

# Patient management positive covid: the central role of clinical nutrition and supplementation of essential amino acids during and after hospitalization..

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## Abstract

**Background** The covid 19 positive patient who is subject to a hyperinflammatory condition associated with lung injury with the development of pneumonia is hospitalized in the intensive care unit. Before resolving and overcoming the “cytokine storm”, with overexpression of pro-inflammatory interleukins (IL-, IL-6), this patient will be intubated for more than 48 hours and therefore needs adequate nutrition. Experimental approach Malnutrition can lead to sarcopenia with a decrease in lean body mass and worsening of the inflammatory state underway. In addition, severe debilitation, if not corrected with adequate nutrition, can greatly lengthen rehabilitation times with prolonged hospitalization, increased costs and reduced turn over already in crisis due to the health emergency caused by coronavirus. **Key Results** The aim of this study is to focus attention on the nutritional importance that must be provided in case of covid 19 together with pharmacological treatments to lower the number of circulating proinflammatory cytokines. **Conclusions** Oral, enteral and parenteral nutrition should always be carried out according to the patient's condition and, in the case of a hyperinflammatory patient, such as the one affected by covid 19, it has been shown that the supplementation of amino acids helps to lower the inflammatory state and promotes normal recovery physiological. **Keywords:** amino acids, nutrition, covid, glutamine, hyperinflammatory, sarcopenia, cytokine.

## Introduction

A newly identified coronavirus (SARS-CoV-2) in China in December 2019 resulted in a significant number of pneumonia resulting in deaths. The spread, as usual of these viruses, is rapidly spreading all over the world with thousands of thousands of deaths. It is no coincidence that the WHO has declared a state of pandemic. For these reasons, worldwide attention is concentrated in the fight against this virus.

The genomic sequence of SARS-CoV-2 is 79.5% of the identity with SARS-CoV. The evidence that caused Cov2 sars infection causes a generalized hyper inflammatory state due to the release of cytokines (“cytokine storm”).

In literature it has been shown that the final stage of infection is the deadly one for humans. In fact, it is not the viral phase that kills but the strong activation of the immune system and the consequent release of cytokines. The patient is thus supported and hospitalized in an intensive care unit (ICU) hoping that he will overcome the “famous storm” and remain alive.

World scientific societies, health professionals, doctors, researchers and scholars are intensifying research to

find a suitable cure to fight the virus, both to prevent infection and to treat the patient before he arrives at death. The vaccine will only be available in several months and at present many drugs are being examined without great success. The latest works give hope about colchicine and hydroxychloroquine/chloroquine also used in combination in order to avoid the release of cytokines with excellent chances of success.

The spontaneous reflection is the possibility of resorting to clinical nutrition and amino acid supplementation both to prevent, support and overcome the infectious phase with greater ease also in combination with pharmacological treatments.

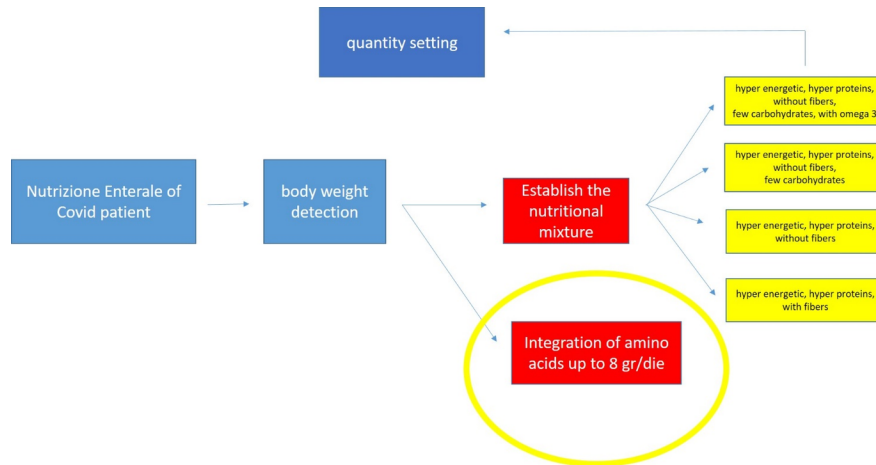
This idea is reinforced by the fact that clinical nutrition and amino acids, in addition to adequately nourishing the patient bedridden in ICU, can modulate the immune system to prevent infection and ensure that the inflammatory state is kept under control with less release of cytokines. Above all, amino acids seem fundamental as an additional contribution in the patient suffering from covid and hospitalized in ICU: on the one hand it mitigates the release of cytokines and on the other it favors a prompt de-hospitalization in the healing phase for a prompt turn-over in the pandemic phase and with consequent savings of indirect and intangible costs (1-2).

### **Hospitalization and nutrition in a positive Covid patient**

COVID-19 disease, caused by SARS-CoV-2 virus infection, can lead to manifestations even severe clinics such as pneumonia with respiratory failure, respiratory distress syndrome acute (ARDS), sepsis and septic shock, which require urgent hospitalization in ICU. ARDS in particular manifests itself as a serious failure hypoxic respiratory accompanied by inflammation, pulmonary edema and risk of dysfunction multi-organ and is often required mechanical ventilation invasive. Generally patients who died from SARS-CoV-2 infection they have an average age of 78 years and 3 or more comorbidities including chronic non-pathologies transmissible diseases such as ischemic heart disease, hypertension, diabetes and chronic obstructive pulmonary disease (COPD).

This is why COVID-19 is the new  $\beta$ -coronavirus, which can lead to various pulmonary phenomena and death (~ 10%) and represents a global health challenge. Medical nutrition therapy is among the pillars of therapeutic principles and a fundamental tool among global therapeutic measures for patients with COVID-19.

Malnourished people with low immunity and chronic diseases have a worse higher prognosis and mortality rates. The relevance of nutritional therapy is important and should be implemented as a first-line treatment and implemented in the anti-Covid-19 clinical practice standard. Good nutrition not only provides the body with immunity to disease, including COVID-19, but it is also the main guarantee for the promotion of the recovery of the disease and the infected patient. However, the indications for nutritional therapy must be tailored. Nutritionists should pay attention to the most appropriate artificial nutrition (AN) approach with enteral nutrition (EN) or parenteral nutrition (PN). Plan, the method, route and formula of nutritional therapy must be adapted dynamically and promptly in accordance with the clinical characteristics of the patient COVID-19. The transition between ONS, EN and PN should be fluid, following the principle that when the EN can satisfy 50% of the target demand, the PN can be constantly reduced and carried out arrested; when the ONS can satisfy 50% of the target demand, the EN it can be progressively reduced and therefore arrested.



**Figure 1:** *Enteral nutritional support in the positive covid patient.*

Advanced age and comorbidity is related to fragility, a syndrome characterized by reduction of functional reserves and decreased resistance to stress. Fragility is connected with loss weight and malnutrition and acute hospitalization without adequate nutritional support can worsen one situation already compromised. All patients hospitalized for more than 48 hours, regardless of the index of initial body mass (BMI) and age, are at risk of malnutrition and need timely and appropriate nutritional intervention. Prolonged hospitalization following catabolism and immobilization, induces a decrease in weight and muscle mass that can result in sarcopenia, condition which in turn helps to reduce respiratory and cardiac function, prolong the hospitalization of the patient and worse prognosis. So counter or prevent malnutrition hospital by improving the patient's response to therapy and facilitating healthcare professionals in the hospital nutrition management by reducing the already high workload due to the state of emergency.

Most patients have severe inflammation and anorexia which leads to one drastic reduction of food intake which then leads to a respiratory failure treated with continuous positive airway pressure. High calorie diets must be readily provided. Oral integration of whey protein and intravenous infusion of multivitamin and multimineral solutions must be implemented at the time of admission. If respiratory conditions worsen, total parenteral nutrition should be considered. To cope with the current emergency crisis, nutritional assistance must be implemented promptly and pragmatically in patients with COVID-19 because it could be neglected although it is necessary for the benefit of clinical and effective results in preventing the consequences of malnutrition in this patient population.



and serum proteins. Immunonutrients can promote patient recovery by inhibiting inflammatory responses and regulating immune function. Glutamine which can modulate and preserve intestinal and lung function, compromised in conditions of severe stress, reducing the production of pro-inflammatory cytokines. Cytokine mediated effects are an essential part response to infection but excessive production of pro-inflammatory cytokines increases the risk of pneumonia and death in Covid-19. The production of pro-inflammatory cytokines (TH1 cytokines: eg tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], IL-1, IL-6, ιντερφερον- $\gamma$  [IFN- $\gamma$ ]) ιν ζοροναϊρυς πνευμονια αρε οερεξπρεσσεδ ιν α στορμ. ηρονις ινφλαμματιον οςζυρς ωην τηε τριγγερινγ φαστορς περσιςτ ορ τηερε ις σομε σορτ οφ ρεσολυτιον φαϊλυρε προζεσσες. Ινφλαμματιον πλαψς α φυνδαμενταλ ρολε ιν τηε παθογενεσις οφ "Ο"ΙΔ-19: αν ιμβαλανζε βετωεεν προ-ινφλαμματορψ ανδ αντι-ινφλαμματορψ ζψτοκινες, λεαδινγ το τηε ζψτοκινε στορμ ις ζυρρεντλψ ζονσιδερεδ το ζοντριβυτε το τηε δεελοπμεντ ανδ προγρεσσιον οφ "Ο"ΙΔ-19.

Μανψ αυτηορς ηαε σηοων τηατ αμινο ασιδς ηαε αντι-ινφλαμματορψ εφφερςτς ανδ τηε ιντεγρατιον οφ αργινινε, γλυταμινε ορ γλψςινε ιμπροες λυνγ δαμαγε ινδυσεδ βψ ινφερςτιονς ορ ανψ οτηερ ινφλαμματορψ εεντ τηυς ζοντριβυτινγ το αλεολαρ ιμπροεμεντ ιν ιτς ιντεγριτψ ανδ φυνςτιον. Ιν παρτιςυλαρ, τηε αδμινιστρατιον οφ γλυταμινε ηας βεεεν σηοων το σιγνιφικαντλψ ρεδυζε ινφλαμματορψ ζψτοκινες ωιτηουτ αφφερςτινγ οτηερ παραμετερς. Αργινινε ορ γλψςινε συππλεμεντατιον μαψ βε α νεω νυτριτιοναλ στρατεγψ φορ ρεδυζε τηε δελετεριους εφφερςτς οφ βακτηριαλ ινφερςτιον ον αλεολαρ φυνςτιον.

Τηε προινφλαμματορψ ζψτοκινες (TNF $\alpha$ , IL-1 $\beta$  and IL-6) and chemotactic cytokines (CXCL-1, MCP-1 and ICAM-1) produced by immune cells are powerful inducers of apoptosis in alveolar epithelial cells and cause a severe inflammatory state and the use of amino acids has reduced mRNA levels for TNF $\alpha$ , IL-1 $\beta$  and IL-6 indicating a reduction inflammatory response. Importantly, IL-6 promotes expression of CXCL-1, which in turn regulates neutrophils accumulation and contributes to lung injury. The administration of arginine or glycine is associated with reduced expression of IL-6, CXCL-1 and decrease in the accumulation of neutrophils in the alveolar epithelium, indicating a regulatory effect of chemokine secretion in lung tissues. Whereas the inhibition of CXCL-1 reduces the accumulation of neutrophils in the lungs tissues and protects against lung injury in clinical patients, arginine or glycine can be used as a new adjuvant nutrient in clinical therapy. Further studies are needed to clarify molecular mechanisms underlying this important modulatory effect of arginine, glycine and glutamine.

Glutamine inhibits the accumulation of white blood cells and Arginine, glycine or glutamine have been reported to inhibit cell death in various studies but the metabolism of amino acids and the production of their metabolites differ from each other in alveolar epithelial cells, thus leading to different responses.

Furthermore, it should be added that malnutrition easily leads to a decrease in the lean body mass and can cause sarcopenia, a frequently encountered disease in the elderly with aggravation of geriatric pathologies. Current opinions consider malnutrition and possible sarcopenia as a consequence of multiple medical, behavioral and environmental factors involving the nervous, hormonal, nutritional system, substitution of muscle proteins, proinflammatory conditions and the load of reactive oxygen species inside of mitochondria. With the intake of amino acids there is a better functional recovery of the muscles and a significant reduction in serum cancer necrosis factor- (TNF-) and a significant increase in both insulin-like growth factor without having significant adverse effects. These preliminary data indicate that dietary supplements with the oral amino acid mixture have significantly increased lean body mass in elderly subjects with and without sarcopenia (10-15).

### *The role of glutamine*

Glutamine is one of the most abundant amino acid in the human organism and it is mostly present in the muscle tissue (about 60%). It is particularly involved in a variety of processes for maintaining body homeostasis: redox processes, acid-base balance and glucose metabolism. Glutamine can become essential and have a positive effect in critically ill patients (e.g. in hospital stay). The effect of Glutamine seems to depend on the route of administration for which the parental one is proven to be the most effective so far. An excessive inflammatory response, oxidative stress, comorbidity such as malnutrition and a catabolic state, could lead to a severe depletion of glutamine. Respiratory diseases are mostly associated with a glutamine in-

crease. Unlike skeletal muscle, which contains significant quantities of free glutamine, the lung synthesizes it *ex novo* from glutamate and ammonia by means of the enzyme glutamine-synthetase. The release of glutamine in stressed lungs is a consequence of the release of glucocorticoids and other mechanical mechanisms and becomes significant due to the massive pulmonary perfusion. Glutamine is synthesized from cytosolic glutamine synthetase (GS) in many tissues, but degraded by mitochondrial glutaminase (GA) and used in large quantities by other tissues that do not synthesize it. The beneficial effects of glutamine on critical diseases is thought to depend on a better expression of thermal shock proteins (HSP). In critically ill patients, the increase in mortality was associated with a decrease in plasma Gln concentration. It is proven that during catabolic stress, the consumption rate of Gln exceeds the supply and both the plasma pools and the skeletal muscle pools present severely reduced free Gln levels. Experimental studies have reported that Gln can protect cells, tissues and whole organisms from stress and injury through the following mechanisms: attenuation of activation of NF (nuclear factor)  $\kappa$ B, a balance between pro and anti-inflammatory cytokines, reduction of neutrophils accumulation, improvement of intestinal integrity and immune cell function and enhancement of heat shock protein expression. In conclusion, high doses of parenteral Gln ( $> 0.50$  g / kg / day) show a greater benefit potential in critically ill patients, although the pathophysiological mechanisms of Gln require clarification (16-17).

### *The role of lactoferrin*

Lactoferrin is a highly conserved natural pleiotropic glycoprotein of 80 kDa and 703 amino acid residues, it binds iron and is expressed and secreted by glandular cells. It can be found in most body fluids the molecule is equipped with *in vitro* antiviral properties against a wide range of viruses including SARS CoV, a virus belonging to the coronavirus family and naturally related to SARS CoV2, responsible for the current Covid19 pandemic. It presents immune-modulating and anti-inflammatory characteristics that can modify the host's responses to infections, thus it can be useful in association with other drugs in the most severe cases. Isolated for the first time in cow's milk and then in breast milk, it is used as a nutritional additive and if administered in doses between 4.5 and 100 mg per day, is free of toxicity. There are also liposomal formulations. The antiviral activity of Lf has been demonstrated for the first time in infected mice where it induced polycythemia of the Friend virus complex in 1980. It attacks naked and enveloped viruses, both DNA and RNA, such as cytomegalovirus, herpes simplex virus, human immunodeficiency virus (HIV), rotavirus, poliovirus, respiratory syncytial virus, hepatitis B and C virus (HCV) parainfluenza virus, alphavirus, hantavirus, human papillomavirus, adenovirus, enterovirus 71, echovirus 6, influenza A virus and the Japanese encephalitis virus, with EC 50 (actual concentration) *in vitro* of Lf generally numbered in the micro-molar when against viruses. The ability of Lf to inhibit viral entry can be explained by the binding with cell's surface molecules (proteoglycans of heparan sulfate, HSPG) or viral particles (see HCV) or both. In addition to preventing the access of the virus, it can contribute by blocking the replication mechanisms of the virus once it enters. The theory according to which children between the ages of 0 and 10, therefore breastfeeding or using milk derivatives containing this molecule, have a reduced incidence of contracting the virus has been demonstrated, although it still needs to be validated. Furthermore, zinc saturated lactoferrin can be used in anti-inflammatory and preventive therapy against Covid19 (18).

### **Conclusions**

The suggestions for proper evidence-based nutritional therapy reported here are for patients with critical COVID-19 conditions and should be included in life-saving therapies. The supplementation of amino acids and lactoferrin should always be accompanied by drug therapies following an ICU hospitalization and its importance cannot be overlooked. Malnutrition phenomena weaken the patient already in poor condition and greatly lengthen recovery and recovery times. Furthermore, the lung damage caused by coronavirus is caused by an overexpression of proinflammatory molecules (cytokines) which, from literature data, has been shown to be lowered by an adequate integration of amino acids. Nutritional therapy together with pharmacological therapy undoubtedly helps the covid patient to overcome the acute phase of the disease first and to shorten recovery times.

### **MAIN STATEMENTS**

I, the undersigned, Francesco Ferrara and any other author, declare that:

- We have no conflict of interest;
- We have not received funding;
- There are no sensitive data and no patients were recruited for this study;
- The document does not conflict with ethical legislation.

Regards

The authors

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