Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 cytokine storm and novel truth

Introduction

While the world is facing an unprecedented crisis with novel coronavirus disease (nCoV) 2019/ COVID-19, there are no proven effective pharmacological agents [1]. Following the detection of Severe Acute Respiratory Syndrome coronavirus [2] (SARS-CoV-2) in December 2019 in Wuhan, China, we witnessed a massive surge in the number of cases globally, until World health organization declared a pandemic on March 11, 2020 [2]. The search for a 'Novel' agent is ongoing and as of 7 April 2020, 'TrialsTracker' project [3] had listed 883 clinical trials on COVID-19, including 344 intervention trials.

COVID 19 Real World Evidence

During an evolving pandemic the real-world evidence can only be obtained from respected sources. Unfortunately, by the time a manuscript is produced and accepted for publication, we might have missed the boat.

World health organization failed us and some governments opted to protect the economy rather than controlling the spread of the COVID 19 pandemic. Investigational journalism had the upper hand in exposing the problem with China and later on, in South Korea and Italy. During the same time the WHO was assuring the world that there was nothing to worry about. When the death rate mushroomed in Italy, everything had exploded, the world knew that a new era had arrived with the greatest lockdown of all time. The novel coronavirus's correction will allow us to get rid of all the dinosaurs for every top position in any organization and to evolve to a new world of trust and confidence.

Based on observations in the USA, Spain, Italy, France and the UK, and from the postmortem of lung involvement in COVID 19, all revealed pulmonary thrombosis, which is not typical of acute respiratory distress syndrome (ARDS). More alarming was that patient hypoxemia was not responding to post end-expiratory pressure (PEEP) but high oxygen flow [4].

Bioinformatics Hypothesis

A Chinese scientist [5] used a bio-informatics model to describe the hypothesis of COVID 19 as methemoglobin, where the SARS-CoV-2 virus structural protein sticks to heme - displaces oxygen - which alters the iron-free ion, leading to inflammation of alveolar macrophages, which culminate in a systemic response ending in a cytokine storm. They suggested that if free radical scavengers and iron chelating agents are added to the protocol of management, these might ameliorate the inflammatory response.

What we must focus on is that SARS-CoV-2 attacks RBCs. Patients have frequently been found to have documented elevated D-Dimer, Troponin, Ferritin, CRP and alanine aminotransferase. Moreover, this has resulted in human body insulin deficiency. The increased rates of renal failure, myocardial infarction, keto-acidosis in euglycemic patients and pulmonary embolisms culminating into multiple organ failure with cytokine storm all point to a complex pathophysiology. The common dominator that all these organs have in common is that all their cells are rich in a cell surface receptor called Angiotensin-converting enzyme 2 (ACE2).

COVID-19 is not 'Pneumonia' nor 'ARDS'

Through the current experience across the world, invasive ventilation is becoming the last resort, as emergency intubation from the Chinese, Italian and American experience evidences higher mortality, not to mention complications from tracheal scarring and stiff lung during the duration of intubation. Furthermore, a new treatment protocol needs to be established in order to control the prolonged and progressive hypoxia of COVID-19 patients.

People are desaturating due to failure of the blood to carry oxygen. This will lead to multi-organ failure and high mortality. The lung damage seen on CT scans is due to the oxidative stress released from the hemolyzed red blood cells, which in turn overwhelm the natural defenses against pulmonary oxidative stress and cause a cytokine storm. There is always bilateral ground-glass opacity in the lungs. Recurrent admission for post-hypoxic leukoencephalopathy strengthens the findings of the Italians, Spanish and Americans [4] that COVID-19 patients are suffering from metabolic hypoxia due to blood capacity failure.

The Chinese hypothesis [5] that had been publicized, theoretically, via bioinformatics modeling, postulated that the catastrophic cascade of oxidative stress explains the vicious cycle as follows:

1) Without the iron ion, hemoglobin can no longer bind to oxygen. Once the hemoglobin is impaired, the red blood cell is essentially unable to carry and deliver oxygen to any tissues. This leads to the destruction of the red blood cells and the patient's oxygen saturation levels drop significantly.

In COVID-19 patients, unlike with carbon monoxide (CO) poisoning in which eventually the CO can break off, the affected hemoglobin is permanently stripped of its ability to carry oxygen. The body compensates by secreting excess erythropoietin to stimulate the bone marrow to secrete new red blood cells. This is the reason we find thrombocytosis, or thrombocytopenia depending on the stage and severity of COVID-19, a high ferritin level and D-Dimer with decreased blood oxygen saturation as the primary indicators of the COVID-19 severity score.

2) The free-floating iron ions [5] are highly reactive and cause oxidative damage. This always happens physiologically and is natural to a limited extent in our bodies, and such cleanup is a defense

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mechanism to keep the balance.

Of the three primary lung defenses to maintain “iron homeostasis”, two are in the alveoli. The first of the two are macrophages that roam around and scavenge the free radicals of the oxidative iron. The second is a lining on the epithelial surface which has a thin layer of fluid packed with high levels of antioxidant molecules such as ascorbic acid.

When too much iron is in circulation, it begins to overwhelm the lungs' countermeasures and the process of pulmonary oxidative stress begins. This leads to damage and inflammation, which leads to the so-called cytokine storm [5]; this can be documented on high-resolution CT scans of COVID-19 patients’ lungs.

The liver attempts its best to remove the iron, but only becomes overwhelmed too. It is starved of oxygen. The liver function will deteriorate with elevated ALT, which is one of the primary COVID-19 severity score indicators.

Worldwide in-time Knowledge

Through extensive discussion with some of our colleagues in Beijing, Milan, Sienna, Paris, Barcelona, London and New York [6–9], we have reached a consensus to recommend that the patient might be better managed on maximum oxygen flow possibly with the aid of hyperbaric oxygen chamber [7,8] on 100% oxygen at double or multiple atmospheres of pressure for 90 min twice per day for five days. The randomized clinical trial of hyperbaric medicine started in USA in the first week of April 2020 [7]. This is in order to give what is left of a patient’s functioning hemoglobin a chance to carry enough oxygen to the organs and keep them alive.

As we do not have nearly enough of those hyperbaric chambers, we might use all the parked grounded airplanes as a ready-made functional hyperbaric chamber with the advantage of providing double atmospheric pressure with an aerosol of prostacyclin as a pulmonary hypertension modulator. Some Chinese physicians tried blood transfusion with packed fresh red blood cells to patients after plasmapheresis [9,10] , and witnessed some amelioration of the cytokine storm.

The main point is that patients will require ventilators if they present late with multi-organ system failure to tide them over this life or death scenario. However, intubation is futile unless the patient's immune system modulates the situation [11]. We must address the root of the illness and avoid using traditional teachings to manage a failing system [12,13].

Armchair pseudo-physicians can no longer sit in their ivory towers proclaiming that chloroquine is an effective COVID19 therapy despite the lack of reliable evidence. A few key opinion leaders advised that Chloroquine lowers the blood pH and interferes with replication of the virus. However, a publication in the New England Journal of Medicine advises against the use of chloroquine [14]. Sweden has decided to halt its use, as have some parts of France. WHO had suspended an international multicenter randomized trial for Hydroxychloroquine, citing higher than expected cardiovascular mortality in the treatment arm. FDA have revoked the emergency use and authorization for Chloroquine and Hydroxychloroquine.

We recommend that if COVID-19 positive patients are conscious, alert and compliant, they should be kept on maximum oxygen. A prone position allows better lung perfusion, and providing the possibility to initiate hyperbaric oxygen as early as possible [8–10].

If we reach the inevitable and need to ventilate, USA pulmonologists [15] have recommended that this should be performed at low pressure but with maximum oxygen flow. We must avoid tearing up the lungs with maximum PEEP as this does more harm to the patient because we may be addressing the wrong organ [16].

SARS-CoV-2 Virus and Diabetes Mellitus

A discussion on Medscape about COVID 19 and diabetes mellitus, illustrated that the virus is attacking the Islets of Langerhans in the pancreas and causing insulin deficiency [17]. As those patients had a good reserve, they present late with diabetic ketoacidosis. The main focus of management in these cases needs to be high oxygen flow with insulin replacement.

It is essential not to miscalculate COVID-19 severity in patients with diabetes in the dearth of established worrying signs and symptoms, and we must develop different clinical early severity scores for patients with diabetes. Although acute inflammatory states and acute stress responses raise glucose levels, the SARS-CoV-2 is damaging the pancreatic islet cells.

A study was done during the SARS 2003 coronavirus outbreak in China in which diabetes developed within two weeks of hospitalization in patients who did not previously have diabetes. Immunostaining in patients who had died after contacting COVID-19 showed intense staining of the ACE2 protein — the coronavirus binding site — in the islets but not the exocrine pancreatic tissue, which means coronavirus causes diabetes by damaging pancreatic islets.

COVID-19 causes insulin deficiency, meaning many patients require markedly elevated insulin drip rates. This is not just pressor/steroid-related. Something else is going on here. We've not seen this pattern of glycemia with associated insulin requirements before. This is a new beast. The degree of glucose toxicity is profound and independent of preadmission diabetes control. Patients with seemingly well-controlled diabetes at home with HBA1c in the single digits experience severe dysglycaemia. Furthermore, COVID19 also affects a subset of patients presenting with diabetes keto acidosis (DKA) with normal lactate, without any other causes of DKA. People with diabetes had higher levels of biomarkers due to an inflammatory “cytokine storm” preceding rapid deterioration of COVID-19 [17,20].

There is a small village in northern Italy where the majority of its population suffers from thalassemia. These individuals have had no deaths, and no cross-community spread due to the abnormal shape of the red blood cells. Moreover, parts of Nepal that are 1 km above sea level are almost COVID-19-free; the same logic applies, abnormal shape of the red blood cell. All the evidence suggests that we are chasing the wrong organ: it is not the lungs, it is a blood problem.

Children, COVID-19 and Kawasaki Shock Syndrome

Concerns among patients and pediatricians are raised, regarding reports of children experiencing Kawasaki disease, tied to the COVID-19 pandemic. The majority of children with COVID-19 are asymptomatic. During the course of April and May 2020, first in Europe, and then in the U.S., children developed a more severe inflammatory syndrome with COVID-19 requiring intensive care [21].

These kids displayed symptoms found in pediatric inflammatory conditions, most notably Kawasaki disease. It is a rare condition that presents with a fever above 38–40 degrees Celsius for 3–5 days, lymph nodes enlargement, vomiting, diarrhea, abdominal pain, conjunctivitis, and a rash. The median age is 9.5 years, but it ranged from 3 to 17 years. Kawasaki disease is the commonest reason for acquired heart disease in children in developed countries [22].

This may progress to persistent fever and evidence of single or multiorgan dysfunction, shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder. All children were tested negative for SARS-CoV-2 on bronchoalveolar lavage or nasopharyngeal aspirates. Despite being critically unwell, with laboratory evidence of infection including elevated CRP, procalcitonin, ferritin, triglycerides, and D-Dimers, with no pathological organism isolated. [21–23]

All these children were in contact with someone with the virus. These kids had either a positive but weak PCR test or a positive serological antibody test that showed contact with the virus dated from 3 or 4 weeks previously.

In adults, the cytokine storm arrives at the start of the second week. However, in children, this exaggerated inflammatory response comes on the third or fourth week manifesting as a hyperinflammatory

syndrome with multiorgan involvement similar to Kawasaki disease shock syndrome.

Prompt treatment prevents significant heart problems. While Kawasaki disease damages the heart and the blood vessels, the heart problems usually go away in 2 months, and children fully recover; rarely, the coronary artery damage persists, resulting in coronary artery aneurysms or myocardial damage [21–23].

Big Data and Artificial Intelligence

We advised a few international organizations that artificial intelligence (AI) and machine learning must be utilized in analyzing Big Data. AI, Big Data analysis and bioinformatics must be harnessed to allow us to scrutinize how we provide the best options for our patients, creating bioinformatics modelling that can surpass any randomized controlled trials. Adaptive platform designs must be structured to promote maximum learning from around the world to adjust how we deliver the best care to our patients [24–30].

People are desaturating due to failure of the blood to carry oxygen [17]. This will lead to multi-organ failure and high mortality due to cytokine storm. We believe that management protocols for ARDS should not be applied for COVID-19 patients [18,19,24–30].

Recommendations

We recommend the following:

1. Inhibit viral growth and replication by any proven means. The star of Remedesivir and corticosteroids, which both have proven effectiveness in ameliorating COVID-19 mortality. Other retroviral therapies are being studied. The less viral load we have, the less severity of the damage with the prevention of cytokine storm.
2. Full heparinization to prevent disseminated intravascular coagulopathy after excluding heparin induced thrombocytopenia.
3. All children with unexplained fever, elevated CRP, leukocytosis, high troponin and D-Dimers, should be carefully monitored.
4. Theoretical use of hyperbaric medicine or pressurized grounded airplanes may prevent rapid ascent into the abyss.
5. Plasmapheresis and blood transfusions may give supportive symptomatic relief when indicated.
6. No international travel until an effective vaccine is available.
7. Cessation of tobacco, vaping and alcohol consumption.

Until we create a sound proven protocol for managing our sick patients and understand why chloroquine and invasive ventilation have failed, as both have been unable to bail out our oxygen-starved patients, the only available option is symptomatic relief.

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Disclaimer

These views are our own. They do not represent the views of NUIG or UHG.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109875.

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