WHAT’S NEW IN INTENSIVE CARE

Ten things we learned about COVID-19

Maurizio Cecconi1,2*, Guido Forni3 and Alberto Mantovani1,2,4

© 2020 Springer-Verlag GmbH Germany, part of Springer Nature

1. The virus
SARS-CoV-2 contains over 30,000 RNA bases. A proof-reading mechanism keeps this large genome from accumulating frequent mutations. The large spike protein (S) forms a sort of crown on the surface of the viral particles. Its receptor-binding domain interacts with high affinity with angiotensin-converting enzyme 2 (ACE2) receptors on the surface of host cells. After the binding, two host cell proteases (Furin and TMPRLRS) cleave spike proteins and their exposed fusion peptides fuse the virus membrane with the membrane of the host cells. The virus RNA enters cells of the upper and lower respiratory tract, and it is translated into viral proteins. Other entry points are under investigation. The cell dies releasing millions of new viruses that infect other cells and other individuals [1].

2. The infection
There are various ways of SARS-CoV-2 spreading. The infection starts with the competition between the SARS-CoV-2 virions arrived in the respiratory mucosa that express high levels of ACE2 receptors and the barrier made by mucus secreted by goblet cells and moved by hair-like cilia and innate immunity reactions. There is evidence for the presence of the virus in cells other than respiratory epithelia, including gastrointestinal epithelial cells, endothelial cells and myeloid cells. We do not know yet how many SARS-CoV-2 is eliminated; however, the effectiveness of the first defence responses determines whether the infection will be benign or will have severe consequences. Figure 1 shows selective determinants of the susceptibility to COVID-19 including viral load, ageing, life style and possibly genetics. If SARS-CoV-2 virions start to replicate, they may reach and destroy the cells of lung alveoli and the gastrointestinal tract. An immune overreaction (cytokine storm) may increase the tissue damage [2, 3]

3. Immunity
Cellular and humoral innate immunity represents a first line of resistance which takes care of most encounters with infectious agents. Evidence from SARS-CoV-1 suggests that these viruses may block interferon-mediated antiviral immunity (Fig. 1). CD8 cytotoxic T cells play a fundamental role in antiviral resistance. Evidence suggests that during COVID-19 T cells undergo functional exhaustion with lymphopenia, skewing towards a Th17 phenotype, inappropriate for antiviral immunity and suppression (Fig. 1) [4]. Antibody production occurs late after exposure (up to 20 days) and after the appearance of symptoms (up to ≈15 days for 100% patients scoring positive) [5]. Intriguingly, IgA antibodies are present in blood and saliva and may play a key role in immunity. There is evidence that symptomatic COVID-19 elicits immunological memory and resistance to reinfection. Based on SARS, one can expect immunological memory to last 2–3 years, a key aspect of immunity that needs to be defined.

4. Inflammation
Inflammation plays a key role in the development of COVID-19 from a SARS-CoV-2 infection. Sensors of viral infection and cellular damage (e.g. inflammasomes; TLR) trigger myeloid cell-dependent production of inflammatory cytokines (e.g. IL-1; IL-6; chemokines). Macrophages and inflammatory cytokines amplify local and systemic inflammation and are major drivers of organ failure (Fig. 1). While the role of inflammation in COVID-19 is obvious, it is not clear whether the modulation of the inflammatory response with drugs could bring
Fig. 1  A schematic representation of the pathogenesis of COVID-19. ACE2 angiotensin-converting enzyme 2, TLR toll-like receptors, Mϕ macrophages, DC dendritic cells, IFN interferon, down arrow interferon low IFN, ARDS acute respiratory distress syndrome, dots indicate more receptors involved (e.g. CD147 for viral entry)
benefits. Several drugs (see session on Therapy) are currently being studied.

5. Thrombosis
Unsurprisingly for a disease characterised by an inflammatory state in response to a viral infection, venous and arterial thromboembolic complications are common in hospitalised patients [6]. Microthrombi are present in lungs, and alterations of the coagulation cascade can be measured at a systemic level. Endothelial dysfunction caused by both direct virus cytopathic effect and inflammatory reaction leads to a pro-thrombotic setting [3, 7]. In hospitalised patients, there should be a low threshold to screen for thromboembolic complications. Further research is needed on the other hand to see the role of anticoagulation regimes vs standard thromboprophylaxis in the treatment of these patients [8].

6. Diagnostic tests
The cornerstone of diagnostic tests is at present the assessment of viral RNA in nasal or bronchoalveolar lavage swabs by RT-PCR. Swab RT-PCR represents a bottleneck, and hopefully, saliva-based assays will address the urgent need of widespread testing.

Over 100 serological assays have been developed in industry or academic institutions, many poorly characterised. Given the timing and characteristics of the antibody response (see above), appropriately validated assays are instrumental for epidemiological studies, evaluation of plasma donations (see below), assessment of memory and response to vaccine, and as a companion diagnostic in RT-PCR-negative patients. No data are available showing that a given antibody level is associated with protection against subsequent exposure to SARS-CoV-2. Therefore, there is no ground for “immunity passports” or “immunity licenses”. A false perception of being “immune” may encourage irresponsible behaviours [9].

7. Clinical aspects
SARS-CoV-2 infection presents a variety of symptoms: it can be completely asymptomatic or present severe symptoms. The incubation period of SARS-CoV-2 is 5.1 (4.5–5.8) days [10]. The prevalence of organ dysfunction varies. ARDS has been reported from as little as 3.4% to more than 10% of positive cases [3, 11, 12].

In Italy, while the country has the highest daily incidence of new cases, about 67% of patients show mild symptoms and about 30% have symptoms that require hospital admission. The most common symptoms are fever and cough. A small percentage of cases reports gastrointestinal symptoms before the onset of the respiratory symptoms.

Older patients with comorbidities are more likely to be severely affected and die. The most common reason for ICU admission is acute respiratory failure. Many patients developed severe ARDS. Involvement of other organs is often present.

8. Therapy
The pillars of treatment are supportive therapy, respiratory support and management of organ failure. Currently, there is no specific treatment for SARS-CoV-2 [13]. Chloroquine and hydroxychloroquine have been used widely; however, more and more evidence is emerging about their lack of efficacy and potential harm.

Studies are currently evaluating the role of antivirals, steroids and immunomodulation therapies. The emerging evidence about high incidence of arterial and venous thromboembolic complications is giving heparin a potential role in preventing these events.

Plasma from recovered patients has been used in China and elsewhere, including Italy, as a source of antibodies, as already done for SARS and MERS. Its safety and efficacy in this disease are currently being studied.

9. Anti-SARS-CoV-2 vaccines
As we still do not know whether the protection towards COVID-19 rests on the action of antibodies or on the activity of T cells, the implementation of about 150 programs for vaccine development based on different technological platforms is fully justified [14]. To verify vaccine efficacy under “emergency use rules”, it has been proposed to vaccinate human volunteers and then intentionally challenge them. WHO is proposing to prioritise the efficacy of the most promising vaccines in coordinated studies. Initially, it might not be physically possible to make enough of the best vaccines for the world’s population. Nevertheless, WHO is trying to make sure that they are shared equitably, a crucial challenge.

10. Preparedness and further research
If one thing is evident from the many deaths of this pandemic, it is that the world was not ready from a structural, political, clinical and research point of view.

Several healthcare workers have lost their lives. This is a very serious loss that no country can afford to repeat.

The two key principles that should be followed for managing a possible increase in sick patients are increasing surge capacity and more importantly containing the virus transmission in the community. During an uncontrolled cluster, the volume of patients requiring ICU admission can be very high and efforts should be put in place to surge while guaranteeing the safety of non-COVID-19 patients and healthcare workers [15, 16].
A wide range of therapeutic approaches have been tested under uncontrolled conditions. Today, like never before, we desperately need to bring back the concepts of precision medicine that took decades to develop. We must continue our efforts to get the right treatment to the right patient at the right time. We should not look for a “magic bullet”, but we should praise the efforts to answer research questions, and if the answer brings new questions, we should praise them even more.

The WHO SOLIDARITY Trial or REMAP-CAP, an adaptive design trial, are a promising way to answer some of these research questions [17].

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-020-06140-0) contains supplementary material, which is available to authorised users.

Author details
1 Humanitas Clinical and Research Center, via Manzoni 56, Rozzano, 20089 Milan, Italy. 2 Humanitas University, via Rita Levi Montalcini, Pieve Emanuele, 20090 Milan, Italy. 3 Accademia Nazionale Dei Lincei, Rome, Italy. 4 The William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK.

Acknowledgement
AM acknowledges support by Dolce & Gabbana fashion company.

Compliance with ethical standards

Conflicts of interest
Alberto Mantovani acknowledges support by Dolce & Gabbana fashion company. Guido Forni and Maurizio Cecconi declare no conflict of interest for this paper.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 12 May 2020 Accepted: 26 May 2020
Published online: 5 June 2020

References
1. Tai W et al (2020) Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. https://doi.org/10.1038/s41423-020-0400-4
2. Ferretti L et al (2020) Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science. https://doi.org/10.1126/science.abb6936
3. Zhou F et al (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062
4. Vabret N et al (2020) Immunology of COVID-19: current state of the science. Immunity. https://doi.org/10.1016/j.immuni.2020.05.002
5. Sethuraman N, Jeremiah SS, Ryo A (2020) Interpreting diagnostic tests for SARS-CoV-2. JAMA. https://doi.org/10.1001/jama.2020.8259
6. Lodigiani C et al (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 191:9–14
7. Varga Z et al (2020) Endothelial cell infection and endotheliitis in COVID-19. Lancet 395(10234):1417–1418
8. Joly BS, Signuret V, Veyradier A (2020) Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. Intensive Care Med. https://doi.org/10.1007/s00134-020-06088-1
9. WHO (2020) WHO “Immunity passports” in the context of COVID-19. https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19. Accessed 24 Apr 2020
10. Lauer SA et al (2020) The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 172(9):577–582
11. Grasselli G et al (2020) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. https://doi.org/10.1001/jama.2020.5394
12. Guan WJ et al (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382(18):1708–1720
13. Alhazzani W et al (2020) Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 46(5):854–887
14. Lurie NM et al (2020) Developing Covid-19 vaccines at pandemic speed. N Engl J Med. https://doi.org/10.1056/NEJMz20025630
15. Shadman Aziz YMA, Waleed A, Laura E, Giuseppe C, Katherine F et al (2020) Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intensive Care Med. https://doi.org/10.1007/s00134-020-06092-5
16. Grasselli G, Pesenti A, Cecconi M (2020) Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA 323(16):1545–1546. https://doi.org/10.1001/jama.2020.4031
17. AA.VV (2020) REMAP-CAP response to novel COVID-19 pandemic. remap-cap.org/coronavirus