



Clinical evidence and therapeutic treatments at the time of the coronaviruses responsible for SARS: a perspective point of view

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(Article begins on next page)

1 *Hypothesis*

2 **Clinical evidence and therapeutic treatments at the**
3 **time of the coronaviruses responsible for SARS: a**
4 **perspective point of view.**

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13

14 **Abstract:** The clinical evolution of the COVID-19 patients highlights a significant minority of subjects with
15 very rapid lethal outcomes with respect to the almost complete healing after coronavirus infections for most
16 of the subjects involved. In addition, the reckless use of some drugs and therapeutic protocols that have not
17 shown any efficacy in reducing mortality in those patients where the progression of the disease was
18 unstoppable suggests a different interpretative way in the pathogenesis of severe cases. Starting from the
19 clinical data already known for almost twenty years on the behavior of human SARS coronaviruses it is
20 possible to advance a new hypothesis. The reference points taken into consideration are: i) the comparison of
21 the histological evidence of the autoptic material; ii) the poor pharmacological response in subjects with
22 severe phenotype of the pathology; iii) the common elements of endotheliitis that a subgroup of the
23 population characterized by the unfortunate clinical outcome expresses during the evolution of the
24 pathology. The tendency to develop a widespread, massive endothelial lesions not responding to any drug
25 therapy or health treatment necessarily play a crucial role in the onset of the systemic and severe stage of the
26 disease. The present hypothesis opens the door to a different therapeutic approach both to the full-blown
27 phase of COVID-19 and to the preventive phase or the very first manifestations of the disease, suggesting
28 greater attention to the protection of the vascular endothelium in subjects who already have it predisposed to
29 the severe evolution of this ailment than to simple antiviral defense.

30

31 **Keywords:** Coronavirus; SARS-CoV-2; COVID-19; Lymphocytopenia; Endothelial cells; Endotheliitis;
32 Prescriptive appropriateness; Personalized medicine

33

34 **1. Introduction**

35 The COVID-19 pandemic took the world's population by surprise, starting with the top
36 decision-makers. The originality of the causal infectious agent (SARS-CoV-2 or 2019-nCoV) has
37 ensured that each of us looks to the future with the presumption of a journey into the unknown
38 with the sharpest technological and pharmaceutical weapons available. Despite this, apart from the
39 initial hesitation of some political leaders, the answer was the lockdown. But what if this pathogen
40 wasn't so completely unfamiliar? But what if such a new positive sense RNA betacoronavirus had
41 left any clue of itself and its etiopathogenesis in any of its ancestors?

42 In late 2002, an unknown, highly virulent respiratory infection originally described as an
43 outbreak of a severe atypical pneumonia appeared in the Guangdong Province of southern China.
44 Such a severe acute respiratory syndrome (SARS) rapidly spread through Southeast Asia, Europe,
45 and North America [1]. Even in that circumstance the state of pandemic was declared and the
46 pathogen belonging to the coronavirus family (namely SARS-CoV) was held responsible.

47 Even if we grant for the sake of argument that there may be translational reasons justifying the
48 substantial difference in size between the two infections [2,3], this is not the purpose of this note.
49 The questions we will try to answer are: i) What scientific evidence have we inherited from
50 previous human coronavirus-mediated diseases? ii) What is the current state-of-the art? iii) What
51 approach will we take to best treat patients with COVID-19?

52 **2. What scientific evidence have we inherited from previous human coronavirus-mediated** 53 **diseases?**

54 From the first cases of SARS, the clinical evidence revealed “worsening in week 2 is unrelated
55 to uncontrolled viral replication but may be related to immunopathological damage” [4]. Going
56 forward, a standard treatment protocol comprising antibiotics, a combination of ribavirin, and a 3-
57 week step-down course of corticosteroids resulted in overall satisfactory outcomes [5]. To
58 understanding SARS pathogenesis, manifestations include systemic vasculitis, apoptosis and
59 swelling of endothelial cells and inflammation in various organs like heart, kidney, liver and
60 adrenal glands. However, the absence of SARS-CoV in these organs where there is an abundant
61 expression of ACE2 allows us concluding that the vascular abnormalities and inflammatory
62 changes in various organs might be related to systemic toxic effects of immunopathological in
63 nature elicited by SARS-CoV infection [4,6]. Therefore, patterns of disease progression in terms of
64 response to different corticosteroid doses [7] and about the quality rather than magnitude of
65 immune response [8] were of interest. To support the latter aspect, the predisposition of the host
66 suffering of Kawasaki disease resulting in the vasculitis from an abnormal clonal expansion of
67 CD8+ T cells in response to the viral agent [9,10].

68 In 2013, the published series “From SARS to MERS: 10 years of research on highly pathogenic
69 human coronaviruses” originated with the stated purpose “that more research is urgently needed
70 to elucidate their replication mechanisms, identify potential drug targets, and develop effective
71 countermeasures” taught us many lessons. However, the hope to change the attitude of researchers
72 and funding policy makers this time around the expected return of a coronavirus pandemic
73 remained in vain, at least until the COVID-19 pandemic state has been declared [11].

74 Eventually, it is worth noticing that over imposable pulmonary CT scan findings were
75 described in SARS patients in 2003 [12], as well as the principal pathological findings associated
76 with acute respiratory distress syndrome [13].

78 **3. What is the current state-of-the art?**

79 Today we are witnessing redundancy in research and reporting in COVID-19, many of which
80 for the sake of publishing [14]. COVID-19 is a viral disease with multi-organ clinical expression
81 where lung injury represents only the first phase of the disease. Nevertheless, in some subgroups of
82 the human population COVID-19 dramatically evolves into a multisystemic disease [15] At this
83 regard, an increasing awareness about COVID-19 immunity, inflammation and intervention is
84 taking shape [16]. Moreover, different respiratory treatments for different phenotypes have been
85 proposed [17], together with prediction models for diagnosis and prognosis [18].

86 From a cell biology perspective, COVID-19 can be divided into three phases that correspond to
87 different clinical stages of the disease [19]. SARS-CoV-2 infects T lymphocytes through its spike
88 protein-mediated membrane fusion [20]. This step, which is crucial in assessing the hazard of the
89 disease in a subgroup of infected people, appears increasingly linked to an alteration of the
90 endothelial cells that cover the entire circulatory tree, at an arterial, capillary and venous level [21].
91 Therefore, the claim suggesting “expanding our understanding of processes that mediate
92 endothelial cell-cell communication is an important step in the approach to treatment of disease
93 processes” is of paramount importance [22].

94 **4. What approach will we take to best treat COVID-19 patients?**

95 Starting from an acquired individual predisposition, it is precisely the ubiquitous presence of
96 vascular endothelial cells in all the parenchyma and tissues of the body to determine modifications
97 of their physiological pattern when they are attacked by the circulating virus [23]. In our opinion,
98 among these changes, an increased degree of molecular freedom at level of membrane bilayer and
99 endothelial cilia structures represents the key to interpretation [24]. From a clinical, laboratory and
100 histopathological viewpoint the altered signal transduction events are the most important factor for
101 the development of these widespread organ, polysystemic lesions and which also involve vascular
102 parietal microthrombosis. Such a cellular adaptation generates an increase in the attraction and
103 uptake stage with firm adhesion to the endothelial surface of the circulating blood bodies [25].
104 Among these, the lymphocytes and platelets are noteworthy: the former, responsible for a massive
105 transendothelial transmigration and the latter through an induction to the phenomena of micro
106 adhesion and the beginning of the thrombotic phases [26]. The first mechanism justifies the
107 phenomenon of lymphocytopenia especially affecting the CD8 + (cytotoxic) and CD4 +
108 subpopulations. In fact, despite the intense lymph node and bone marrow production of
109 leukocytes, compared to a significant increase in circulating neutrophils which rapidly rise up to
110 90% of the white blood cells present in the blood, and temporary increases also in the circulating
111 lymphocytes, the latter decrease both in percentage and in absolute numbers at values comparable
112 to an acquired immunodeficiency syndrome. The drop is prevalent in the T lymphocyte line. This
113 immediately has two effects:

114 1) The first is to have an intense perivascular lymphocellular infiltrate spread in all organs,
115 with toxic effects on tissue parenchyma both for immediate hypoxemia which prevents organ cells
116 from continuing to perform their normal functions and for direct damage by cytotoxic CD8 +
117 lymphocytes at the level of the same parenchymal cells [4,16]. In fact, the function of these immune
118 cells is to attack cancer and virus infected cells.

119 2) The second is an immunosuppression effect, also by reducing T helper lymphocytes and
120 circulating natural killer cells. So, the response times of the immune system to COVID-19 are longer
121 than the time expected for the body's normal antibody reaction to infections [27].

122 In this context, it is not clear why glucocorticoid drugs continue to be administered even at
123 massive doses which further reduce the antiviral capacity of the residual lymphocyte population
124 [28].

125 The thrombotic phenomena will then determine consequent diffuse microembolies since the
126 attraction and surface ligands of the shear stress endothelial cells may or may not retain the
127 thrombotic structures formed. This hypothesis is supported by the fact that despite the intense and
128 sometimes preventive administration of heparin even in large doses, this does not prevent or limit
129 the dramatic effects of the intravascular disseminated coagulation [29,30]. The precapillary terminal
130 arterial vessels are extremely widespread, and they are necessarily present in all parts of the body
131 because the microcirculation must touch all the cells of the body since the need of oxygen to
132 survive. They have an endothelium consisting of simple monolayer paved epithelial tissue of
133 mesenchymal origin whose functions are multiple. In addition to those of constituting an important
134 blood pressure regulation organs actively participating in the changes of the blood flow at the
135 terminal level through the phenomena of dilation and contraction of the vascular lumen, they also
136 perform two important functions strictly connected to each other by the ability of their cytoplasmic
137 membrane to easily adapt to these purposes: i) the mitotic function of cell duplication linked to
138 neovascularization and ii) the structural modification that occurs in the phase of the transcellular
139 passage of lymphocytes from the vascular lumen to the perivascular parenchymal tissue. These two
140 phases are necessarily regulated by physiological regulatory mechanisms. However, they can be
141 modified and altered by various agents such as the toxic action generated by both infectious,
142 especially viral, and autoimmune diseases, by chemical stress related to the metabolic or/and
143 pharmacological action, by cellular senescence, just to name the most important [31-33].

144 According to the pathogenetic mechanism proposed by us for COVID-19, the clinical
145 manifestations of the pathological pictures resulting from these endothelial alterations are mainly
146 linked to the exaggerated lymphopenia that we find in phase 2, that is, in the phase of the multi-

147 organ tissue damage of which we have previously reported [21]. In this regard, it should be
148 reiterated that this pathological situation cannot occur without an active participation of endothelial
149 cells and therefore we will have to talk about endotheliitis, where the occasional binding phase of
150 circulating lymphocytes immediately turns into a close adhesion of the former and in the
151 subsequent passage transendothelial of the latter.

152 The accelerated migration stage is necessarily related to a mechanism of reduction of
153 membrane rigidity in analogy to the rearrangement of molecules in the cholesteric, smectic, nematic
154 phases of liquid crystals [34-36]. It allows rapid penetration of the large lymphocyte corpus (6-8 μm
155 in diameter) through the thin barrier of the endothelial cell whose thickness does not exceed 1 μm
156 [37]. Such a phase transition could occur due to the changes in the apical cell polarity that the
157 mechanical force of shear stress, exerted by the blood flow on the lymphocyte closely attached to
158 the endothelium, is plausibly capable of generating [38]. By doing so, the structure of the
159 endothelial cytoplasmic membrane is modified, initiating a phagocytosis/exocytosis process and
160 allowing a mitotic-like membrane separation [39]. These phenomena are functional and
161 physiological in endothelial cells, but in this step of the pathology they instead become exaggerated
162 and out of control, hence the rapid and massive passage of T-lymphocytes through the endothelial
163 cell body into the perivascular tissue with all resulting pathological consequences [40].

164 Moreover, to further confirm the phase of "tight" adhesion between lymphocyte and
165 endothelium there are some parameters that during COVID-19 should always be carefully
166 monitored. They are the blood values of the calcium ion and haptoglobin. Ca^{2+} is also responsible
167 for molecular adhesion when the relationship concerns actin filaments such as those present in the
168 cilia present on the surfaces of endothelial cells [24,41]. In COVID-19 patients, calcemia is always
169 below normal values. On the contrary, the presence of high haptoglobin values even in the absence
170 of haemolysis phenomena suggest a liver release during the pathogenic challenge [42]. The role of
171 haptoglobin in the genesis of thrombotic phenomena needs more in-depth studies.

172

173 5. Conclusions

174 On the basis of clinical observations from COVID-19 patients, the severity of COVID-19 is
175 determined by the viral attack but becomes truly dramatic when it is associated with endotheliitis
176 triggered by the presence of risk factors at level of vascular endothelium such as aging, and/or
177 concomitant pathologies, therapies and immune-based diseases [43]. For this reason, we suggest
178 that the therapeutic action in COVID-19 cannot ignore personalized medicine. The elderly, patients
179 subjected for a long time to pharmacological treatments with a potential degree of endothelial
180 toxicity and patients with diseases that act heavily on the endothelium and which generally
181 manifest themselves as microangiopathies are at risk. In addition to both trying to limit the viral
182 action with the use of effective antiretrovirals for RNA viruses and improving the antibody
183 response with immunostimulation using specific monoclonal antibodies, it should mainly focus on
184 the defense of patients with diabetes, scleroderma microangiopathy, Raynaud disease, obliterating
185 arteritis, Kawasaki disease.

186 We are also convinced that if COVID-19 is observed with this attention to its deeper
187 etiopathogenetic mechanisms, the social protection measures currently in place in this pandemic
188 can be tailored and re-evaluated.

189

190

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193 of the manuscript

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