
COVID-19 War, Cytokines Storms Enigma

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Globally, Scientific's research and development is suppressed, while subjects are suffering from the COVID19 pandemic attack with its surprising infection/ death ratio, and no standard cure/ care against it still exist. Furthermore, how systemic blood is attacked by provoked cytokines storm in different patients, and their response to Covid19-related organs' shut down is also not clarified completely.

Generally known that in some people with COVID19, an overreaction of their immune system can damage their lungs, and an anti-inflammatory drug may help reduce this damage and keep them off a ventilator, while the Food and Drug Administration of US has also given the green light to clinical trials of compounds that were still being studied for use in other similar conditions. Beside, mainly steroids are the best anti-inflammatory drugs prescribed when a patient shows signs of a 'cytokine storm', classically.

Ultimately no standard treatment is available routinely yet to cure/care of 8 million COVID19 infected patients (15 June 2020).

Previously we introduced the pathogenesis of the COVID19 virus, which was divided in 4 pathophysiologic pathways [1,2]. Now it became obvious that cytokines storm might intensifies organs shut down, prematurely; and subsequently might increase random deterioration of in- hospital stay patients' condition toward increased risks of mortality and morbidity, however. Whether in-hospitals' staying worsening of clinical

symptoms is side effect of (unfitting) treatments is not clarified yet [1-3]. The main questions still remained namely “what would be the best diagnostic biomarker of the COVID19 infection? And what would be the standard cure/care of infected patients?

In addition, most clinical published data has focused on the classical biomarkers i.e. TNF alpha, IL-6 and IL-8, underlying signal transduction mechanisms that provokes destruction of random tissue and cell are not elucidated as well. Different simultaneously activated processes might aggravate appropriate diagnostics/cure/care due to for instance I. premature apoptotic processes, II. go- /nogo orders from the unfolded protein response (UPR) and its associated genetically expressed signaling III. Premature phosphatidic Serine (PS)-flip-flop, and at least but not last IV. Unexpected release of interleukins- correlated signaling [4,6].

When host's Brain-Gut-Heart axis being involved in immunological responses, central nervous system monitors via Vagus nerve, the longest of the cranial nerves, and controls human's inner nerve center - the parasympathetic nervous system. Although, it is remarkable how COVID19 enters subjects' body and dysregulates microbiota hemostasis, and their combination, randomly. Consecutively, any changes that eventually might affect endogenous hormonal and immunological reaction in infected subject might turned off/on, in advantage of the COVID19 (mutants) eventually.

To understand and highlight more in details about possible connections between a certain disease and possible options to cure/care an infected patient, it might be useful to know that the endogenous defense systems and protective hormonal reactions mainly are regulated by 5 different compensation systems, post-infections namely rehabilitation via 1. respiratory 2. metabolic 3. microbiota 4. central vagal 5. peripheral regulated (un-)known systems. Moreover, the Brain-Gut-Heart axis might being involved to express certain genes, proteins and induce appropriate respiratory and/or metabolic compensation systems. In subjects infected with COVID19 vibrant responses of microbiota and their intervention with the COVID19 (re-) actions, might offer therapeutic strategies, against cytokine storm if subject' physical condition would be fit enough and contain fitting antiviral factors. One might wonder whether bacterial flora of patients could become blocked post-COVID19 infection, and their capability to prevent cytokine storm and/or sudden septic onset, intentionally.

In the last 6 months there are different drugs introduced as best medicine i.e. Favipiravir, or Avigan, Remdesivir, Avifavir, Chloroquine hydrochloride, and different so-called anti-Covid19 therapies and/or drugs like OZON, statins, Warfarin, NOACS, convalescence plasma, etc., which none of them were standardized as best routine treatment against COVID19, without side effects. Speculatively, when (para-) Medici are planning to treat any random COVID19-patients by prescribing routine antibiotics to manage their infection and inflammation, unspecific usage of the general bactericides administration instead of bacteriostatic antibiotics might additively and/or synergistically deteriorate shut down signal transduction of restoration and rehabilitation, however.

Up to now there are limited studies over how (Para-)Medic can reduce the risk of mix-infection [1,5]. Disappointingly, limited investigation is carried out to evaluate the probability of the COVID19 origin and mechanism of action, which directing all changes in human- or environmental microflora and microbiota combination, concomitantly. As during previous pandemics (severe acute respiratory syndrome and Middle

East respiratory syndrome), corticosteroids are not routinely recommended and might exacerbate COVID19-associated lung injury [6]. Different cytokines storm provocations are reported to aggravate tissue damages [4-6]. The main secreted known interleukins and cytokines are ILs 1,2,6,8,10 and TNF α , while Secondary haemophagocytic lymphohistiocytosis (HL) is an under-recognized, hyper-inflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with random shut down of subjected organs [4-6]. A cytokine storm might be associated with COVID19 disease severity, as well. Different endogenous releasates and secretoms considered to be involved in an increased IL-2, IL-7, granulocyte colony stimulating factor, interferon- α inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumor necrosis factor- α [4,6] which are also very important in COVID19 severity.

Looking at most quick published data of last months, One might wonder why all Basic Scientists from big Pharmaceutical Companies still have no idea how they can prevent COVID19 pandemic second and third waves, in the near future. Limiting budget and foundation of the most Researchers toward an economic-based Science has resulted in a world with political-based- Science decision which bring whole humanity (co-)existence in dangerous situation. One might hope all conspiracy theories for no-existency are illusions and hopefully we all enjoy appropriate remedy as soon as possible, world widely.

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