WHAT'S NEW IN INTENSIVE CARE

Ten things we learned about COVID-19

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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

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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
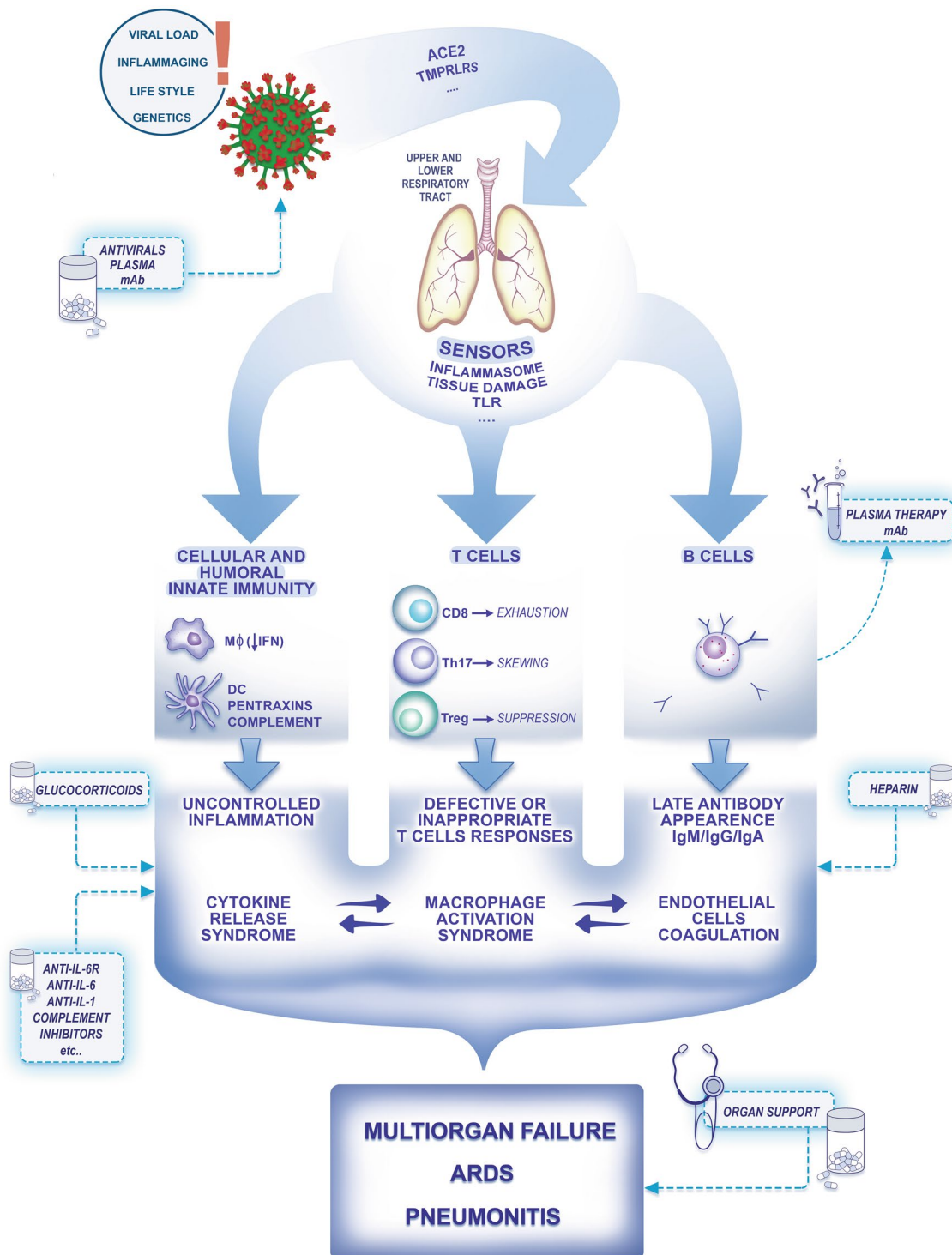
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Fig. 1 A schematic representation of the pathogenesis of COVID-19. *ACE2* angiotensin-converting enzyme 2, *TLR* toll-like receptors, *Mφ* macrophages, *DC* dendritic cells, *IFN* interferon, *down arrow interferon* low IFN, *ARDS* acute respiratory distress syndrome, dots indicate more receptors involved (e.g. CD147 for viral entry)

Your guide to COVID-19 testing
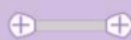### An overview for NHS staff and test requesters

The Antigen PCR Test

Tests for the presence of **virus** in a patient

infection

PCR test window

DAYS post symptom onset

	0	5	10

Optimal testing time between 2 days before and 7 days after symptom onset

Test can be carried out using:
Nose swabs
Throat swabs

⊕—⊕ Positive

Continue PPE use and follow Trust policies in terms of patient pathway if admitted

Does not tell you
how ill the patient will become, or when they contracted the virus

⊖—⊖ Negative

Test is **only 75% accurate** - symptomatic patients with high suspicion of infection should be **re-tested 2-3 days later**

If high suspicion of COVID-19 and repeat PCR negative, could consider antibody test

UHB: Test for patients requested through microbiology. Test for staff requested via line manager and Occupational Health

The Antibody Test

Tests if the patient has been **previously infected** with the virus and has had an immune response

Antibody test window

15	20	25	30+

Optimal testing time at least 14 days after symptom onset

Test can be carried out using:
A blood sample

⊕ Positive

Patient has previously been exposed to COVID-19 and mounted an immune response

Does not tell you
if the patient is protected from becoming ill again if exposed to COVID-19, or how long protection may last

You must still [keep 2m apart] 🧍🧍

⊖ Negative

Test is **80% accurate in mild disease** (but higher in severe disease) so false-negatives may occur

The patient may have failed to mount an antibody response and is still susceptible

UHB: Test for patients through laboratory request form/electronic requesting. Test for staff requested via antibody.testing@uhb.nhs.uk

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 been 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].

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Compliance with ethical standards

Conflicts of interest
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