Special edition

Focus on COVID-19
Strategies for impact reduction

Introduction

With almost 380,000 deaths to date and just over 6 million confirmed cases, coronavirus disease 2019 (COVID-19) continues its global spread. In many countries, the first peak in cases has been reached or surpassed, and governments around the world are taking their first tentative steps towards easing lockdown restrictions as they attempt to find the difficult balance between public health and economic priorities.

The scientific effort to tackle the pandemic has brought new insights into the epidemiology and course of the disease, including several new reports detailing the link between COVID-19 and cardiac disease. Multiple studies have been initiated in the search for a vaccine and at least 15 clinical trials are already entering Phase I/II. Additionally, the antiviral remdesivir has become the first drug approved by the FDA for the treatment of COVID-19. Here, we summarise the latest use of cutting-edge science in the fight against COVID-19.

Section 1: New insights into COVID-19 pathogenesis

Much is known regarding the structure of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its host cell adhesion and virulence. The pathogenesis, however, is less clear. Based on reports from clinicians and pathologists, many severely or critically ill patients with COVID-19 display clinical signs of shock without evidence of bacterial or fungal co-infections. This led researchers to suggest a role for viral sepsis in more severe cases of the disease.

A new aspect has been investigated in a Chinese study, which found that patients with severe COVID-19 had high viral load and a long virus-shedding period, indicating that viral load may be a useful marker of disease severity and prognosis.

Reactivation of the SARS-CoV-2 virus has also been reported in small number of patients. Although this cannot be generalised to the wider populations it merits attention during the relaxation of social distancing measures.

On the other hand, a recent study demonstrated that 100% of convalescent COVID-19 patients can mount a robust CD4+ T-cell response to anti-SARS-CoV-2 immunoglobulin G and A. Furthermore, SARS-CoV-2 reactive T cells were observed in 40–60% of healthy individuals suggesting cross-reactive T-cell recognition between circulating 'common cold' coronaviruses and SARS-CoV-2 indicating the potential for some pre-existing immunity in the population.

Coronavirus cases

Worldometer – Coronavirus.

https://bit.ly/36h42fi

Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment

Boopathi S *et al. J Biomol Struct Dynam.* 2020; April 30.

https://bit.ly/367GtVY

COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses

Shereen MA *et al. J Adv Res.* 2020; **24:** 91–98.

https://bit.ly/2LEUp0o

SARS-CoV-2 and viral sepsis: Observations and hypotheses

Li H *et al. Lancet.* 2020; **395:** 1517–1520.

https://bit.ly/3689noU

Edwards

Viral dynamics in mild and severe cases of COVID-19

Liu Y *et al. Lancet Infect Dis.* 2020; March 19.

https://bit.ly/2LCMH6P

Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation

Ye G *et al. J Infect.* 2020; **80:** e14–e179.

https://bit.ly/2ybmtFq

Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals

Grifoni A *et al. Cell* 2020; doi: 10.1016/j.cell.2020.05.015.

https://bit.ly/2ZILWBo

Section 2: COVID-19 and cardiac diseases

An association between COVID-19 and cardiovascular complications is now recognised, but the underlying mechanisms are not understood. Recent evidence suggests that SARS-CoV-2 infection causes endotheliitis in multiple organs as a direct result of viral infection of endothelial cells.

In addition to the cardiovascular complications related to COVID-19, the pandemic may also impact individuals with cardiac disease, reducing their willingness to seek medical attention. In northern Italy, a significant decrease in hospitalisations and increase in non-COVID-19-related mortality was observed among individuals with acute coronary syndrome.

There is an urgent need for cardiac surgeons to provide a safe healthcare service, both for patients and healthcare workers, in the COVID-19 environment. As an example, Italian physicians have outlined a roadmap for restarting cardiac surgery, based on assessing the level of spread and severity of COVID-19 in any given area (using the COVID-19 Spread and Severity Index), and developing a COVID-free pathway to mitigate the risk of hospital infection.

COVID-19 and the cardiovascular system

Zheng YY *et al. Nat Rev Cardiol.* 2020; **17:** 259–260.

https://go.nature.com/3gaaE3t

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study

Zhou F *et al. Lancet.* 2020; **395:** 1054–1062.

https://bit.ly/2TgMb2I

Out-of-hospital cardiac arrest during the COVID-19 outbreak in Italy

Baldi E *et al. N Engl J Med.* 2020; April 29.

https://bit.ly/3g2CmyW

Endothelial cell infection and endotheliitis in COVID-19

Varga Z *et al. Lancet.* 2020; **395:** 1417–1418.

https://bit.ly/3bJwck5

Reduced rate of hospital admissions for ACS during COVID-19 outbreak in northern Italy

De Filippo O *et al. N Engl J Med.* 2020; April 28.

https://bit.ly/2zLlQCX

Safety for all: Coronavirus disease 2019 pandemic and cardiac surgery: A roadmap to 'phase' 2

Parolari A *et al. Eur J Cardiothorac Surg.* 2020; May 11.

https://bit.ly/3emFEvs

Section 3: Vaccines and prospective treatments

An effective vaccine and/or treatment for COVID-19 would be a game-changer, helping societies to alleviate the social and economic impacts of the pandemic. The search for a COVID-19 vaccine has gathered momentum in the past two months, driven by significant collaborations between academic, industry and government partners, and several prospective vaccines are now moving towards Phase II clinical trials (Table 1). Notably, a range of approaches to identify new candidates (e.g. inactivated viruses, proteomic 3D modelling) have been employed, and strategies to facilitate rapid delivery have been proposed. Initial promising data have indicated a protective effect of a novel vaccine against COVID-19 in rhesus macaques, offering hope for the global effort to find a vaccine in humans.

On 1 May 2020, the FDA approved remdesivir (Gilead Sciences Inc.) for emergency use in the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalised with severe disease. This approval was based on preliminary data

Table 1: Selected SARS-CoV-2 vaccination clinical trials entering Phase I and II

Experimental vaccine	Sponsor	Phase	Link
ChAdOx1 nCoV-19 (COV001)	University of Oxford, UK	I/II	https://bit.ly/NCT04324606
LV-SMENP-DC (Minigene vaccine)	Shenzhen Geno-Immune Medical Institute, China	I/II	https://bit.ly/NCT04276896
SARS-CoV-2 inactivated vaccine	Sinovac Research and Development Co, China	I/II	https://bit.ly/NCT04352608
BNT162	Biontech SE, Pfizer, USA	I/II	https://bit.ly/NCT04368728
SARS-CoV-2 rS	Novavax, Queensland, Australia	I/II	https://bit.ly/NCT04368988
bacTRL-Spike	Symvivo Corporation, Canada	I	https://bit.ly/NCT04334980
mRNA-1273	National Institute of Allergy and Infectious Diseases, USA	II	https://bit.ly/NCT04283461

indicating a 31% faster time to recovery in patients receiving remdesivir compared with those receiving placebo ($p<0.001$) in the Adaptive COVID-19 Treatment Trial.

Other proposed treatments, including hydroxychloroquine and lopinavir–ritonavir, have shown no consistent benefit in patients with COVID-19. In the case of hydroxychloroquine, which gained significant attention following anecdotal positive reports in small studies, larger studies have failed to demonstrate a significant benefit in patients with mild to moderate disease, or in patients requiring oxygen, and recent trials have been halted pending safety review because of the higher risks of cardiac complications and death.

Of particular relevance to cardiology, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are the first-choice drugs for a range of conditions including hypertension and heart failure. They increase angiotensin converting enzyme 2 expression, the receptor for SARS-CoV-2, causing concern that their use may increase the susceptibility of patients to SARS-CoV-2 infection. Studies from North America, Europe and Asia have confirmed that there is no link between the use of ARBs/ACEIs and risk of contracting COVID-19, or between these drugs and the severity of COVID-19.

Myocardial injury is frequently seen in COVID-19 and worsens prognosis. When deciding on treatment it is important to differentiate between the different causes of myocardial injury. The effects of various potential therapies on the cardiovascular system must be considered.

A strategic approach to COVID-19 vaccine R&D

Corey L *et al. Science.* 2020; May 11.

https://bit.ly/2WE06Sq

The race for coronavirus vaccines: A graphical guide

Callaway E. *Nature.* 2020; **580:** 576–577.

https://go.nature.com/3bJycZD

Reverse vaccinology approach to design a novel multi-epitope vaccine candidate against COVID-19: An *in silico* study

Enayatkhani M *et al. J Biomol Struct Dyn.* 2020; May 2.

https://bit.ly/2XdzJ58

COVID-19 shot protects monkeys

Cohen J. *Science.* 2020; **368:** 456–457.

https://bit.ly/2zPmbEy

NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19

NIH News Release, April 29 2020.

https://bit.ly/3dX8tP0

Hydroxychloroquine in patients mainly with mild to moderate COVID-19: An open-label, randomized, controlled trial

Tang W *et al. medRxiv.* 2020; May 07.

https://bit.ly/2zJNh06

A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19

Cao B *et al. N Engl J Med*. 2020; **382:** 1787–1799.

https://bit.ly/2WI11Be

Cardiovascular disease, drug therapy, and mortality in COVID-19

Mehra MR *et al. N Engl J Med*. 2020; May 1. doi: 10.1056/NEJMoa2007621.

https://bit.ly/2XakDgo

Response to COVID-19 and ACEI/ARB: NOT ASSOCIATED?

Schriffin EL *et al. Am J Hypertens*. 2020; May 16. doi: 10.1093/ajh/hpaa077.

https://bit.ly/3gcXBy8

Renin–angiotensin–aldosterone system blockers and the risk of COVID-19

Mancia G *et al. N Engl J Med*. 2020; May 1. doi: 10.1056/NEJMoa2006923.

https://bit.ly/2AJCvqV

Cardiovascular manifestations and treatment considerations in COVID-19

Kang Y *et al. Heart*. 2020; April 30. doi: 10.1136/heartjnl-2020-317056.

https://bit.ly/36i1pd2

Section 4: Epidemiology-based strategies

Throughout the response to the COVID-19 pandemic, governments have used modelling data to estimate the potential spread of the disease and to develop measures to reduce the impact of the pandemic on society. Non-pharmaceutical interventions to reduce the impact of the disease fall into two categories – **mitigation** approaches to reduce peak healthcare demand and protect the most vulnerable individuals, and **suppression** of the virus to reverse pandemic growth. One model estimated that up to 120,000 deaths were averted by March 31, 2020 as a result of social distancing measures introduced across Europe. The challenge for governments is to gauge how much and how quickly to reopen society in the absence of an effective vaccine or treatment, while minimising the risk of a second wave.

Despite the success shown among the European countries during the first phase of releasing the lockdown measures, a word of caution is needed. Current evidence suggests that warmer weather is unlikely to reduce transmission of the virus sufficiently to negate the need for additional interventions. Furthermore, atmospheric pollution has been linked to higher mortality in patients with COVID-19, which may impact strategic decisions in relation to larger cities and industrial centres. Countries considering relaxing preventative measures need to engage with scientists to analyse the situation and form plans to deal with the pandemic.

The decision on whether to reopen schools for the summer term is hotly debated. A recent systematic review highlights data collected from the SARS outbreak in Asia, which suggests that school closures contributed minimally to controlling the epidemic. Furthermore, modelling data for COVID-19 indicate a modest 2–4% reduction in deaths associated with school closures. However, the article emphasises the need for policy makers to be aware of equivocal evidence in relation to school closures for COVID-19.

Another issue facing patients with cardiovascular disease is that while the focus of healthcare systems is on COVID-19, there is a risk that non-COVID-19 patients with cardiovascular conditions may suffer from the reduction in care. As resources are directed towards containing the pandemic, and because of concerns of disease transmission among healthcare providers and patients, elective cardiovascular procedures and outpatient visits have been cancelled.

Patient reluctance to seek medical care because of concerns of SARS-CoV-2 infection in hospital has resulted in delays in time from symptom onset to treatment, increasing complication rates. In addition, Italian investigators observed a 58% increase in out-of-hospital cardiac arrests.

Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries

Flaxman S *et al.* Imperial College COVID-19 Response Team.

https://bit.ly/2X76MYf

COVID-19: Are we ready for the second wave?

Ali I. *Disaster Med Public Health Prep*. 2020; May 7.

https://bit.ly/2AzxwZP

Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand

Ferguson NM *et al*. Imperial College COVID-19 Response Team.

https://bit.ly/3dX1ZQ1

Effective transmission across the globe: The role of climate in COVID-19 mitigation strategies

O'Reilly KM *et al. Lancet Planet Health*. 2020; May 6.

https://bit.ly/3cIGfqY

Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in northern Italy?

Conticini E *et al. Environ Pollut.* 2020; **261:** 114465.

https://bit.ly/3dTg1Cj

School closure and management practices during coronavirus outbreaks including COVID-19: A rapid systematic review

Viner RM *et al. Lancet Child Adolesc Health.* 2020; **4:** 397–404.

https://bit.ly/3dZHVwC

One train may hide another: Acute cardiovascular diseases could be neglected because of the COVID-19 pandemic

Huet F *et al. Arch Cardiovasc Dis*. 2020; **113:** 303–307.

https://bit.ly/2XvMQyL

Cardiovascular implications of the COVID-19 pandemic: A global perspective

Boukhris M *et al. Can J Cardiol*. 2020; May 10. doi: 10.1016/j.cjca.2020.05.018.

https://bit.ly/2LOJHnW

Out-of-hospital cardiac arrest during the COVID-19 outbreak in Italy

Baldi E *et al. N Engl J Med*. 2020; April 29.

https://bit.ly/3g2CmyW

Section 5: Cutting-edge digital science on the frontline

A prominent feature of the COVID-19 response has been the growing use of digital technologies.

Track-and-trace apps have been used in several countries to identify individuals with COVID-19 symptoms, to track their social interactions, and to inform their recent contacts who may be at risk of developing COVID-19 symptoms. These digital tools have the potential to not only provide valuable information for at-risk individuals, but also to allow policymakers to track the spread of the disease and to instigate control measures accordingly. Provided these tools are used correctly and ubiquitously, they may also help to contain pandemics without requiring mass quarantines that are damaging to society.

Telemedicine, in which physicians use virtual tools to evaluate, diagnose and treat patients, is a developing field which is already used in specific settings to support healthcare provision. In the context of the COVID-19 pandemic, telemedicine could help to provide workforce sustainability, to limit exposure of healthcare workers, and to reduce the requirements for personal protective equipment. While this approach requires a significant investment in IT infrastructure and operational support, the current crisis offers a valuable opportunity to lay the groundwork for telemedicine within institutions to improve care for patients, not only in the current pandemic but also in future emergency healthcare situations.

Real-time tracking of self-reported symptoms to predict potential COVID-19

Menni C *et al. Nat Med.* 2020; May 11.

https://go.nature.com/36aSNVJ

Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing

Ferretti L *et al. Science*. 2020; **368:** May 08.

https://bit.ly/2WEQW8c

Keep calm and log on: Telemedicine for COVID-19 pandemic response

Doshi A *et al. J Hosp Med*. 2020; **15:** 302–304.

https://bit.ly/3fZRuNS

The value of remote monitoring for the COVID-19 pandemic

Watson AR *et al. Telemed e-Health.* 2020; May 7.

https://bit.ly/3e2Akxj

Implementation guide for rapid integration of an outpatient telemedicine program during the COVID-19 pandemic

Smith WR *et al. J Am Coll Surg.* 2020; April 30.

https://bit.ly/3dVdXJV

Turning the crisis into an opportunity: Digital health strategies deployed during the COVID-19 outbreak

Sust PP *et al. JMIR Public Health Surveill.* 2020; **6:**e19106. May 4.

https://bit.ly/2ThlNFO

Conclusion

The rapid spread of SARS-CoV-2 over the past five months has placed significant pressures on families, healthcare systems and economies around the world. However, the pandemic has also triggered an unprecedented global response from the scientific community to understand, to track, and to tackle the virus. We are beginning to see progress in our understanding of COVID-19 and we are driving forward research efforts at a rapid pace to combat the disease. The pandemic is also providing an opportunity to consider new approaches (such as telemedicine and mHealth) to the way we provide healthcare, which should be applicable both to the current crisis and to future healthcare emergencies.

Abbreviations

ACEIs: angiotensin-converting enzyme inhibitors
ARBs: angiotensin receptor blockers
COVID-19: coronavirus disease 2019
FDA: US Food and Drug Administration
mHealth: mobile health
NPIs: non-pharmaceutical interventions
SARS: severe acute respiratory syndrome
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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