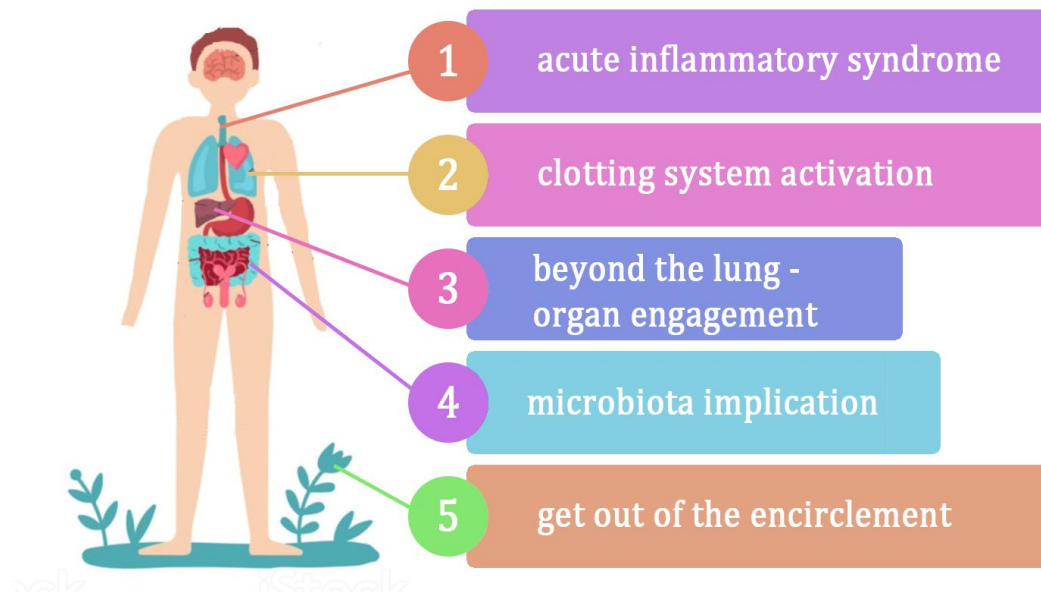


SARS-COV-2 INFECTION HALLMARKS AND POSSIBLE REMEDIES

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SARS-CoV-2 infection has launched a worldwide debate about health care in general. Recent reports² have pointed out that a clear understanding of the mechanisms of the disease and complications leading to the death of some patients could change our preventive and therapeutic strategies.

Of course, most infected patients will deal with the infection with no, mild or moderate symptoms. The problem is that of severe cases that trigger so many mediatic reactions. What happens in such cases ?



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² How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. Wadman M, Couzin-Frankel J, Kaiser J, Maticic *Science* Apr. 17, 2020.

- **First step : acute inflammatory syndrome**

In the first place this virus is unknown to the human immune system and, for some individuals, an « overreaction » of the immune system can lead to severe symptoms. This is typically the picture of an uncontrolled acute inflammatory reaction similar to that observed in sepsis or « acute respiratory distress syndrome », ARDS.

This acute inflammatory reaction involves high levels of IL-6, IL-1, TNF-alpha and interferons (the « cytokine storm »).³

- **Second step : clotting system activation**

Generalized engagement of **blood vessel walls leads to massive endothelial damage**⁴ that could be at the origin of pulmonary thrombo-embolism through involvement of the coagulation cascade. This can lead to severe organ damage and failure.

Due to the exaggerated inflammatory reaction and consequent overstimulation of the clotting system, pulmonary thrombo-embolism has now been reported by many studies in severe cases, with dramatically high peripheral levels of D-dimers⁵.

- **Third step : beyond the lung - organ engagement**

- As blood clots can break apart and lodge in the **brain**, stroke may occur.
- **Heart attack** symptoms have been indeed described in an Italian patient⁶.
- Heart lesions have been reported in nearly 20% of 416 hospitalized patients in Wuhan⁷ and 44% of 138 hospitalized patients had **arrhythmias**⁸,

³ “The fact that some studies have shown elevated levels of these inflammation-inducing cytokines in the blood of hospitalized COVID-19 patients, has drawn to the conclusion that the real morbidity and mortality of this disease is probably driven by this out of proportion inflammatory response to the virus” (Jamie Garfield, Temple University Hospital), *art cit*.

⁴ Endothelial cells are lining the vascular wall and are responsible for immune cells recruitment, but also exposed to the cytokine storm of an acute inflammatory activation.

⁵ High incidence of thrombotic complications in ICU patients with COVID-19 pneumonia. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Klok FA, Kruip Mjha, Van Der Meer Njm et al. - *Thrombosis Research* 2020, <https://doi.org/10.1016/j.thromres.2020.04.013>

⁶ In Brescia, Italy, a 53-year-old woman walked into the emergency room of her local hospital with all the classic symptoms of a heart attack, including telltale signs in her electrocardiogram and high levels of a blood marker suggesting damaged cardiac muscles. Further tests showed cardiac swelling and scarring, and a left ventricle so weak that it could only pump one-third its normal amount of blood. But when doctors injected dye in the coronary arteries, looking for the blockage that signifies a heart attack, they found none. Another test revealed why: the woman had COVID-19.

⁷ Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. *JAMA Cardiol*. Published online March 27, 2020.

⁸ Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD; Xing Liu, MD; Jing Zhang, MD; Binbin Wang, MD; Hui Xiang, MD; Zhenshun Cheng, MD; Yong Xiong, MD; Yan Zhao, MD; Yirong Li, MD; Xinghuan Wang, MD; Zhiyong Peng, MD *JAMA*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585

- **Fourth step : microbiota implication**

Suddenly, but obviously, also the microbiota steps into the SARS-CoV-2 infection : scientists communicate about changes in the intestinal flora as possibly related to the severity of the disease.

Infected patients with severe symptoms – already highly inflamed and full of clots - seem to experience a shift in their intestinal microbiota strains composition. *Bifidobacteria* and *Lactobacilli* disappear, especially in the aged population. Instead, bacteria of the *Prevotella* genus seem to prevail.

Indeed, gut and lung microbiota belong to the mucosal immunity and communicate to such a point that in the SARS-CoV-2 infection it seems that a mixed contamination takes place, involving both of them in the thrombo-embolic mechanism.

- **Fifth step : some simple suggestions to get out of the encirclement**

The University of Zhejiang has proposed a strategy of “The 4 anti and the 2 maintain ” which can be summarized as :

- The 4 “anti” are : anti-viral, anti-shock, anti-hypoxemia and anti-infectious,
- The 2 “maintain” are : maintain the electrolytic and microbiotic balance.

Therefore, in Western terms, this would mean to supplement in essential vitamins (B3, C, D) and oligo-elements (zinc) as well as prebiotics (fibers) and probiotics (*Lactobacillus brevis* shown to be able to inhibit *Prevotella's* biofilm formation). In the supplementation of pre- and probiotics also known as “psycho-biotics” as they importantly are able to modulate mood⁹, fibers are strategic, without regular intake of fibers, probiotics are useless.

This can be summarized in these five steps:

- take care of stress in the first place
- treat inflammation (IL-6)
- control coagulation
- take care of intestinal dysbiosis
- help restore good strains of the microbiota (fibers).

⁹ Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF and Philip W.J. Burnet. *Trends in Neurosciences*, November 2016, Vol. 39, No. 11 <http://dx.doi.org/10.1016/j.tins.2016.09.002>

Could a preventive treatment with AISA moleculum Capsules contribute to improve the immune response to SARS-CoV-2?

In a large European study¹⁰, the AISA active compound¹¹ contained in AISA moleculum® Capsules has been shown, in a selected population of 65-85 years old of age people of both genders, to be able to improve a baseline chronic inflammation involving elevated levels of IL-6, one of the most important pro-inflammatory cytokines.

In the same study, blood fibrinogen levels (another marker of inflammation also crucial for coagulation) were decreased upon consumption of AISA moleculum capsules. This study did not involve any patient with acute inflammation, but the decreases of IL-6 and fibrinogen were significant.

The immune system challenged by SARS-CoV-2 infection represents, for a probably small population of infected individuals, a condition of stress leading to deleterious effects. For other individuals, it seems reasonable to assume that some added value can be derived from the use of this natural anti-inflammatory molecule:

- ❖ AISA **anti-stress** action is largely beneficial to the immune system.
- ❖ AISA overall **anti-inflammatory** action can possibly avoid « the cytokine storm » in individuals likely to develop it.
- ❖ AISA **anti-fibrinogen** activity¹², although interpreted as a consequence of the anti-inflammatory properties of AISA compound, could possibly prevent – such as LMWH¹³ or anti-factor Xa drugs¹⁴ - the pro-thrombotic effects of acute reactions following SARS-CoV-2 infection in some individuals.
- ❖ The AISA moleculum compound has been shown to be able to **reverse dysbiosis**, thus contributing to the restoration of the gut barrier function¹⁵.

¹⁰ The RISTOMED study is an FP7 Capacities study comparing different nutritional strategies according to the claim « healthy aging by nutrition ». Impact of diet and nutraceutical supplementation on inflammation in elderly people. Results from the RISTOMED study, an open-label randomized control trial. Ostan R, Béné MC, Spazzafumo L, Pinto A, Donini L, Pyren F, Charrouf Z, Valentin L, Lochs H, Bourdel-Marchasson I, Blanc-Bisson C, Buccolini F, Brigidi P, d'Alessio PA. *Clin Nutr.* 2016;35:812-818.

¹¹ Natural mono-terpene cocktail, collected in bio collections and reconditioned by AISA corporate know-how.

¹² Within the clotting cascade Fibrinogen is the substrate for fibrin formation (the end product of thrombus formation) and at the same time the ligand for the platelet receptors, thus promoting platelet aggregation.

¹³ Low Molecular Weight Heparin whose rebound effect excludes it from therapy, at the exclusion of urgency.

¹⁴ *Ex gr* Rivaroxaban a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathways of the blood clotting cascade, thereby inhibiting thrombin formation and thrombus development.

¹⁵ Oral administration of *d*-Limonene controls inflammation in rat colitis and displays anti-inflammatory properties as diet supplementation in humans. d'Alessio PA, Ostan R, Bisson JF, Schulzke JD, Ursini MV, Béné MC. *Life Sciences.* 2013;92:1151-1156.