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COVID-19 IN INTENSIVE CARE

How COVID-19 will change the management of other respiratory viral infections

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Started with a local outbreak of pneumonia in Wuhan, China, coronavirus disease-19 (COVID-19) has spread globally over a short time, to become one of the largest known pandemic in human history. In parallel, and within less than a year and a half, there have been great advancements in understanding the pathophysiology, management, and prevention of COVID-19. The speed of progress has far exceeded what has been made in many other diseases, including other severe respiratory viral infections (RVIs). This progress was driven largely by the pressing urgency created by the unprecedented global pandemic. However, at the same time, many advancements would not have been possible without the coordinated research response; a response that has built on knowledge and networks already present.

While we are still in the midst of the COVID-19 pandemic, and there is much to learn about this disease, the experience from COVID-19 should transform the approach to addressing future research on RVIs. There are many biologic similarities and differences between COVID-19 and other RVIs, which translate to similarities and differences in management. Here, we focus on selected lessons learned in COVID-19 management and how they may be relevant for research in other RVIs (Fig. 1; Table S1).

Antiviral therapy

Treatment of viral infections with agents with antiviral properties seems intuitive, but COVID-19 has proven that the issue is more complicated. Several agents including (hydroxy)chloroquine, remdesivir, lopinavir/ritonavir, and interferon-beta were suggested for COVID-19 therapy based on in vitro and observational studies. Hydroxychloroquine was widely promoted based on limited data until several large randomized controlled trials (RCTs) showed that it was not effective, and probably harmful [1]. Except for RCTs showing a possible benefit of early remdesivir in hospitalized patients with COVID-19 and early inhaled interferon-beta in patients with mild COVID-19, COVID-19 antiviral therapies have been disappointing [2]. This reinforces, once again, the concept that clinical management should not be based solely on preclinical and observational studies, and the importance of performing well-designed RCTs. This also prompts the question about the role of antivirals in other RVIs, where RCT data are limited with a few exceptions [3]. Different RVIs may have different responses to antiviral therapy given the different pathophysiology, viral kinetics and patient populations. Notably, data on the effectiveness of neuraminidase inhibitors for influenza in critically ill patients remains largely observational despite years of use [4].

Corticosteroids

Several RCTs have demonstrated a beneficial effect of corticosteroid therapy in patients with severe COVID-19, although important questions remain regarding the dose, time, duration, and drug and the association with infection and long-term outcomes. On the other hand, corticosteroid therapy in influenza has been greatly debated. The evidence is based mainly on observational studies and to a lesser extent on RCTs in which critically ill patients were either excluded or a minority; time is overdue for properly powered and conducted RCTs.

Specific immune modulation

Immune modulation has emerged as an important therapeutic target for COVID-19. In particular, RCTs have

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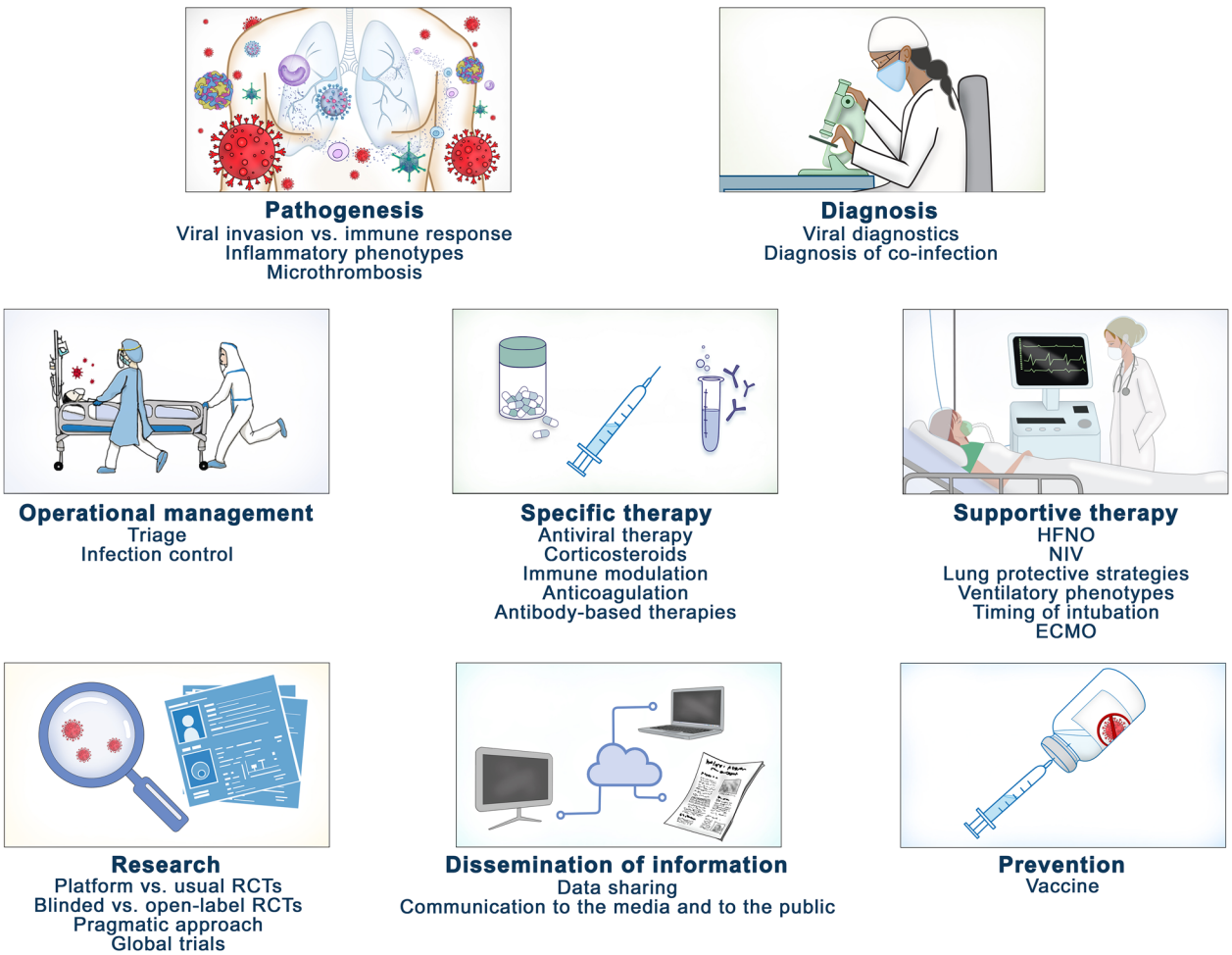

Fig. 1 Examples of what questions were raised during COVID-19 pandemic that would need to be addressed regarding other respiratory viral infections (RVIs). HFNO: high-flow nasal oxygen, NIV: noninvasive ventilation (NIV), ECMO: extracorporeal membrane oxygenation, RCT: randomized controlled trial

demonstrated that IL-6 receptor antagonists (IL-6ra) among critically ill patients and deteriorating hospitalized patients with signs of inflammation reduce mortality and improve time on organ support [5, 6]. However, some discrepancies between studies require consideration, as other trials did not demonstrate benefit. In addition, the RECOVERY trial demonstrated heterogeneity of treatment effect of IL-6ra by concomitant corticosteroid therapy, and the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial demonstrated no heterogeneity of treatment effect by of C-reactive protein (CRP) levels [5, 6]. Further studies are needed to understand the interaction of different therapeutics, and to define phenotypes that may respond differently to IL-6ra among patients in the intensive unit (ICU) with COVID-19.

How about immune modulation in other RVIs? The mortality reduction reported with INF-beta-1b in hospitalized patients with Middle East Respiratory Syndrome (MERS) in the recent MIRACLE ((MERS-CoV Infection Treated with a Combination of Lopinavir–Ritonavir and Interferon Beta-1b) trial may be related to immune modulation of interferon beta-1b, and not just to its antiviral properties [3]. Similar questions about the role of immune modulation in other RVIs and about the presence of phenotypes should guide further research [7].

Anticoagulation

In COVID-19, thrombotic abnormalities are common and seem to be intertwined with an exaggerated inflammatory response [8, 9]. Whether the coagulation abnormalities in COVID-19 can be addressed by immune modulation or anticoagulation (and by which method,

heparin vs antiplatelet) or both is currently unknown. For critically ill patients, recent trials demonstrated that therapeutic anticoagulation was not better compared to thromboprophylaxis given according to usual care, and that intermediate-dose prophylactic anticoagulation was not better compared to standard-dose prophylactic anticoagulation [10, 11]. The divergent result in less severely ill patients, who benefit from therapeutic anticoagulation, shows that differential treatment effects occur for patients at different timepoints during their course of disease, underpinning the need for research in the most critically ill patients as a separate group [12]. Further research is needed to better understand to what extent endothelitis and micro-thrombosis are part of the pathogenesis of other RVIs.

Respiratory support

There are several outstanding questions on the best supportive respiratory care for patients with COVID-19 and other RVIs, including the role of high-flow nasal oxygen (HFNO) and noninvasive ventilation (NIV), awake proning, the timing of intubation and the risks of delaying intubation, extracorporeal membrane oxygenation (ECMO) and invasive ventilation strategies [13–15]. RCTs (RECOVERY and COVIDICUS, NCT04344730, COVI-PRONE NCT04350723, Helmet-COVID NCT04477668 and others) are awaited. On the whole, even though non-invasive ventilation techniques have already been used in several respiratory virus outbreaks (severe acute respiratory syndrome [SARS], MERS, H1N1), supportive evidence is limited.

The big picture

By far, one of the greatest lessons from COVID-19 is related to how to address research questions. Most of the practice-changing advancements have come from collaborative pragmatic international multicenter adaptive platform trials that can address multiple questions at the same time, resulting in efficient answers. In particular, the RECOVERY (https://www.recoverytrial.net/) and REMAP-CAP (https://www.remapcap.org/) have, thus far, addressed more than 10 interventions, and others are undergoing study. At the same time, it has become evident that these trials can carry additional design complexity compared to traditional RCTs and have their specific limitations. Novel study designs are an evolving area, and there is much to learn and improve, especially in the interpretation and presentation of the results of complex statistical models to clinicians. These designs are likely to increasingly find their way into clinical research, addressing important questions, some of which have been long-awaited, in other RVIs.

Supplementary Information
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Declarations

Conflict of interest
YMA: Investigator on REMAP-CAP trial, Investigator on COVI-PRONE trial, Principal investigator on Helmet-COVID trial, member of Member of the COVID-19 guideline committee SCCM/ESICM/SSC.LPGD: EU FP7-HEALTH-2013-INNOVATION-1, PREPARE grant number 602525, H2020 RECOVER grant agreement No 101003589, Dutch ZonMw grant (ANACOR-IC) Projectnr 10150062010003, Chair of the EU RMC, ITSC member and involved in several DSWGs REMAP-CAP, Member of the COVID-19 guideline committee SCCM/ESICM/SSC, Member of the ESICM COVID-19 taskforce, Chair of the Dutch intensivists (NVIC) taskforce infectious threats.JFT is the PI of the COVIDICUS academic research program comparing 2 doses of corticosteroids and oxygenation modes (NCT04344730).JFT participated to 2 advisory boards and antiviral therapies directed against sars-Cov2 (Merck and Gilead).

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