Dance Round COVID-19

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

COVID-19 AS AN OXYGEN-DEPRIVATION DISEASE

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*Since the last year, the epidemic with the new coronavirus SARS-CoV-2 has accumulated a wealth of data. The genetic structure of the virus, the epidemiological characteristics of the spread, the main clinical manifestations, the risks of the healing process, and the approaches for therapeutic intervention, etc. are the main areas into which the information can be parsed. The experimental and clinical data confirm the view that the new coronavirus causes pathogenic changes, which can be summarized as hypoxic syndrome. In this Dance Round, I shall succinctly justify this claim. **Biomed Rev 2020; 31: 113-116***

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BEFORE THE ONSET OF VIRAL ATTACK

Coronavirus disease-19 (COVID-19) was regarded as an infective-inflammatory viral disease, which mainly affected lungs. SARS-CoV-2 virus attacked cells containing angiotensin-converting enzyme2 (ACE2), particularly surfactant-producing alveolar type II cells. The clinical signs from this attack are dry cough, fever and most importantly: difficulty breathing, lack of „air“.

A careful analysis of the clinical picture of “oxygen deprivation” in a number of seriously ill people strongly suggests that the functions of hemoglobin and iron are also marred in the pathogenesis of COVID-19. One of the main physiologic roles of iron is to serve as a component of hemoglobin, the carrier of oxygen to body tissues.

Hemoglobin is composed of four subunits, 2- α and 2- β , and each subunit has an iron-bound heme. When iron is divalent (reduced), hemoglobin can release carbon dioxide and capture oxygen atoms in alveolar cells. When hemoglobin reaches other parts of the body through blood circulation, it can release oxygen molecule and capture carbon dioxide.

I hope that this short description of oxygen, the elixir of life, and its journey to the diverse cells of the human body, serves as a foundation for understanding the pathogenesis in COVID-19.

THE VIRUS IS ALREADY AT OUR “FRONT” DOOR

Here’s how SARS-CoV-2 comes in action. The transcribed, non-structural SARS-CoV-2 proteins ORF (Open Reading

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Frame) 8, 3a, 10 play critical roles during infection (viral replication) and disease pathogenesis (stimulate NF- κ B mediated inflammation and immune responses). ORF proteins interact with 1-beta chain of hemoglobin (BCH), which leads to the malfunction of heme. As a consequence, iron ion is “disassociated” (released) from the hemoglobin protein (1, 2). This is bad for several reasons:

- **Without the iron ion, hemoglobin can no longer bind to oxygen.** The end result is a lot like carbon monoxide poisoning, in which CO is bound to the hemoglobin, making it unable to carry oxygen. In such cases, ventilators aren’t treating the root cause; the patient’s lungs aren’t “tiring out”, they’re pumping just fine. The red blood cells just can’t carry O₂. The body compensates for this lack of O₂ carrying capacity by having the kidneys release hormones like **erythropoietin**, which tell our bone marrow factories to ramp up production of new red blood cells with fully functioning hemoglobin.
- The released ‘free iron ion’ is highly reactive, and it increases interleukin 6 (IL-6) levels, causing oxidative damage and inflammation. During active infection, increased **ferritin** level signifies a vital host defense mechanism that attempts to remove viral growth and defends immune cell function.
- Free iron attacks the **liver cells**, and hampered its efforts to remove the free iron ‘safely’. The result of this “tussle” is the release of higher alanine aminotransferase (ALT) amounts.
- An important diagnostic detail is the picture of the lung. Viral inflammation is diffuse in both lobes of the lungs. Normally, **pneumonia** develops in one lobe.

It is worth mentioning that there are published *in vitro* docking data demonstrating the possible interaction of SARS-CoV-2 spike protein (S1-RBD) with FDA-approved iron oxide nanoparticles (IONPs) as drugs for anemia treatment (3). This information indirectly enabled the process of tracking hemoglobin iron “released” in the coronavirus pathology.

WHAT ARE THE MOST COMMON CLINICAL SIGNS OF COVID-19 OBSERVED BY THE ATTENDING PHYSICIAN?

In 48 hours or so, COVID-19 causes prolonged and progressive **hypoxia** (starving the body of oxygen) by decapacitating hemoglobin in patient’s red blood cells. Patients desaturate oxygen (losing O₂ in their blood), and this is what eventually leads to fatal organ failures, not any form of acute respiratory distress syndrome (ARDS) or pneumonia.

Prognostic significance of **hemoglobin level** in SARS-CoV-2 infection: Patients with lower hemoglobin levels (Hgb < 12.5 g/dL) admitted in intensive care units (ICU) had a higher mortality compared with non-anemic ICU patients (4). This fact indicates that monitoring changes in the level of hemoglobin during the therapeutic process would have great prognostic significance for the outcome of therapy (5). It is important to note that patients with SARS-CoV-2 with reduced iron content in physiologically significant active components (such as: serum iron, ferritin, and transferrin total iron-binding capacity) pose increased risk of pathological changes in the cardiovascular, hepatic and renal systems (6). In a clinical trial with two groups of patients suffering from pneumonia, the group of patients showing PSR positive test (that are COVID-19 positive group) have several times higher levels of serum **porphyrin** (7).

All the damage to the lungs seen in CT scans are from the release of oxidative iron from the hemes. This overwhelms the natural defenses against pulmonary oxidative stress and causes the always-bilateral ground glass opacity in the lungs.

A huge meta-analysis from 6 bibliographic databases included 189 unique studies, with data from 57 563 COVID-19 patients, evaluated biomarkers of anemia and iron metabolism (hemoglobin, ferritin, transferrin, soluble transferrin receptor, hepcidin, haptoglobin, unsaturated iron-binding capacity, erythropoietin, free erythrocyte protoporphyrin, and erythrocyte indices). It showed a correlation of lower hemoglobin and increased ferritin levels with increasing proportion of mortality in second group (8).

An interesting question would be whether abnormalities of BCH, quantitative in thalassemias, and qualitative in Sick-Cell-Disease (SCD), influence the outcome of virus attack? Only a few confirmative data is available in this regard (9). From 18 350 Iranian beta-thalassemic patients only fifteen confirmed cases reported mild to moderate disease of COVID-19 (10).

WHAT THERAPEUTIC APPROACHES DOES THE CURRENT PARADIGM OFFER?

- Quick **blood transfusion** with fresh red cells and hemoglobin. As therapies used for anyone with abnormal hemoglobin or malfunctioning red blood cells.
- Use recombinant **erythropoietin (rhEPO)** for combating anaemia.

Chloroquine (CHQ) is suspected to bind to DNA and interfere with viral attack on hemoglobin and prevents viral

ORF proteins from attacking heme and forming porphyrin (11). Hydroxychloroquine (an advanced descendant of regular old chloroquine) lowers the pH which can interfere with the replication of the virus (see Yanev, Zhelyaskova, Chaldakov's *Dance Round* in this volume of *Biomedical Reviews*). Ideally, some form of treatment is needed to inhibit viral growth and replication. In this context, **CHQ+ZPAK (azithromycin 3 day pak) +ZINC** or other retroviral therapies are being studied. Lower the virus, lesser hemoglobin loses its iron, and this in turn, lowers the severity and damage (12).

COVID-19 is a part of the **hyperferritinemic syndrome spectrum**, like secondary haemophagocytic lymphohistiocytosis, catastrophic antiphospholipid syndrome, adult onset Still's disease, and septic shock. To explore this, two clinical trials are under way to test the efficacy and safety of deferoxamine in comparison with standard treatment or to tocilizumab (NCT04333550, NCT04361032) (13, 14). The final results of these studies are awaited.

Iron chelators: By binding the excess iron, several effects were achieved. Iron chelators help to obtain effectively functioning hemoglobin and improve tissue oxygenation. At the same time, they reduce the level of free iron required for virus replication; inhibit endothelial inflammation, prevent pulmonary fibrosis and lung insufficiency *via* reduction of pulmonary iron accumulation (15). Manipulation of the cellular iron level by iron chelators or *via* increasing iron exporter ferroportin expression, has been shown to have promising effectiveness as adjuvant antiviral therapy of AIDS (16). **Deferoxamine** is the only drug form for s.c and i.v administration (17). It can also be helpful with its immunomodulatory affect, in adjunction to antiviral drugs used to treat COVID-19 (18).

The hypoxic state of the body in the conditions of viral infection is further complicated by the oxidative hemolysis of erythrocytes induced by SARS-CoV-2 spike (S) protein binding to broadly expressed **CD147 receptors on erythrocytes** (19; also see Yanev et al's *Dance Round* in this volume of *Biomedical Reviews*). That effect, together with altered calcium signaling from SARS-CoV-2 ion channel activities, may contribute to hypercoagulation, thrombosis, and cardiac remodeling, ultimately resulting in heart failure. **Melatonin** as effective endogenous antioxidant was proved to be useful, with success in prevention and attenuation of hemoglobinopathies, refractory hypoxemia and myocardial injury during critical COVID-19 infections (19).

- Clinicians must be careful with the emergency ventila-

tion! The key principle should be to set low pressure with O₂.Max. Protect the lungs and don't tear them up! Give immunity the time to do its job!!

- Spend as much time as possible in the fresh air, no matter where, at home near open windows, in the park or on the mountain. And when you are in such an environment, do not wear the masks so that oxygen exchange is facilitated.
- Anyone can find answers or raise questions related to their own practice and professional awareness. As they say, *the floor is yours*. I hope the discussion will be useful to everyone, particularly to curious minds, scientists and medical practitioners.

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