HEALTH CARE

e-Compendium

Volume - II
January - April 2021

Current Issues in Patient Care

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FROM THE DESK OF THE EDITOR-IN-CHIEF

Knowledge shared = Knowledge^2

Sharing knowledge and inspiration is equally important in every professional sphere. More so in the field of patient care, where every hour innovative products and technology are used for early diagnosis and complete recovery. It can foster the vision and strengthen professional ties. When you share your knowledge and experiences with others, it helps expand your own knowledge and engrains what you know. This has become more relevant when we have faced COVID-19 pandemic where scientists and researchers have risen above the geographical boundaries to pool their brains for saving humanity.

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 contributions of all the doctors, DPSRU faculty members and DRSC team who helped in bringing out this second issue of *Healthcare e-Compendium.*

CONTENTS

Recent Advancement in COVID-19 Vaccine and their Role in Controlling Spread of Corona Virus Pandemic

Abstract

Recent spread of SARS-CoV-2 pandemic has caused many casualties. Many measures to control the spread are based on prevention and symptomatic treatment. Apart from many attempts in finding the cure, there is still no approved medicine which can cure this deadly viral infection. The most promising options the vaccine, which helps in developing immunity against the infection from SARS-CoV-2. Various researches are going on for development of potent vaccines and are evaluated clinically for their efficacy.

Keywords: *SARS-CoV-2 pandemic, COVID-19 vaccine, Treating coronavirus.*

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Introduction

Coronavirus disease 2019 (COVID-19) has spread globally at a rapid pace since the novel coronavirus was first reported in late December 2019 in Wuhan, China, and was declared a pandemic by the World Health Organization on March 11, 2020 [1]. COVID-19 disease caused by the SARS-CoV-2 virus spreads from country to country, following modern travel routes [2]. A demographic study in late December of 2019 showed that the percentages of the symptoms were 98% for fever, 76% for dry cough, 55% for dyspnoea, and 3% for diarrhoea; 8% of the patients required ventilation support [3]. The diagnosis of SARS-CoV-2 infection is achieved through detection of viral RNA from a nasal pharyngeal swab or saliva, by nucleic acid tests (NATs) or tests that detect viral protein antigens. In infected individuals, the results are only positive for a relatively short time window, on average until the 14th day after symptom onset [4-5].

Contact tracing is a core public health intervention that plays an important role in the control of COVID-19 [6]. The aim of contact tracing is to rapidly identify potentially newly infected persons who may have come into contact with existing cases, in order to reduce further onward transmission. Contact tracing consists of three steps [7] (figure 1):

Contact identification: To identify persons who may have been exposed to SARS-CoV-2 as a result of being in contact with an infected person.

Contact listing: To trace and communicate with the identified contacts and to provide information about suitable infection control measures, symptom monitoring and other precautionary measures such as the need for quarantine.

Contact follow-up: To monitor the contacts regularly for symptoms.

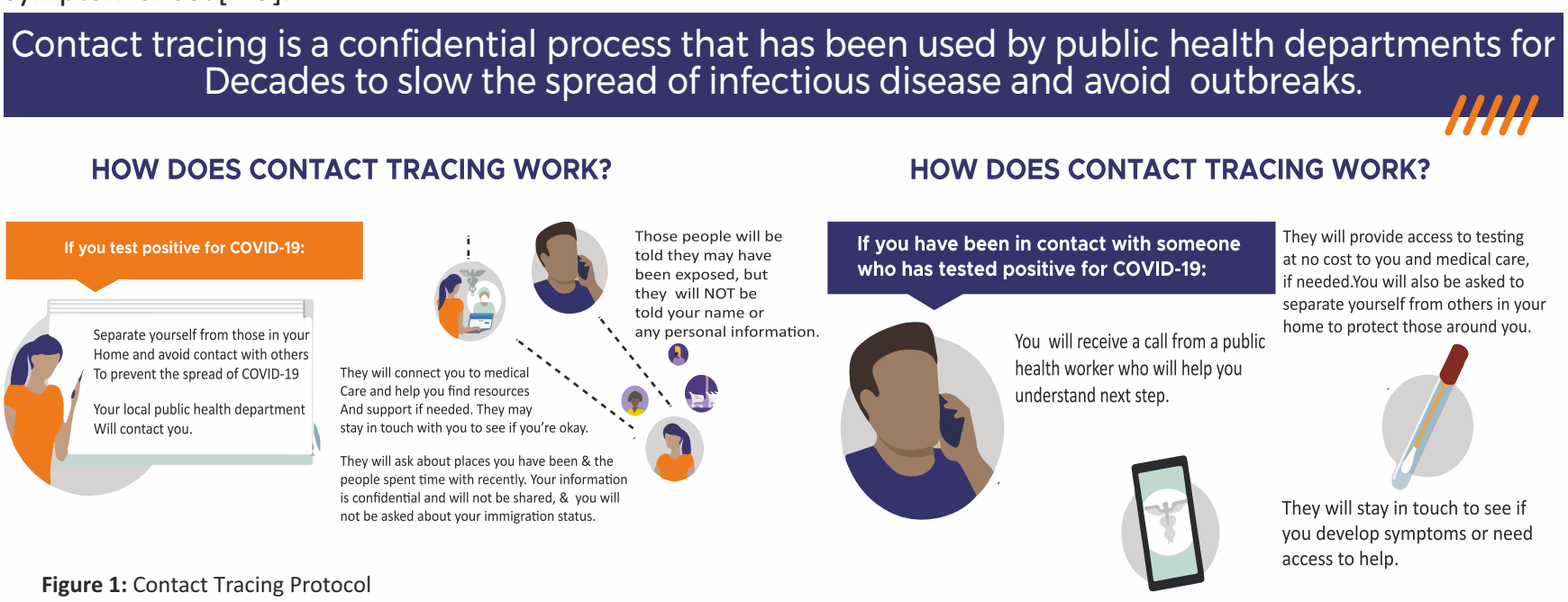

Figure 1: Contact Tracing Protocol

Treatment Options

Therapeutic options for coronavirus disease 2019 are desperately needed to respond to the ongoing SARS-CoV-2 pandemic. Various researches are going on for finding the cure; meanwhile many potential medicines are being used for managing the symptoms and viral load in infected patients. Both antiviral drugs and immunomodulators might have their place in the management of coronavirus disease 2019 (table 1). Unfortunately, no drugs have been approved yet to treat infections with human coronaviruses [8].

- **Antivirals:** Various antiviral agents with apparent in vitro activity against SARS-CoV and MERS-CoV were used during the SARS and MERS outbreaks, with inconsistent efficacy [9] and are also being considered for SARS-CoV-2.
- **Corticosteroids:** The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and acute respiratory distress syndrome (ARDS) [10]. Observational studies in patients with SARS and MERS reported no associations of corticosteroids with improved survival, but demonstrated an association with delayed viral clearance from the respiratory tract and blood and high rates of complications including hyperglycaemia, psychosis, and a vascular necrosis [11].
- **Immunomodulators:** Monoclonal antibodies directed against key inflammatory cytokines or other aspects of the innate immune response represent another potential class of adjunctive therapies for COVID-19. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs and other organs is caused by an amplified immune response and cytokine release, or "cytokine storm" [12].
- **Plasma Therapy:** Convalescent plasma (CP) has been used successfully to treat many types of infectious disease, and has shown initial effects in the treatment of the emerging SARS-CoV-2. CP therapy is a form of passive immunization in which antibody-rich blood is collected from recovered patients and then processed to transfuse into infected patients. As of now, it is a potentially effective treatment for COVID-19 [13].

Table 1: Therapeutic options consideration for treating SARS-CoV-2

Therapeutic considerations for COVID-19 management		
Antiviral	**Anti-inflammatory**	**Convalescent Plasma**
Remdesivir Favipiravir Lopinavir – Ritonavir Ribavirin Chloroquine and Hydroxychloroquine	Glucocorticoids Tocilizumab Siltuximab	Serum-containing neutralizing antibodies

Vaccines

Vaccination is the best way to prevent an infectious disease, the development of an effective vaccine against SARS-CoV-2 can not only reduce the morbidity and mortality associated with it, but can also lessen the economic impact.

It is estimated that 60–70% of a population would need to be immune to achieve herd immunity against SARS-CoV-2. The safest and most controlled way for effective and sustainable prevention of COVID-19 in a population is to have an efficacious and safe vaccine and the majority of the population successfully vaccinated [14].

Researching of vaccines has to faces multiple challenges during its development. Traditional way of development is a time taking process. So in times of emergency pandemics the process needs to be accelerated for early development of cure (figure 2). This has led to the modified approach towards development of vaccine with many phases going on simultaneously [15].

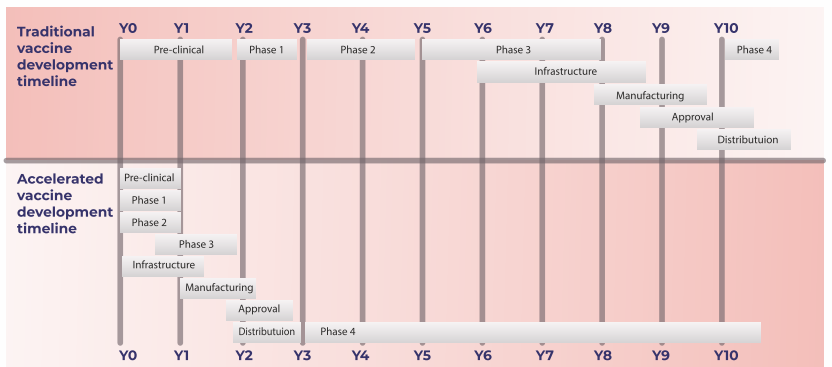

Figure 2: Various phases of vaccine development (traditional and accelerated) with timeline.

Development of Vaccine

Different measures for development of vaccine are considered, this leads to many types of vaccines to be considered for manufacturing process.

Live-Attenuated Vaccines

Live attenuated vaccine (LAV) is the most immunogenic vaccines that do not require adjuvant to gain optimal response due to its effectiveness to provoke immunity mimic to the natural infection [16]. Several LAVs are found in the market to protect various disease including mumps, rubella, measles and varicella vaccines. LAV is not suitable for infants, immune-compromised patients, and elderly people due to the risk of reversion to virulent strain [17]. Codagenix Biotec Inc collaboration with the Serum Institute of India Ltd developing a live-attenuated SARS-CoV-2 vaccine in which the sequence of the target gene of interest has been changed by swapping its optimized codons with non-optimized ones [18].

Inactivated Whole-Virus Vaccine

Inactivated whole-virus comprises the entire disease-causing virion which is inactivated physically (heat) or

chemically. It has several antigenic parts to the host and can induce diverse immunologic responses against the pathogen [19]. IWV is conventional vaccines with mature technology and may become the first SARS-CoV-2 vaccine put into clinical use. There are three inactivated whole-virus vaccines against SARS-CoV-2 reached phase 1/2 clinical trial. These phase 1/2 clinical trials are done by the Beijing Institute of Biological Products, Sinovac and Wuhan Institute of Biological Products [20].

Subunit Vaccines

Subunit vaccines contain pathogen-derived proteins (antigens) with immunogenicity that can elicit the host immune system. Subunit vaccine is safe and easily manufactured by recombinant DNA techniques but requires adjuvant to enhance an immune response [21].

Novavax, Inc. developed a candidate vaccine based on S protein. So far, Clover Biopharmaceuticals constructed a SARS-CoV-2 S protein trimer vaccine (S-Trimer) by using its patented Trimer-Tag© technology [22].

mRNA Vaccines

mRNA carries instruction from the protein-encoding DNA to the proteins translating ribosomes. There are two types of mRNA vaccines platform: non- replicating mRNA and self-amplifying mRNA that encodes not only the required antigen but also the viral replication machinery.

mRNA vaccine is a promising alternative to traditional vaccine approaches due to their safety, potency, quick vaccine-development time, and low-cost production. The procedures to develop the mRNA vaccine include the screening of antigens, the optimization of sequences, modified nucleotides screening, delivery systems optimization, evaluation safety, and immune response [23-24].

Duke-NUS Medical School and Arcturus Therapeutics partnered to develop a self-replicating mRNA vaccine candidate, currently in a preclinical trial. BioNTech and Pfizer are collaborating to co-develop mRNA-based vaccine candidate BNT162 [25].

DNA Vaccine

DNA vaccines (DVs) have a plasmid into which a particular gene incorporated that encodes the antigens that identified from the pathogenic microorganism. DVs elicit both the cell-mediated and humoral immune system. DVs induce long-lasting immunity that defends the diseases effectively in the future. DVs are very stable, can be produced within weeks because they do not need culture or fermentation; instead used synthetic processes and began clinical trial within months. Currently, DNA vaccine not approved for the market [26]. Inovio Pharmaceuticals developed a DVs candidate termed INO-4800, which is in phase 1 (NCT04336410) clinical trial. Takis/Applied DNA Sciences/Evvivax and Zydus Cadila are developing a DVs candidate for COVID-19 disease which is now in preclinical studies [27].

Viral Vector-Based Vaccine

Viral vector vaccine works by carrying a DNA express or antigen(s) into host cells, thereby eliciting cell-mediated immunity in addition to the humoral immune responses. Viral Vectors Vaccines are characterized by strong immunogenicity and safety [28]. Several viral vectors are available for vaccine development including vaccinia, modified vaccinia virus Ankara (MVA), adenovirus (Ad), adeno-associated virus (AAV), retrovirus/lentivirus, alphavirus, herpes virus, Newcastle disease virus, poxvirus, and others. Viral vectors can be replicating or non-replicating viruses [29].

Currently, Can Sino Biological Inc. and the Beijing Institute of Biotechnology are developing Ad5- vector COVID-19 vaccine candidate in Phase 1(ChiCTR2000030906). Another adenovirus vectored vaccine developed by Chen Wei group entered in phase 1 clinical trial (NCT04313127). Johnson & Johnson is developing an adenovirus vectored vaccine using AdVac®/PER.C6® vaccine platforms. Shenzhen Geno-Immune Medical Institute also developing two lentivirus vector based vaccine candidates named COVID-19/aAPC and LVSMENP- DC [30].

Synthetic Peptide or Epitope Vaccine

Synthetic Peptide vaccines are chemically produced from fragments of antigens that elicit the immune response. These vaccines are inexpensive, easy for preparation, and quality control. But display low immunogenicity, thus antigen modification and adjuvant required during formulation [31].

Several pharmaceutical companies like Generex Biotechnology developing peptide based vaccines against SARS-CoV-2 viruses by producing synthetic peptides that mimic crucial antigens from a virus that is chemically bonded to the 4-amino acid Ii-Key to ensure robust immune system activation [32].

Virus-Like Particles Based Vaccine

Virus-like particles (VLPs) are “hollow-core” virus particles formed by the viral structural component with self-assembly character into nanostructure. VLPs represent advanced subunit vaccine with increased immunogenicity because they contain the structural protein of the virus [33]. VLP-based vaccines produced

Table 2: COVID-19 Vaccine candidates in phase III trials [35]

Candidate Vaccines in Phase III Clinical Evaluation	Vaccine Platform	Location of Phase III Studies
Sinovac	Inactivated virus	Brazil
Wuhan Institute of Biological Products / Sinopharm	Inactivated virus	United Arab Emirates
Beijing Institute of Biological Products / Sinopharm	Inactivated virus	China
University of Oxford / AstraZeneca	Viral Vector*	United States of America
CanSino Biological Inc./ Beijing Institute of Biotechnology	Viral Vector*	Pakistan
Gamaleya Research Institute	Viral Vector	Russia
Janssen Pharmaceutical Companies	Viral Vector	USA, Brazil, Colombia, Peru, Mexico, Philippines, South Africa
Novavax	Protein subunit	United Kingdom
Moderma / NISID	RNA	USA
BioNTech / Fosun Pharma / Pfizer	RNA	USA, Argentina, Brazil

for greater than 30 different viruses including GlaxoSmithKline's Engerix® (hepatitis B virus) and Cervarix® (human papillomavirus), and Merck and Co., Inc.'s Recombivax HB® (hepatitis B virus) and Gardasil® (human papillomavirus) [34].

COVID-19 Vaccines under Development

As of October 2020, there are 42 COVID-19 candidate vaccines in clinical evaluation, of which ten are in Phase III trials. There are another 151 candidate vaccines in preclinical evaluation. Phase III trials which usually require 30,000 or more participants, are undergoing. All top candidate vaccines being considered are given for intra-muscular injection. Most of the developed vaccines are designed for a two-dose schedule (exceptions with asterisk (*) in table 2 are single dose).

Conclusion

COVID-19 pandemic is increasing on massive scale on day to day basis. Spread of SARS-CoV-2 infection can be avoided by following good social practices and maintaining proper hygiene. The casualties are being controlled by providing the immediate medical attention and treating symptomatically. But for eradicating such a deadly virus a proper cure needs to be discovered. Many current researches on development of vaccine for COVID-19 is going on and have proceeded for third phase clinical trials. These potential candidate vaccines hold a promising ray of hope against finding a cure for COVID-19.

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Role of Thymosin Alpha 1 as an Immunoregulator Preventing Oxidative Stress and Cytokine Storm

Abstract

Thymosin alpha 1 (Tα1), a 28-amino acid peptide, which enhances T-cell, dendritic cell (DC) and antibody response, modulates cytokines as well as chemokines production and blocks the steroid-induced apoptosis of thymocytes. Tα1 is also proven to decrease tumor cell growth both in vitro and in vivo and has demonstrated therapeutic usefulness in several types of cancer. Tα1 exhibits a dual mechanism of action as an immunomodulator and antiviral. Recently many clinical applications have been researched to prove the efficacy of Tα1 as either a mono or adjuvant therapy in treatment and diagnosis of diseases associated with deficiencies and/or imbalances of the immune system.

Keywords: *Thymosin alpha-1, Immunomodulator*

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Introduction

Thymosin alpha 1 (Tα1), a 28-amino acid peptide (fig. 1), was first described and characterized from calf thymuses in 1977. This peptide enhances T-cell, dendritic cell (DC) and antibody response, modulates cytokines and chemokines production and block the steroid-induced apoptosis of thymocytes [1].

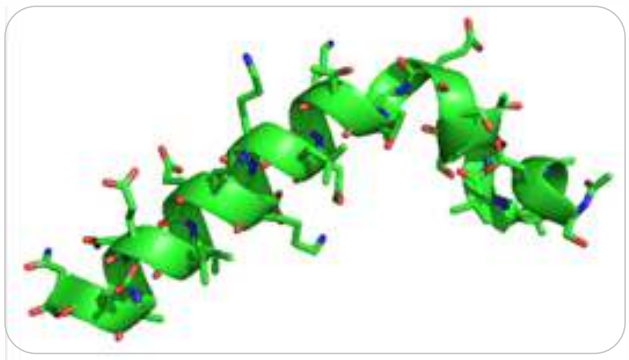

Figure 1: Thymosin alpha 1 (Tα1), a 28-amino acid peptide

Thymosin alpha-1 (thymalfasin) is produced endogenously by the thymus gland which increases T cell-mediated immune responses by several mechanisms (fig. 2), including stimulation of T cell, activation of natural killer cells and dendritic cells, and stimulation of proinflammatory cytokine release [2].

The research process of Tα1 began along with the study on the thymus, which is a vital organ for homeostatic maintenance of peripheral immune system. In 1966, *Goldstein et al*. first isolated and described a lymphocytopoietic factor from calf thymus, which was termed “thymosin”. The multiple action of thymosin on the immune, endocrine and central nervous systems was revised by Goldstein and Badamchian. Further purification of this factor led to the isolation of a heat-stable acetone-insoluble preparation, termed thymosin fraction 5, which could induce T cell differentiation, enhance immunological function and induce apoptosis of neuroendocrine tumor cells. The promising results seen with TF5 provided the scientific rationale to further isolate and characterize the molecules in TF5 responsible for the reconstitution of T-cell immunity. Hence, Tα1 was first purified from TF5 in 1977 and has been found to be 10–1000 times as active as TF5 evaluated *in vivo* and *in vitro* [1].

Due to its pleiotropic biological activities, Tα1 has gained interest in recent years and has been used for the treatment of various diseases in clinic. Accordingly, there is an increase in the demand for the production of this peptide. So far, Tα1 used in clinic is synthesized using solid phase peptide synthesis. Here, we summarize the genetic engineering technique to produce Tα1 using prokaryotic or eukaryotic expression systems. The effectiveness of these biological products in increasing the secretion of cytokines and in promoting lymphocyte proliferation were investigated *in vitro* studies. This opens the possibility for biotechnological production of Tα1 for the research and clinical applications [1].

Tα1 administration has been efficacious for SARS patients in controlling the development of the disease. Studies show that the treatment with thymosin α1 could decrease 28-day mortality in critical type COVID-19 patients, which suggest that thymosin α1 might improve host immune dysfunction and the poor prognosis of critical type patients [3]. Critical COVID-19 patients developed uncontrolled inflammatory activation, resulting in an increase in neutrophils and a decrease in the total number of lymphocytes, which are more significant in critical cases [4]. Whereas, lymphocytes play an important role in antiviral processes by balancing the fight against pathogens and decreases lymphocytes which are related to poor prognosis in many diseases [5][6].

CyTOF and microfluidic qPCR revealed that severe COVID-19 patients showed a decreased T-cell proportion, and T-cell activation as well as differentiation-related genes were downregulated [7]. Studies suggest that critical type COVID-19 patients with lower lymphocyte counts could obtain a significant benefit from thymosin α1 therapy.

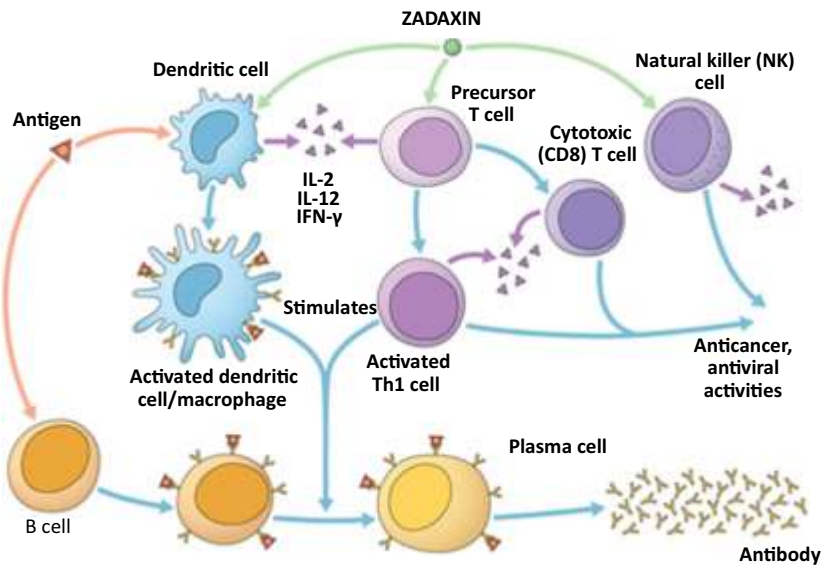

Figure 2: Immune-stimulating mechanism of action of Tα1.

Biological Activity

Immunoregulation

Many studies have been performed to identify the immunoregulatory activity of Tα1 *in vitro* and *in vivo*(fig. 3). Evidence suggest that T1 increased the efficiency of T cell maturation, stimulated precursor stem cell differentiation into the CD4+/CD8+ T cells and balanced CD3/CD4+/CD8+ T cells of peripheral blood mononuclear cells (PBMCs). By stimulating natural killer (NK) cells and cytotoxic lymphocytes (CD8+ T cell), Tα1 could directly kill virally infected cells [8].

Antitumor

Tα1 has been shown to decrease tumor cell growth both *in vitro* and *in vivo* and has demonstrated therapeutic usefulness in several types of cancers. Tα1 was observed to exhibit anti-proliferative effects on HepG2 human hepatoma cells and SPCA-1 lung adenocarcinoma cells. Moody et al. investigated the effects of Tα1 on mammary carcinogenesis in fisher rats and found that Tα1 could reduce mammary carcinoma incidence and prolong survival time [9].

Protection against oxidative damage

Tα1 had protective effects against oxidative damage. Tα1had a positive influence on liver superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity and thereby limited free radical damages to hepatic tissue. Similarly, it was reported that Tα1 could improve streptozotocin-induced pancreatic lesions and diabetes by reducing malondialdehyde (MDA), increasing GSH level and enhancing the activities of both SOD and catalase (CAT), suggesting that Tα1 treatment could greatly enhance the overall antioxidative capability of pancreatic tissues [10].

Other functions

Tα1 possesses the ability of influencing the central nervous system [11]. Its modulatory effect on the excitatory synaptic transmission in cultured hippocampal neurons was found [12]. Similarly, when it was combined with chemotherapeutics in treating cancers, Tα1 could prevent patients from chemotherapy-induced neurotoxicities [13]. Moreover, Tα1 has potent effects in promoting endothelial cell migration, angiogenesis as well as wound healing [14].

How Does Thymosin Alpha 1 Work?

Although the mechanism of action of thymosin has not been totally defined, but it primarily exhibits dual mechanism of action as immunomdulator and antiviral. Tα1 as immunomodulator increases the efficiency of T-cell maturation and to increase the ability of T-cells to produce lymphokines such as IFN, IL-2 and IL-3 following antigen and/or mitogen activation and to upregulate and express high affinity lymphokine receptors [15]. Thymosin is classified as a biological response modifier on the basis of these effects on lymphocyte markers and lymphocyte functional activity both in vivo and in vitro. Initial studies demonstrated that thymosin at induced markers of mature T-cell differentiation on lymphocytes from the bone marrow of adult thymectomized mice [16]. Subsequent studies defined thymosin to act as antiviral as it inhibits viral replication and also increases MHC class1 expression. This dual activity is perhaps the reason why Tα1 exhibits such a wide range of bioactivities.

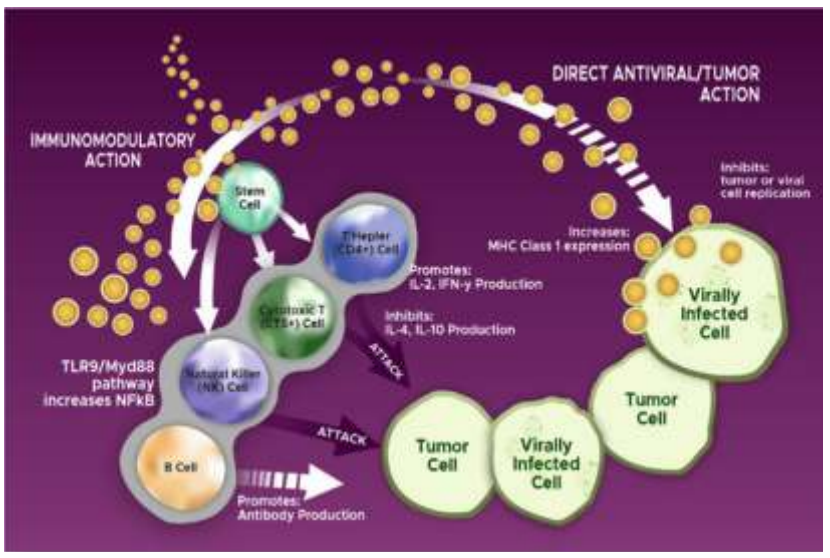

Figure 3: Immunoregulation and antiviral action of Tα1

Latest Studies on Use of Thymosin Alpha 1 in Treating Covid-19 Patients in Elderly Renal Dialysis Patient

Patients with end-stage renal disease (ESRD) on hemodialysis, in addition to their intrinsic kidney disease and frequent burden of comorbidities, also have increased risk of exposure to communicable diseases as they are treated several times each week at hemodialysis centers with several other patients and clinic staff in attendance. The majority of patients are over 60 years of age and many are receiving immunosuppressive medications. Accordingly, ESRD patients are particularly susceptible to COVID-19 infection.

Thymosin alpha 1, Tα1 is a naturally occurring peptide that has been evaluated for its immunomodulatory activities and related therapeutic potential in several conditions and diseases, including infectious disease and cancer. Tα1 has been used clinically in pilot studies for treatment of severe acute respiratory syndrome (SARS) and other lung infections including acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disorder (COPD), as well as infections after bone marrow transplant. Larger clinical trials have shown significant efficacy for treatment of severe sepsis and hepatitis B, along with certain cancers such as melanoma, hepatocellular, and lung cancer. Tα1 has also demonstrated improvement in response to vaccines in the elderly and in patients immunocompromised by renal disease. The beneficial clinical effects of Tα1 result from activation of toll-like receptor (TLR) 9 in dendritic and other immune system cells, resulting in augmentation of T helper (Th1) function, natural killer (NK) cell activity, and increased antibody responses to T-cell dependent antigens. Importantly, Tα1 also leads to an increase in IL-10 producing regulatory T cells, which create feedback inhibition of cytokine production, hence dampening immune response and preventing a pro-inflammatory cytokine storm.

It is our hypothesis that a course of Tα1 administered to individuals at high risk for COVID-19 infection (hemodialysis patients 60 years and older) will reduce the rate of COVID-19 infection and severity of infection with COVID-19, compared to untreated individuals in the same hemodialysis units with comparable risk. The study will also evaluate the need for hospitalization in those patients who do not become infected with COVID-19 [17].

Clinical Effect of Thymosin Alpha-1 on Various Diseases

Recently many clinical applications have been researched to prove the efficacy of Tα1 as either a mono or adjuvant therapy in treating and diagnosis of diseases associated with deficiencies and/or imbalances of the immune system. The many fields of

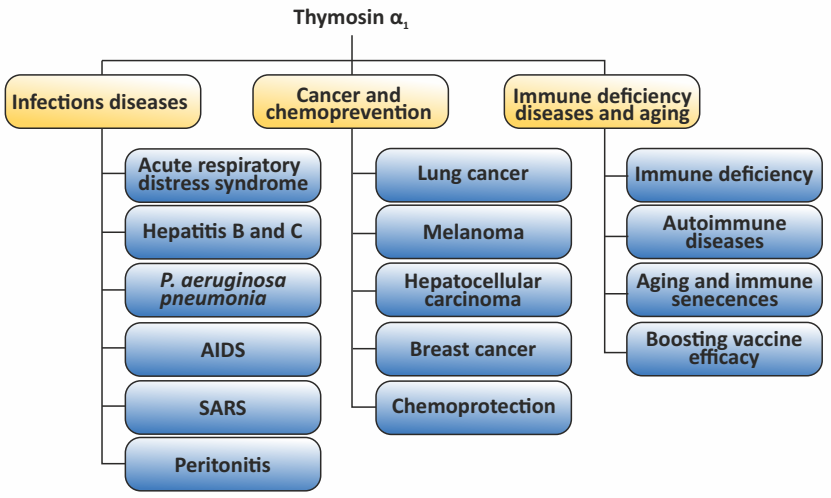

Figure 4: Emerging clinical applications of Thymosin α1 [1]

applications are shown in the figure 4 [18].

Infectious Diseases

Tα1 has been effective in improving immune responses and in arresting the progression of many viral, bacterial, and fungal infections in mice [19]. Moreover, many studies have been reported that indicate that Tα1 alone and/or in combination with other biological response modifiers (BRMs) is clinically effective in treating different infectious diseases [20].

Severe sepsis

Using Tα1 as a single agent, *Chen et al*, have reported that Tα1 upregulated immune function in patients with severe sepsis. Researchers observed that that using Tα1 in combination with standard antimicrobial therapy had significantly higher cumulative survival rate and it also shortened time of mechanical ventilation, use of antibiotics, and stay in the intensive care unit (ICU) [21]. *Zhao et al*, have reported similar results, with addition there were significant improvements in the number of lymphocytes and CD14+ monocytes and HLA-DR [22].

Acute Respiratory Distress Syndrome (ARDS)

ARDS has extremely high mortality rate and with patients on ventilation support. Study on ARDS patient who had recent renal transplant suffering from severe pneumonia found that after receiving Tα1 showed an improved outcome [23]. In a follow up trial, *Ji et al*, observed the death rate was significantly reduced; and also found that Tα1 significantly increased the number of CD4+ and CD8+ lymphocytes, suggesting that repairing cellular immunity reinforces resistance to CMV [24].

Severe Acute Respiratory Syndrome (SARS)

SARS is caused by novel coronaviruses, and the cure is still under development. *Gao et al*, in a study reported out that timely administration of a cocktail of antivirals, steroids and immuno-enhancers, including IFNα-2b and Tα1, to SARS patients was efficacious in helping to control the development of the disease and in improving patients' prognosis and controlling the spread of SARS [25].

Acquired Immune Deficiency Syndrome (AIDS)

Various studies suggest that thymosin may be useful in treating AIDS in combination with antivirals. A pilot study showed that Tα1 was effective in significantly increasing functioning immune responses [26]. In multicenter studies, a combination of Tα1 and zidovudine with IFN-α was found to improve and maintain CD4 counts and to reduce HIV virus titers [27].

***Pseudomonas aeruginosa* Pneumonia**

Pseudomonas infections are major clinical problems of immunocompromised and aging populations. Clinical report of Tα1 on critically ill hospitalized patients was carried out by *Huang et al*. They found a significant decrease of infection rate, white blood cell (WBC) count, C-reactive protein, TNFα, and IL-6 in their study [28].

In a follow up study patients were treated with Sulperazone and Tα1; *Li et al*, reported that immunological function improved and reduced inflammation, and had a synergistic effect on drug-resistant *P. aeruginosa* pneumonia [29].

Hepatitis B and C, Severe Chronic Hepatitis, and Spontaneous Peritonitis

Thymosin has been clinically indicated for treating the infections by hepatitis viruses. In the first reported pilot study, Tα1 was found to significantly improve the remission rate in advanced chronic hepatitis B [30]. Tα1 in combination with IFN-α and/or antivirals have also shown promise [31]. Study on patients with HCV, the remission rates in patients treated with Tα1 in combination with interferon were greater than those obtained with interferon alone [32]. In addition, other biochemical responses at the end was seen to be improved.

An interesting pilot trial in patients with severe chronic hepatitis (SCH) has been reported by *Gao et al*. They observed patients receiving Tα1 in addition to conventional therapy had improved survival [33].

Cancer

Many cancers are associated with significant deficiencies in cellular immunity [34]. In addition, standard treatments for cancer (i.e., surgery, radiotherapy and chemotherapy) usually depress cellular immunity.

Lung Cancer

The first randomized double-blind Phase II trial by *Schulof et al*, found Tα1 as an adjuvant to conventional radiation therapy significantly prolonged survival and increase the disease-free interval particularly in patients with nonbulky tumors, and with NSCLC [35]. Similar beneficial effects of Tα1 as an adjuvant to chemotherapy and IFN-α have been reported, along with an added ability to reduce the toxicity of conventional chemotherapy, in patients with NSCLC [36-37].

Melanoma

Late-stage metastatic melanoma is resistant to most forms of therapy. In the first trial of Tα1 by *Rasi et al*, they studied Tα1 in combination with DTIC and natural IFN-α. Patients showed an improved overall response rate with a shortened mean duration of response [38]. In the second trial by Lopez et al, done using Tα1 in combination with DTIC and IL-2; patients showed better response rate and lesser median time to progression [39].

In Phase II multi-center, randomized open-label study of patients with stage IV melanoma, trial was designed to evaluate different dose levels of Tα1 in combination with DTIC chemotherapy, with/without low-dose IFN-α. It was observed Tα1 at all dose levels was well-tolerated in all treated patients, with no serious adverse events attributed to the drug. Results reported as tripled overall response rate and extended overall survival time [40].

Hepatocellular Carcinoma (HCC)

There is a strong connection between HCC and chronic hepatitis B and C [41]. The first Phase II trial of Tα1 in patients with HCC was reported in Italy by Stefanini et al. They observed the addition of Tα1 following chemotherapy with doxorubicin significantly increased the survival obtained by transcatheter arterial chemoembolization (TACE) [42]. Many other subsequent clinical studies observed similar results.

Chemoprotection during Lung and Breast Cancers Treatment

The addition of Tα1 therapy appears to offer protection from some of the toxicities of chemotherapy. In a study by *An et al*, on patients with advanced lung or advanced breast cancer treated with chemotherapy found that Tα1 given before and after chemotherapy reduced neurotoxicities in patients [43].

In another study focusing on quality of life (QoL) issues in patients receiving chemotherapy by *Chen*, obtained results of significant increase in QoL scores in terms of appetite, sleep, fatigue, daily activity and overall feeling of well-being, and reduced depression [44].

Immune Deficiencies

Thymosin's modulate immune activity and may be used to restore depressed immune systems. Most of the congenital immune deficiencies are T-cell-dependent; that is, the defective immune activity is due to a partial or complete absence of mature T-cells, resulting from a deficiency of thymus hormone production [45-46]. Tα1 has been used to stimulate the formation and development of an effective T-cell immunity.

Autoimmune Diseases

Autoimmune diseases are distinguished by an abnormally sensitive and over-responsive immune system. In preclinical studies, Tα1 restored immune balance and increased the level of suppressor T-cells. Tα1 has been found to be safe and without either significant side effects or a narrow therapeutic index. In pilot clinical studies, Tα1, has relieved symptoms in rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome [47].

Aging and Immune Senescence

Immunity basically declines with age with contributing factors including a decline in thymus-related cellular function, an accumulation of memory cells, and dysregulated inflammatory mediators. Of these, T-cells, are most affected by age. This may be linked to the universally occurring age-associated thymus gland involution and resultant shrinkage of the naïve T-cell compartment [48-49].

A decline in T-cell immunity and possibly serum levels of Tα1 appears to correspond with an increase in immune senescence associated with aging, and studies suggest that Tα1 may be possible to improve immunologic responses in the elderly by manipulating the blood levels of thymus hormones [49].

Boosting Vaccine Efficacy

An early example of the use of Tα1 as an adjuvant to boost the efficacy of a vaccine in an immunodeficient patient population with renal disease on hemodialysis was carried out by *Shen et al*. They observed the patients receiving Tα1 responded positively with protective antibody levels to the hepatitis vaccine [50]. *Ershler et al* found that they could significantly enhance antibody responses and immunity to influenza with Tα1 [51]. Many other trials had similar results of the greater antibody levels with no toxicity observed.

Conclusion

Role of Tα1 in improving the immune response is long known since the discovery of the molecule over the last century. The advances in our knowledge of potential clinical application has improved since. Tα1 alone or in combination with other drugs or standard therapies offer many opportunities to boost and regulate the immune responses improving the outcomes. Recently many clinical studies support the use of Tα1 which in synergy with other treatment options; and are providing broad and novel insights into understanding the underlying mechanisms as well. Utilizing this knowledge we will be able to grow the ability to intervene in a number of serious life-threatening and/or chronic diseases with the ways in which the immune system affects disease processes.

This translate into the successful treatment of many diseases that have a high morbidity and mortality, while improving patients' quality of life.

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COVID-19 Pandemic and Management of Wound Care Patients in Home-Setting

Abstract

The COVID-19 (severe acute respiratory syndrome SARS CoV-2) pandemic has presented a great challenge and global threat. A wound is a disruption of the normal structure and function of the skin, possibly extending more deeply, and may be regarded as acute and chronic. The management of wounds in the present pandemic is a great challenge for the healthcare professionals. Multiple studies have shown that patients who have wounds also have comorbidities including diabetes, blood pressure, pneumonia, heart disease, respiratory disease, and are at greater risk of COVID-19. Due to multiple comorbidities, wound patients are at an increased risk for the most extreme complications of COVID-19 and healthcare professionals must focus on reducing their exposure risk by providing them proper care with less movement to the hospitals.

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Keywords: *COVID-19, SARS COVID-19, Wound, Wound Care, Pandemic, Ulcers.*

Introduction

First reported in December 2019 in Wuhan, China, COVID-19 has spread quickly, with confirmed COVID-19 cases in 220 countries worldwide till date [1, 2]. COVID-19, has disrupt normal healthcare setup bringing out extreme changes in the healthcare guidelines, healthcare practice, and hospitalization procedures. This has hampered the established best practices, affecting patients with critical, chronic, and other life-threatening disease who require continuous treatment and monitoring [3] leaving a large population without treatment and care [3, 4]. Particularly, the patients who require general medical and nursing support for injuries like the wound care management have been affected badly due to changed out-patient hospitalizations. Although, low-priority wounds can be managed in the home-settings by providing additional support to the patient through visiting nurse services with physician oversight through telehealth. High-priority wounds on the other hand will require additional services available in the clinic or hospital setting. Wound care centers have thus started the procedures of wound management from the home-setting. This has been done to minimize the chances of COVID-19 exposure among these vulnerable population as they may have cardiac, hypertension, chronic renal failure, chronic lung disease, neurological problems, and diabetes, which may worsen the existing diseased condition [5].

A wound could be an injury to the skin or underlying tissues, organs due to bruises, cut, friction or sheer force, pressure or as a result of disease (leg ulcers or carcinomas) or during a surgery [6]. The injury could rupture the skin preventing its protective function, continuous loss of epithelium which may or may not involve underlying connective tissues (i.e., bone, muscles, or nerves) [7]. A wound can be classified based on its etiology, anatomical location, or its severity (acute or chronic), presenting symptoms, method of closure, or the appearance of the predominant tissue types in the wound bed [8].

Chronic wounds are commonly occurring in 1 to 2 per 100,000 populations in the United States. Furthermore, in patients with diabetes and those over 65 years, lower extremity chronic ulcers predominate [9] with a prevalence ranging from 0.18-2% and up to 5% in patients over 65 years [10]. For managing chronic wounds during COVID-19 pandemic, modern dressing, use of technology such as negative pressure wound therapy, and tele-medicine could be an effective way to manage along with avoiding the exposure risk of COVID-19 [11].

The lower extremity wounds could be classified as follows [12]:

1. Wounds related to ischemic wounds
2. Wounds related to lymph venous problems
3. Diabetic foot ulcer (DFU)
4. Pressure ulcer

In the present paper, the management of different kinds of wounds described above is presented.

Ischemic Wounds: Cause and Management

Ischemic wounds occur as a result of blocked blood supply to vascular beds in the body. Most often these types of wounds occur on the legs, feet and toes. Particularly they occur on the shins, tops or sides of feet as well as the tips of toes or between the toes (where the skin tends to rub together). The increased consumption and insufficient supply of oxygen in the infected tissue lead to necrosis, resulting in spread of infection and deterioration of patient's health condition. In case of the infection and necrosis is not salvageable, amputation (trans metatarsal, below-the knee, or above-the-knee) should not be postponed. Blood flow to the extremity, age, general condition of the patient, comorbidities, anticipated length of postoperative hospital stay, and the anticipated need for re-amputations, and postoperative morbidity are the factors that influence the decision to amputate. The level of amputation is determined by a multidisciplinary team consisting of vascular surgeon, infectious diseases physician, orthopedic surgeon, plastic surgeon, endocrinologist or dialectologist, interventional radiologist (if present), podiatrist (if present), and hyperbaric oxygen physician (if present).

In patients with acute limb ischemia and wet gangrene with progressively tissue loss and ascending cellulitis, urgent surgical debridement should be performed to diminish the bacterial load. Broad spectrum antibiotics treatment must be administered immediately and continued postoperatively. In patients with chronic limb ischemia and non-salvageable limbs urgent surgery amputation is recommended. Non-salvage ability can be attributed to advanced lower extremity arterial disease, advanced tissue loss, poor health status of the patients precluding timely intervention or all of the above.

Patients admitted to vascular surgery outpatient ward with chronic peripheral vascular disease may have claudication with non-healing ulcers, while some may have pain in the lower extremity with ulcer or infected toes. The best medical care for this group includes revascularization followed by amputation of the affected toes and wound care [13]. Postponing surgical interventions follow-up on the outpatient basis is recommended. Revascularization and surgical debridement should be postponed, unless the wound are infected [13]. Zinc oxide can be used to prevent moist in the perimeter of the wound.

Prophylactic antibiotic treatment can be initiated in case of suspicion or history of secondary infection. If the non-healing wound (healing slow with a granulated wound bed), skin grafting procedure may be considered. The patients and/or their caregivers should be trained to apply wound care and change the dressings, preferably daily to avoid wound infection.

If the caregiver does not live with the patient, he/she should be trained about social distancing, providing wound care under sterile conditions, using a face mask all the time during wound treatment, and ventilating the room during or after each visit by the caregiver. The patient or the caregiver should be informed about how to use telemedicine such as clicking and sharing photographs with the healthcare staff.

Lymphovenous Wounds: Management Procedure

Compression therapy is the mainstay of the treatment for both venous and lymphedema ulcers, as edema, exudation, and exudation-related skin problems are common in these ulcers. Lymphovenous edema causes a dry, itchy skin, which may lead to loss of skin integrity and a rise in bacterial infection even after an unnoticeable physical trauma such as insect bite or itching. Once the infection starts, the wound enlarges rapidly, and the exudation increases. American Venous Forum Guidelines recommend a three component approach for the optimal treatment of lymphovenous wounds, as described below [14]:

- Treating the underlying venous disorder surgically, when possible
- Compression therapy
- Best wound care

Most of the lymphovenous bleeding episodes can be stopped with prolonged topical compression on the site of bleeding or suturing the veins under local anesthesia. It is strongly recommended to postpone all the venous surgical procedures during COVID-19 pandemic, with profuse bleeding of the varicosities being the only exceptional case to follow the recommended optimal treatment approach.

For the hospitalization need, it is recommended that priority should be given to the wounds: (i) with signs of systemic infection (ii) heavily exuding wounds with local skin infection requiring dressing change more than once a day; and (iii) Lymphovenous wounds with arterial insufficiency (mixed wounds) that need urgent revascularization, close follow-up, and intravenous administration of broad-spectrum antibiotics. The patients with lymphovenous ulcers are usually treated at the outpatient clinics where compression treatment is applied either with two or four-layer bandages which are changed twice a week [14, 15].

In addition to this, wound status and exudation volume, patient's social circumstances and economic status, or availability of the healthcare facilities determines the hospital visits. However it is recommended that during the pandemic or war times, the indications should be narrowed and the frequency of dressing should be reduced for the rest of the lymphovenous ulcer patients.

Shifting from bandages to compression hosiery and wraps

The patients and their caregivers should be encouraged to change their own dressings. Absorbent dressings such as alginates, hydro fibers, and foams, which can stay on the wound for more than three days may be preferred. Silver dressings can be combined to treat local infections or to prevent the wound from getting infected [15]. The frequency of dressing change can be determined according to the amount and nature of the exudation. In case of a suspicion of a local infection and highly exudation, it would be wise to perform daily wound cleansing and dressing. Swap cultures from the exudation or tissue cultures from different sites of the wound should be obtained in each hospital visit. Antibiotics should be given, when a local infection is suspected or systemic signs of infection are present.

Having said this, it is quite unusual for a patient or non-medical personnel to apply two or four-layer compression bandages in the right manner alone. Compression wraps for highly exuding wounds, infected wounds, and wounds with wound dermatitis that need frequent dressing change and application of creams are thus recommended. The most reasonable and frequently used options are compression hosieries and self-adjustable wraps. However, they have their own pros and cons. For example, ulcer stockings are difficult to wear, particularly in highly edematous legs, ulcers with stasis dermatitis, highly exuding or infected ulcers, irregular shaped extremities, in patients with peripheral arterial disease, or with orthopedic problems; and in elderly population with reduced muscle power who are unable to wear these tight stocking alone and in large ulcers due to pain caused by the stockings [16]. Self-adjustable wraps are available in the market for more than five years and their use has been increasing worldwide in elderly individual.

Shifting to more sparse follow-up intervals by keeping the bandages *in situ* for more than 4 days (between 5 to 7 days at most)

In patients who are not capable of changing their dressings and applying any form of compression treatment at home for any reason prolonging the follow-up intervals is recommended. For these patients superabsorbent dressings made of polymer and cellulose or multi-layers of standard absorbent dressings such as alginates, hydro fibers and foams should be used to avoid leakages, ruining the integrity of the bandages, and precluding dressing change earlier than planned. Non-adherent paraffin or silicon embedded interface dressings should be preferred in low exuding or dry wounds to avoid sticking of the gauze or other types of dressings to the wound.

Silver-containing dressings can be chosen in suspicion of local wound infection or bacterial contamination. If the patient or the caregiver desire to apply his/her own multilayer bandage, he/she can be trained in the outpatient clinic on how to apply bandages.

If passive wound dressings are not available, negative pressure wound treatment (or vacuum-assisted closure) can be used under compression bandages as an option, unless the patient has accompanying peripheral arterial disease. The foam can be left in place up to five to seven days.

Diabetic Foot Ulcer (DFU): Management Strategies

Although, diabetic foot ulcer treatment procedures, debridement, and amputations during pandemic circumstances can be neglected owing to increased risk of mortality from COVID-19. However, it should be noted that these are a fragile group at high risk of getting infected, losing a limb, or die if not treated promptly [18].

Prevention of DFU is not possible without active daily involvement of the patient, given the following recommendations: foot care, hygiene, and their glycemic index must be in control use of prescribed shoes and avoidance of dangerous conditions (i.e., hot sand in the summer). Education in DFU care may guarantee that the patient has adequate knowledge of self-foot care and may motivate the patient in daily prevention. For many years, the goal of DFU care was to heal wounds to avoid major amputations [4]. Therefore, a rehabilitation specialist should be responsible for diabetic patients who need to return to walking after a long period of immobility in both primary prevention (when neuropathy is responsible for the initial changes in standing and walking) and secondary prevention.

For managing the diabetic foot ulcers triaging the diabetic foot patients according to the presence of infection and limb ischemia is recommended. The triaging system was suggested to help inform the best setting in which to treat patients. This system applicable based on variety of wound etiologies and complications with only minor modification. The triage categories are presented below [3]:

- **Critical**- Temperature >38°C, tachycardia, tachypnea, abnormal white blood cell count, (or failed initial therapy), moderate infections (systemic signs), gas gangrene, sepsis, and acute limb-threatening ischemia should receive care in a hospital setting [5].
- **Serious**- Patients with mild to moderate infections including with osteomyelitis, chronic limb ischemia, dry gangrene, worsening foot ulcers, and acute

charcot foot should receive care in an outpatient's clinic, office based lab, surgery center, or podiatry office.

- **Guarded**- Patients with improving foot ulcer and inactive charcot foot (yet not stable in foot wear) could receive care in a podiatry office, or at home with oversight through telehealth.
- **Stable**- Patients with uncomplicated venous leg ulcers, healed foot wounds or amputation, and inactive Charcot (in stable footwear) can be treated at home or through telehealth.
- **Possible limb-threatening ischemia**- For patients with lower extremity wounds and possible chronic limb-threatening ischemia (CLTI), the wound ischemia, foot infection threatened limb classification system can also help stratify and triage patients. If the patients present with foot ulcer, severe systemic infection and acute limb-threatening ischemia, these patients are considered to have a high risk for mortality and limb loss; hence, urgent debridement followed by the revascularization procedure is advised. These patients must be hospitalized and treated with short-acting insulin promptly and intravenous broad spectrum antibiotic therapy [19]. If the patients present with foot ulcer with mild/moderate infection and acute/chronic limb ischemia, they should be accepted to have a moderate risk for limb loss and these patients must be hospitalized and the same aforementioned algorithm must be followed and elective revascularization must be performed during the hospitalization period.

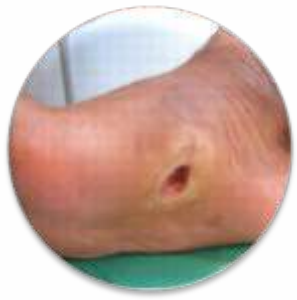
The other group of patients with infection are the ones who present with acute/chronic osteomyelitis or acute charcot foot. These patients belong to the low-risk group; however both require timely elective foot surgery and proper offloading with total contact casts.
Patients who develop the following conditions associated with wounds should be treated in a hospital setting:

- Some moderate and all severe infections, systemic inflammatory response syndrome, sepsis
- Wet or gas gangrene
- Limb-threatening ischemia (acute-on-chronic disease)

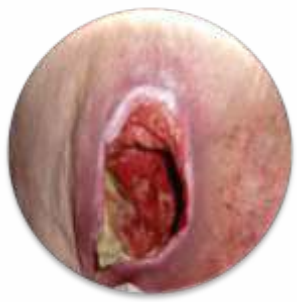
In addition to using mandated precautions to prevent person-to-person transmission of SARS-CoV-2, care of these patients may be modified in the following manner [20, 21]:

- For patients presenting with lower extremity wounds and without evidence of limb-threatening infection (e.g. wet gangrene) or acute ischemia, requiring surgical revascularization, may be deferred until after managing the acute wound issue.
- For patients with wound infection or cellulitis in association with chronic venous insufficiency or lymphedema, wound debridement, compression therapy, and antimicrobial therapy can be initiated. Vascular evaluation can be deferred to outpatient setting.
- For patients with localized osteomyelitis, debridement and antimicrobial therapy may be sufficient in the interim, allowing definitive management to be delayed.

Local wound care is initiated as the patient is discharged, and step-by-step instructions are provided for follow-up either in person or via telehealth. Clinicians must determine on a case-by-case basis whether hospital-based diagnostic studies (e.g. vascular ultrasound, computed tomographic, and magnetic resonance angiography) can be postponed. Diagnostic tests should only be performed if their results will change immediate management.



1a. Usually occurs on foot; Higher risk for amputation; Neuropathy inhibits the perception of pain and sensation.



1b. Patients bedridden for long time; Pressure on sites such as the heels, shoulder blades

Figure 1: Ulcers (a) Diabetic Foot Ulcer, (b) Pressure Ulcer

Pressure Ulcers

Pressure ulcers are caused by tissue compression over a bony protuberance or by inadequate perfusion. The wound is formed after a decrease in blood supply to the concerned tissue, or vascular damage to the tissue arteries. Tissues with a compromised blood supply or oxygenation are at risk for ischemia, leading to necrotic tissue formation. Any necrotic tissue should be removed as it promotes bacterial growth and delays wound healing. The patient should also avoid too little or excessive moisture. Protecting periwound skin is

helpful and most importantly reducing pressure over the wound area is suggested [22].

Step 1: Wounds should be covered with transparent film and warrant immediate preventative treatment: minimize friction at the wound site, using pressure-reducing products and correcting any existing malnutrition.
Step 2: Wound treatment consists of a moist dressing over the wound dressing. If necrotic tissue is present, consider occlusive dressings such as hydrogels to promote dead tissue enzyme digestion (autolytic debridement) rather than manual debridement.
Step 3 and 4: Wounds require debridement with a dressing, antibiotics if infected, then referral to the emergency department.
During this pandemic, wound care should not be overlooked and wound care with a regular follow-up needs to be considered as an essential service, requiring a regular provider-patient interaction only if very urgent to avoid the risk of getting infected [23].

Conclusion:

COVID-19 is now a worldwide pandemic presenting a considerable challenge for healthcare workers. In this context along with other chronic disease and delayed elective surgeries, the treatment of wound has also limited. The present guidance is based on practical experience and clinical treatment guidelines during the pandemic and guideline of relevant clinical experts. Wound should not be overlooked, must be cleaned with disinfectant and prevent from moisture. The diagnosis and treatment strategies described here should ensure that patient receive timely and reasonable treatment with effective COVID-19 prevention and control. It includes reasonable treatment and diagnostics of diabetic foot ulcer, lymph wound and ischemia wounds. In cases of any serious issue prefer to consult physician.

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Fosfona: Technically Superior Multilayer Sachet Packaging of Fosfomycin Granules to Preserve its Stability and Efficacy to Treat Resistant Infections

Abstract

Urinary tract infections (UTIs) are the most globally prevalent disease affecting all age groups. The recent emergence of resistant pathogens has led to the increased cause of morbidity and healthcare expenditure. Limited options of novel antibiotic agents and broad spectrum effectiveness of fosfomycin against the bacterial species has re-evaluated its position as potential therapy. With the advances in technology, the technically superior multilayer packaging of fosfomycin granules helps to preserve its stability and effectiveness to treat the resistant infections.

Keywords: *Fosfomycin, Urinary tract infection, Multilayer sachet packaging*

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Introduction

Urinary tract infections (UTI) are the most common type of infection found in outdoor patients. It is most prevalent in women than men with lifetime incidence rate of 50-60% [1]. The prevalence increases with age with approximately 20% over 65 years of age. It is the leading cause of morbidity and healthcare expenditures in persons of all ages globally.

UTI is the infection of urinary tract affecting both lower and upper tract. It may be community acquired or hospital acquired [2]. The causative agent behind infections are the bacteria. Different measures can be employed to treat and prevent the infections, but due to high pervasiveness of resistant bacterial strains the complete elimination of infection becomes difficult and the incidence of recurrence increases.

Urinary Tract Infection (UTI)

Urinary system constitutes the urethra, urinary bladder, ureter and the kidney. UTI is an infection that can affect any of these parts. If the part of lower tract consisting urinary bladder is affected, it is termed as bladder infection or cystitis. If the part of upper tract consisting of kidney is affected, it is termed as kidney infection or pyelonephritis [3]. The most common symptom of UTI is fever. Other symptoms of lower urinary tract infection include pain with urination, frequent urination, and feeling the need to urinate despite having an empty bladder [4]. Usually in addition to the symptoms of a lower UTI, kidney infection includes fever and flanking pain [3]. Clinically the UTI is diagnosed by the presence of cloudy urine with foul smell; and further confirmation can be done by urine culture identifying the bacterial strain in urine [5]. If infection in upper tract is suspected, complete blood count and blood cultures are required for confirming the source of infection via blood. Risk factors include female anatomy, sexual intercourse, diabetes, obesity, and family history [6]. Kidney infection is usually followed by a bladder infection, but may also result from a blood-borne infection. Females are more susceptible due to the short length of urethra, pregnancy, absence of prostatic secretion and feasible contamination of the tract with faecal flora due to nearby vicinity [7]. During infection, bacteria typically enter the bladder through the urethra and attach to bladder wall to form biofilm (figure 1), that can resist the body's immune response [8].

E. coli is most common organism causing UTI which accounts for up to 90% of cases. *P. mirabilis*, *Klebsiella species*, *P. aeruginosa* and *Enterobacter species* are less frequent offenders. Gram-positive organisms are less common which includes Group B *Streptococcus*, *S. aureus*, *S. saprophyticus* and *S. haemolyticus* [9].

Figure 1: Showing bladder infection of lower urinary tract

UTIs, Treatment and Resistance to Antibiotics

Clinically UTI is divided into two categories – uncomplicated UTI and complicated UTI. These categories can be further sub divided into – asymptomatic bacteriuria, acute uncomplicated cystitis, acute uncomplicated pyelonephritis and recurrent uncomplicated UTIs.

Uncomplicated UTI mostly affects healthy individuals, who does not have any structural or neurological urinary tract abnormalities; which includes cystitis and pyelonephritis. Complicated UTI happens to individual due to the factors that compromise the urinary tract; which include pregnancy, neurological disease causing urinary retention, renal failure, urinary obstruction, renal transplantation and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices [10].

Treatment of UTIs mainly include antibiotics, as UTI is commonly caused due to bacterial infections. The form of antibiotic used to treat a bacterial UTI usually depends on part of the urinary tract involved. Lower tract UTIs can usually be treated with oral antibiotics. Upper tract UTIs require intravenous antibiotics, which are directly inserted into veins. At times the patient does not respond to the course of antibiotic treatments going on, for this the specific strain of bacteria which has infected the patient needs to be determined for choosing the right type of antibiotic treatment. Besides this, bacteria may develop resistance to antibiotics. To reduce the risk of antibiotic resistance, it is essential to choose the shortest treatment course possible, and should typically last not more than 1 week

Commonly used antibiotics, includes trimethoprim/sulfamethoxazole (TMP/SMX), nitrofurantoin, or fosfomycin; are typically first line therapy [11]. Cephalosporins, amoxicillin/clavulanic acid, ceftriaxone, or a fluoroquinolone, ciprofloxacin may also be used [12]. However, antibiotic resistance to fluoroquinolones among the bacteria causing urinary infections has been increasing. Phenazopyridine can occasionally be prescribed for managing the pain during the therapy, along with acetaminophen to control fever.

Currently UTI is mostly managed empirically without urine culture or susceptibility testing.This may lead to the frequent misuse of antibiotics. The overuse or misuse of antibiotics is often the reason for antibiotic resistance. Antibiotic resistance makes the treatment ineffective, increasing the severity of the disease and incidence of high mortality rate.

Antimicrobial resistance remains the major problem in the therapy for UTI throughout the world. Fundamental mechanism of antibiotic resistance may be due to enzymatic degradation of antibiotics, alteration of bacterial proteins or changes in the membrane permeability to antibiotics. Antibiotic resistance can appear spontaneous because of random mutation or more commonly following gradual build up over time [13].

Fosfomycin

Fosfomycin is an antibiotic primarily used to treat bladder infections, generally prescribed orally. It was first discovered in 1969 and approved for medical use in 1996. It is on the World Health Organization's List of Essential Medicines; classified under critically important for human medicine. It was originally produced by certain types of *Streptomyces*, although it is now made synthetically [14].

Fosfomycin is a broad spectrum antibiotic, derived from phosphonic acid. It is considerably active against both gram-negative and gram-positive bacteria. Specially, fosfomycin is considered active against *Enterococcus spp.* (irrespective of vancomycin resistance), *Staphylococcus aureus* (irrespective of methicillin resistance), and *S. epidermidis* [15]. Fosfomycin also exhibits considerable activity against Gram-negative pathogens, including *E. coli*, *Salmonella spp., Shigella spp., Serratia spp., Citrobacter spp., Proteus mirabilis, Klebsiella* and *Enterobacter spp.* [16]. It is effective in treating the UTI infection caused by *Escherichia coli* and *Staphylococcus saprophyticus.*

Fosfomycin, Bridging the Gap

In recent times, the emergence of resistance pathogens has complicated the therapeutic approach to serious infections. Also, resistant pathogens are frequently being encountered in easily treated infections, like that of acute cystitis due to ESBL *E. coli* isolates. Limited options of novel antibiotic agents have necessitated the re-evaluation of fosfomycin, as a potential therapeutic option for infections caused by contemporary isolates with advanced antimicrobial resistance [17].

Observations have been made in regards to few bacterial species of resisting the intracellular killing after phagocytosis from neutrophils and persisting inside the host cell. Therefore, they can cause relapse of infections after few days resulting into recurrent diseases [18]. Based on studies, fosfomycin was been observed to penetrate inside the cells and assist in

to other antimicrobials, fosfomycin was more active than glycopeptides and daptomycin [19].

Fosfomycin, Mechanism of Action

Fosfomycin has bactericidal activity. It inhibits bacterial cell wall biogenesis by inactivating the enzyme UDP-N-acetylglucosamine-3-enolpyruvyltransferase, also known as MurA [20]. This enzyme catalyses the committed step in peptidoglycan biosynthesis, namely the ligation of phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-N-acetylglucosamine. This pyruvate moiety provides the linker that bridges the glycan and peptide portion of peptidoglycan.

Fosfomycin enters the bacterial cell through the glycerophosphate transporter [21]. After entering the cell, fosfomycin (aPEP analog) inhibits MurA by alkylating an active site cysteine residue (Cys 115 in the *Escherichia coli* enzyme) [22]; which prevents the formation of N-acetylmuramic acid, an essential element of the peptidoglycan cell wall.

Fosfomycin, Pharmacokinetics

The concentration of fosfomycin in serum is higher when it is administered before intake of food. Pharmacokinetic parameters indicate that absorption is significantly reduced after food intake. 58% of the administered dose is found in the urine within 24 hours [23-25].

Urinary concentration is high and may exceed 2000mg/L after administration of a single dose. Urinary levels remain high for a prolonged period (over 24hours) constituting an argument in favour of its use in the treatment of common urinary tract infections [25, 26].

Fosfomycin, Pharmacodynamics

Fosfomycin has demonstrated concentration-dependent killing in two different *in vitro* models. Fosfomycin activity uses kill curves at concentrations from 1x MIC to 64x MIC for isolates of *E. coli* and *P. mirabilis* [27]. When bacterial growth was assessed from time 0 to 24 hours, bacterial inhibition was directly proportional to fosfomycin concentration [27]. For *E. coli*, complete eradication was observed at 6–8 hours at fosfomycin concentrations ≥4x MIC [28].

Improved Bioavailability of Fosfomycin with Trometamol

When Fosfomycin is administered orally, it is partially absorbed by the small intestine by two mechanisms- (i) a saturable carrier-mediated system associated with a phosphate transport system, and (ii) a non-saturable process with first-order kinetics [29]. Studies with fosfomycin calcium have shown that before reaching the small intestine, fosfomycin undergoes acid-catalyzed hydrolysis in the stomach, where intra-gastric acidity and gastric emptying rate can affect the extent of fosfomycin's hydrolytic degradation and consequently its bioavailability [30].

Whereas, trometamol is a pH (i.e., alkaline) organic compound believed to slow acid-catalysed hydrolysis. As mentioned, fosfomycin trometamol is the most preferred oral formulation due to its improved properties compared to fosfomycin calcium, including higher bioavailability (F) which ranges from 33% to 44% [31] compared to 12–37% for the calcium salt [32]. It has been observed that when bioavailability was taken into account from urinary excretion data following oral and parenteral administration of fosfomycin trometamol, values as high as 58% have been calculated [33]. Despite the fact that the bioavailability of the two salts is diminished when taken orally, following food when taken under fasting conditions, serum concentrations of the trometamol salt are around 2–4 fold higher than the calcium formula of fosfomycin [34, 35].

Fosfona, Technological Advancement

The increased bioavailability of fosfomycin in granules form is considered for better treatment of urinary tract infections before the complicated UTI. It was taken into account that the improved bioavailability of fosfomycin has better patient compliance and will help in reducing the frequent hospital stays of patients for parenteral administration. Further, the complications with the granules were found with its stability and packaging of it. The hygroscopic granules of fosfomycin trometamol formed chunks and caking of the granules by absorbing moisture in different geographical conditions.

With further advancement of technology and studies, the outer and inner packaging is fused for a dual packaging of four layers. The packaging which comprises an inner layer having high water vapour permeability for packaging article, an outer layer having no or low water vapour permeability. The new advancement in packaging of the fosfomycin trometamol prevent the granules from caking into chunks and having a better stability in the long run, while the layers also serve as desiccants, while in storage. The technological advancement in the packaging led to the granules having caking properties which can be stored for a long term of over six months, especially over one year without accompanying occurrence of caking. The overall quality of the packaging helped the molecule reached to superiority in terms of quality for the reach to patients. The new sachet form with four layers has increased the shelf-life of the molecule in an unopened sachet for 3 years.

Dosage and Administration

The benefit of a single dose regimen and granule formulation with better bioavailability, fosfomycin has achieved an important place in the world of antibiotics. Fosfomycin trometamol is currently approved for use in several European countries and is approved as a single 3-g dose for treating uncomplicated UTIs in women, specifically UTIs due to *E. coli* infection [36]. The molecule has also been investigated as a potential therapy for surgical prophylaxis in order to prevent prostate infection and even as a treatment for prostatitis due to MDR Gram-negative bacteria [37]. The use of a multiple-dose regimen with fosfomycin trometamol has emerged as a potential strategy for treating of complicated and/or recurrent UTI, as well as infections due to MDR bacteria [38]. A study has suggested that a single dose of 3 g of fosfomycin trometamol in every 72 hours is sufficient to achieve the appropriate concentration to treat resistant pathogens causing recurrent UTI [39].

In premature infants, the recommendation is 100 mg/kg/day divided into 2 doses; for full-term newborns, 200 mg/kg/day in 3 doses is recommended. Starting at 12 years of age or 40 kg of weight, the dosage is the same as for adults. In the case of infections by multidrug-resistant microorganisms, there are no specific recommendations for children, while for adults the recommendation is 8-12 g/day for Gram-positive microorganisms and 16-24 g/day for Gram-negative microorganisms [40].

Fosfomycin is recommended as the first-line treatment of uncomplicated lower urinary tract infection due to broad spectrum, low resistance of uropathogens, high safety profile and good compliancy [41].

Fosfomycin trometamol should be taken immediately after dissolving the 3 g of granules in a glass of water.

Conclusion

The World Health Organization currently perceives that antibiotic resistance is one of the significant dangers confronting worldwide general wellbeing, especially given the decrease in the number of powerful antibiotics. In this regard, rethinking and re-examining of old antibiotics, fosfomycin has been proposed as a potential molecule in treating resistant bacterial infection of urinary tract. The emerging multi-drug resistance strains of *E. coli* and ESBLs can be treated with fosfomycin trometamol, with its low resistance chance due to its unique mechanism of action. Oral fosfomycin in a multiple-dose regimen has emerged as a potential strategy for treating complicated UTIs and prostatitis. The convenient single dosage and administration of fosfomycin is also an added advantage to the women, who are at higher risk of getting infected by UTI once in a lifetime. Due to the resistance rate of antibiotics, fosfomycin is an old and unique antibiotic that can reduce the burden of hospital stays and recurrent UTI. In the meantime, using fosfomycin as a monotherapy should be avoided due to the rapid development of resistance *in vitro*.

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Complipro - 1st Innovative and Patented Intra-Dialytic Protein Supplement for Patients on Dialysis

Abstract

Chronic Kidney Disease (CKD) is a progressive disorder associated with decreased Glomerular Filtration Rate (GFR) and/or increased urinary albumin excretion. In advanced kidney disease , dialysis leads to disturbance of nutritional and metabolic arrangement of the body. Protein-energy wasting (PEW) is increasingly becoming a clinical problem in maintenance hemodialysis patients and guidelines call for nutritional interventions. The complications make it a problem with high prevalence and treatment cost. The present article focuses on the various aspects of dialysis, its requirement, advantages and disadvantages, nutritional loss and their management, intradialytic nutrition, its advantage and recently developed new product which could be beneficial to the dialysis patients in replenishing protein and nutritional requirements.

Keyword: *Complipro, Intra-dialytic nutritional supplement, Chronic kidney disease, Hemodialysis, Protein supplement*

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Introduction

Chronic kidney disease (CKD) is a progressive disorder associated with the decreased glomerular filtration rate (GFR) and/or increased urinary albumin excretion [1]. Its global prevalence is considered as 8% to 16% [1]. The complications associated with CKD make it a problem with high prevalence and treatment cost [2]. The situation in India is not different from world and many factors directly contribute to high prevalence of CKD.

The core contributors to the CKD include:

- Low birth weight
- Malnutrition and hypovitaminosis A [3]
- Congenital anomalies and obstructive or reflux nephropathy
- Environmental factors and nephrotoxins
- Growing incidences of hypertension and diabetes mellitus
- Family history [4]

Chronic kidney disease refers to the 5 stages of kidney damage starting Stage 1 (eGFR > 90) to Stage 5 (eGFR < 15). A patient needs dialysis when he/she develops end stage kidney failure, that is loss of 85% to 90% kidney function and a GFR below 15 (Stage 5).

Dialysis is a process of eliminating excess solutes and toxins from the blood in patients whose kidneys fail to perform the functions naturally.

Dialysis can be used as a temporary measure in either acute kidney injury or in patients due for kidney transplant and as a permanent measure for patients ruled out for transplant [5]. The kidneys perform an important task of maintaining the body's internal equilibrium of water and minerals while produce erythropoietin, calcitriol, and rennin, function as a part of the endocrine system. Dialysis does not correct the compromised endocrine functions of the kidney but replaces few of the functions through diffusion and ultrafiltration [6] while using highly purified water [7]. Advanced kidney disease and its dialysis lead to disturbance of nutritional and metabolic arrangement of the body.

Dialysis and its Prevalence

The global burden of CKD continues to rise, enabling the need for cost-effective treatment along with it. According to the Global Burden of Disease (GBD) 2015 study, 12 lakh deaths, 1.8 crore years of life and 1.9 crore disability-adjusted life-years were lost from cardiovascular diseases, directly attributing to reduced glomerular filtration rates [8, 9]. The Global Burden of disease (GBD) 2015 study also estimated around 1.2 million deaths from kidney failure, with an increase of 32% in 10 years [9].

In 2010, 2.3–7.1 million deaths were estimated in people with end-stage kidney disease due to no access to chronic dialysis [10]. World Health Organization (WHO) estimated around 1.7 million deaths per year due to acute kidney injury [11]. According to WHO, 2.62 million patients received dialysis globally in 2010, and the need for dialysis was projected to double by 2030 [10]. The greatest increase in peritoneal dialysis utilization was reported in China, Thailand, and the USA in the past decade and it decreased in European parts and Oceania [12]. Asian countries have reported the largest absolute growth in patients on dialysis [12].

In India, GBD 2015 ranks chronic kidney disease as the eighth leading cause of death [13]. It is estimated that the population requiring dialysis is increasing at 10-20% annual rate with only 55,000 patients on dialysis in India [14].

As of 2017, over 1,30,000 patients were reported to receiving dialysis and the number is increasing by about 232 per million populations [15]. In countries like India, the screening of CKD patients is quite challenging and due to poor access to healthcare facilities, around 50% CKD patients are first reported when GFR is 15 ml/min per 1.73 m2 [15]. This is an alarming situation and there is an immediate need of robust screening of CKD patients.

Protein Loss in Dialysis Patients

In case of kidneys failure, the patient will need to start dialysis or have a kidney transplant to survive. Each treatment has its pros and cons. The decision to choose the treatment is based on the medical conditions, lifestyle, and personal preference.

The major pros of dialysis include maintenance of fluid balance, removal of wastes, and control of blood pressure while major disadvantage associated with dialysis is loss of 6-15 g amino acids [16] during each session and the loss of amino acids exert a great influence on hemodialysis membranes (fig. 1).

Malnutrition in Dialysis Patient

The CKD patients are prone to risk of malnutrition manifested by protein energy wasting and micronutrient deficiency. The various studies revealed high prevalence of malnutrition in paediatric and adult CKD patients in both developing and developed countries [17]. The paediatric CKD patients are stunted and malnutrition is considered responsible for growth failure in this population [18]. Based on subjective global assessment scale, a study reported that almost 31% adults with CKD (including dialysis and non-dialysis patients) had protein energy wasting [19].

The pathogenesis of nutritional loss or malnutrition during dialysis depends on various factors. Though it is not fully understood, the common pathway for all the nutritional and metabolic derangements is considered to be related to extensive protein degradation and a reduced rate of protein synthesis. The various etiological factors include reduced protein and energy intake due to anorexia, high protein catabolism, decreased anabolism, chronic inflammation, metabolic acidosis and hormonal imbalances [20-23]. Chronic inflammatory state in CKD result in resting energy expenditure, which in turn promotes catabolism of protein and reduced anabolism. The published studies revealed that during dialysis, resting energy expenditure increase (12-20%) [24], resulting increased demand for protein and energy intake.

High protein losses through dialysis, protein catabolism, and reduced albumin synthesis result in negative nitrogen balance and muscle wasting [20, 25]. If the loss of amino acids continues in CKD patient, it can lead to weight loss, muscle wasting, and reduced ability to fight against infections, which can ultimately lead to high mortality rates in hemodialysis patients. Reduced intake of dietary nutrients is a common aspect of advanced CKD. The epidemiologic published literature shows that prevalence of increased levels of inflammatory markers is high in CKD patients. Malnutrition is considered to exert serious consequences in patients with ESRD treated with maintenance dialysis and they are advised to be managed vigorously.

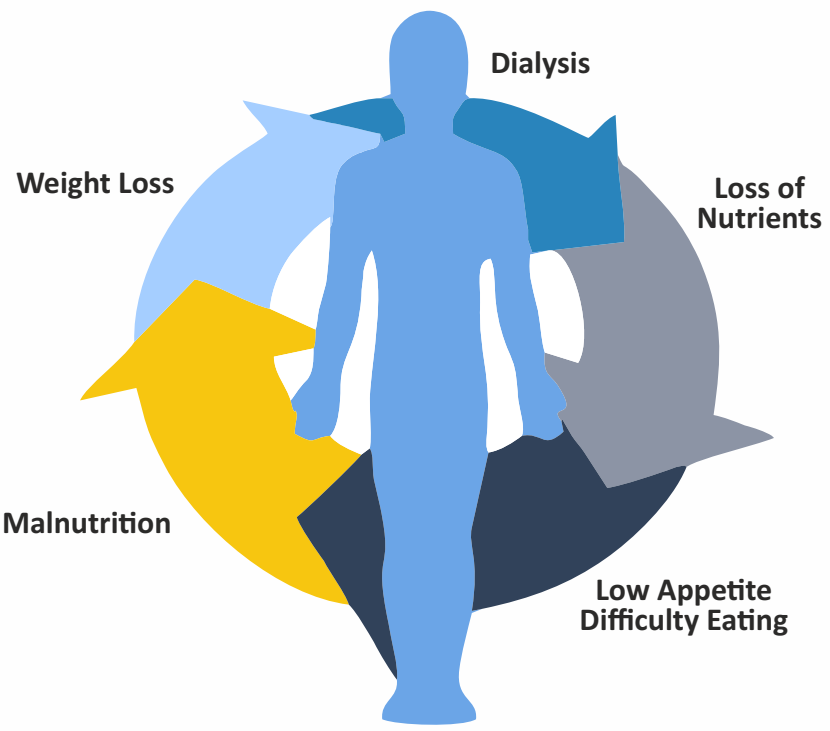

Figure 1: Cycle of protein loss and malnutrition in dialysis patients.

Current Management of Nutrition in Dialysis Patients

In CKD patients, malnutrition treatment requires a multidisciplinary, multifaceted and individual customized approach. Evaluation of the nutritional status is a key criterion to initiate the supplementation as per requirement. A clinically meaningful evaluation of the nutritional status can identify the risks and underlying causes and can help in choosing the possible benefits from the nutritional interventions [26]. For management of CKD during dialysis, nutrient intake through dietary supplements is increased. These supplements can be given by oral route or by parenteral route. The oral therapy includes intradialytic meals, oral nutritional supplements outside dialysis sessions, and tube feeding. If no improvement is reported then management can be done by intradialytic parenteral nutrition, intraperitoneal nutrition, and total parenteral nutrition.

Challenges Faced in the Current Nutritional Loss Management

Most of the appetite stimulating agents (megestrol acetate, dronabinol, cyproheptadine, melatonin, thalidomide and ghrelin) are available but the published data in CKD patients is not available; however, these agents are used in other catabolic illnesses [27]. Short and long-term benefits of oral nutritional supplements include improvement in whole-body and skeletal muscle protein balance [28]. The current nutritional supplements have risk of hypotension, quality of protein which may disrupt dialyzer settings, overall low quality profile with deleterious potential, and low compliance due to poor acceptability. The risk of hypotension may frighten nephrologists to recommend these supplements. Apart from low blood pressure, the other disadvantages reported were risk of aspiration and other respiratory complications; infectious control and hygiene issues; logistics constraints; and availability of a fraction of required meal [29]. The artificial flavors, certain additives have deleterious potential while powders requiring reconstitution and taste problems may compromise with acceptability. The benefits of nutritional supplements include corrections of intra- and post dialysis catabolism; an improvement in control of dietary phosphorus, potassium, salt and fluid; enhanced adherence to hemodialysis; and improved quality of life.

High protein dietary intake may result in higher intraglomerular pressure and glomerular hyperfiltration which in turn can damage glomerular structure leading to or aggravating CKD [30]. Hence, it is recommended to provide supplements with a low protein diet (LPD) of 0.6 0.8 g/kg/day for the management of CKD [30]. The LPD exerts favorable metabolic effects, which preserve kidney function and control uremic symptoms [31-33]. For rapid decline of GFR and initiation of dialysis, LPD as proper dietary regimen is recommended. In non-dialysis days, essential amino acids or their keto-analogs, along with supplemented LPD may be used for incremental transition to dialysis [30].

Innovative Approach to Protein Loss Management

Intradialytic Nutrition

Patients with end-stage renal disease often experience malnutrition as a result of decreased dietary intake; inadequate dialysis; loss of nutrients into the dialysate; abnormal protein, carbohydrate, and lipid metabolism; and concomitant diseases, which may contribute to an increase in morbidity and mortality. Intradialytic parenteral nutrition (IDPN) is being used to improve nutritional status, in conjunction with other methods of nutritional supplementation. The biggest advantage of IDPN is probably its convenience since it is administered during dialysis treatment and thus does not require additional clinic visits or prolonged dialysis time. IDPN has ability to improve nutritional status and reduce morbidity and mortality in patients with end-stage renal disease is promising.

Intradialytic nutritional support has been used for more than 30 years both in critically ill patients with acute renal failure and during maintenance hemodialysis. Present knowledge allows better estimation of its metabolic and nutritional efficacy, as well its effect on patient outcome. Recent data showed that intradialytic nutritional support is able to counteract these effects of dialysis on protein metabolism and to improve both nitrogen and energy balance. In maintenance hemodialysis patients, the improvement of nutritional status during nutritional support was shown to improve long-term survival. In critically ill patients with acute renal failure, protein sparing is one of the main therapeutic goals. The effect of nutritional support on patient outcome is not demonstrated. Recent data, however, showed that the improvement of nitrogen balance may be associated with a better outcome [34].

Advantages of Intradialytic Nutrition

There is a strong need of high protein product without other ingredients which could compensate amino acids losses and could also prevent the hyper catabolism. The published data suggest that use of optimal diet can prevent protein-energy wasting and enteral nutritional supports primarily targeting dietary protein intake. Intradialytic oral nutrient support can help in maintaining optimal protein preventing the muscle wasting and can enhance survival rate with reduced

hospital stay. Intradialytic oral protein supplementation helps in improving outcomes of dialysis which include improved nutritional biomarkers in CKD patients, decreased missed dialysis treatments, decreased all-cause mortality rates by at least 30% in dialysis patients, decreased hospitalization rate, and increased survival rate (fig. 2) [35].

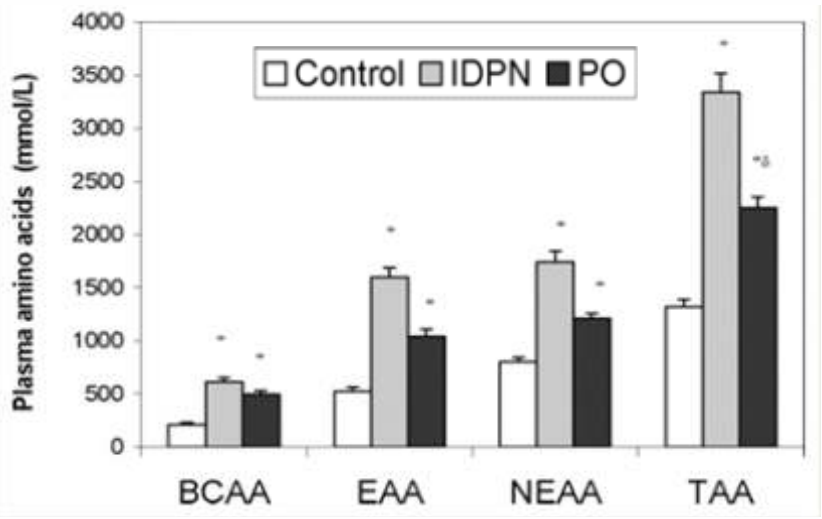

Figure 2: Total plasma amino acid concentrations by functional groups during hemodialysis (HD), comparing control, intradialytic parental nutrition (IDPN), and oral supplement (PO). Units are mol/L.*P<0.05 versus control; p<0.05 versus IDPN, BCAA, branched-chain amino acids; EAA, essential amino acids; NEAA, nonessential amino acids; TAA, total amino acids

COMPLIPRO: Innovative Ready-to-Drink High Protein Oral Supplementation

Intra-dialytic Protein Supplements- Right Choice, Right Proportion (COMPLIPRO)

Currently available intradialytic oral protein supplementations need reconstitution before consumption. The supplements available in powder form needs to be dispersed in calculated quantity of water which can be tedious to patients and can cause loss of nutrients while reconstitution.

Presently no marketed product is formulated or positioned as ready-to-use high protein oral supplement. Alniche, in collaboration with DPSRU, government of NCT has developed India's first intradialytic oral nutritional supplement, Complipro.

Importance and Benefits

Complipro helps to compensate the intradialytic amino acids losses in dialysis patients. During dialysis, Complipro prevents the hyper-catabolism through maintaining a positive amino acid balance during the whole dialysis session. Complipro prevents high protein loss by maintaining the intradialytic plasma amino-acid balance against replenishing the protein capital post-dialysis in comparison to the current products.

Complipro contains HIGH QUALITY protein that forms spherical complex structures (SCS) of 0.04 to 0.3 µm in diameter in homogenized form in liquid form. These are porous structures that allow the water/milk to move freely in and out of these spherical structures.

These SCS are stable yet dynamic structures that do not settle in solution while remain dissolved. They can be heated to boiling or cooled without adverse effects or affecting the nutritional properties of the protein. These contains all the essential amino acids in right proportion that body is unable to produce naturally. Most importantly, it provides a high amount of leucine, which initiates muscle protein synthesis.

SCS in Complipro are fairly simple in their structure, lacking the high degree of coils, turns, and folds found in many other proteins. In theory, they should move through the stomach quickly and transfer their amino acids into the bloodstream soon after ingestion. However, SCS are "Time Release Proteins" and assimilate slowly providing amino acid for longer period.

SCS, has hydrophilic (water-loving) portions of the protein on the outside of the sphere and the hydrophobic (water-fearing) portions on the inside. With hydrophilic structures on the outside, the spherical globules are soluble in water/milk. But when SCS reach the stomach, "one of the most ingenious events in nature takes place". Chymosin is a digestive enzyme that snips one of the bonds on the exterior protein (known as the kappa subunit), leaving only the hydrophobic subunits inside. Without their outer layer, now these proteins form a semi-solid structure. Thus, by effectively turning a liquid into a semi-solid, that passed on to small intestine for absorption and is the key of better assimilation.

In comparison to fast assimilating proteins, the SCS reduced the total amount of protein burned for fuel over a four to five-hour period leading to an improved net protein balance, a key factor for muscle growth and retention in dialysis patients. SCS is anti-catabolic, reduces protein breakdown within the body due to its slow digestion rate and sustained supply of amino acids to muscle cells for longer period and absorbed from microvilli of small intestine to keep dialysis patient satiated.

PDCAAS value (Protein Digestibility Corrected Amino Acid Score) of Complipro is one. This score means after digestion of the protein; it provides per unit protein 100% or more of the indispensable amino acid required.

Protein in Complipro remains completely dissolved in liquid and are passed on to small intestine to be absorbed through microvilli. Protein in Complipro is 100% assimilated, thus, patients will not have a feeling of flatulence and heaviness.

In addition, Complipro does not contain soya, added sugar, stabilizers and preservatives which is safe, long-lasting and cost-effective product. Complipro, is patient friendly and is available in single dose (1 "Tin can" ~ 150 mL/dialysis), can be stored at ambient temperature for 6 months with burnt coffee flavor.

Reconstituted Protein Powder: Inconvenience to Patients

While reconstituted Protein powders when dissolved in milk or water have following problems [36]: -

1. Incomplete dissolution: Addition of Protein powder in hot, cold or normal water/milk leads to formation of flakes or lumps because of improper wetting, sinking, dispersion and dissolving. This is due to two factors. Firstly, the surface of protein powder has hydrate-forming components forming a gel like structure around the powder preventing liquid to penetrate inside the protein powder. Secondly, hydrophobic layer or fat layer on the protein molecule prevents complete dissolution. Both these factors result in incomplete or inconsistent dissolution or even sinking of the protein powder at bottom of the glass while trying to reconstitute it.

2. Heaviness and Formation of Gas: The undissolved or undigested protein or 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 patients have tendency to pass foul gas too frequently.

3. Use of Agglomeration and Lecithination (Emulsifiers): These two techniques are being used, in order to make protein powers dissolve properly in water/milk. These methods have their own undesirable effects.

   - Agglomeration increases wetting property of protein powder, but repeated drying of protein powder also increases its denaturation
   - Lecithin is used to enhance the properties of instant milk powders. This involves dissolving lecithin in butter oil and spraying over the agglomerated milk powder, either internally or in a fluidized bed, and outside the dryer. It can cause some side effects including diarrhea, nausea, abdominal pain, or fullness.

Conclusion

The imbalance between protein synthesis and degradation seems to be the major driver for the disturbance, which can be mitigated by various anabolic strategies. Nutritional supplementation administered orally or parenterally, is an effective approach. Ready-to-use high protein oral supplement can be proven as an effective measure to prevent the amino acids loss during dialysis.

The demand for dialysis and renal replacement therapy is increasing rapidly.

Providing intradialytic meals or oral nutritional supplements to patients undergoing dialysis and other nutritional interventions can be one of the most promising interventions to increase serum albumin and to improve longevity and quality of life in this patient population. Ready-to-use high protein intradialytic oral nutritional supplement (Complipro) effectively helps in preventing high protein loss by maintaining plasma amino acid balance during dialysis. The current article throws light on the management of protein and energy intake in patients undergoing dialysis in a limited manner. Though these are the symptomatic preventive measures, the robust screening to detect the disease at the early stage and proper evaluation of the nutritional status of the patients undergoing dialysis are some of the key factors to manage the patients with kidney disease and government initiatives may play an important role in mitigating the disease.

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NIZRAL®- A Time Tested Globally Accepted Therapy for Seborrheic Dermatitis

ABSTRACT

Seborrheic dermatitis is a common inflammatory condition mainly affecting scalp, face, chest, back, axilla, and groin, characterized by a chronic relapsing course. Treatment with antifungal agents such as topical ketoconazole is the mainstay of therapy for seborrheic dermatitis. Nizral 2% formulated with micronized ketoconazole, a NHS-recommended ingredient for anti-dandruff shampoos, effectively relieves and prevents the symptoms of seborrheic dermatitis. Nizral 2% micronized ketoconazole shampoo solution is effective in the treatment of moderate to severe dandruff; however, ketoconazole 2% shampoo appears to be better tolerated. Many Antidandruff shampoos simply wash the dandruff away, but Nizral 2% addresses the root of the problem by helping treat the underlying cause of the condition and restoring the scalp to its normal healthy state. Yeast malassezia is responsible for dandruff/seborrheic dermatitis and using a treatment such as Nizral 2% helps to control it. Nizral 2% is a global brand of Ketoconazole shampoo solution, mentioned in most of the medical textbooks, with clinical legacy of 35 years.

Keywords: *Seborrheic dermatitis, Antifungal, Ketoconazole*

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Introduction

Seborrheic dermatitis (SD) is a chronic inflammatory dermatologic condition that usually appears on areas of the body with a large density of sebaceous glands, such as the scalp, face, chest, back, axilla and groin. Although it can be associated with human immunodeficiency virus infection and neurologic disease (e.g. cerebrovascular event, Parkinson disease) [1], seborrheic dermatitis typically occurs in healthy persons. Its prevalence is 1-3% in the general population and 34-83% in immunocompromised persons [2]. It has a bimodal distribution, with peaks at 2-12 months of age and in adolescence and early adulthood [2]. It is more common in men and is typically more severe in cold and dry climates and during periods of increased stress [3].

Seborrheic dermatitis (SD) is a multifactorial disease that requires several predisposing factors for its progress. Presence of these factors leads to reproduction of opportunistic yeast *Malassezia spp.* [4]. The fungus uses lipids from the skin surface to produce unsaturated and saturated fatty acids which, when left in the individual's skin milieu, induce an inflammatory response. The sebum in the skin aids the growth of *P. ovale (i.e. Malassezia)* and hence the development of SD.

Dandruff and SD are considered the same basic condition differing only in magnitude [5]. The development of effective drugs for treating dandruff/SD requires appropriate outcome assessment measures like presence and level of skin flakes for the quantitation of the condition of the scalp and assessment of therapeutic resolution [6]. Other such outcome assessment measures employed by various studies establishing the efficacy of a drug in SD mainly include total clearance of lesions at the end of treatment phase/maintenance phase, mean change in symptom scores, i.e. erythema score, scaling score & pruritus score and patient assessment methods (usually visual analogue score method) [7].

Diagnosis

Seborrheic dermatitis is a clinical diagnosis that is based on appearance of lesions and the location. In infants, it may present as thick white or yellow greasy scales on the scalp; it is usually benign and resolves spontaneously. In adolescents and adults, seborrheic dermatitis typically presents as flaky, greasy, erythematous patches on the scalp (Figure 1a), nasolabial folds (Figure 1b), ears, eyebrows (Figures 1c and 1d), anterior chest, or upper back [3].

The differential diagnosis is lengthy but the correct diagnosis can usually be made clinically by the characteristic distribution of lesions and varying course of the disease [8]. If the diagnosis is uncertain, a biopsy demonstrating parakeratosis in the epidermis, plugged follicular ostia and spongiosis can confirm the presence of seborrheic dermatitis.

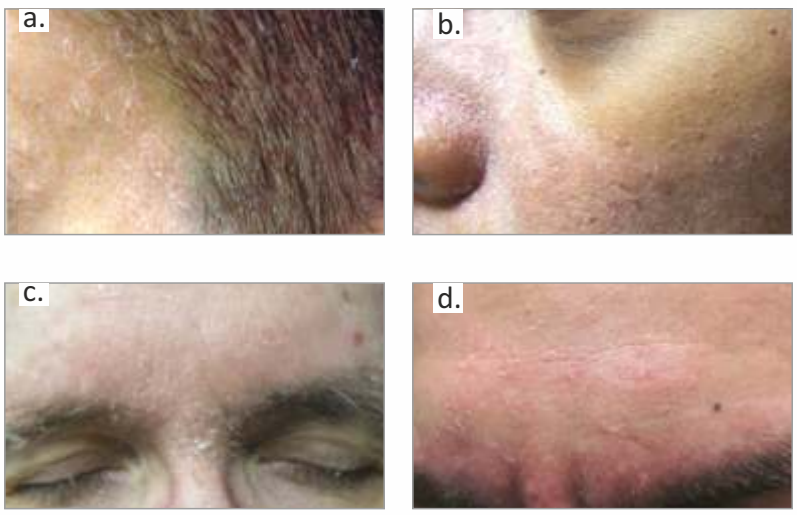

Figure 1: Clinical Diagnosis of Seborrheic Dermatitis: (a) Seborrheic dermatitis of the scalp; (b) Seborrheic dermatitis of the nasolabial folds; (c) Seborrheic dermatitis of the eyebrows; (d) Seborrheic dermatitis of the eyebrows

[GARY W. C et al., Diagnosis and Treatment of Seborrheic Dermatitis, Am Fam Physician. 2015;91(3):185-190]

Treatment Considerations for Seborrheic Dermatitis

Ketoconazole - A Topical Antifungal for Seborrheic Dermatitis Treatment

Seborrheic dermatitis (SD) is caused by yeast belonging to *Malassezia species*, which comes under fungal based classification. This mainly affects the skin surface producing excessive sebum (oily textured secretion) by sebaceous gland. In response to which formation of dead skin cells spreads up, which further flourishes fungal colony at the site of infection. Hence leading to characteristic symptoms, such as inflammation, flaky, greasy, erythemous patches with dandruff on oily skin surfaces [9].

Fungal infections can be tough to fight. There are many antifungal medicines which can be used for the treatment, such as selenium sulfide, zinc pyrithione, bifonazole, or clobetasol propionate. Steroids are also used for topical application. They are used to treat fungal infections, but total eradication does not occur and the site of infection on skin is prone for reinfection. Ketoconazole is an antifungal agent belonging to azole group of antifungal which is highly effective in treating such type of fungal infections [10].

Ketoconazole - Mechanism of Action

Fungal cell consists of outer cell wall and cell membrane. Ergosterol (ergosta-5,7,22-trien-3β-ol) is a sterol found in fungi. It is a component of yeast and other fungal cell membranes, functions as maintaining the membrane integrity, where it regulates permeability and fluidity [11]. Fungus cannot survive without ergosterol, and the enzymes that synthesize it have become important targets for drug discovery. As ergosterol is the main sterol of fungal membrane and yet is absent in animal cells, hence, a useful target for antifungal drugs [12].

Ketoconazole belongs to the azole group of antifungals. It is a fungistatic agent which causes growth arrest in fungal cells thereby preventing growth and spread of the fungus throughout the body. Ketoconazole inhibit the synthesis of ergosterol (the main fungal sterol) [13]. Ketoconazole targets the enzyme used for synthesis of ergosterol. The mechanism of action is believed to be based on the inhibition of fungal cytochrome P450 enzyme. This in turn impairs the biosynthesis of ergosterol (fig. 2). Ergosterol is a vital component of fungal cell membranes and changes the composition of other lipid components in the membrane. Impaired synthesis of ergosterol eventually leads to cell death and elimination of the fungus [14].

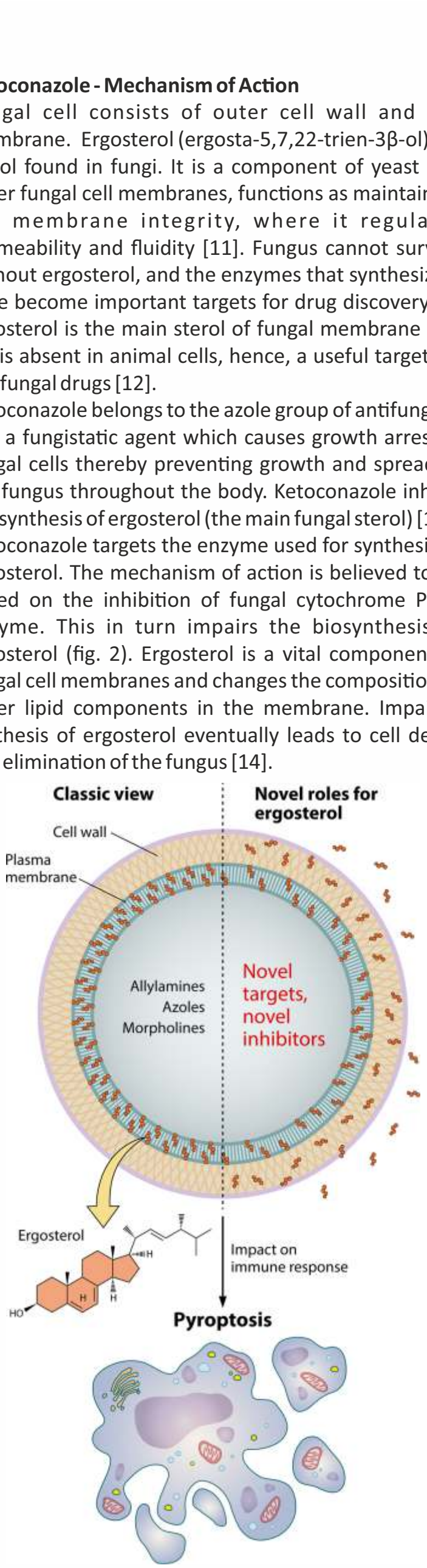

Figure 2: Ketoconazole inhibiting the synthesis of ergosterol (the main fungal sterol).

Research Studies on Ketoconazole for Seborrheic Dermatitis Treatment

Efficacy Study

For treatment of seborrheic dermatitis, topical solutions containing ketoconazole are found to improve the symptoms.

When severity of symptom is considered, many studies on ketoconazole shampoo compared with placebo are done. They showed ketoconazole shampoo is more effective than placebo at improving scalp symptoms such as scaling, itching, redness, and dandruff at 4 weeks in people with seborrhoeic dermatitis of the scalp [9, 15]. As per the Cochrane database of systematic reviews, the treatment with ketoconazole showed lowered side effects when compared with treatment done using steroids [10].

A multicentre study performed to investigate the efficacy of ketoconazole 2% shampoo in the treatment and prophylaxis of seborrhoeic dermatitis, observed that medication was well tolerated in all patients. Further, study conclude the therapy to be highly effective, not only in clearing scalp seborrhoeic dermatitis and dandruff, but also in preventing relapse of the disease when used prophylactically once weekly [16]. These results were supported by other study, in addition also mentioned the use of ketoconazole shampoo reduces hair greasiness significantly [17].

Comparative Analysis Study

Beside Ketoconazole there are other antifungal also which are active against *Malassezia species* yeast infections, and are believed to play an effective role in dandruff and seborrheic dermatitis treatment. But the efficacy of therapy varies and depends on the type of antifungal used.

A study was based on randomized, double-blind, placebo-controlled trial of ketoconazole 2% shampoo and selenium sulfide 2.5% shampoo for the treatment of moderate to severe dandruff. Results showed a decline in mean total adherent dandruff score throughout the treatment period with both ketoconazole 2% and selenium sulfide 2.5% shampoos significantly better than placebo, with overall reduction in irritation and itching. Data suggested ketoconazole was statistically superior to selenium sulfide. However, few adverse experiences during treatment phase were observed with selenium sulfide 2.5% shampoo; but not with ketoconazole. Henceforth, ketoconazole 2% shampoo appears to be better tolerated [18].

A 12-week long randomized parallel single center clinical trial was conducted on patients who presented moderate to severe dandruff. This comparative study was based on the prolonged antifungal effect of three proprietary shampoos containing either 2% ketoconazole, 1.5% zinc pyrithione or 2.5% selenium sulfide. The fact that ketoconazole 2% binds to keratinized structures of hair and skin; therefore, high concentrations remained on hair keratin (i.e. on hair shaft) up to 3 days after shampoo application. After following a 6-week antifungal shampoo treatment, data showed the increased duration of yeast reduction for the ketoconazole shampoo over the two other formulations [19].

Comparing the efficacy and safety of ketoconazole 2% and zinc pyrithione 1% in shampoo formulations for the alleviation of severe dandruff and seborrheic dermatitis, an open multicentre randomized parallel-group trial was conducted. Clinical assessments showed that beneficial effects were evidenced for both medicated shampoos, but the effect was significantly better for ketoconazole 2%, and recurrence rate of the disease was also significantly lower. The results of the study complied with previous finding; and were noticeable and consistent. This concluded that after a 4-week treatment, ketoconazole 2% shampoo was significantly superior to zinc pyrithione 1% shampoo for treating severe dandruff or seborrheic dermatitis of the scalp [20].

Guidelines for Ketoconazole

<u>International – WHO 2014 guidelines</u> [21]

- "Topical ketoconazole is safe with an excellent benefit v/s side effect profile."
- "Topical ketoconazole 2% was graded as a strong recommendation for mild seborrheic dermatitis, and topical corticosteroids graded as a strong recommendation for severe seborrheic dermatitis."
- "Ketoconazole is the most studied and has the strongest evidence for its effectiveness."

<u>Asia</u>

- Cheong 2015 [22]: "Treatment of Seborrheic Dermatitis in Asia: A Consensus Guide."
- Ketoconazole recommended for treatment of mild-moderate SD of scalp and non-scalp SD.

<u>Danish Dermatology Society Guidelines [23]</u>

- Give highest strength recommendation for use of ketoconazole 2% in SD & PV based on highest quality available evidence.

<u>United Kingdom</u>

- NICE CKS [24]: recommend treatment with Ketoconazole 2% shampoo for SD.
- British Association of Dermatologists [25]: recommends the use of ketoconazole shampoo for scalp and body SD.

Product Unique Features

1. <u>Micronized Ketoconazole:</u> Nizral is manufactured using micronized technology. No particle of

ketoconazole observed above 50 microns. This unique formulation/technology leads to better penetration. Nizral (Micronized Ketoconazole) gets uniformly distributed in the affected dermis/epidermis resulting in greater degree of efficacy.

2. Potent Antifungal: Effectively kills the fungus that causes dandruff. Nizral contains ketoconazole which belongs to the "azole" group of antifungals. Ketoconazole acts by intervening ergosterol (the main component of *Malassezia* cell membrane) biosynthesis. By inhibiting ergosterol synthesis, the cell membrane function is disrupted, increasing permeability of the cell, leading to cell death.

3. Anti-inflammatory & Anti-proliferative: Relieves itching associated with seborrheic dermatitis and dandruff. Also reduces flaking, scaling and ensures higher cure with lower recurrence rates.

4. High Keratinophilicity: Nizral exhibits a strong activity against the yeast *Malassezia ovalis* and is most active antidandruff shampoo with prolonged effect. Persists in hair up to 72 hours.

5. Low viscosity: Nizral's molecular makeup results in very little friction when it is in motion which allows easy spreadability on the scalp.

6. Convenient dosage: One application per wash

How to Use Nizral 2%:

1. Apply Nizral to wet hair and massage gently to loosen flakes from scalp.
2. Leave Nizral on your scalp for 3 – 5 minutes.
3. Rinse thoroughly with water.

Dosage & Administration

As a shampoo for seborreic dermatitis and dandruff	For child 12-17 years & adults
Treatment	Apply twice weekly for 2–4 weeks, Leave preparation on for 3–5 minutes before rinsing
Prophylaxis	Apply every 1–2 weeks, Leave preparation on for 3–5 minutes before rinsing

As a shampoo for pityriasis versicolor	For child 12-17 years & adults
Treatment	Apply once daily for maximum 5 days, Leave preparation on for 3–5 minutes before rinsing
Prophylaxis	Apply once daily for up to 3 days before sun exposure, Leave preparation on for 3–5 minutes before rinsing

How to use Nizral® 2%

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TREAT

THE ROOT CAUSE OF
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- Anti-fungal, Anti-inflammatory, Anti-proliferative and Sebostatic[2,3]
- Relieves redness, flaking and itch[4]

#1 Hald, M., Arendrup, M. C., Svejgaard, E. L., Lindskov, R., Foged, E. K., & Saunte, D. M. L. (2015). Evidence-based Danish guidelines for the treatment of Malassezia-related skin diseases. Acta dermato-venereologica, 95(1), 12-19.
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nailKALM®, Nature-based Solution for Onychomycosis: A Widely Prevalent yet Underdiagnosed Disease

ABSTRACT

Onychomycosis is a fungal infection of nails. It is most common disease accounting up to 50% of nail disorders and effecting 10% of world population. Mild forms of onychomycosis are typically considered a cosmetic issue, but it can develop into a serious health risk if not addressed early, especially for diabetics and the elderly. The disease is highly contagious and is caused by a group of fungi – dermatophytes, moulds and yeasts. Current treatments are potentially toxic or have low efficacy. A novel topical agent, nailKALM®, based on a naturally-derived extract (AMYCOT®) from the microalgae Spirulina, is a promising addition to the arsenal in the fight against onychomycosis.

Keywords: *Onychomycosis, Fungal Infection, Tinea unguium, Arthrospira maxima, nailKALM, AMYCOT*

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Introduction

Onychomycosis is the fungal nail infection which causes nail's discoloration, thickening and separation from nail bed to occur. It takes place in both fingernails or toenails but the most commonly takes place in toenails. It is caused by variety of organisms but in most of the cases it is caused by dermatophytes. Widely, onychomycosis is considered to be a cosmetic problem but it can be more harmful and can cause cellulitis in older adults [1] and foot ulcers in patients with diabetes. [2] Onychomycosis can cause discomfort, disturbance and pain and serious physical limitations may occur.

Onychomycosis significantly affect negatively patient's social, emotional and occupational status. Patients affected by onychomycosis may experience embarrassment socially and occupationally due to their unclean and unhygienic nails. Employment also suffers in the cases, if field of work is related to interacting with persons, food handling or modelling. In this case, possibility of transferring pathogen from infected person to unaffected always exists. In persons with low immunity such as HIV patients or Dialysis patients, onychomycosis may cause severe health problems [3].

Epidemiology

Onychomycosis was found to be the most common fungal disease in foot diseases in a 2003 survey of 16 European countries and its universality in that survey estimates at 27% [4, 5]. Almost one in three of diabetics is affected by onychomycosis [6] and is 56% more frequent in people suffering from psoriasis [7].

Around 5-10% of the global population is estimated to be suffering from onychomycosis [8-14]. It is prevalent in hot and humid areas but is also known to persist in temperate regions, especially during the winter months. During this time, the feet are heavily covered from the cold, generating a moist environment from sweat and poor aeration, which promotes fungal growth.

The incidence of onychomycosis is observed to be increased with age, 20% among 60-year old adults and 50% of any adult older than 70 years [12]. Incidence among children is very low at <0.5% but with increasing incidence of tinea infections among infants in India this may change. Surveys indicate that onychomycosis is more prevalent among adults than children below 18 years old.

Risk Factor

The major risk factors for onychomycosis are age, obesity and diabetes. The correlation of increasing age and incidence of the disease can be attributed to changes in the nail structure related to poor blood

circulation, auto-immune disease, reduced immunity and even altered biomechanics that may cause nail trauma. These factors may increase an individual's susceptibility to fungal infection [8-14].

The disease is also common among pregnant or nursing women which may be related to their increased risk for diabetes. Neuropathy or decrease in the sense of touch including poor circulation among diabetics, increase their risk to nail trauma which makes them susceptible to onychomycosis.

Weakened immune system is also a major risk factor for this condition. Cancer [15], immunodeficiency [16] and peripheral arterial disease [17] have been associated with increased susceptibility to onychomycosis. A genetic predisposition to susceptibility to onychomycosis has also been identified [18].

Onychomycosis is highly contagious. Community spread is a major source of transmission of the disease. Going bare foot in damp places like shower rooms, gyms, swimming pools, having minor skin or nail injury, sweating heavily, as well as shared clothing and gear; are also a risk factor for the infection. Therefore, basic hygienic practice can go a long way in preventing transmission and contracting the disease [11-14].

Clinical Impact

Onychomycosis may initially appear as a blemish or cosmetic defect on the nail. However, if it is left untreated, it can worsen into nail dystrophy, which can lead to pain, discomfort and disfigurement. These complications can lead to physical and occupational limitations as well as reduction of quality of life. If onychomycosis is not managed well, especially among diabetics, it can develop into serious complications such as cellulitis, paronychia and gangrene which can eventually lead to limb loss or amputation [11-14].

Since onychomycosis is readily transmitted, early treatment and management of the disease can prevent the disease from spreading within the household and to the community [11-14].

Onychomycosis

Onychomycosis often arises from a damaged nail that is infected by a fungus or develops from pre-existing fungal skin infections of the hand and feet spreading towards the nail bed or cuticle and eventually penetrating the nail plate (Figure 1b) [13-14].

Almost 90% cases of onychomycosis of toenails and 50% of the fingernail infections are caused by Dermatophytes. Dermatophytes includes the members of genera *Microsporum, Trichophyton*, and *Epidermophyton.* Onychomycosis is due to a dermatophyte infection on nails, it is termed tinea unguium. But Onychomycosis can also be caused by non-dermatophyte molds (such as *Scytalidium* and *Scopulariopsis*) on skin, nail or hair [19] and is termed as Dermatomycoses; estimated to cause 2% of fungal nail infection. The other agent being yeasts (mainly *Candida*) accounting for 8% of total onychomycosis cases.

Anatomy of Nail

Nail is a keratinous structure at the tip of the fingers and toes. Anatomy of nail (Figure 1a) consists of the structures as cuticle, matrix, nail plate (commonly called the nail), proximal and lateral folds, nail bed, and hyponychium.

- The nail matrix is the origin of the nail and the site where nail cells multiply and keratinise (formation of the nail) before incorporated into the fingernail or toenail. The matrix starts under the skin below the area of the cuticle where the finger or toe skin meets the nail (nail fold) and covers the half-moon shaped area (lunula).
- The cuticle is an area of modified skin where the finger or toe meets the nail. The cuticle acts as a protective barrier for the nail matrix against infection
- The nail plate is actual nail and protects the nail bed.
- The nail bed is the tissue under the nail plate and serves as an anchor to the nail plate.

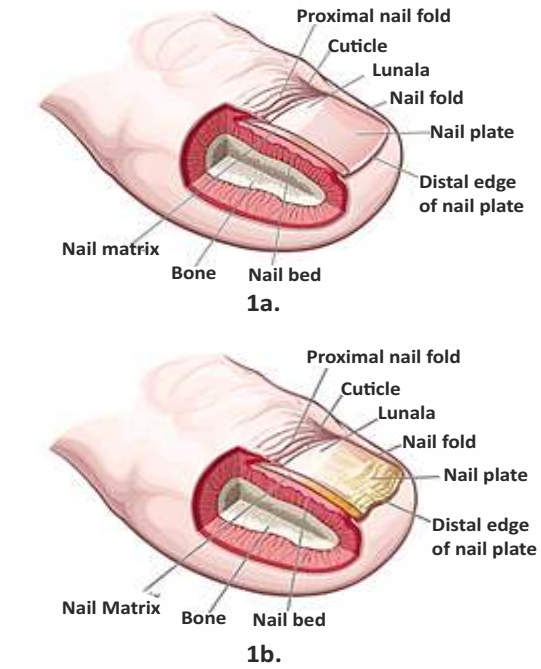

Figure 1: Anatomy of a human nail and onychomycosis

Classification of Onychomycosis

Onychomycosis can be classified into 5 different types (Figure 2) depending on its location, morphology, aetiological fungal agent and progression of the disease [14]. Patients can have one or a combination of the different subtypes in different digits of the patient's hands or feet. Total dystrophic onychomycosis is the most advanced form among the different subtypes and typically presents itself as a thickened, opaque and yellowish-brown nail.

Distal Lateral Subungual Onychomycosis (DLSO): The most common form of tinea unguium. Commonly caused by *Trichophyton rubrum*, which invades the underside of the nail plate and nail bed [19]. The infected nail is usually yellowish-white in colour. Streaks of yellow or yellowish onycholytic areas are observed in the central portion of the nail plate.

White Superficial Onychomycosis (WSO): This is usually confined to toenails. Commonly infected by moulds; but T*richophyton mentagrophytes*, a dermatophyte is the common aetiological agent. It is caused by invasion of the superficial layers of the nail plate to form 'white islands' on the plate and can progress into the nail bed. Typically, small, white, speckled or powdery patches are observed on the surface of the nail plate which roughens the nail and makes it to crumble easily.

Proximal Subungual Onychomycosis (PSO): It is a very rare infection and the least form of tinea unguium but can be found more commonly when the patient is immunodeficient [19]. Characterised by white lines or dots near proximal nail fold in newly formed nail plate that moves distally with nail growth. Fungi (mainly dermatophytes, especially *Tricophyton rubrum*) invade the cuticle and then penetrate the nail plate.

Endonyx Onychomycosis (EO): It is characterized by Leukonychia, a condition where white lines or dots appears on finger or toe nails, along with a lack of subungual hyperkeratosis or onycholysis [20]. Fungi invade the nail plate via direct spreading from the skin instead of the nail bed.

Candidal Onychomycosis: It is the invasion of the fingernails by Candida species. It is typically found on fingernails and usually occurs in the persons whose hands frequently comes in contact with or immersed in water. Prior damage of the nail by infection or trauma is normally required in this.

Figure 2: Different types of onychomycosis, a fungal infection

Antifungal Therapy for Onychomycosis

Treatment can range from direct killing of the fungi (fungicidal) or limiting fungal cell division and propagation (fungistatic) or to removal of the infected nail (debridement). The approaches range from pharmaceutical, physico-mechanical and natural agents.

Oral Anti-Fungal Drugs: The most effective class of anti-fungal drugs against onychomycosis are oral anti-fungals which act systemically. This class of drugs inhibit certain metabolic enzymes of fungi required for its growth and survival. However, these drugs have serious liver toxicity limiting its application especially for the elderly, diabetics, children and women. Terbinafine, Itraconazole and Griseofulvin are examples of these drugs.

Topical Anti-Fungal Drugs: Although local and topical application of anti-fungal drugs would be more convenient and safe than the oral route, re-formulation of known effective drugs such as terbinafine as topical agents have been not as successful to date. The major challenge has been the difficulty of the drug penetrating the tough nail plate and its keratinous structure. Given the limited efficacy of topical anti-fungal drugs, they are often prescribed for treating mild to moderate onychomycosis and is not used with patients with total dystrophic onychomycosis. Ciclopirox, Amorolfine, Efinaconazole and Tavaborole are few drugs under this category.

Debridement: Debridement is the physical removal of an infected nail bed or viable nail plate. It is a common practice among podiatrists and represents an option for 30% of onychomycosis patients [21]. The practice can be applied mainly to improve appearance of the nail and comfort, but does not necessarily cure the infection. Thus, any residual fungal spores or fungi may not be totally eliminated, therefore the possibility of recurrence is high.

Laser Therapy: Laser therapy is an emerging modality for treating onychomycosis [10, 14]. There are limited clinical studies to validate its efficacy, but it is considered a promising option. Lasers improve cosmetic appearance by increasing the clarity of nail in the patients with onychomycosis. Thus are approved for the temporary clearance [10], as noted that there is insufficient data to confirm the fungicidal property of lasers.

Natural Treatment: There have been reports of natural treatments for onychomycosis such as vinegar (acetic acid) and tea tree oil. In addition, there are numerous

generic formulations of OTC onychomycosis treatments that contain an organic acid such as lactic acid, undecylenic acid and acetic acid. It is known that organic acids have anti-fungal activities. However, there are limited controlled clinical studies demonstrating the efficacy of these treatments [13].

Combination Therapy: Since most of therapies have low efficacies, combination therapy may have an additive effect especially if the modalities have different mechanisms of action and can complement each other. For mild to moderate infections, a combination of an oral and topical drugs is the current strategy employed in India. However, this may not be an option for pregnant or nursing women due to toxicity concerns with the oral drugs. However, a combination of laser therapy or debridement with topical agents may offer a better alternative.

Managing Onychomycosis and Educating Patients to Avoid Relapse

Relapse of onychomycosis is relatively high due the presence of fungal spores which may not be eliminated from the different treatments. Furthermore, fungi are ubiquitous and one can readily contract either the organism or its spores. Once the right conditions of humidity and temperature are reached, fungal growth can readily initiate. Therefore, it is important to avoid contraction as well as keeping a clean and well-ventilated environment for the hands and feet [11-13].
Educating patients about their role in treatment plays a very crucial role in eradicating the infection. Patient should take appropriate measures for the nail care like new healthier habits should develop instead of old bad habits to support the treatment and to prevent from reinfection. Physician support staff plays a very important role in educating the patients about the treatment which is going on and the preventions they should take to prevent from reinfection.

nailKALM® Dermaceutical Lotion: A Novel Treatment for Onychomycosis

nailKALM is a very effective topical antifungal agent indicated for relief of onychomycosis. It consists of AMYCOT, a patented key ingredient derived from naturally occurring species of spirulina.

AMYCOT®: Naturally Occurring Key Ingredient, Patented

AMYCOT is a proprietary extract derived from Spirulina, a microalgae or cyanobacterium, specifically from the *Arthrospira maxima* species. It is the most widely produced microalgae in large-scale production. It is a single celled, water borne plant that has a long history of being used as a food source in different parts of the world. It is high nutritious source of food containing very high levels of essential vitamins and anti-oxidants.

AMYCOT®: Mode of Action

The antifungal activity of AMYCOT is due to a putative enzymatic action that destroys the chitin/chitosan polymers, the structural component of the fungal cell wall. Damage to the polymers causes the fungal walls to collapse, eventually killing the fungus (fungicidal). However, AMYCOT is composed of a complex variety of proteins, lipids and carbohydrates that have been known to collectively exhibit anti-fungal properties. Thus, it is possible that all of these molecules act synergistically to manifest efficacy [22].

AMYCOT®: Efficacy

In vitro studies of AMYCOT has shown its efficacy against fungi associated with onychomycosis such as *Trichophyton mentagrophytes*, *Trichophyton rubrum, Candida albicans, Epidermophyton floccosum,* and *Microsporum canis.* Additional clinical studies confirmed AMYCOT efficacy against other related mycological skin infections such as Tinea cruris, Tinea corporis, Tinea pedis and Tinea capitis.
In vitro studies indicate that AMYCOT has no skin irritating side effects; stimulates the growth and protein synthesis of skin cells such as keratinocytes; and has anti-inflammatory properties. Moreover, AMYCOT does not stimulate the cellular immune response indicating that it is most likely non-allergenic. These multi-functional properties of AMYCOT address the inflammation associated with onychomycosis, and is one of nailKALM unique attributes which may help explain its high efficacy against onychomycosis.

AMYCOT®: Safety

Spirulina (*Arthrospira maxima*), the source of AMYCOT, has been ingested orally as human food for centuries. There has been no reported toxicity even with up to 8 grams consumed per day [23, 24]. AMYCOT has no skin irritating side-effects and show anti-inflammatory properties. Thus, the application of a Spirulina extract such as AMYCOT as a topical agent may be considered relatively harmless and may be an option for immuno-compromised patients such as the elderly, infants, diabetics and pregnant women.

AMYCOT®: Clinical Trials

One of the study conducted in Germany (2005) shows the antifungal effect of AMYCOT preparations (8% Lotion and 12% Cream) tested in ten patients with heavy to moderate infections for 14 days. In the beginning of the trial all the subjects showed an extreme fungal activity (< 96%, assessed by spore count). One week after beginning the treatment, the degree of infection reduced to less than 72% and all the

symptoms. The fungal activity had reduced to less than 18% at the end of the study (14 days later) in nearly all test subjects. This study shows that the AMYCOT preparations are more effective than previously known medications [25].

Another study conducted in 2011 (Queensland) showed 100% clearance of onychomycosis when treated with nailKALM. This is the independent trial conducted with 10 subjects diagnosed with Onychomycosis (verified by microscopy and/or culture) and treated with nailKALM Lotion over 3 months with a follow up at 6 months. 100% clearance on 70% of the subjects after 3 months, 100% clearance of 80% of the subjects after 6 months and 20% of the subjects did not complete the treatment. nailKALM Lotion has a definite clinical benefit in the treatment of Dermatophyte Onychomycosis infections [25].

The clinical efficacy of AMYCOT was confirmed in a randomized double-blind, placebo-controlled trial of subjects with severe to very severe tinea and onychomycosis infections, who were treated with different AMYCOT formulations. The subjects treated with AMYCOT showed significantly greater than 90% mycological cure and 100% clinical cure rates compared with the subjects treated with placebo. There was no reported adverse effect associated with the treatment [26].

Applications and Benefits of nailKALM®

nailKALM has been used as a stand-alone product for managing onychomycosis with high rates of success. The product has also been found to work anecdotally as well on other nail problems such as nail damage and nail psoriasis, presumably due to its skin repair and anti-inflammatory properties. Moreover, these aforementioned properties of AMYCOT may contribute in helping the new nail to grow after the fungi are eliminated. Concomitantly, nailKALM can hasten nail re-growth as well as reduce any inflammation arising from treatment such as laser therapy. Due to the natural source of AMYCOT and apparent safety profile, nailKALM can be used as a combination treatment with other modalities.

Conclusion

Onychomycosis is a highly contagious disease with no effective treatment to date. Although the disease initially appears as a cosmetic problem, it poses a serious health risk if not addressed early. With an aging population and rising incidence of diabetes, onychomycosis represents a disease with an unmet need in search for more safe and effective treatments. nailKALM is made up of AMYCOT and has a definite clinical benefit in the treatment of onychomycosis infections. AMYCOT has skin repair abilities, anti-inflammatory properties and no skin irritating side effects. This means nailKALM is harmless for skin.

Beside these, various studies showed that AMYCOT preparations are more effective than previously known medications. nailKALM represents a new option and/or an adjunct to current modalities available in the management of onychomycosis.

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*Freeman AM and Freeman MG. Nailkalm (Arthrospira maxima) for the treatment of dermatophyte nail infections. Australian Journal of Derjmatology 2011;52 Suppl 1:25

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SCAN ME

Cerebroprotein Hydrolysate: New Paradigm in Management of Neurological Problems

Abstract

Cerebral ischemia is known to be one of the most common causes of death worldwide. This is caused when proper amount of oxygen and nutrient rich blood does not reach the brain cells. Although various options are available for the management of such condition, efficiency of these methods is not established. On the other hand, Cerebroprotein Hydrolysate is novel therapy option for the patients suffering from such disorder. It provides faster and better recovery of repairing neurons and their growth than other neurotrophic agents.

Keywords: *Cerebroprotein hydrolysate, Cerebral ischemia, Traumatic brain injury, Brain stroke, Management of neurological problem*

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Introduction

Cerebral ischemia is the most common cause of mortality and morbidity across the globe. It is caused due to restricted flow of oxygen and nutrient rich blood towards brain. The insufficient supply of blood towards brain does not meet its metabolic demand, causing damage to brain cells [1]. This leads to impairment in vision, body movement, speaking and may also lead to unconsciousness, weakness in body and irreversible damage to brain.

Epidemiological Consideration

Strokes are considered to be the major public health concern globally. As per the Global Burden of Diseases (GBD) study in 1990, it was the second leading cause of death worldwide [2]. Subsequent update in 2010 showed the rise of 26 percent in past two decades. With this rising increase in proportionality of mortality, stroke has remained the second leading cause of mortality [3]. According to the study data by GBD (2001) the incidence of stroke is most prevalent in the low and medium income countries [4]. In India, a study showed the cardiac disease, diabetic mellitus, hypertension, smoking, tobacco chewing and low haemoglobin to be associated as the risk factor for incidence of ischemic stroke [5].

What is Cerebral Ischemic Injury?

Cerebral ischemic injury is also known as brain ischemia or ischemic stroke. This is mainly caused due to blockage in artery supplying blood to brain. This leads to depriving the oxygen supply to brain, which causes damage to brain cells. If the blood flow is not restored, the permanent damage to brain cells occurs as a result of cerebral hypoxia.

The damage to brain cells may lead to temporary loss of function, the condition is known as transient ischemic attack (TIA), or mini-stroke. This loss of function can return to normal state by restoring the oxygen rich blood supply to brain. This is characterised by the temporary blockage of cerebral blood flow (CBF) due to formation of blood clots which damages the inner walls of brain vasculature [6]. However, they do not cause any permanent damage but one third of the patients are expected to suffer from cerebral ischemic condition within a year [7].

When the blood flow is interrupted for approximately 10 seconds, it causes unconsciousness; if this interruption is prolonged for few minutes, it may cause irreversible damage to the brain cells. This kind of damage leads to death of brain tissue resulting into loss of brain function permanently. This is known as ischemic stroke.

Ischemic strokes are the most common type of strokes accounting for approximately 87 percent of all strokes, in comparison to 23 percent of haemorrhagic strokes resulting from rupturing of blood vessel inside brain [8].

Types, Causes and Symptoms of Cerebral Ischemia

Ischemic stroke can effect different regions of the brain. If the effect is confined to a particular region, it comes under focal ischemia. But if the effected region is widespread and encompasses the larger area, this is termed as global ischemia.

The function of the blood vessels in the brain is to provide oxygen and nutrient rich blood to the brain cell to work properly; and carry out a particular and specified task. There are various small capillaries which following a certain path ensures that each and every area of the brain is covered. If these vessels due to any

reason get blocked or start bleeding, it causes deprivation of blood to the respective areas leading to malfunctioning or even death of that particular region. The major cause for cerebral infarction or cerebral stroke is the blockage of blood vessel by the clot of blood or plaque of fat molecules. This situation can arise due to the result of thrombosis, embolism or hypoperfusion; or any other associated condition which may restrict the oxygen supply to brain tissue. Such as high blood pressure, atherosclerosis, high cholesterol, atrial fibrillation, prior heart attack, sickle cell anemia, clotting disorders, congenital heart defects, etc. Other risk factors may be associated with diabetes, smoking, obesity, heavy alcohol misuse, use of certain drugs, such as cocaine or methamphetamines. Anything from trauma to tumour, which may cause blood loss or compression of blood vessel resulting in reduced nutrient and oxygen-rich blood to brain, causes cerebral ischemic strokes.

Symptoms of ischemic stroke depends on which part of the brain is affected. But the common one expressed by patients are vision problems (such as blindness in one eye or double vision), weakness (or paralysis in limbs, which may be on one or both sides), dizziness, vertigo, confusion, loss of coordination, drooping of face on one side, slurred speech, loss of consciousness, sudden or strong headaches. Once the symptoms are observed it is necessary to take immediate action to prevent permanent damage of brain tissues.

Pathophysiology of Neurons

Various mechanism underlying the cerebral ischemia are known, as follows:

1. **Excitotoxicity and apoptosis/necrosis**

Glutamate, the most abundant excitatory neurotransmitter in the brain, is a major contributor to cerebral ischemia-induced excitotoxicity (excitatory amino acids-induced neurotoxicity) and subsequent apoptosis/necrosis [9]. Cerebral ischemia alone can induce overexpression of the death receptor ligands (i.e., tumour necrosis factor (TNF)-α and FasL), as a result of serine/threonine-protein kinase 1-mediated neuronal necroptosis [10].

Furthermore, enhanced expression of c-Jun N-terminal kinase (JNK, a stress-activated protein kinase) after cerebral ischemia can activate Fas- and Bim-mediated pro-apoptotic signals leading to neuronal cell death [11, 12].

2. **Reperfusion injury and neuro-inflammation**

Reperfusion injury occurs when a tissue/organ encounters deprivation of blood supply followed by a restoration of blood flow to the ischemic area. This however, causes secondary injury due to excessive formation of reactive radical oxide species (ROS) and/or peroxynitrite and activation of the immune system [13, 14].

In terms of ischemia induced neuro-inflammation, infiltrating immune cells release inflammatory mediators to recruit multiple immune and glia cells.

Moreover, pro-inflammatory cytokines increase neurotoxic molecules and free radicals (i.e., ROS), reactive nitrogen species, cyclooxygenase-2 and inducible nitric oxide synthase to cause secondary neuronal cell death [15, 16].

Damage associated molecular patterns, such as high-mobility group box1 protein and ATP are released from the cytoplasm upon tissue injury and/or cell death to initiate series of innate immune responses, as a result of excessive production of pro-inflammatory cytokines/chemokines, which causes peroxynitrite- and ROS-mediated lipid peroxidation, DNA damage and cell dysfunction/death [17].

3. **Impaired axonal regeneration**

One of the major hallmarks of cerebral ischemia is the inherent glial scar formation. Glial scar (a tissue barrier) is formed by reactive astrocytes, microglia, and infiltrating immune cells to protect survival neurons from the harmful environment (i.e., nitric oxide toxicity and glutamate-induced cellular excitotoxicity) [18].

However, the immune-reactive cells, in particular astrocytes, become hypertrophic and release chondroitin sulfate proteoglycans (an inhibitory extracellular molecule) in response to cerebral ischemia [19], which restricts axonal regeneration and neuronal survival via RhoA/ROCK-mediated pathways [20].

In addition to glial scar, myelin (the laminated membrane structure that surrounds the axon) is also responsible for the failure of axonal regeneration. Numerous studies have shown that myelin-associated glycoproteins, such as oligodendrocyte-myelin glycoprotein and nogoA are actually detrimental to axonal regeneration and sprouting after cerebral ischemia [21].

Current Options for the Management of Cerebral Ischemia

Legions formed in brain due to stroke are classified into two parts – the ischemic core and the surrounding penumbra [22]. The irreversible cell death occurs in ischemic core area, while the studies on management are targeted to prevent neuronal cell death in the hypo-perfused penumbra region [23]. Details on these studies of neuro-regenerative agents (Table 1) and other novel factors/therapies (Table 2) are mentioned as follows:

Table 1: Neuro-regenerative agent in cerebral ischemia [23]

Neuro-regenerative agents	Rationale	Applications
Fibroblast growth factors (FGFs)	FGF are group of structurally similar polypeptide mitogens, which promote tissue repair, angiogenesis, neurogenesis, axonal growth, embryonic development, and various endocrine signaling pathways. Administration of FGF-2 (based on experimental studies) has shown to increase the number of neurons and markers for neurogenesis. Up-regulation of FGF-2 via adeno-associated viral vectors in the infarct area can increase the number of proliferating cells and motor behaviour.	MCAO induced ischemic brain injury
Nicotinamide adenine dinucleotide (NAD)	NAD is a coenzyme of vitamin B3 critical for many biochemical reactions including energy production, ion homeostasis, and biosynthesis of glucose and fatty acids. NAD+ depletion and subsequent ATP loss during/after cerebral ischemia result in energy failure and cell death, this suggests that repletion of NAD+ is beneficial.	MCAO induced ischemic brain injury
Melatonin (N-acetyl-5-methoxy tryptamine)	Melatonin plays a crucial role in the regulation of sleep and wake cycles and has been widely used for the treatment of sleep disorders. Also recent studies suggest that melatonin provides other non-sleep/wake cycle related pharmacological effects, such as anti-nitric oxide (NO) production, anti-oxyradicals, and anti-peroxynitrite effects. Oxyradicals, NO, and peroxynitrite play a crucial role in the pathological progression of neuronal cell death following cerebral ischemia, suggesting melatonin use may provide neuroprotection against cerebral ischemia.	MCAO induced ischemic brain injury; bilateral common carotid artery occlusion induced cerebral ischemia
Resveratrol	Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a poly-phenol found in many plants. Numerous studies show it has multifactorial effects including anti-inflammation and anti-oxidation. Other studies suggest that resveratrol attenuates ischemic brain injury via inhibition of myeloperoxidase levels, pyrin domain-containing 3 inflammasome formation, cerebral TNF-α production and markers for apoptosis, indicating resveratrol has potential for treatment of cerebral ischemia.	MCAO and bilateral common carotid artery occlusion induced cerebral ischemia
Protein kinase C (PKC) isozymes, δPKC and εPKC	There is an enhanced expression of δPKC after cerebral ischemia, and subsequent studies suggest that inhibition of δPKC via δPKC specific inhibitor (δV1-1) can alleviate neuronal cell death and CBF derangements, showing the neuroprotective effects of δPKC inhibition after cerebral ischemia. While εPKC (another PKC isozyme) expression is actually enhanced during therapeutic hypothermia and ischemic preconditioning, which suggest εPKC's has possible neuroprotective role in ischemic brain injury.	Oxygen and glucose deprivation; ACA and bilateral common carotid artery occlusion induced cerebral ischemia
Pifithrin-α (PFT-α)	For a study PFT-α (p53 inhibitor) was synthesized to evaluate the therapeutic potentials of p53 inhibition on ischemic brain injury. According to this study, it was observed that PFT-α can reduce neuronal cell death in the CA1 region of the hippocampus, suggesting its use may have therapeutic potential against cerebral ischemia in the near future. Few studies reported that PFT-α can stimulate angiogenesis and neurogenesis after MCAO, while other studies suggest PFT-α reduces infarct volume and neurological and locomotor deficits via vascular endothelial growth factor-mediated pathways	MCAO induced ischemic brain injury

Table 2: Neuro-regenerative factors/therapies in cerebral ischemia [23]

Neuro-regenerative factors/therapies	Rationale	Applications
Hypothermia	In a study it was found that hypothermia treatment (at 33 and 30°C) significantly reduced neuronal metabolic demand and glutamate release, ultimately attenuating neuronal cell death in the CA1 region of the hippocampus after cerebral ischemia. Another experiment shows that moderate hypothermia significantly reduces intracranial pressure, cerebral edema, and neurological deficits in patients with severe middle cerebral artery infarction. Further studies reported hypothermia to reduce apoptosis, autophagy, and inflammation, as well as blood-brain barrier leakage and brain metabolism after cerebral ischemia.	MCAO and bilateral common carotid artery occlusion induced cerebral ischemia; traumatic brain injury; patients with middle cerebral artery infraction
Fatty acids	Palmitic acid methyl ester (PAME) released from the sympathetic nervous system is a novel vasodilator and CBF mediator. Since hypoperfusion (decrease in CBF) following cerebral ischemia plays a crucial role in the pathological progression of neuronal cell death and neurological deficits, the vasodilatory properties of PAME suggest its therapeutic potential in the treatment against cerebral ischemia.	MCAO and ACA induced cerebral ischemia
Attenuation of sympathetic nervous system	Surgical interruption of perivascular sympathetic nerves via decentralization of superior cervical ganglion (a sympathetic ganglion that innervates cerebral arteries) can alleviate ACA-induced hypoperfusion and brain injury. Interruption of cervical sympathetic chain in the superior cervical ganglion has been shown to reduce neurological deficits after aneurysmal subarachnoid haemorrhage in humans.	ACA induced cerebral ischemia; aneurysmal subarachnoid haemorrhage
Neuro-modulation therapy	Neuromodulation therapy is a novel technique that utilizes implantable neuromodulatory device/stimulator to deliver electrical or magnetic stimuli directly upon injured neurons. Recent clinical studies suggest that non-invasive brain stimulation via transcranial direct current stimulation (tDCS) or theta burst stimulation (TBS, a neuromodulatory device that provides continuous theta frequency low-intensity stimuli into target brain regions) can facilitate motor and language recovery after chronic stroke.	MCAO induced cerebral ischemia; patients with ischemic stroke
Traditional Chinese therapies	Traditional Chinese therapies (i.e., plant-based medicines and acupuncture) are considered novel therapies against stroke/cerebral ischemia due to their multifactorial effects. They can inhibit cerebral ischemia-induced excitotoxicity, inflammation, and apoptosis, while promoting angiogenesis and cerebral blood flow after cerebral ischemia.	MCAO induced cerebral ischemia; patients with acute stroke
Stem cell therapy	Stem cells has self-regenerative, differentiating, and multifunctional properties; and can be divided into endogenous and exogenous therapies. Endogenous therapies utilize neurotrophic and growth factors, such as epidermal growth factor, glial cell-derived neurotrophic factor, FGF-2, insulin-like growth factor-1, and brain-derived neurotrophic factor to enhance vascular regeneration and brain synaptic plasticity, while it stimulates the reparative abilities of the endogenous neural stem cells (NSCs) in the injured dentate gyrus and subventricular zone (SVZ), thus reducing lesion size and locomotor deficits. Exogenous therapies use tissue extraction, in vitro cultivation, and subsequent stem cell transplantation into damaged brain regions caused by stroke/cerebral ischemia.	MCAO induced cerebral ischemia; patients with acute stroke

What is Cerebroprotein Hydrolysate?

Cerebroprotein hydrolysate is a mixture of peptides and free amino acids extracted from porcine brain tissue which has been proved to be effective in inhibiting microglial activation, neuro-inflammation and free radical formation and it has been shown to promote neuronal sprouting and stimulate neurogenesis [24, 25]. Moreover, it can penetrate biological membranes easily and pass through the blood brain barrier to improve neuronal survivals, regulate neuronal plasticity and repair neurons [26-28]. Hence, cerebroprotein hydrolysate is widely regarded as a potential neurotrophic and neuroprotective drug in treatment of vascular dementia, traumatic brain injuries and ischaemic in clinical [29-31].

Cerebroprotein hydrosylate helps in Neuronal differentiation and protection against ischaemic and neurotoxic lesions. It regulates and improves neuronal metabolism. It reduces excitotoxic damage, blocks over-activation of calcium dependent proteases, and scavenges free oxygen radicals. It has been found in animal studies that early intervention with cerebroprotein hydrosylate reduces blood-brain and blood-cerebrospinal fluid barrier permeability changes, attenuates brain pathology and brain edema, and mitigates functional deficits caused by traumatic brain injury [30]. It improved brain bioelectrical activity, i.e. reduced EEG ratio by increasing fast frequencies and reducing slow activities and also improves cognitive performance in tasks, evaluating attention and memory functions in post-acute traumatic brain injury patients [31].

Mechanism of Action and Pharmacological Effects

It acts by multiple mechanisms viz. [33]:-

- Regulation and improvement of the neuronal metabolism
- Modulation of the synaptic plasticity
- Neuronal differentiation and protection against ischemic and neurotoxin lesion
- Cerebroprotein hydrolysate reduces excitotoxic damage, blocks over activation of calcium dependent proteases, and scavenges free oxygen radicals
- Cerebroprotein hydrolysate has been shown to counteract the negative effect of the elevated EGF-2 on neurogenesis and neuromodulator

Pharmacokinetics

It is given in a dose of 60 -180 mg once daily for 10-20 days. It should be slowly infused in 250 ml saline in 60-120 minutes. Maintenance doses (30 mg) can be given by I.M. route. It should not be mixed with amino acid solutions in the infusion bottle. Doses of antidepressants should be reduced if used with cerebroprotein hydrolysate.

Adverse Effects and Contraindications

Studies have revealed that most of the side effects are minor. Most common side effects include headache, nausea, vertigo, increased sweating, agitation, fever, hallucinations, confusion, and flu like syndrome. Contraindications include hypersensitivity, epilepsy and severe renal impairment. Safety has not been established in pregnancy and lactation.

Drug Interactions

Based on cerebroprotein hydrolysate's pharmacological profile, special attention should be paid to possible additive effects when used in conjunction with anti-depressants or monoamine oxidase inhibitors (MAOIs). In such cases, it is recommended that the dose of the antidepressant is lowered. Cerebroprotein hydrolysate should not be mixed with balanced amino-acid solutions in one infusion [34].

Indications [35]

- Acute ischemic stroke
- Traumatic brain injury
- Vascular dementia
- Alzheimer's disease

Cerebroprotein Hydrolysate in Traumatic Brain Injury, Acute Ischemic Stroke, Vascular Dementia, Extrapontine Myelinolysis and Alzheimer's disease

There are very few medications that can reduce the functional disability caused by traumatic brain injury. The complex study of cognitive and emotional status, levels of serum serotonin and brain-derived neurotrophic factor (BDNF) performed in 72 patients with acute traumatic brain injury, with a special focus on moderate brain injuries (MBI), treated with cerebrolysin found that cerebrolysin improves outcomes of closed craniocerebral injury by promoting activation of neurotrophic processes [36]. Cerebroprotein hydrolysate-augmented proliferation, differentiation, migration of adult SVZ neural progenitor cells results in increased number of neural progenitor cells and neuroblasts which contribute to neurogenesis. The beneficial effect seen in traumatic brain injury and acute ischaemic stroke may be due to this mechanism. A double-blind, placebo-controlled, randomized study showed that cerebrolysin improves the cognitive function of patients with mild traumatic brain injury (MTBI) at 3rd month after injury, especially for long-term memory and drawing function tested on Mini-Mental Status Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) scores.

Conclusion

Cerebroprotein hydrolysate is the first drug with neurotrophic factors which are small proteins that

exert survival promoting and trophic action on neuronal cells. It consists of short biological peptides, which act like endogenous neurotrophic factors. Neurotrophic activity can be detected up to 24 h after a single injection. It is the only medication indicate in dementias that acts at a neuronal level unlike others that act at neurotransmission and neurotransmitter levels. In our case series, we continued the medications that patients were on and improvement that was not noticed earlier was seen after starting cerebroprotein therapy.

Cerebroprotein hydrolysate is a medication that acts at a brain level and provides us with an effective tool for improving levels of activities of daily living in such patients with various neurological disorders and decreasing their dependence on caregivers though further research in larger populations and clinical trials is warranted. Initial experiences show promising results for cerebroprotein hydrosylate but it is still in its early stages and will require extensive randomized controlled trials before its efficacy is proved.

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HOW IT SPREADS

- Droplets from cough & sneezes
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- Contact with contaminated surfaces of objects, followed by touching own mouth, nose or face

SYMPTOMS OF COVID-19

Fever

Cough

Shortness of breath

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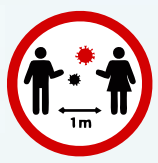

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