that the achievement of >90% of target protein intake in the early phase of illness associated with improved ICU outcomes in mechanically ventilated critically ill patients.

Keywords: *EZEPRO, Ready-to-Drink protein, ICU-induced weakness, Critically ill patients*

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Introduction

In three macronutrients, protein is one which the body needs in higher quantities. The other macronutrients are fat and carbohydrates. Proteins are made up of hundreds or thousands of minor units termed amino acids, which are attached to one another in long chains. There are 20 diverse types of amino acids that can be combined to make a protein. The arrangement of amino acids decides each protein's unique 3-dimensional structure and its exact function.

Proteins are large, complex molecules that play many critical roles in the body. Proteins do most of the work in cells and are vital for the structure, function, and regulation of the body's tissues and organs.

In every single body cell, protein is present and an ample protein intake is essential for keeping the muscles, bones, and tissues healthy.

Consequences of Low Protein in Critically ill Patients:

Critical illness, a life-threatening multisystem process, can result in significant morbidity or mortality; common complications involve increased infectious morbidity, multi-organ failure, and prolonged hospitalization [1]. Critical illnesses give rise to severe metabolic stress and the suffering patients often develop systemic inflammation. It causes increase in muscle proteolysis leading to amino acid catabolism and urea synthesis, which subsequently disrupt the body nitrogen balance and make it strongly negative [2].

If there is deficiency of protein and energy for long time during illness, it leads to the condition known as protein energy malnutrition [3] and starvation disease [4]. Protein-energy malnutrition is a prevalent consequence of hospitalization, especially in critically ill patients admitted to the intensive care unit (ICU). It is a global problem with prevalence 50.8% and 78.1% in developed and developing countries, respectively [5]; the situation is no better in India and the published evidences suggest reported rate ranges from 39% to 50% [6,7,8]. The published evidences also revealed that more than half of all ICU patients globally are significantly underfed, which worsen the condition [9]. The prolong malnutrition is associated with adverse clinical outcomes, increased rates of morbidity, mortality, and reduced quality of life with longer hospitalization [10,11]. Economically, protein malnutrition leads to significant increase in healthcare costs and utilization of resources.

Dramatic alterations are witnessed in protein metabolism with all critically ill patients like alterations in metabolic balance, with catabolic responses being consistently higher than those associated with protein anabolism. The scale of the loss of protein during illness is proportional to the harshness of injury [12]. In its most severe cases, mostly in critical illness, the catabolic response linked with protein loss leads swiftly to the exhaustion of existing protein contained within cells and tissues with the subsequent advancement to protein malnutrition.

Severe protein malnutrition is associated with poor clinical outcomes, including severe muscle deconditioning, ventilator dependency, poor wound healing, immune dysfunction, incompetence to maintain activities of the daily living, and ultimately death [13]. An inordinately elevated incidence and prevalence of protein malnutrition is observed in hospitals. This poorly recognized condition is also called hospital-acquired or disease- acquired malnutrition. Up to 30% or even more of all patients in hospitals are known to have significant protein malnutrition. Protein malnutrition expressively increases healthcare costs and utilization of precious healthcare resources. Thus, it is a crucial priority to find solutions that overcome protein malnutrition.

Role of Protein in Speedy Recovery of Critically ill Patients

Protein: A fundamental element of metabolism in seriously ill patients.

In the milieu of critical illness, evidence advocates that exogenous protein/amino acid supplementation has the potential to favorably impact whole body protein balance [14,15].

The American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) nutrition guidelines recommend 1.2 to 2.0 g/kg/day [16]. Some experts conclude that up to 2.0–2.5 g/kg/day of protein, and even higher doses in severe burn and trauma patients, is safe and could be considered an ideal dose [17]. Yet existing observational studies document that critically ill patients are being prescribed much less than that, an average of 1.3 g/kg/day, and getting only 55% of what is prescribed on average (approximately 0.7 g/kg/day) [18].

Numerous physiometabolic deviations occur in critically ill patients. These deviations may increase the risk of malnutrition [19]. Decrease in total calories and protein intake confuses the deteriorating clinical condition. Rise in sepsis, rise in inflammatory biomarkers, and metabolic imbalance may result in multiple organ failure, shock, and mortality. Detailed assessment of critically ill patients will help in deciding the strategy of nutritional support and further increase the patient outcomes.

Nutritional support becomes vital to fulfill the macro- and micro-nutrient necessities in such patients. Route-of-feed administration (enteral or parenteral) needs to be decided based on the calculation of hemodynamic status and gastrointestinal functioning [20]. This will avoid risks linked with the faulty feeding methods. Early enteral nutrition (EEN) in critically ill patient is found to be allied with many benefits and at the same time, with reduced risk of complications [21].

Patient outcomes in Intensive Care Unit (ICU) are affected by proper timing of initiation, amount and type of nutrition. Initiating feeding within 24–48 h of critical illness is defined as early nutrition intervention.

Route of Nutrition (Enteral vs. Parenteral): Preference in Critical-care Settings

EN is preferably commended over PN as early nutrition in critically ill patients [22]. The route of nutrition delivery governs the effect of the nutritional intervention. Enteral route is more physiologic, providing nutritional benefits without unfavorably disturbing structural–functional integrity of gut and intestinal microbial diversity. EN has limitation in the acute disease phase and gastrointestinal dysfunction due to its probable lower nutritional adequacy. In contrast, the intended nutritional requirement is better secured with PN but hyper-alimentation, hyperglycemia and infectious complications remain the key challenges [23].

In critically ill patients, supplemental PN at the end of the 1st week after ICU admission is advisable when full EN support is not possible or fails to deliver caloric targets of up to 60% [24].

Current Available Therapy

Because of worries in tolerating, digesting, absorbing whole protein and have need of reconstitution it is seen that critically ill patients may not be able to attain adequate macronutrient or micronutrient protein requirements through oral powder formulations of protein.

Therefore, in hospitals, dietary meal with high protein and energy content are given to ICU patients (Table 1). The normal feed for patients comprises of eight feeds of 150-250ml per session at equal breaks of 2hrs. This is not only lumbersome, but involves proficiency to make the precise quality and quantity of preferred amount of meal. Additionally, dals and cereals comprises one less vital amino acid in content, which does not help in making of protein. So the comprehensive meal is essential with tallying of rice or chapatti.

There are however definite challenges with meals for example egg is a good source of protein, however other components in egg may not be suitable for critical ill patients. One large egg (50gm) comprises approx. 6gm of protein, 70mg of sodium, 70mg of potassium, 100mg of phosphorus, apart from high calories and carbohydrates [26].

Potential challenges with other meals, especially non-vegetarian include postprandial hypotension and other hemodynamic instabilities, aspiration risk, gastrointestinal symptoms, hygiene issues, staff

Table 1: Foods containing potential amino acid are following [25]:

Food	mEq per g of protein
1. Oatmeal	0.82
2. Egg	0.8
3. Walnuts	0.74
4. Wheat (whole)	0.69
5. White Rice	0.68
6. Barley	0.68
7. Tuna	0.65
8. Chicken	0.65
9. Corn	0.61
10. Milk	0.55
11. Soy	0.4
12. Peanuts	0.4
13. Almonds	0.23
14. Potato	0.23

burden, reduce solute removal, and increased costs. Differing in-centre nutrition policies exist within organizations which is a possible challenge for meal in the critical ill patients.

Patients also resort to oral protein supplements (powders). There are certain challenges with powder supplements as it causes constipation and bloating in the patients, there is a hassle of reconstitution each time as the powder needs to dissolve in a definite volume of liquid, the main problem with reconstitution is that it does not let the right quantity of protein reach the system, proteins in powder forms leads to poor absorption in critical ill patients and they also have electrolytes exceeding the limits prescribed to the patients (lipids, sugars, carbohydrates, sodium, phosphorus and potassium content).

Some oral protein supplement has the dairy protein source containing whey and casein. Whey is the quick digesting and fast assimilating protein within short duration. It provides the rapid source of amino acids and is good for instant requirement. While casein coagulates in the gastrointestinal tract giving the feeling of satiety. It is slow assimilating protein providing the sustained release of amino acid in the body within longer duration. However, the unbalanced formula does not meet the required criteria for critical ill patients.

Additionally, current available products may have high levels of sodium, potassium and phosphates potentially deleterious for the procedure that involves in ICU patients. Some protein supplements may contain artificial flavours like maltodextrin and additives like sodium benzoate. Powders requiring reconstitution into semi-liquid food and are not adapted to patients in intensive care, Problems of taste/palatability which causes low compliance.

Moreover, the undissolved or undigested protein lumps of protein not only makes patient feel gut heavy or gut discomfort, but microbes in colon act on these lumpy undigested protein particles and try breaking them down leading to formation of fermented metabolites like thiols, phenols, ammonia, indoles and amines which are undesirable substances due to which these patient have tendency to pass foul gas too frequently and experience gastritis, flatulence etc.

Considering above challenges and while interacting with doctors, it has been established that Ready-to-Drink protein supplement offers following advantages over other available supplements like:

- Short and long term benefits of protein supplements in critical ill patients include improvement in whole body an skeletal muscle protein balance
- Ready-to-drink protein supplements can bridge the protein nutrition gap when eating enough food and powder proteins are not feasible
- Sole source of protein nutrition for critically ill patients who are at risk of malnutrition, particularly those with high energy and protein requirements and powder protein restrictions.
- Integral component of diabetes management improved glycemic control and lower diabetic complications.
- Supports malnutrition, growth and early recovery in critical ill patients as Protein needs are increased during critical illness.
- Improving outcomes of chronic disease which require more protein to recover and decreases all-cause mortality, hospitalization rate and increased survival rate.

Ezepro, Ready-to-drink Protein Formula for Management of Protein Loss in critically ill patients

Foods have slow digesting proteins due to which amino acids are not stored but are taken up by the body cells for the synthesis of proteins. Slow digesting protein is absorbed at a rate which doesn't induce much muscle

protein synthesis. To overcome these issues, Alniche has developed a Ready-to-Drink oral protein supplement (Ezepro) for improving the health of critically ill patients due to protein loss.

EZEPRO is the patented, 1st Ready-to-Drink protein formula, with right-quantity of slow assimilating high-quality protein with high biological value (BV) and PDCAAS* value equal to 1(highest possible score). This helps in slow assimilation of protein ensuring near 100% absorption in the body. This score means after digestion of the protein; it provides per unit protein 100% or more of the indispensable amino acid required. In addition, Ezepro delivers 55.12 Kcal and is low in sodium, potassium and phosphorus; with no added soya and sugar; hence suitable for diabetic patients as well.

Ezepro pack is uniquely designed to ensure stability, patient convenience and most importantly it is environmental friendly pack. Patient can carry and consume Ezepro anytime, anywhere without anyone's help. Currently available protein powders in market needs reconstitution and has many problems like:

- Every time, it is difficult to measure right quantity of powder in scoop. To level the scoop, patient or attendant or nurse touches powder resulting in high chances of contamination that even multiplies with every touch
- Cleanliness of glass is questionable
- Pure sterile drinking water is must
- Chances of powder taking moisture and gets solidify
- Carrying bulky powder box

So, Ezepro is a tailored readymade protein drink for the critically ill patients that prevents rapid loss of muscle mass, ensures energy intake. Ezepro has optimally balanced formula of right quality and quantity of 100% assimilated protein suitable to ICU patients suffering from ICU acquired weakness.

Conclusion:

In conclusion, there is good evidence to support protein in the ICU is beneficial although delivery must be individualized. An upper range of 2.5g/kg/day is considered safe. Optimal protein intake may be different in the acute compared to the prolonged phase of illness. Due to the heterogeneous nature of the ICU population decisions must be made on an individual basis. Aggressive protein delivery combined with resistance exercise may improve muscle kinetics, metabolism and regeneration.

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Colloidal Albumin Properties and Its Impact on Osmotic Pressure: A Rational For Using Albuzest in Liver Disease

Abstract

Human serum albumin, a negatively charged small globular protein encoded on chromosome 4, is the most abundant protein in the blood. Albumin accounts for about 75% of plasma oncotic pressure. Albumin has showed valuable role in managing various disease. Albumin is utilized in patients with liver cirrhosis, hepatic encephalopathy and hepatorenal syndrome. Albuzest an effective plasma volume expander containing albumin 20%, manufactured by SK plasma group which is the second largest business group in Korea. Overall, albumin is effective in treatment of hepatorenal syndrome, hepatic encephalopathy and cirrhosis.

Keywords: *Albumin, Liver cirrhosis, Hepatic encephalopathy, Hepatorenal syndrome, Albuzest*

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Introduction

The most abundant protein in the blood is albumin. Albumin accounts for about 50% of all plasma proteins. Albumin is a small globular protein consisting of a single chain of 585 amino acids organized in three repeated homologue domains (sites I, II and III), each of which comprises two separate sub-domains (A and B).

Under physiological conditions, about 10-15 grams of albumin is produced in the liver by the hepatocytes. Different hormones such as insulin, cortisol and growth hormone stimulates the synthesis of albumin, while pro-inflammatory substances including interleukin-6 and tumor necrosis factor do the inhibition of its synthesis. [1,2]

Albumin has been used for many years in the management of patients with cirrhosis and ascites as it is an effective plasma volume expander due to its high oncotic activity and prolonged half-life in the intravascular compartment [3].

The main physiologic function of albumin is to maintain colloid osmotic pressure, but in the past few years, many other functions have been recognized. These other function include ligand binding and transport of various molecules, in addition to antioxidant and anti-inflammatory actions [4]. These functions of albumin could be applied to various clinical situations, including septic shock.

Functions of Albumin

Colloidal Osmotic Pressure

Albumin is essential for maintaining the oncotic pressure in the vascular system. A decrease in oncotic pressure due to a low albumin level allows fluid to leak out from the interstitial spaces into the peritoneal cavity, producing ascites [5].

Antioxidant Effects

The major extracellular source of thiols is albumin. Thiols are scavengers of reactive oxygen and nitrogen species. Albumin can also limit the production of reactive oxidative species by binding free copper (an ion known to be particularly important in accelerating the production of free radicals) [5].

Transport

Albumin is negatively charge, but binds weakly and reversibly to both cations and anions. Therefore, it functions as a transport molecule for an outsized number of metabolites, including fatty acids, ions, thyroxine, bilirubin and amino acids. The glycosylation of albumin, which is to a particular extent age-dependent, affects its charge and therefore, may influence capillary permeability characteristics [1]. Albumin acts as a transporter vehicle and binds with drugs given in Table 1.

Endothelial Stabilization

Albumin has the ability to reduce injury to the endothelium caused by reactive oxygen and nitrogen species which means it may stabilize the endothelium and help to maintain capillary permeability. It also interferes with neutrophil adhesion to the capillary endothelium [5], thereby reducing inflammation and aiding the maintenance of endothelial integrity.

Table 1: Albumin acts as a transporter vehicle and binds with drugs [1]

Transport vehicle for	Albumin interacts with
1. Cholesterol	1. Phenytoin
2. Bile pigments	2. Non-steroidal anti-inflammatory drugs
3. Nitric Oxide	3. Digoxin
4. Fatty acids	4. Midazolam
5. Metals	5. Thiopental
	6. Antibiotics

Albumin Impact on Osmotic Pressure

Colloid osmotic pressure, or oncotic pressure, is a form of osmotic pressure which is induced by proteins, mainly albumin, in a blood vessel's plasma that displaces water molecules, thus creating a relative water molecule deficit with water molecules moving back into the circulatory system within the lower venous pressure end of the capillaries. Oncotic pressure has the opposing effect of both hydrostatic blood pressure, pushing water and small molecules out of the blood into the interstitial spaces within the arterial end of capillaries, and interstitial colloidal osmotic pressure, pressure exerted by fluids within the interstitial fluid. These interacting forces determine the partition balancing of total body extracellular water between the blood plasma and the larger extracellular water volume outside the blood stream.

Dissolved compound throughout the body have an osmotic pressure. As large plasma protein cannot cross through the capillary walls so their effect on the osmotic pressure of the capillary interiors will balance out the tendency for fluid to leak out of the capillaries, means the osmotic pressure tends to pull fluid into the capillaries.

The large majority of oncotic pressure in capillaries is generated by the presence of high quantities of albumin. The total oncotic pressure of an average capillary is about 28 mmHg with albumin contributing approximately 22 mmHg of this oncotic pressure.

As blood proteins cannot escape through capillary endothelium so oncotic pressure of capillary beds tends to draw water into the vessels. It is necessary to understand the oncotic pressure as a balance; because the blood proteins reduce interior permeability so that less plasma fluid can exit the vessel [6].

Use of Albumin in Liver Cirrhosis

The reduced albumin concentration is typically a feature of cirrhosis and represents an important and adverse prognostic factor. It results from both a decreased hepatocyte production and various events closely related to the course of the disease. For example, renal sodium and water retention leads to plasma volume expansion and dilution of extracellular fluid protein content, thus contributing to lower serum albumin concentration. Another factor, at least in the most advanced stage of cirrhosis, is represented by an increase in the trans-capillary escape rate of the molecule that leads the protein to be lost towards the extravascular space.

Albumin has been used as the treatment for many complications of cirrhosis and ascites, such as spontaneous bacterial peritonitis and HRS [7, 8]. As the basic pathophysiological process that leads to the development of ascites is a reduction of the effective arterial blood volume, [9] it makes physiological sense to use albumin in the management of ascites, although this has been controversial.

One randomized, controlled trial checked out the effect of albumin along with standard diuretic therapy in cirrhotic patients with ascites; weekly infusion of 25g of albumin added to diuretic produced a significantly better diuretic response, shorter hospital stays and a lower likelihood of readmission to hospital, but no effect on survival [9] when compared with diuretic alone. Suppression of the activity of anti-natriuretic systems, particularly the renin-angiotensin aldosterone system, probably accounts for a rise in the natriuretic response to diuretics with repeated albumin infusions [9]. Survival, however, was not affected by the addition of albumin [6]. Moreover, compared with the simple performance of paracentesis during a day-care unit, the logistic problems of intravenous albumin administration on a weekly basis, and its lack of cost-effectiveness, render this indication unjust and impractical in clinical practice [10]. For this reason, there's currently no standard recommendation to use albumin as an adjunct therapy to diuretics within the treatment of uncomplicated ascites [6].

Albumin in Hepatic Encephalopathy

Neuropsychiatric syndrome – Hepatic encephalopathy plays a prime role in complicating acute and chronic liver dysfunction and is associated with a wide range of other severe manifestations. In course of cirrhosis, hepatic encephalopathy is very common [11]. Three types of hepatic encephalopathy are noted, type A (acute liver failure), type B (portosystemic shunting), and type C (cirrhosis) [12].

According to the West-Haven criteria, the severity of hepatic encephalopathy is categorized into grade I, II, III and IV [13].

The occurrence of hepatic encephalopathy in patients having liver cirrhosis is apparently 30-45% [14-16]. Numerous substances (mostly ammonia) are liable for the pathophysiology of hepatic encephalopathy which are produced in GUT and metabolized by liver. Newly, other reasons, such as inflammation driven by bacterial translocation and oxidative stress have assumed to play a vital role [17].

Clinical trial was done including 15 patients having hepatic encephalopathy prompted because of diuretic, 4.5% of human serum albumin infused has shown a noticeable progress in hepatic encephalopathy beside showing a reduction in oxidative stress indicators as matched to colloid group. By using volume expansion, the levels of plasma ammonia exhibited a decrease and there was an increase in urinary excretion of ammonia. The noticeable progress in the albumin group may propose an antioxidant role of albumin in the treatment of hepatic encephalopathy [18].

In a current multicenter prospective double blind control trial, 56 cirrhotic patients having acute hepatic encephalopathy were randomized to take either albumin (1.5 g kg–1 on day 1 and 1 g kg–1 on day 3) or isotonic saline in addition to the standard treatment. The results came with negotiable difference in percentage of patients with hepatic encephalopathy on 4th day (albumin 57.7% vs. 53% in saline), But there was a pointedly improved survival rate after three months of continuation in the albumin group [19]. Improvement in hepatic encephalopathy is more frequent and earlier with extracorporeal albumin dialysis [20]. In added prospective randomized controlled multicenter trial, albumin dialysis with molecular adsorbent recirculating system displayed progress in hepatic encephalopathy, but the outcome was non-noteworthy [21].

Albumin in Hepatorenal Syndrome

Development of renal failure in patients with severe liver disease is prominent with Hepatorenal syndrome. It is a life-threatening state with poor prognosis.

Hepatorenal syndrome is a possibly reversible renal failure considered by severe intra-renal vasoconstriction that develops in patients with advanced cirrhosis and ascites [22-23]

Hepatorenal syndrome (HRS) is classified into two types. Type 1 hepatorenal syndrome is well defined as the severe, rapid worsening in renal function in which there is doubling of serum creatinine value in less than two weeks and achieving a final value more than 2.5 mg dl-1 in the absence of reasons of renal failure. This typically happens secondary to an acute insult for example spontaneous bacterial peritonitis or acute gastrointestinal bleed and brings a poorer prognosis than type 2 Hepatorenal syndrome. Type 2 hepatorenal syndrome is a slow progressive worsening of renal function with creatinine levels ranging between 1.5 and 2.5 mg dl-1. Even though it may be caused by a precipitating incident. Ascites and hyponatremia is typically more frequent in these patients. In the existence of an acute insult such as spontaneous bacterial peritonitis type 2 hepatorenal syndrome can convert into type 1. In a study by Gines et al., the rate of hepatorenal syndrome was found to be around 18% at one year and 39% at five years in 234 non-azotemic patients with cirrhosis and ascites [24-26].

There is an upsurge in the efficacy of vasoconstrictor drugs by using albumin. Treatment of cirrhotic patients with hepatorenal syndrome for several days or weeks with a combination of vasoconstrictors and plasma volume expansion with albumin grades a noticeable progress in circulatory and renal functions in most cases, with normalization of plasma levels of vasoconstrictor factors and serum creatinine have been illustrated by two studies. Yet, the need for a plasma expander agent as a co-therapy remains uncertain. The administration of vasoconstrictors with albumin has been shown to reverse type 1 hepatorenal syndrome and stabilize renal function in 60-70% of treated patients. Small numbers of patients were there in these studies, some of whom were not randomized, and the impression on long-term (> 1 month) survival survival has not been shown. Type 2 hepatorenal syndrome treatment data are much uncommon than for type 1 hepatorenal syndrome [27-28]. To achieve the advantageous effect of vasoconstrictor therapy in hepatorenal syndrome by using albumin is not well-known. But, the therapeutic efficacy of vasoconstrictors probably to be improved with albumin, as the improvement in circulatory and renal functions is more noticeable in patients preserved with terlipressin and albumin than that in patients preserved with terlipressin alone. Specified that albumin has volume-expanding, antioxidant and ligand-binding properties,

it appears sensible to use albumin infusions in the treatment of hepatorenal syndrome except there is evidence that albumin actually does some harm. As per the American Association for the Study of Liver Disease (AASLD) infusion of albumin plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type 1 hepatorenal syndrome (level II-I) [13].

Albuzest – An Effective Plasma Volume Expander

Albumin is an effective plasma volume expander due to its high oncotic activity and prolonged half-life in the intravascular compartment. Seeing these aspects, it is not astonishing that albumin has been used for many years in the management of patients with cirrhosis and ascites [5]. Albuzest 20% contains human serum albumin 20g in each 100mL. Human serum albumin in Albuzest is broadly used in treatment of serious burn injuries, hypoproteinemia, hemorrhagic shock, fetal erythroblastosis and ascites caused by liver cirrhosis [3]. Albuzest is manufactured by SK plasma group which is the second largest business group in Korea, and had revenue of 154 billion US dollar in 2019. SK plasma is contributing 12.9% to the Korean economy. Albuzest is approved by European union standard and USA plasma pool.

Albuzest Dosage and Administration

Albuzest 20% injection 125-375mL, equivalent to human serum albumin 25-75g should be administered by intravenous drip infusion or by slow direct intravenous injection. The recommended infusion rate is 2-4mL/min. It may be diluted with 5% glucose and 0.9% sodium chloride when necessary.

The dosage may be adjusted according to body weight, age, symptoms and existing comorbid conditions of patient (table 2).

Conclusion

The most abundant protein in the blood is albumin that constitutes about 50% of the total plasma protein. Albumin is essential for maintaining the oncotic pressure in the vascular system. Albumin can also limit the production of reactive oxidative species by binding free copper and it also stabilize the endothelium. For cirrhosis there's currently no standard recommendation to use albumin as an adjunct therapy to diuretics within the treatment of uncomplicated ascites. Albumin dialysis with molecular adsorbent recirculating system displayed progress in hepatic encephalopathy, but the outcome was non-noteworthy. Infusion of albumin plus administration of vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type 1 hepatorenal syndrome (level II-I). Overall, the use of albumin seems to be useful in the patients with liver cirrhosis, hepatic encephalopathy & hepatorenal syndrome.

Table 2: Dosing of Albumin in different diseases [29-30]

ADULTS DOSE:	
Cirrhotic Ascites and Paracentesis	Human albumin 6-8 g/liter of removed ascites if paracentesis >4 liter
Spontaneous Bacterial Peritonitis	Human albumin 1.5 g/kg at diagnosis and 1 g/kg on third day + antibiotic therapy
Hepatorenal Syndrome	Human albumin 1 g/kg at diagnosis followed by 20–40 g/die +vasoconstrictors
Hypovolemia	Initial dose 25 g (125 mL of a 20% solution), repeat after 15–30 minutes if necessary
Acute Respiratory Distress Syndrome	25 g of albumin IV over 30 minutes, every 8 hours for 3 days
Hypoproteinemia	50–75 g daily, larger amounts may be required in those with severe hypoproteinemia who continue to lose albumin
PEDIATRIC DOSE:	
Hypovolemia	Initial dose of 0.5–1 g/kg or 2.5–12.5 g, repeat after 15–30 minutes if necessary
Hypoproteinemia	0.5–1 g/kg given over 0.5–2 hours and repeat after 1–2 days if necessary

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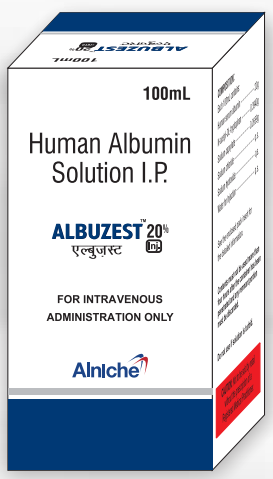

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COMBIKLAS - The Most Versatile TPN to Reduce Complication and Negative Outcome in Patients at Nutritional Risk during COVID-19 Treatment

Abstract

Malnutrition among critically ill patients is very prevalent. The metabolic response to stress, injury, surgery, or inflammation cannot be accurately predicted and these metabolic alterations may change during the course of illness. Underfeeding and overfeeding both are very common in Intensive Care Unit (ICU), and this resulting in large energy and other nutritional imbalances. Better understanding of human nutrition and metabolic process has led to formulation of scientific parenteral solutions to suit specific situations. This article shows the negative consequences due to lack of nutrition and how Total Parenteral Nutrition can be helpful for the critically ill patients.

Keywords: *Parenteral Nutrition, Total Parenteral Nutrition*

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Introduction

The feeding of nutritional product to a person intravenously, bypassing the usual process of eating and digestion is known as Parenteral nutrition. When no significant nutrition is obtained by other routes then the person will receive a nutritional formula that contain nutrients including glucose, salts, amino acids, lipids and added vitamins and dietary minerals. It is called total parenteral nutrition (TPN). Total parenteral nutrition (TPN) supplies all daily nutritional requirements.

The interruption in the continuity of gastrointestinal tract or the impairment in the absorptive capacity of gastrointestinal tract can be treated by total parenteral nutrition (TPN). TPN is also used to prevent malnutrition in patients who are unable to obtain adequate nutrients by oral or enteral route.

JW Lifesciences is a Korea-based company, primarily engaged in manufacture and distribution of Intravenous(IV) fluid products and infusion solutions. The Company offers product that contents amino acids, lipids, proteins, vitamins, and minerals which is used in special cases. The company is also engaged in manufacture of total parenteral nutrition (TPN) products and others. COMBIKLAS is unique “Three-in-One” formulation, scientifically designed by JW Lifesciences.

Negative Consequences Regarding Lack of Nutrition

According to WHO, Nutrition is the pillar of human life, health and development across the entire life span. The body requires many different vitamins and minerals that are crucial for both body development and preventing disease. Nutrients aren't produce naturally in the body, so you have to get them from your diet. An unhealthy diet increases the risk of many diet-related diseases. Basic nutrients for all life activities are carbohydrates, fats, and proteins. These constitute the carbon skeleton of numerous useful molecules, and deliver energy through oxidative decomposition. The main aim of nutrition is to prevent and treat nutritional deficiencies.

i) In Critically Ill Patient

The critical ill patients are at high risk of malnutrition because of stress catabolism and inadequate or delayed nutrition intake. Catabolic hormones (such as glucagon, cortisol, and catecholamines) are secreted in the early stage of critical illness to mobilize body nutrition reserves (muscle and adipose tissue) for the generation of endogenous energy substrate (glucose, amino acids, and free-fatty acids) and to prioritize the delivery of these energy substrates to vital organs (such as the brain or the heart). Proinflammatory cytokines such as Interleukin (IL)-1, IL-6 and tumor necrosis factor-α are also secreted at the same time in response to the body's acute insult and further exaggerate the catabolism process [1] During such inflammatory states, the provision of nutrition is not able to completely reverse the loss of body cell mass [2].

Such conditions make critically ill patients more prone to develop a risk of malnutrition (loss of body cell mass to a critical level), and the risk of complications is significantly increased if malnutrition develops [3]. At this stage, the priority is to provide nutrition support to support vital organ system functions and preserve appropriate host responses while the underlying disease is treated [4].

Depending on the patients' history, the patients may already have features of malnutrition with a reduced or restricted food intake long before intensive care unit (ICU) admission the reason behind could be either underlying chronic conditions (such as chronic obstructive pulmonary disease, cancer, or chronic renal failure) or have reduced intake from a hospital stay prior to ICU admission [4,5].

Moreover, in the ICU, the patients may continue to have restricted nutrition intake and thus they may experience prolonged fasting or frequent feeding interruptions due to various ICU procedures [5].

These two factors, preexisting malnutrition and iatrogenic underfeeding, may further complicated the nutrition status and worsen clinical outcomes.

ii) In Bacterial Infected Patients

Infection and malnutrition have always been intricately linked. Malnutrition is the primary cause of immunodeficiency worldwide, with infants, children, adolescents, and the elderly most affected. Malnutrition and infection shows a strong relationship,

because poor nutrition leaves individual underweight, weakened, and vulnerable to infections, primarily because of epithelial integrity and inflammation (figure 1) [6].

Malnutrition can make a person more susceptible to infection, and infection contributes to malnutrition, which causes a vicious cycle (figure 2). An inadequate dietary intake leads to weight loss, lowered immunity, mucosal damage, invasion by

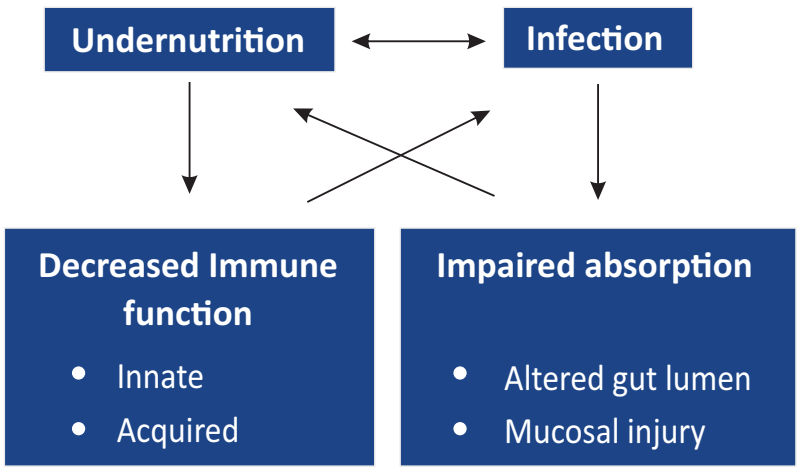

Figure 1: Interactions between malnutrition and infection

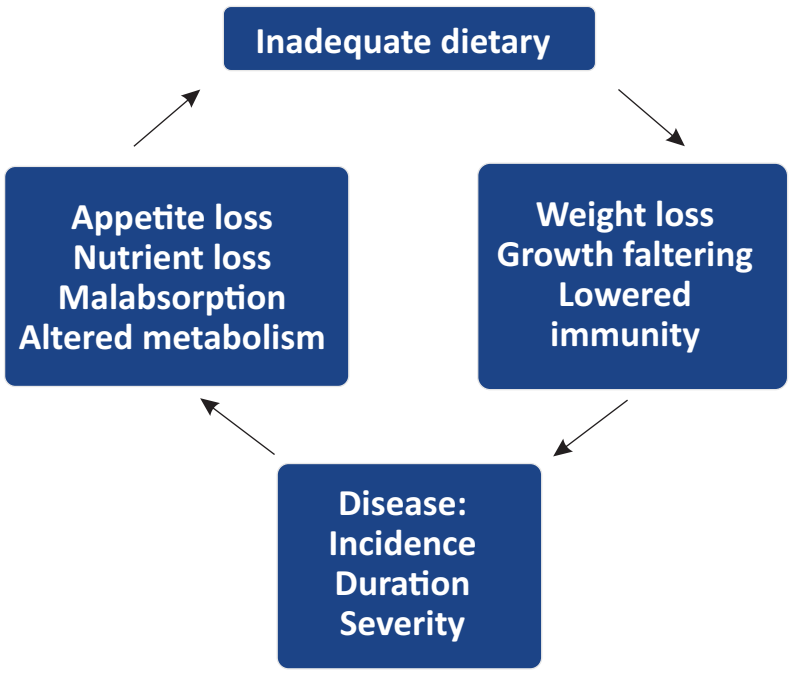

Figure 2: The “vicious cycle” of malnutrition and infection

pathogens, and impaired growth and development in children. A sick person's nutrition is further aggravated by diarrhea, malabsorption, loss of appetite, diversion of nutrients for the immune response, and urinary nitrogen loss, all of which lead to nutrient losses and further damage to defense mechanisms. This results in the reduction of dietary intake. In addition, fever increases both energy and micronutrient requirements. Malaria and influenza, for example, have mortality rates proportionate to the degree of malnutrition [7].

iii) In GI tract disease

Nutrition and intestinal function are intimately interrelated. The chief purpose of the gut is to digest and absorb nutrients so as to take care of life. Consequently, chronic gastrointestinal (GI) disease commonly leads to malnutrition and increased morbidity and mortality.

Practical Guidance for Nutritional Treatment

1. All the critically ill patients should undergo nutrition assessment, on admission. [8]
2. Observation of signs of malnutrition (e.g., cachexia, edema, muscle atrophy, BMI <20 kg/m2) is critical. [9]
3. EN should be started early, preferably within first 24–48 h. [8]
4. In case the nutrition requirement is not met adequately with EN even after 7 days of ICU admission, then usage of parenteral nutrition (PN) may be considered. [8]
5. Nutritional support should to be considered as of therapeutic benefits and not just supportive or adjunctive. [8]
6. Electrolytes should be strictly monitored in the patient on nutrition therapy. [10]
7. Assessment of drug–nutrient interaction to be done on daily basis. [11]

TABLE 1: Three chambers of COMBIKLAS

CHAMBERS	COMPOSITION	ROLE
Chamber 1	Dextrose solution	It is for fluid replenishment and caloric supply
Chamber 2	Amino acids solution with Electrolytes	It comprises essential and nonessential amino acids provided with electrolytes
Chamber 3	Intralipid® 20% (a 20% Lipid Injectable Emulsion)	It is prepared for intravenous administration as a credit of calories and essential fatty acid

8. Tube feeding to be considered if even 50%–60% of nutrition targets are not met adequately within 72 h of oral nutrition support.

COMBIKLAS

Combiklas is the most versatile TPN designed by JW Lifesciences. It is a sterile hypertonic emulsion, for central venous administration, in a three chamber bag with no added sulfites.

Route of Administration (Peripheral and Central)

JW Lifesciences, introduced Combiklas in both variants peripheral parenteral nutrition (Peri) and total parenteral nutrition (Central). Depending on which vein to be used, this procedure is often referred to as either total parenteral nutrition (TPN) or peripheral parenteral nutrition (PPN). [12] Total Parenteral Nutrition (TPN) and Peripheral Parenteral Nutrition (PPN) are provided to patients who do not have any other source of nutrition. Both the TPN and the PPN are provided through IV route (figure 3). Though the two are used to provide the required nutrition to a patient, they are different various ways.

When a patient is on Total Parenteral Nutrition, he relies on it completely. On the other hand, Peripheral Parenteral Nutrition, or PPN, is only partial. This means that the patient may be getting nutrition from other sources along with the PPN.

Another difference that can be seen is that Total Parenteral Nutrition comes in a higher concentration, and can only be administered through a larger vein. On the contrary, Peripheral Parenteral Nutrition comes in a lesser concentration, and can be delivered through a peripheral vein. Generally, the TPN is administered in the larger vein in the chest or neck.

PPN is not a preferred nutritional supplement for a long time. This is because it is not safe to use hyperosmolar solutions in peripheral veins for a very long time. However, the TPN can be used for a longer duration as it is delivered through a central vein.

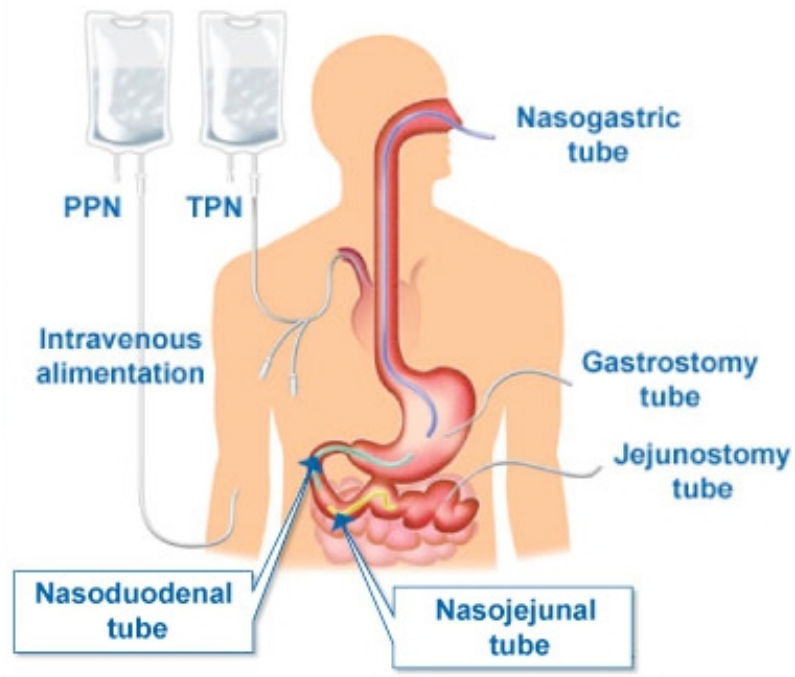

Figure 3: Routes of Feeding

Total Parenteral Nutrition is given to patients who are suffering from digestive disorders, or who are having any extended consequences of surgery or accident. The Peripheral Parenteral Nutrition is prescribed if a person's digestive system has been blocked, or if the patient is not getting enough nutrition during an extended stay in the hospital. [13]

Indication and Pack Specified Usage

Combiklas indication remains same for every variant of pack size available but the use of different pack size depends upon the patient's medical condition. Some of the most discussed indications are mentioned below:

1. Newborns with gastrointestinal anomalies such as tracheoesophageal fistula, massive intestinal atresia, complicated meconium ileus, massive diaphragmatic hernia, gastrochisis, omphalocele or cloacal exostrophy, and neglected pyloric stenosis.
2. Failure to thrive in infants with short bowel syndrome, malabsorption, inflammatory bowel disease, enzyme deficiencies and chronic idiopathic diarrhea.
3. Other paediatric indications include necrotizing enterocolitis, intestinal fistulae, severe trauma, burns, postoperative infections and malignancies.

Table 2: Comparison between TPN and PPN [14]

Parameter of Comparison	Total Parenteral Nutrition (TPN)	Peripheral Parenteral Nutrition (PPN)
Meaning	It is a process in which the patient is given nutrients through veins when they do not have other nutrition sources.	It is a process of providing supplements with the other source of obtaining/receiving nutrients.
Time period	It is long-term therapy.	It is normally a fourteen days' process. It is a short-term therapy.
Alkalinity	TPN is more caustic as it has minerals, glucose, and electrolytes.	It is not very caustic as compared to TPN.
Manage	TPN can only be applied in larger veins near the chest or neck of the patient.	PPN can only be applied to be in a short vein in a patient body.
Operate	TPN can be given to a person who has a digestive disorder, accident, or has critical surgery.	PPN can be given to a person whose digestive system has been blocked or unable to take a sufficient amount of nutrientsfrom other sources.

4. Adults with short bowel syndrome secondary to massive small-bowel resection or internal or external enteric fistulae.
5. Malnutrition secondary to high intestinal obstruction for example achalasia, oesophageal strictures and neoplasms, pyloric obstruction and gastric neoplasms.
6. Prolonged ileus due to medical or surgical causes (for example post-operative, following abdominal trauma or polytrauma).
7. Malabsorption secondary to sprue, enzyme & pancreatic deficiencies, regional enteritis, ulcerative colitis, granulomatous colitis, and tuberculous enteritis.
8. Functional gastrointestinal disorders like idiopathic diarrhoea, psychogenic vomiting, anorexia nervosa.
9. Patients with depressed sensorium (for example, following head injury or intracranial surgery) in whom tube feeding is not possible.
10 Hypercatabolic states secondary to severe sepsis, extensive full - thickness burns, major fractures, polytrauma, major abdominal operations etc.
11. Patients with malignancies in whom malnutrition may jeopardize successful delivery of a therapeutic option (surgery, chemo- or radiotherapy).
12. Paraplegics/quadriplegics with pressure sores in pelvic or perineal regions where fecal soiling is a problem. [15]

Available Pack Size

1. Combiklas 384 ml – Given to pediatric patients as well as to the patients with Fluid Restriction in cases such as:
   - Acute Kidney Failure
   - Acute Respiratory Syndrome
   - Congestive Heart Failure
   - Malnourished Patients
2. Combiklas Peri 1440 ml – Preferred during short duration of treatment (3-5 days) where patient body weight is less than or up to 60kg
3. Combiklas Peri 1920 ml – Preferred during short duration of treatment (3-5 days) where patient body weight is more than 60 kg
4. Combiklas Central 1540 ml – Preferred during long duration of treatment (6-12 days) where patient body weight is less than or up to 60kg
5. Combiklas Central 2053 ml – Preferred during long duration of treatment (6-12 days) where patient body weight is more than 60kg

Benefits of Fulfilling the Nutritional Requirement of Patient through TPN

The development of parenteral nutrition (PN) contraindicated a long-held belief that nutritional administration entirely through the veins was impossible, impractical, or unaffordable. The ability to supply nutrients to patients lacking a functional GI tract ultimately saved lives that would have otherwise been lost due to malnutrition.

The major advantages of parenteral nutrition are:

- Provision of adequate nutrients during gastrointestinal dysfunction
- Useful during fluid restriction since caloric density can be increased with a central venous catheter
- Generally indicated when patient cannot eat enough or be fed adequately by tube

Macronutrient Composition:

Patient with severe symptoms needs ICU admission and also after intensified conditions by extended stay during hospitalization; consequently, leads to the demand of nutritional therapy based on their health conditions. Following recommendation are based on international guidelines for critically ill patient treatment which must be considered:

Carbohydrates are the primary source of energy for the human body. The brain and neural tissues, erythrocytes, leukocytes, the lens of the eyes, and the renal medulla either require glucose or use it preferentially. The base of all PN solutions is carbohydrates, most commonly dextrose monohydrate. Dextrose provides 3.4 kcal/kg and is available in concentrations from 5% to 70%, with higher concentrations used primarily for patients on fluid restrictions.ry source of energy for the human body.

Protein is necessary to maintain cell structure, tissue repair, immune defense, and skeletal muscle mass. Protein is provided in the form of crystalline amino acids in concentration ranging from 3% to 20%. Amino acids provide 4 kcal/kg.

Amino acid solutions are usually a physiologic mixture of both essential and nonessential amino acids. Disease-specific amino acid solutions are available and are primarily used for renal and hepatic disease. Patients with declining kidney function who are not yet candidates for dialysis are at risk for urea nitrogen accumulation when infused with nonessential amino acids. These patients receive only essential amino acids. Patients with severe hepatic encephalopathy may benefit from branch-chain amino acids (BCAAs). BCAAs are oxidized primarily in the muscle, rather than the liver, preserving hepatic metabolic pathways in case of liver failure. In general, disease-specific amino acid solutions offer an incomplete amino acid profile and should not be used for more than 2 weeks.

Lipids in oil-in-water emulsion concentrations ranging from 10% to 30% provide fats in PN. Lipid solutions currently available in the United States contain long-chain triglycerides (LCT) in the form of soybean or safflower oil, egg phospholipids as an emulsifier, water, and glycerol to create an isotonic solution.

Inclusion of lipids in IV nutrition prevents essential fatty acid (EFA) deficiency. Solutions that provide up to 4% of total calories from linoleic acid or 10% of total calories from safflower oil-based emulsions will meet daily EFA requirements. Patients who receive PN without lipids, usually those with an egg allergy, should be monitored for EFA deficiency.

Fluid volume 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 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. [16]

Conclusion

MALNUTRITION among hospitalized patients has been associated with increased morbidity, prolonged hospital stay, and increased costs to the health care system.

Understanding of human nutrition and metabolic processes has led to formulation of total parenteral solutions to suit different conditions. Total parenteral nutrition (TPN) has been used in clinical practices for over a century. It has restructured the management of potentially fatal condition like the short bowel syndrome in adults as well as infants. Total Parenteral nutrition is helpful in reducing the complications rate, especially in malnourished patients.

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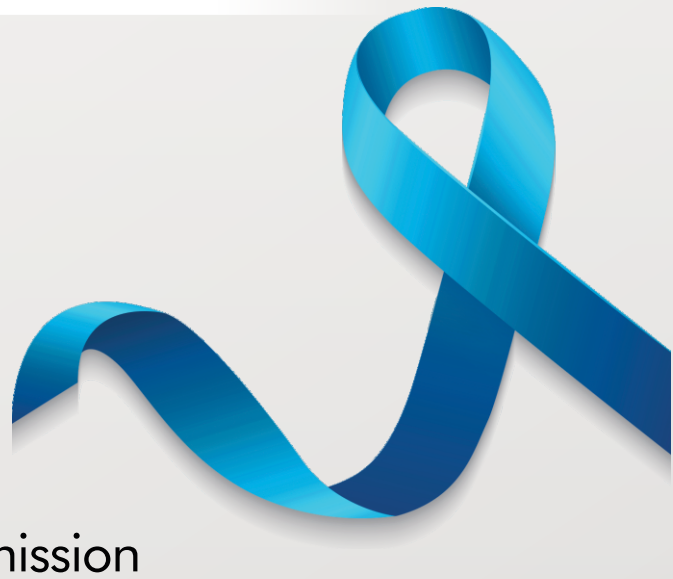

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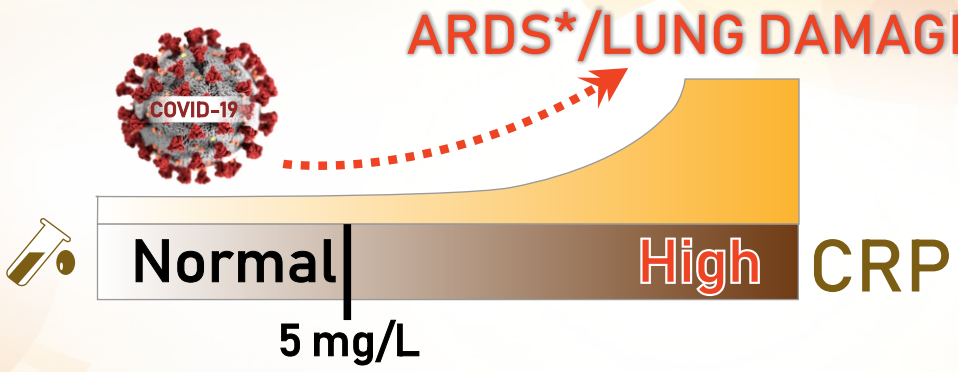
Novel coronavirus (2019-nCoV) seems to increase C-reactive protein (CRP) levels significantly[1]



Curcumin Supplementation Reduces CRP Levels by 79% in Covid-19 Patients[2]

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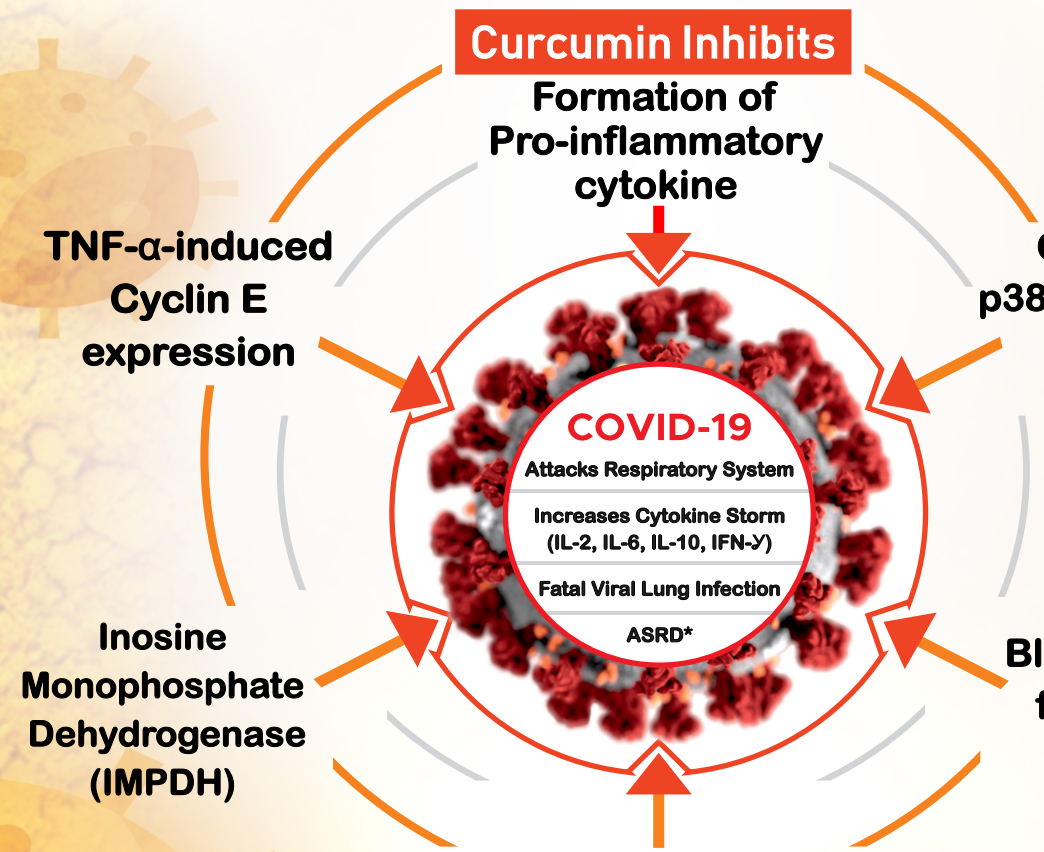

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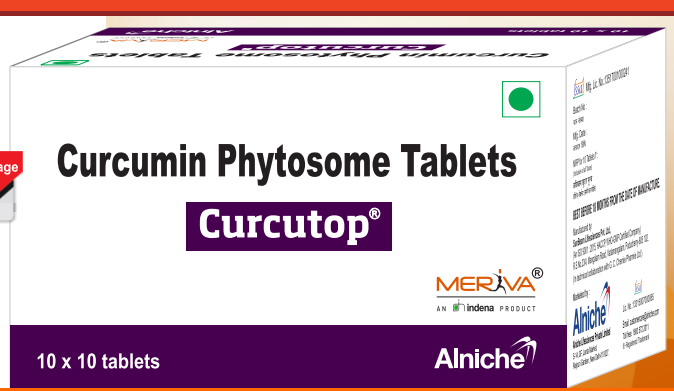

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