

## Tribulations of the Sars-Cov-2 over the Globe

Ilai Goshen MA<sup>1</sup>, Assaf Benharroch<sup>2</sup>, Daniel Benharroch MD<sup>3\*</sup><sup>1</sup>The Psychotherapeutic Institute, Shaar HaNegev and Sapir College, Sderot, Israel<sup>2</sup>Kibbutz Gal On, Israel<sup>3</sup>Department of Pathology, Soroka University Medical Center and Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, IsraelDOI: [10.36347/sjams.2020.v08i04.027](https://doi.org/10.36347/sjams.2020.v08i04.027)

| Received: 05.04.2020 | Accepted: 24.04.2020 | Published: 30.04.2020

\*Corresponding author: Prof. Daniel Benharroch

### Abstract

### Review Article

In this review, the unique peculiarities of the SARS-CoV-2 were screened, in an attempt at defining the most relevant features of the virus that might explain its erratic and deviant behavior. The characteristics of COVID-19 were likewise scrutinized, in order to associate them with one of the footsteps of the virus in its voyage around the planet. Although a hypercytokinemia is certainly an inherent part of the disease, we have suggested that the 'cytokine storm' may not be an integral part of COVID-19, and, while microthrombosis may be accounted for by the CAC/DIC secondary to viral sepsis, various degrees of bleeding have been reported.

**Keywords:** Tribulations, Sars-Cov-2 hypercytokinemia.

**Copyright @ 2020:** This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

## INTRODUCTION

SARS-CoV-2 is probably more contagious than the associated viruses, SARS-CoV and MERS-CoV, which are, by contrast, more pathogenic [1]. The novel coronavirus' contagious capacity is expressed by the transmission rate ( $R_0$ ). The latter represents the number of newly infected people contaminated by one individual case. At the beginning of this year,  $R_0$  varied between 1.4 and 2.5, but it has later reached 3.5, with an epidemic doubling time of about 6.4 days [2]. The next aggressiveness marker, the case fatality rate (CFR), the proportion of cases terminating in death, varies from 2 to 3%. Asymptomatic transmission represents a further criterion, since by this means, the pandemic progresses unattended. An additional difference between the three coronaviruses features is that, with COVID-19, the patient will exhibit a normal temperature in 12-30% of the cases, while fever is the rule for the other two viruses' features. However, to this day, temperature is still measured for medical and security enforcement [2].

The incubation period for the novel coronavirus ranges from 2 to 10 days or according to other sources, 2-14 days, while during the lapse between day 10 and day 14, the individual is highly contagious. Recovery time of one month is found in 90% of patients; in mild cases, the malady lasts about two weeks and severe disease endures 3-6 weeks.

Some pathogenic features may be attributable to SARS-CoV-2 adaptation to humans in a more

efficient manner. Regarding the genetic basis of this skill, the virus will undergo frequent mutations, both normal and benign in character. Recently it has been suggested that this virus mitotic rate is lower than assessed previously. But this comparison refers most probably to the mitotic ratio of SARS-CoV [2].

Other issues on COVID-19 have been subject to controversy, including a possible role for children in the virus dissemination. In order to refrain from pinning down stigmata onto any age or ethnic group, we will discuss instead the role of asymptomatic individuals, only to note that this fraction of the population has not been properly estimated. The viral load in asymptomatic carriers may be low. Involvement of the gut by the novel coronavirus is infrequently detected, but might represent the site of a carrier state [2].

Several aspects of COVID-19 and of SARS-CoV-2 are, thus, abstruse and they are the subjects of our review.

## OF SOME OBSCURE ASPECTS OF COVID-19

### *Asymptomatic infections*

An estimation of the number of infected individuals has been accounted for in Iceland [3], at the Stanford Medical Center [4] and in a small town in Germany. By performing large numbers of serologic tests to measure IgM, IgG antibodies and the antigens of SARS-CoV-2, these scientists have evaluated the true figures of the pandemic, as well as the rate of

asymptomatic patients. Together with other groups, they displayed the ratio of asymptomatic infections that has varied from 10-30% in Hong Kong; 18% on the Diamond Princess cruise ship [5]; 67% in Northern Italy, 50% in Iceland and up to 75% in the early Chinese studies [3]. These last reports showed that the Chinese patients became symptomatic, soon after the tests performance. These groups have raised the issue of the transmission capacity of the asymptomatic carriers [2, 6].

In contrast to the novel coronavirus, the SARS-CoV and MERS-CoV spread less efficiently and mostly via symptomatic patients. Overall, the range of asymptomatic individuals varies for the novel coronavirus from 5 to 80%, although the figures may not be entirely reliable.

#### ***Presymptomatic carriers***

The incidence of these carriers is probably high and upon 5 days of follow-up, these persons may start to display symptoms. During the week preceding the appearance of symptoms, these carriers may shed very large amounts of the novel coronavirus.

#### ***RNA viruses and their mutation rate***

SARS-CoV-2 mutates about every 15 days. It is by the bias of its swift mutation rate that the virus has infected most areas of the world. Genomic data obtained during the pandemic progression, highlight the chronologic advance of the virus.

However, these mutations are not to be accounted for the harmful effect of the novel coronavirus. These mutations are benign. It is the virus' RNA itself that dictates its infective behavior and the means by which it harms the host. Its high affinity for human cells accounts among others for its behavior in the carrier state.

When the SARS-CoV-2 reaches a new area of the globe, inhabited by slightly different humans, it undergoes mild mutations, which increase its capacity to acclimatize to the new environment and the new host. The virus adapts to various populations through mutations and that is why it is capable of infecting so many mortals.

#### ***RNA viruses, genetic diversity and the quasispecies theory***

Several viruses of serious medical impact, like influenza, hepatitis C or HIV are RNA viruses. They all show very high mutation rates. Moreover, this includes a notable genetic diversity, which encourages the viral population to adjust to a changing habitat. In addition, these faculties might evoke a cutting resistance to treatments and to the synthesis of vaccines [7, 8].

For more than 30 years, the quasispecies theory has attempted to provide a background for understanding the behavior and progression of RNA viruses, among others. The quasispecies is meant to mingle numerous viral variants, genetically related through mutations, which show a common crosslinking activity, each component contributing to the characteristics of the collectivity. It is of note that many forecasts of this theory stand out against the laws of classical microbiology, while they help explaining the behavior of viral diseases.

Thus, our ability to foresee the outcome of an infection and the therapeutic solution thereof, from exclusive observations of an isolated clone, is deemed to fail. In RNA viruses, a marked mutation rate means that a fast proliferating virus will result in genetically diverse offsprings, which might be less fit than their parents to predict the RNA virus behavior. Therefore, fitness of biological viral clones is reduced in comparison with complete population fitness, from which the clone originated [9].

Next generation sequencing, should improve significantly the ability to study the configuration of the range of viral mutants of a quasispecies in animals or in human. SARS-CoV-2, being an RNA virus, endowed with a very high mutational ability, should be exposed to the quasispecies theory, more specifically, while using for this purpose the next generation sequencing technology. This approach has been applied, including for the analysis of the novel coronavirus [10].

#### ***Coagulation disorders as they relate with viral infectious diseases***

Coagulation disorders may be associated with bacterial, as well as non-bacterial (about 42%) infectious diseases [11]. The most prominent disorder in this context disseminated intravascular coagulopathy (DIC), is followed by multiorgan failure, and other conditions: HUS – hemolytic uremic syndrome; TTP – thrombotic thrombocytopenic purpura. The viral hemorrhagic fevers (Dengue, Ebola etc..) are related to these disorders [12].

These conditions are usually associated with systemic infections, mainly sepsis. In the context of viral infectious diseases, a systemic viral disease might probably activate the coagulation cascade and initiate coagulation and even bleeding. The coagulation cascade pathology might look like DIC. Indeed DIC may be of viral origin.

Cytokines have been attributed several roles herein. One possible task of the cytokines in severe systemic disorders has been related to the 'cytokine storm'. Indeed high levels of inflammatory cytokines have been detected in critical COVID-19 patients suspected to have developed this syndrome [13].

Although viral sepsis has been poorly categorized, one should be reminded, that 42% of infectious diseases presenting with coagulopathy, are non-bacterial, a significant proportion of these cases being of viral origin. Therefore, it is not excluded that a sizeable part of sepsis cases with DIC might be of viral origin. An excess of TNF- $\alpha$  and of IL-6 with IFN- $\gamma$  deficit might inflict damage to the patient. If viral sepsis is suspected in a COVID-19 patient, broad spectrum antibiotics should be administered [14].

COVID-19-associated coagulopathy (CAC) might be slightly different from DIC. However, it has been proposed to name the entity CAC/DIC. The prognosis of these patients is poor, reflecting coagulation activation from sepsis, with positive feedback of proinflammatory cytokines, reminiscent in a way of a cytokine storm. These patients should be monitored with platelets count, PT/PTT, fibrinogen, and mainly with D-dimers.

## DISCUSSION

SARS-CoV-2 has been proven the agent responsible for the worst global infectious disease in more than 100 years. In spite of its relationship with two different coronaviruses which have also caused pandemics, several years ago, we face huge gaps in our knowledge and understanding of this novel coronavirus.

The comparison carried out in this review, between the three coronaviruses has shed little light. SARS-CoV-2 is more contagious, but less pathogenic; it is endowed with a higher mutation rate, and a stronger affinity for human tissues. However, the extent and significance of the asymptomatic and presymptomatic conditions have not completely been deciphered. The origin of COVID-19 in an RNA virus compounds our attempts at understanding the disease, and the novel coronavirus might hamper our efforts at developing specific treatment and a vaccination modality.

Last we have tried to decipher the issue of CAC/DIC. We believe that the basic condition, preceding this form of coagulopathy, is most probably consistent with a viral sepsis. The subsequent hypercytokinemia may be due to this viral sepsis, as well as to the COVID-19-related coagulopathy (CAC/DIC). However, it has been inferred, that the 'cytokine storm' stands up for itself, in spite of additional sources of cytokines.

Italian hematologists have suggested a complex terminology for a severe pulmonary involvement by COVID-19, which they called also microCLOTS. For practical purposes, the hematologists may be referring to the same CAC/DIC coagulopathy as we do [15].

Is it possible that no independent source of cytokines exists beyond that related with CAC/DIC and the viral sepsis and that a 'cytokine storm' might have never developed? How could we explain the extensive microvascular thrombosis described at the autopsy? Aren't the viral sepsis and the CAC/DIC coagulopathy reasons enough for the hypercytokinemia and the vascular pathology?

## ACKNOWLEDGEMENTS

Thanks to Kibbutz Sde-Boker for a productive debate. The authors declare 'no conflict of interest exists'. Funding was not necessary for this review.

## REFERENCES

1. Rehman Su, Shafique L, Isban A, Liu Q. Evolutionary trajectory for the emergence of novel coronavirus SARS-CoV-2. *Pathogens*. 2020;9:240.
2. Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. SARS-CoV-2 and COVID-19: The most important research questions. *Cell & bioscience*. 2020 Dec;10(1):1-5.
3. Tara John, CNN World, April 3, 2020. Iceland lab's testing suggests 50% of coronavirus cases have no symptoms.
4. Gregory Barber, (Stanford), Science 21.04.2020. Serologic tests show that COVID-19 is more prevalent than expected (50 to 85 times more).
5. Mizumoto K, Kagay K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board of the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill*. 2020; 25:pil=2000180.
6. Bai Y, Lingshen Y, Tao W. Letter: Presumed asymptomatic transmission of COVID-19. *JAMA*. 2020;323:1406-1407.
7. Andino R, Domingo E. Viral quasispecies. *Virology*. 2015;479-480:46-51.
8. Phan T. Genetic diversity and evolution of SARS-CoV-2. *Infection, Genetics and Evolution*. 2020;81:104260.
9. Lauring AS, Andino R. Quasispecies theory and the behavior of RNA viruses. *PLoS Pathog*. 2010;6:e100.
10. Lu NI, Muller CP, He FQ. Applying next-generation sequencing to unravel the mutational landscape in viral quasispecies. *Virus Res*. 2020; 283:197963.
11. COVID-19 and coagulopathy: FAQ. COVID-19 recommendations from the International Society for Thrombosis and Hemostasis. April 14, 2020.
12. Van Gorp ECM, Suharti C, ten Cate H. Review: Infectious diseases and coagulation disorders. *The Journal Infect Dis*. 1999; 180:176-186.
13. Van der Poll T, de Jonge E, ten Cate H. Cytokines as regulators of coagulation. *Madame Curie Bioscience Database*. 2000-2013.

14. Lin G-L, McGinley JP, Drysdale SB, Pollard AJ. Epidemiology and immune pathogenesis of viral sepsis. *Front Immunol.* 2018; 9:2147.
15. Ciceri F, Beretta L, Scandroglio AM. Microvascular COVID-19 lung vessels obstructive thromboinflammation syndrome (microCLOTS): an atypical acute respiratory distress syndrome working hypothesis. *Crit Care Resusc.* 2020 [Epub ahead of print].