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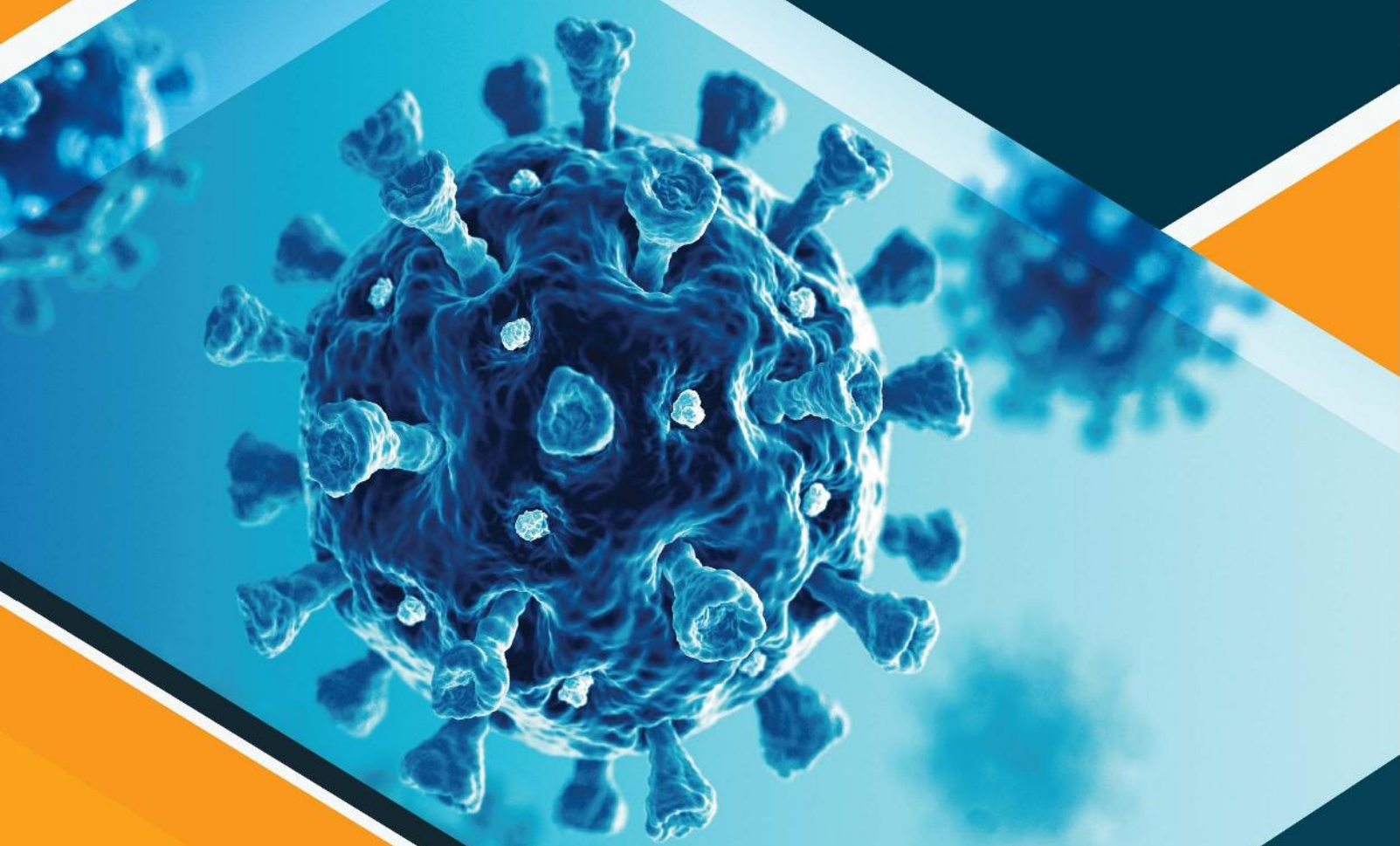

COVID-19

Recent Update

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EDITORIAL

Dear Doctor

Some eventful months have again passed and we are happy to presents yet another issue of Info Medicus with the recent updates of COVID-19. We would like to focus on several topics covered in these issue compiled from different renowned journals.

This issue is arranged in six different sections with amazing blend of subjects. We start with patient handout which explains a few questions on thrombosis that may be helpful in your daily practice. Health news features current development on COVID-19 Vaccine. Moreover, symptoms of COVID-19 that are mistaken with the symptoms of influenza have been discussed.

This issue consists of two Review articles that has been arranged with the latest updates on the pathophysiology, transmission, diagnosis and treatment of COVID-19 along with management of post-acute COVID-19 in primary care.

The research section is about the patterns of IgG and IgM antibody response in COVID-19 patients. Which we believe will enrich your knowledge.

Your constructive suggestions are always solicited.

Stay Safe!

With warm regards

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COVID-19 and thrombosis: What do we know about the risks and treatment?

How common is thrombosis in critically ill patients with COVID-19?

A recent Dutch study of 184 patients with COVID-19 pneumonia admitted to an Intensive Care Unit (ICU) found a 49% cumulative incidence of thrombotic complications mainly changes seen on Computed Tomography (CT) pulmonary angiograms. The level was "remarkably high," given that all patients received at least standard doses of thromboprophylaxis. Other studies from France and the Netherlands have also suggested that thrombosis occurs in 20% to 30% of critically ill COVID-19 patients, even with prophylaxis. "The extent of thrombosis we are seeing with COVID is extraordinary" Roopen Arya, clinical director for haematology at King's College Hospital, told The BMJ. "I would say that one third of those severely affected with COVID in critical care is a conservative estimate".

Why are COVID-19 patients at particular risk of thrombosis?

COVID-19 causes massive inflammation boosting cytokines which increase the liver's production of clotting factors, explains Beverley Hunt, medical director of Thrombosis UK and a practicing clinician. For example, fibrinogen levels in a severely ill COVID-19 patient are 10 to 14 g/L, compared with 2 to 4 g/L normally and 5 to 6 g/L in a pregnant woman. "A COVID patient's blood is enormously sticky," she told The BMJ.

Is the rate of thrombosis in COVID patients higher than in non-COVID patients in critical care?

"All patients in critical care are at increased risk from clots because they are immobile and when you are sick you have sticky blood," says Hunt. Studies of venous thromboembolism rates among non-COVID patients in critical care show that rates of thrombosis can be as high as 28% if patients are not given any prophylaxis. Among patients given prophylaxis the rates are halved. So, it seems to be significantly higher rates of thrombosis in COVID patients.

Is thrombosis contributing to the COVID death rate?

"Thrombosis is definitely contributing to the high mortality rate from COVID," says Hunt. "Not only can it lead to a pulmonary embolism, which can be fatal, but there are also higher rates of strokes and heart attacks."

Are the clots in COVID patients different from those seen in other critically ill patients?

Postmortem studies are finding clots in the capillaries of the lungs in COVID-19 patients, restricting the oxygenated blood from moving through the lungs. Hunt says, "We are not only seeing high rates of

deep vein thrombosis and pulmonary embolisms in COVID patients but we are also seeing immunothrombosis with lung destruction because of inflammation."

How should COVID-19 patients be treated to prevent thrombosis?

In the NHS, anyone coming into hospital is routinely assessed for risk of hospital associated venous thromboembolism and given appropriate prophylaxis with blood thinners. "However, we are still seeing these high rates of deep vein thrombosis, pulmonary embolism and immunothrombosis in COVID patients and some people are arguing that we should be giving bigger doses," says Hunt. Without evidence from randomised controlled trials, however, it is not clear what the correct dose should be. Some UK hospitals are going ahead and using a higher treatment dose of heparin, rather than a prophylactic dose, for seriously ill patients with COVID. "It's like the Wild West out there with lots of different protocols," says Arya. "But giving a higher dose could increase the risk of bleeding. Our hospital is taking a pragmatic approach. Instead of giving the standard prophylactic dose of heparin we are giving half the treatment dose." You should definitely use a treatment dose in patients who have had a pulmonary embolism, Hunt advises. But she also favours intermediate doses for other patients because of the as yet unknown risk of bleeding with higher doses. However, she says that clotting is right down the chain of events with COVID. "If you have less viral load, you would have less inflammation, less sticky blood and less venous thromboembolism and immunothrombosis," she says.

Reference: BMJ, 21 May 2020, Vol. 369

Vaccines of COVID-19

Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Researchers are testing 36 vaccines in clinical trials on humans and at least 90 preclinical vaccines are under active investigation in animals. Antibody is produced in response to a vaccine. Work began in January with the deciphering of the SARS-CoV-2 genome. The first vaccine safety trials in humans started in March, but the road ahead remains uncertain. Some trials will fail and others may end without a clear result. But a few may succeed in stimulating the immune system to produce effective antibodies against the virus.

Russian vaccine

Russia became the first worldwide to register the vaccine against the coronavirus which was named Sputnik V on August 11. Russian scientists presented preliminary results of the first two phases of clinical trials of two different forms of the Sputnik V vaccine on 76 volunteers which confirmed that both forms of the vaccine are safe for humans and stimulate their immune system to develop antibodies to SARS-CoV-2. The vaccine is highly immunogenic and induces strong humoral and cellular immune responses in 100% of healthy adult volunteers with antibody titers in vaccinated participants higher than those in convalescent plasma. The study results were published in the Lancet journal. To form a powerful immune response against SARS-CoV-2, it is important that a booster vaccination is provided. However, booster vaccinations that use the same adenovirus vector might not produce an effective response because the immune system may recognise and attack the vector. The booster shots were administered approximately five days after the first injection. They elicited a number of mild side effects, such as pain at injection site or elevated body temperature but over 42 days of trials the researchers have registered no potentially life threatening complications. The preparation was developed by the Gamaleya National Research Center and passed clinical trials in June to July. It is based on a known platform previously used for other vaccines. On August 15, the Healthcare Ministry announced the production launch of the preparation. The third post registration phase of clinical trials of the vaccine began on August 25. Some volunteers received injections of rAd26-S and rAd5-S cultures which were stored in a frozen form and others were vaccinated with a freeze dried form of a vaccine. The researchers weakened those pathogens and modified their genomes in such a way so that they deliver the coronavirus RNA fragments to human cells forcing them to produce a large amount of its membrane proteins. These molecules infiltrate immune cells making them produce antibodies to SARS-CoV-2.

Overall, both vaccine formulations turned out to be approximately equally effective causing all volunteers to develop antibodies to the coronavirus and teaching T-cells to recognise this threat. According to the scientists the booster dose has elevated significantly the effectiveness of the Sputnik V vaccine since after a single injection the antibodies were developed in only 60% of volunteers. The researchers hope that the vaccine developed by them will be equally successful during larger scale clinical trials approved on August 26. Over 40,000 volunteers of all age groups will participate in them.

UK vaccine

A phase 1/2, single blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18 to 55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19 like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection. A protocol amendment in two of the five sites allowed prophylactic paracetamol to be administered before vaccination. Ten participants assigned to a non randomised, unblinded ChAdOx1 nCoV-19 prime boost group received a two dose schedule, with the booster vaccine administered 28 days after the first dose. Humoral responses at baseline and following vaccination were assessed using a standardized total IgG ELISA against trimeric SARS-CoV-2 spike protein, a multiplexed immunoassay, three live SARS-CoV-2 neutralisation assays (a 50% plaque reduction neutralisation assay [$PRNT_{50}$]; a microneutralisation assay [MNA_{50}, MNA_{80} and MNA_{90}] and Marburg VN) and a pseudovirus neutralisation assay. Cellular responses were assessed using an ex vivo interferon-γ enzyme linked immunospot assay.

The co-primary outcomes are to assess efficacy, as measured by cases of symptomatic virologically confirmed COVID-19 and safety as measured by the occurrence of serious adverse events. Analyses were done by group allocation in participants who received the vaccine. Safety was assessed over 28 days after vaccination. Here, it was reported the preliminary findings on safety, reactogenicity and cellular and humoral immune responses. The study is ongoing and was registered at International Standard Randomised Controlled Trials Number (ISRCTN), 15281137 and ClinicalTrials.gov, NCT04324606. ChAdOx1 nCoV-19 showed an acceptable safety profile and homologous boosting increased antibody responses. However, phase 3 clinical trials of coronavirus vaccine, developed by AstraZeneca and Oxford University, have been temporarily halted on 09 September 2020 due to a suspected serious adverse reaction in a participant in the United Kingdom.

Chinese vaccine

A vaccine against the coronavirus developed by CanSino Biologics Inc and China's military research unit appears to be safe and induced immune responses in most subjects in a closely watched mid stage study, researchers said on 20 July 2020. The CanSino candidate, Ad5-nCOV, which was tested in 508 subjects, is one of a handful of vaccines that have shown some promise in early human testing prior to much larger trials to demonstrate efficacy. Others also gearing up for such pivotal vaccine trials include Moderna Inc, BioNTech SE in partnership with Pfizer Inc. CanSino's vaccine uses a modified common cold virus to carry genetic material from the new coronavirus into the human body, a method also used by the Oxford or AstraZeneca vaccine.

Both vaccines elicited antibody and T-cell immune responses and neither prompted any serious side effects. T-cells are an important component of the immune system's attack against foreign invaders, such as viruses. Results of both trials were released in the medical journal the Lancet. Both studies augur well for the large Phase III trials, where the vaccines will be tested on thousands of subjects to assess their efficacy and safety, Naor Bar-Zeev and William Moss, from the International Vaccine Access Center at Johns Hopkins Bloomberg School of Public Health, said in an accompanying editorial. "Overall, the results of both trials are broadly similar and promising," they said.

Separately, BioNTech and Pfizer said data from an early stage trial of their experimental coronavirus vaccine showed that it prompted an immune response and was well tolerated, similar to results seen in prior early test. CanSino's vaccine received the greenlight to be used by China's military despite not yet undergoing the type of large scale testing needed to prove its ability to prevent infection.

USA vaccine

Moderna develops vaccines based on messenger RNA (mRNA) to produce viral proteins in the body. They have yet to bring one to the market. The government has bankrolled Moderna's efforts on a coronavirus vaccine with nearly $1 billion. In partnership with National Institutes of Health, they found that the vaccine protects monkeys from the coronavirus. In March, the company put the first COVID-19 vaccine into human trials, which yielded promising results. After carrying out a phase 2 study they launched a phase 3 trial on July 27. The final trial will enroll 30,000 healthy people at about 89 sites around the United States. On August 11, the government awarded the company an additional $1.5 billion in exchange for 100 million doses if the vaccine proves safe and effective. In July Moderna lost a patent dispute over some of their vaccine technology. The following month, the company stated that it could not be certain it was the first to make the inventions claimed in their patents, including its coronavirus vaccine.

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COVID-19 and Messenger RNA (mRNA) vaccines First large test for a new approach

On January 10, Chinese researchers posted the novel coronavirus RNA sequence on a preprint server. Immediately scientists who study genetic vaccines turned their efforts to the emerging pathogen that causes Coronavirus Disease 2019 (COVID-19). They knew that rapid response genetic platforms could save precious weeks to months off development, crucial during a pandemic.

When the first US clinical trial for a vaccine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) began just 66 days later, volunteers received mRNA-1273, a messenger RNA (mRNA) candidate codeveloped by biotechnology company Moderna, Inc and the National Institute of Allergy and Infectious Diseases (NIAID).

On July 27, based on encouraging early results, mRNA-1273 and another mRNA vaccine candidate, BNT162b2 from BioNTech and Pfizer, both entered phase trials, which together will enroll an estimated 60,000 volunteers. The milestone came "at a remarkably rapid pace compared to the usual pace for vaccine preparation," National Institutes of Health (NIH) Director Francis Collins, MD, PhD said at a press briefing that day. Results could be available as early as this fall NIH officials said.

Despite the unprecedented speed, mRNA vaccines are clinically unproven. No commercially available vaccines use the platform and until now, it hasn't been tested in large scale human trials. With COVID-19, that's all set to change. Experts said in interviews that if the technology pans out the pandemic could help to usher in a new plug and play approach to vaccinology.

The genetic advantage

Current antiviral vaccine designs can be described as falling into 2 camps: protein based or gene based. Protein based vaccines deliver the immune system stimulating antigen to the body. This category includes whole inactivated (killed) vaccines as in the polio and flu shots and subunit vaccines and virus like particles, like in the hepatitis B and human papillomavirus vaccines.

Gene based vaccines take a different tack. They carry the genetic instructions for the host's cells to make the antigen, which more closely mimics a natural infection. In the case of coronaviruses, the antigen of interest is the surface spike protein the virus uses to bind and fuse with human cells. "You're not giving them the protein you're giving them the genetic material that then instructs them how to make that spike protein, to which they make an antibody response that hopefully is protective," University of Pennsylvania vaccinology professor Paul Offit, MD, explained in a JAMA live stream in June. The approach isn't entirely unfamiliar. In live attenuated vaccines,

like the measles, mumps and rubella shot, weakened viruses incorporate their genetic instructions into host cells, causing the body to churn out viral copies that elicit antibody and T-cell responses. In newer gene based designs viral vector, DNA and mRNA vaccines scientists synthesize and insert genetic instructions from the pathogen of interest to induce immune responses.

The viral vector technique transports genetic information in a less harmful virus often a common cold causing adenovirus that's sometimes engineered so it can't replicate in the host. DNA and mRNA vaccine designs deliver naked nucleic acids or more recently encapsulate them in a carrier nanoparticle. Within each of these versatile platforms, the same production and purification methods and manufacturing facilities can be used to make vaccines for different diseases.

These highly adaptable techniques were waiting in the wings when COVID-19 hit. "The people who jumped on this right away are the people who had vaccine platforms that were conducive for this that were simply sitting there," said Louis Picker, MD, associate director of the Oregon Health & Science University's Vaccine and Gene Therapy Institute. "All they had to do is basically figure out what part of the virus they were going to put in the vaccine and then run with it."

Thanks to research beginning in 2002 on the severe acute respiratory syndrome coronavirus and then the Middle East respiratory syndrome coronavirus, which emerged a decade later, scientists knew to focus their initial attention on the novel coronavirus spike protein. They also already knew which genetic modifications would stabilize the spike in its "prefusion" configuration important for a robust and safe antibody response and those that would make the mRNA less inflammatory and therefore safer. They had also learned how to purify mRNA to rid it of contaminants and how to protect it from degrading too quickly in the body by encasing it in lipid carrier molecules. These delivery vehicles already in use with therapeutic small interfering RNAs, also help mRNA cross the cell membrane and may even have an immune stimulating adjuvant effect.

Unlike conventional vaccines, mRNA vaccines aren't grown in eggs or cells, a time consuming and costly process. At their essence, these vaccines are simply chemicals catalyzed in test tube or a tank. This makes them easier to develop quickly and at least theoretically at scale, although they've never been mass produced before.

"We were making RNA within a week or so of the SARS-CoV-2 sequence being published" said Drew Weissman, MD, PhD, who researches mRNA vaccines at the University Of Pennsylvania Perelman School Of Medicine. That speed propelled development according to Weissman, both groups currently testing nucleic acid based vaccines in phase 3 trials licensed his team's mRNA formulation from the university.

Why mRNA?

As of August 20, thirty potential vaccines against COVID-19 were in clinical trials, with another 139 in preclinical development, including both gene and protein based candidates. But genetic approaches have a potential immunological advantage. In addition to eliciting antibodies and CD4+ helper T cells, they recruit CD8+ cytotoxic T cells, also known as killer T cells, through the major histocompatibility class I pathway.

According to Otto Yang, MD, an infectious disease researcher and clinician at the University of California, Los Angeles, David Geffen School of Medicine, the body's cells only display viral proteins on their surface through this pathway if those cells themselves have produced the proteins. "If you just inject a protein or inject a dead virus, it doesn't get into that pathway and doesn't get displayed that way and so the T cells don't get stimulated," he said.

Even among the gene based platforms, distinct advantages exist. In cutting out the viral vector, both DNA and mRNA vaccines eliminate the risk of pre-existing immunity against it, which can limit effectiveness. "If your immune system clears a vector before it will actually get into the cells, that's a big problem," Yang said. Such immunity could also be more common in some geographic areas than others, rendering a vectored vaccine more or less effective depending on the region.

Pre-existing immunity could explain why a non replicating viral vector COVID-19 candidate from CanSino Biologics Inc and several Chinese institutions elicited less than impressive neutralizing antibody levels in a phase 1 trial. Pre-existing neutralizing antibodies to the vector, the human adenovirus 5 known as Ad5, ranges from up to 69% in the US to 80% in Africa. Of additional concern, Offit said in an August livestream, more than a decade ago, men with pre-existing Ad5 immunity had an increased risk of acquiring HIV infection after receiving an experimental Ad5 vectored HIV vaccine.

To get around these issues, ChAdOx1 nCoV-19, a non-replicating viral vector candidate in phase 3 trials from AstraZeneca and the University of Oxford, uses an adenovirus that infects chimpanzees instead of humans. But, it's possible that cross reacting pre-existing immunity to human adenoviruses could still diminish the response.

According to Weissman, mRNA vaccines also have a leg up on DNA vaccines. In a DNA vaccine, the genetic material must first enter the host cell's nucleus. From there, messenger RNA is created, which travels out of the nucleus into the cytoplasm, where protein is formed from it. However, genetic information can only enter the nucleus when the cell is dividing, making the process inefficient.

Reference: JAMA, 3 September 2020

Influenza in the COVID-19 era

The annual influenza epidemic substantially affects health care systems worldwide and has resulted in an estimated 12,000 to 61,000 deaths annually since 2010 just in the US. The extent of the morbidity and mortality in any given year reflects the degree of genetic drift or shift in the dominant strain of the influenza virus and the efficacy and coverage of vaccination. With the Coronavirus Disease 2019 (COVID-19) pandemic, clinicians face a second respiratory virus associated with morbidity and mortality several fold higher than that of influenza, in part due to its spread in an immunologically naive population. A looming threat of concurrent influenza and COVID-19 epidemics is a major concern for public health officials and clinicians.

A population perspective

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19 and influenza are vastly different pathogens, but there are important areas of overlap (Table-1). Both viruses are primarily transmitted by respiratory droplets. Thus, the adoption of Nonpharmacologic Interventions (NPIS), such as mandated face coverings in public, closure of schools and retail spaces and restrictions on movement would be expected to influence the incidence of both infections to varying degrees. Studies have consistently shown a pattern of decreased influenza incidence in 2020 (January through May) after adoption of NPIS as compared with prior seasons. A similar trend has occurred in the US, with the number of influenza like illnesses for the 2019 to 2020 season decreasing earlier than expected. Caution should be taken when interpreting these data because the rates of testing for non-SARS-CoV-2 respiratory viruses were greatly curtailed during the initial pandemic wave.

Effects on clinical practice

Although no specific clinical manifestations reliably distinguish between early influenza disease and COVID-19, it will be important to identify the viral etiology in clinical practice. First, the approach to management of the 2 viruses is different. Influenza can be treated with a neuraminidase inhibitor or a cap dependent endonuclease inhibitor, neither of which have antiviral activity against SARS-CoV-2. Remdesivir is available for treatment of COVID-19 under an Emergency Use Authorization, but because it is administered parenterally, it is reserved for hospitalized patients. It is also essential to confirm a diagnosis of COVID-19 to

Table-1: Comparison between seasonal influenza and SARS-CoV-2

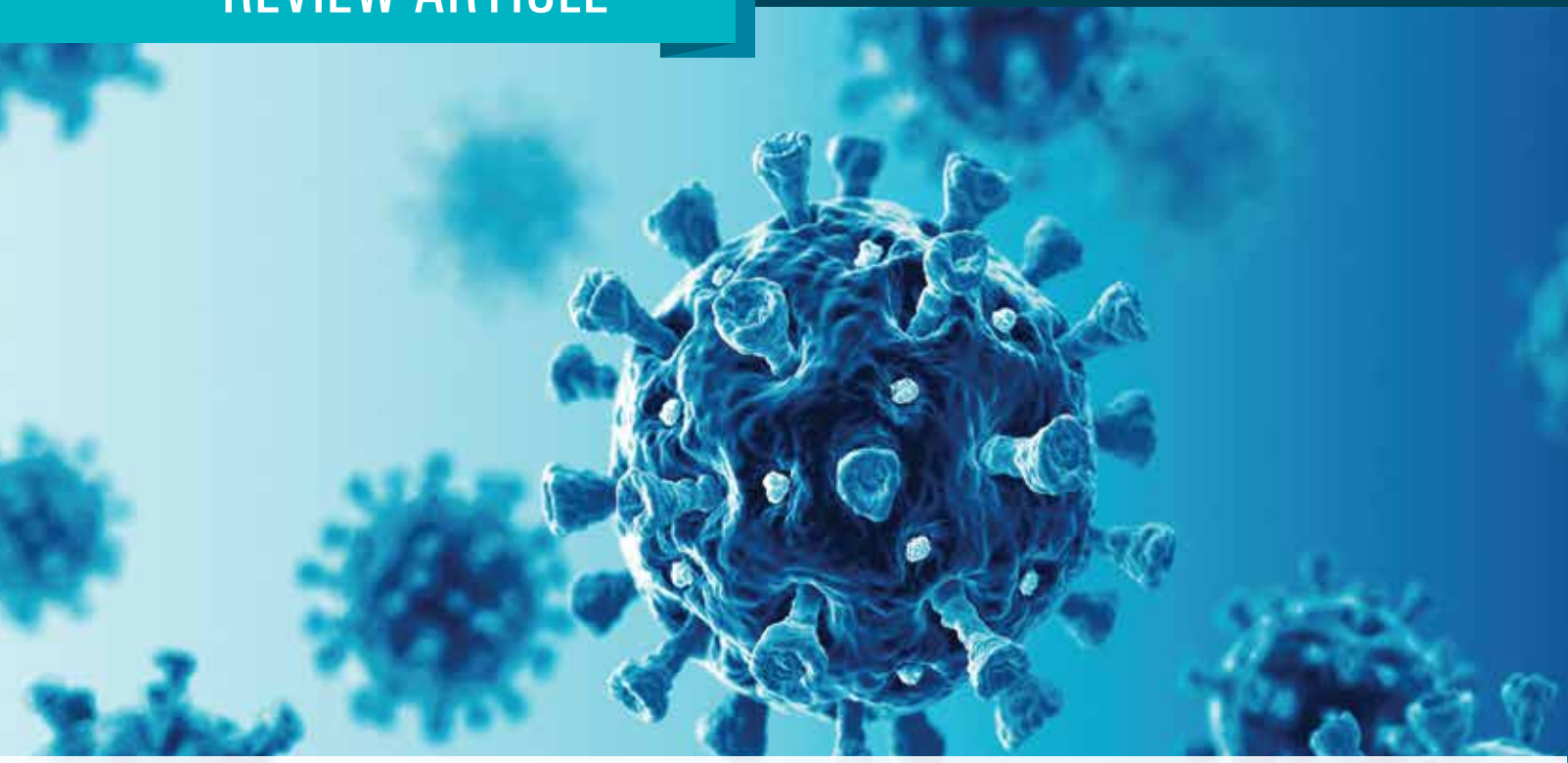
Characteristics	Seasonal influenza viruses	SARS-CoV-2
Primary route of transmission	Droplet	Droplet (airborne, fomite and fecal oral transmission possible but less important)
Overall infectivity	Less contagious	More contagious
Dynamics of infectivity	Patients are most infectious after symptom onset	Patients are most infectious starting 48 hours prior to symptom onset
Incubation period	1 to 4 days (median, 2 days)	2 to 14 days (median, 5 days)
Risk factors for severe disease	• Age > 65 years and < 2 years • Immunosuppression • Pregnancy (through 2 weeks postpartum) • Morbid obesity • Chronic lung disease, cardiac disease, advanced liver disease, chronic kidney disease • Residence in nursing home or long term care facilities • American Indian or Alaska Native heritage	• Advanced age (risk increases with age) • Male sex • Obesity • Hypertension • Chronic lung disease, cardiac disease, type 2 diabetes, cancer, chronic kidney disease, advanced liver disease • Surgery during incubation period • Residence in nursing home • Structural racism, poverty
Most common clinical manifestations	Fever, chills, headache, myalgias, cough, nasal congestion, sore throat and fatigue	Fever, chills, headache, myalgias, cough, shortness of breath, fatigue and anosmia
Pediatric disease	• Common, especially high risk in children < 2 years • Children play a leading role in propagating outbreaks	• Uncommon, with typically mild disease • Multisystem inflammatory syndrome has been observed in children, but is rare • Limited evidence on children as a source of infection
Case fatality rate	≈ 0.1%	≈ 0.25% to 3.0%
Dynamics of symptoms	Symptoms typically peak during first 3 to 7 days of illness	Symptoms can peak during week 2 or 3 of illness
Vaccine	Multiple approved	No vaccine currently licensed
Clinical diagnostics	Nucleic acid amplification and antigen based assays from respiratory samples	• Nucleic acid amplification and antigen based assays from respiratory samples • Serologies
Available antiviral agents	• Neuraminidase inhibitors • Cap dependent endonuclease inhibitors • M2 channel blockers	Nucleoside analogue (remdesivir)

encourage early participation in clinical trials, especially for patients who may have contraindications to remdesivir.

Second, the syndrome caused by each virus follows a different course. Patients with influenza typically experience most severe symptoms during the first week of illness, whereas patients with COVID-19 may experience a longer duration of symptoms with a peak during the second or third week of illness. Distinguishing between the viruses could allow clinicians to provide patients with anticipatory guidance about how symptoms are expected to evolve and can help identify complications later in the disease course.

Third, correctly identifying the virus has important infection control implications, including appropriate guidance regarding isolation and quarantine, return to school and work recommendations and COVID-19 case identification and contact tracing.

Reference: N. Eng. J. Med., 07 May 2020, Vol. 382, N.19



Pathophysiology, transmission, diagnosis and treatment of Coronavirus Disease 2019 (COVID-19)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused a sudden significant increase in hospitalizations for pneumonia with multiorgan disease. COVID-19 is caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection may be asymptomatic or it may cause a wide spectrum of symptoms such as mild symptoms of upper respiratory tract infection and life threatening sepsis. COVID-19 first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognized in Wuhan, China. As of July 1, 2020, SARS-CoV-2 has affected more than 200 countries, resulting in more than 10 million identified cases with 508,000 confirmed deaths. This review summarizes current evidence regarding pathophysiology, transmission, diagnosis and management of COVID-19.

Pathophysiology

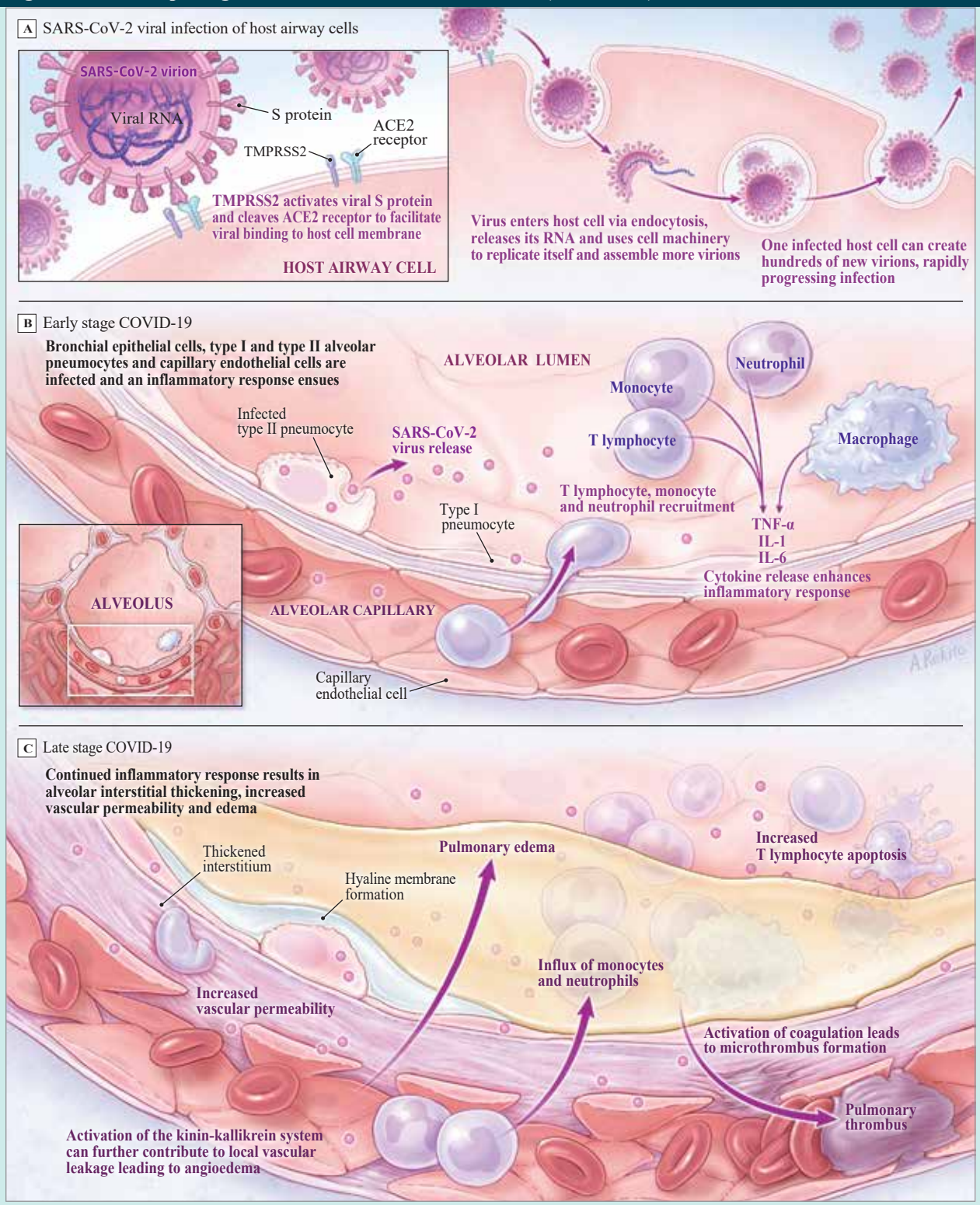
Coronaviruses are large, enveloped, single stranded RNA viruses found in humans and other mammals such as dogs, cats, chicken, cattle, pigs and birds. Coronaviruses cause respiratory, gastrointestinal and neurological disease. The most common coronaviruses in clinical practice are 229E, OC43, NL63 and HKU1 which typically cause common cold symptoms in immunocompetent individuals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans to spread globally in the past 2 decades. The first coronavirus that caused severe disease was Severe Acute Respiratory Syndrome (SARS), which was thought to originate in Foshan, China and resulted in the 2002-2003 SARS-CoV pandemic. The second was the coronavirus caused Middle East Respiratory Syndrome (MERS), which originated from the Arabian peninsula in 2012.

SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm giving the virions the appearance of a solar corona. Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARS-CoV-2 via an intermediate host, such as the pangolin.

The host defense against SARS-CoV-2

Early in infection, SARS-CoV-2 targets cells such as nasal and bronchial epithelial cells and pneumocytes through the viral structural spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor (Figure-1). The type 2 Transmembrane

Figure-1: Immunopathogenesis of Coronavirus Disease 2019 (COVID-19)



Current understanding of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) induced host immune response. SARS-CoV-2 targets cells through the viral structural spike (S) protein that binds to the Angiotensin Converting Enzyme 2 (ACE2) receptor. The Serine Protease Type 2 Transmembrane Serine Proteas (TMPRSS2) in the host cell further promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein. In the early stage, viral copy numbers can be high in the lower respiratory tract. Inflammatory signaling molecules are released by infected cells and alveolar macrophages in addition to recruited T lymphocytes, monocytes and neutrophils. In the late stage, pulmonary edema can fill the alveolar spaces with hyaline membrane formation, compatible with early phase acute respiratory distress syndrome.

Serine Protease (TMPRSS2), present in the host cell, promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which mediates coronavirus entry into host cells. ACE2 and TMPRSS2 are expressed in host target cells, particularly alveolar epithelial type II cells. Similar to other respiratory viral diseases, such as influenza, profound lymphopenia may occur in individuals with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells. In addition, the viral inflammatory response consisting of both the innate and the adaptive immune response (comprising humoral and cell mediated immunity), impairs lymphopoiesis and increases lymphocyte apoptosis. Although upregulation of ACE2 receptors from ACE inhibitor and angiotensin receptor blocker medications has been hypothesized to increase susceptibility to SARS-CoV-2 infection, large observational cohorts have not found an association between these medications and risk of infection or hospital mortality due to COVID-19. For example, in a study 4,480 patients with COVID-19 from Denmark previous treatment with ACE inhibitors or angiotensin receptor blockers was not associated with mortality.

In later stages of infection when viral replication accelerates epithelial endothelial barrier integrity is compromised. In addition to epithelial cells, SARS-CoV-2 infects pulmonary capillary endothelial cells, accentuating the inflammatory response and triggering an influx of monocytes and neutrophils. Autopsy studies have shown diffuse thickening of the alveolar wall with mononuclear cells and macrophages infiltrating airspaces in addition to endothelialitis. Interstitial mononuclear inflammatory infiltrates and edema develop and appear as ground glass opacities (Figure-2) on computed tomographic imaging. Pulmonary edema filling the alveolar spaces with hyaline membrane formation follows, compatible with early phase Acute Respiratory Distress Syndrome (ARDS). Bradykinin dependent lung angioedema may contribute to disease. Collectively, endothelial barrier disruption, dysfunctional alveolar capillary oxygen transmission and impaired oxygen diffusion capacity are characteristic features of COVID-19.

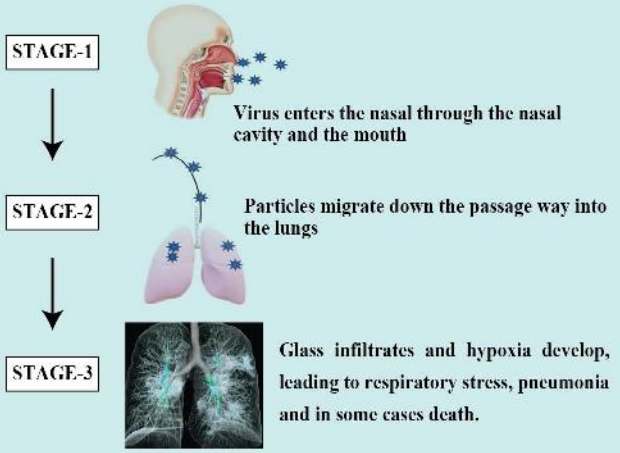
In severe COVID-19, fulminant activation of coagulation and consumption of clotting factors occur. A report from Wuhan China, indicated that 71% of 183 individuals who died of COVID-19 met criteria for diffuse intravascular coagulation. Inflamed lung tissues and pulmonary endothelial cells may result in microthrombi formation and contribute to the high incidence of thrombotic complications such as deep venous thrombosis, pulmonary embolism and thrombotic arterial complications (e.g., limb ischemia, ischemic stroke, myocardial infarction) in critically ill patients.

Transmission of SARS-CoV-2 infection

Epidemiologic data suggest that droplets expelled during face to face exposure during talking, coughing or sneezing is the most common mode of transmission (Table-1). Prolonged exposure to an infected person (being within 6 feet for at least 15 minutes) and the briefer exposures to individuals who are symptomatic (e.g., coughing) are associated with higher risk for transmission, while brief exposures to asymptomatic contacts are less likely to result in transmission. Contact surface spread (touching a surface with virus on it) is another possible mode of transmission. Transmission may also occur via aerosols (smaller droplets that remain suspended in air), but it is unclear if this is a significant source of infection in humans outside of a laboratory setting. The existence of aerosols in physiological states (e.g., coughing) or the detection of nucleic acid in the air does not mean that small airborne particles are infectious. Maternal COVID-19 is currently believed to be associated with low risk for vertical transmission. In most reported series, the mothers' infection with SARS-CoV-2 occurred in the third trimester of pregnancy, with no maternal deaths and a favorable clinical course in the neonates.

The clinical significance of SARS-CoV-2 transmission from inanimate surfaces is difficult to interpret without knowing the minimum dose of virus particles that can initiate infection. Viral load appears to persist at higher levels on impermeable surfaces such as stainless steel and plastic than permeable surfaces such as cardboard. Virus has been identified on impermeable surfaces for up to 3 to 4 days after inoculation. Widespread viral contamination of hospital rooms has been documented. However, it is thought that the amount of virus detected on surfaces decays rapidly within 48 to 72 hours. Although the detection of virus on surfaces reinforces the potential

Figure-2: Schematic diagram representing the stages involved in the pathogenesis of COVID-19.



The virus enters the respiratory system through the nasal cavity and the mouth. The innate immune system is triggered to activate inflammation, which results in blockage of the alveoli. This results in hypoxia and ground glass opacities and subsequent death.

for transmission via fomites (objects such as a doorknob, cutlery or clothing that may be contaminated with SARS-CoV-2) and the need for adequate environmental hygiene, droplet spread via face to face contact remains the primary mode of transmission.

Viral load in the upper respiratory tract appears to peak around the time of symptom onset and viral shedding begins approximately 2 to 3 days prior to the onset of symptoms. Asymptomatic and presymptomatic carriers can transmit SARS-CoV-2. In Singapore, presymptomatic transmission has been described in clusters of patients with close contact (e.g., through church going or singing class) approximately 1 to 3 days before the source patient developed symptoms. Presymptomatic transmission is thought to be a major contributor to the spread of SARS-CoV-2. Modeling studies from China and Singapore estimated the percentage of infections transmitted from a presymptomatic individual as 48% to 62%. Pharyngeal shedding is high during the first week of infection at a time in which symptoms are still mild, which might explain the efficient transmission of SARS-CoV-2, because infected individuals can be infectious before they realize they are ill.

Although studies have described rates of asymptomatic infection, ranging from 4% to 32% it is unclear whether these reports represent truly asymptomatic infection by individuals who never develop symptoms, transmission by individuals with very mild symptoms or transmission by individuals who are asymptomatic at the time of transmission but subsequently develop symptoms. A systematic review on this topic suggested that true asymptomatic infection is probably uncommon. Although viral nucleic acid can be detectable in throat swabs for up to 6 weeks after the onset of illness, several studies suggest that viral cultures are generally negative for SARS-CoV-2 8 days after symptom onset. This is supported by epidemiological studies that have shown that transmission did not occur to contacts whose exposure to the index case started more than 5 days after the onset of symptoms in the index case. This suggests that individuals can be released from isolation based on clinical improvement. The Centers for Disease Control and Prevention recommend isolating for at least 10 days after symptom onset and 3 days after improvement of symptoms. However, there remains uncertainty about whether serial testing is required for specific subgroups, such as immunosuppressed patients or critically ill patients for whom symptom resolution may be delayed or older adults residing in short or long term care facilities.

Clinical presentation

The mean (interquartile range) incubation period (the time from exposure to symptom onset) for COVID-19 is approximately 5 (2 to 7) days. Approximately 97.5% of individuals who develop symptoms will do so within 11.5 days of infection. The median (interquartile range) interval from symptom onset to hospital admission is 7 (3 to 9) days. The median age of hospitalized patients varies between 47 and 73 years with most cohorts having a male preponderance of approximately 60%. Among patients hospitalized with COVID-19, 74% to 86% are aged at least 50 years.

COVID-19 has various clinical manifestations (Table-1). In a study of 44,672 patients with COVID-19 in China, 81% of patients had mild manifestations, 14% had severe manifestations and 5% had critical manifestations (defined by respiratory failure, septic shock, and/or multiple organ dysfunction). A study of 20,133 individuals hospitalized with COVID-19 in the UK reported that 17.1% were admitted to high dependency or Intensive Care Units (ICUs).

Although only approximately 25% of infected patients have comorbidities, 60% to 90% of hospitalized infected patients have comorbidities. The most common comorbidities in hospitalized patients include hypertension (present in 48% to 57% of patients), diabetes (17% to 34%), cardiovascular disease (21% to 28%), chronic pulmonary disease (4% to 10%), chronic kidney disease (3% to 13%), malignancy (6% to 8%) and chronic liver disease (< 5%).

The most common symptoms in hospitalized patients are fever (up to 90% of patients), dry cough (60% to 86%), shortness of breath (53% to 80%), fatigue (38%), nausea or vomiting or diarrhea (15% to 39%) and myalgia (15% to 44%). Patients can also present with non classical symptoms, such as isolated gastrointestinal symptoms. Olfactory and or gustatory dysfunctions have been reported in 64% to 80% of patients. Anosmia or ageusia may be the sole presenting symptom in approximately 3% of patients.

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney and coagulation system. COVID-19 can lead to myocarditis, cardiomyopathy, ventricular arrhythmias and hemodynamic instability. Acute cerebrovascular disease and encephalitis are observed with severe illness (in up to 8% of patients). Venous and arterial thromboembolic events occur in 10% to 25% in hospitalized patients with COVID-19. In the ICU, venous and arterial thromboembolic events may occur in up to 31% to 59% of patients with COVID-19.

Approximately 17% to 35% of hospitalized patients with COVID-19 are treated in an ICU, most commonly due to hypoxemic respiratory failure. Among patients in the ICU with COVID-19, 29% to 91% require invasive mechanical ventilation. In addition to respiratory failure, hospitalized patients may develop acute kidney injury (9%), liver dysfunction (19%), bleeding and coagulation dysfunction (10% to 25%) and septic shock (6%).

Table-1: Transmission, symptoms and complications of coronavirus disease 2019 (COVID-19)

- Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) occurs primarily via respiratory droplets from face to face contact and to a lesser degree via contaminated surfaces. Aerosol spread may occur but the role of aerosol spread in humans remains unclear. An estimated 48% to 62% of transmission may occur via presymptomatic carriers
- Common symptoms in hospitalized patients include fever (70% to 90%), dry cough (60% to 86%), shortness of breath (53% to 80%), fatigue (38%), myalgia (15% to 44%), nausea or vomiting or diarrhea (15% to 39%), headache, weakness (25%) and rhinorrhea (7%). Anosmia or ageusia may be the sole presenting symptom in approximately 3% of individuals with COVID-19
- Common laboratory abnormalities among hospitalized patients include lymphopenia (83%), elevated inflammatory markers (e.g., erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-α, IL-1, IL-6) and abnormal coagulation parameters (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer [46% of patients] and low fibrinogen)
- Common radiographic findings of individuals with COVID-19 include bilateral, lower lobe predominate infiltrates on chest radiographic imaging and bilateral, peripheral, lower lobe ground glass opacities and or consolidation on chest computed tomographic imaging
- Common complications among hospitalized patients with COVID-19 include pneumonia (75%), acute respiratory distress syndrome (15%), acute liver injury characterized by elevations in aspartate transaminase, alanine transaminase and bilirubin (19%), cardiac injury including troponin elevation (7% to 17%), acute heart failure, dysrhythmias and myocarditis, prothrombotic coagulopathy resulting in venous and arterial thromboembolic events (10% to 25%), acute kidney injury (9%), neurologic manifestations including impaired consciousness (8%) and acute cerebrovascular disease (3%) and shock (6%)
- Rare complications among critically ill patients with COVID-19 include cytokine storm and macrophage activation syndrome (e.g., secondary hemophagocytic lymphohistiocytosis)

Approximately 2% to 5% of individuals with laboratory confirmed COVID-19 are younger than 18 years, with a median age of 11 years. Children with COVID-19 have milder symptoms that are predominantly limited to the upper respiratory tract and rarely require hospitalization. It is unclear why children are less susceptible to COVID-19. Potential explanations include that children have less robust immune responses (e.g., no cytokine storm), partial immunity from other viral exposures, and lower rates of exposure to SARS-CoV-2. Although most pediatric cases are mild, a small percentage (< 7%) of children admitted to the hospital for COVID-19 develop severe disease requiring mechanical ventilation. A rare multisystem inflammatory syndrome similar to Kawasaki disease has recently been described in children in Europe and North America with SARS-CoV-2 infection. This multisystem inflammatory syndrome in children is uncommon (2 in 100,000 persons aged < 21 years).

Assessment and diagnosis

Diagnosis of COVID-19 is typically made using polymerase chain reaction testing via nasal swab. However, because of false negative test result rates of SARS-CoV-2 PCR testing of nasal swabs, clinical, laboratory and imaging findings may also be used to make a presumptive diagnosis.

Diagnostic testing: Polymerase chain reaction and serology

Reverse transcription polymerase chain reaction based SARS-CoV-2 RNA detection from respiratory samples (e.g., nasopharynx) is the standard for diagnosis. However, the sensitivity of testing varies with timing of testing relative to exposure. One modeling study estimated sensitivity at 33% 4 days after exposure, 62% on the day of symptom onset and 80% 3 days after symptom onset. Factors contributing to false negative test results include the adequacy of the specimen collection technique, time from exposure and specimen source. Lower respiratory samples such as bronchoalveolar lavage fluid are more sensitive than upper respiratory samples.

Several serological tests can also aid in the diagnosis and measurement of responses to novel vaccines. However, the presence of antibodies may not confer immunity because not all antibodies produced in response to infection are neutralizing. Whether and how frequently second infections with SARS-CoV-2 occur remain unknown. Whether presence of antibody changes susceptibility to subsequent infection or how long antibody protection lasts are unknown. IgM antibodies are detectable within 5 days of infection, with higher IgM levels during weeks 2 to 3 of illness, while an IgG response is first seen approximately 14 days after symptom onset. Higher antibody titers occur with more severe disease.

Laboratory findings

A systematic review of 19 studies of 2,874 patients who were mostly from China (mean age, 52 years), of whom 88% were hospitalized, reported the typical range of laboratory abnormalities

seen in COVID-19, including elevated serum C-reactive protein (increased in > 60% of patients), lactate dehydrogenase (increased in approximately 50% to 60%), alanine aminotransferase (elevated in approximately 25%) and aspartate aminotransferase (approximately 33%). Approximately 75% of patients had low albumin. The most common hematological abnormality is lymphopenia (absolute lymphocyte count < 1.0×10^9/L), which is present in up to 83% of hospitalized patients with COVID-19. In conjunction with coagulopathy, modest prolongation of prothrombin times (prolonged in > 5% of patients), mild thrombocytopenia (present in approximately 30% of patients) and elevated D-dimer values (present in 43% to 60% of patients) are common.

Imaging

The characteristic chest computed tomographic imaging abnormalities for COVID-19 are diffuse, peripheral ground glass opacities (Figure-3). Ground glass opacities have ill defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura. Early in the disease, chest computed tomographic imaging findings in approximately 15% of individuals and chest radiograph findings in approximately 40% of individuals can be normal. Rapid evolution of abnormalities can occur in the first 2 weeks after symptom onset, after which they subside gradually.

Chest computed tomographic imaging findings are nonspecific and overlap with other infections, so the diagnostic value of chest computed tomographic imaging for COVID-19 is limited. Some patients admitted to the hospital with polymerase chain reaction testing confirmed SARS-CoV-2 infection have normal computed tomographic imaging findings, while abnormal chest computed tomographic imaging findings compatible with COVID-19 occur days before detection of SARS-CoV-2 RNA in other patients.

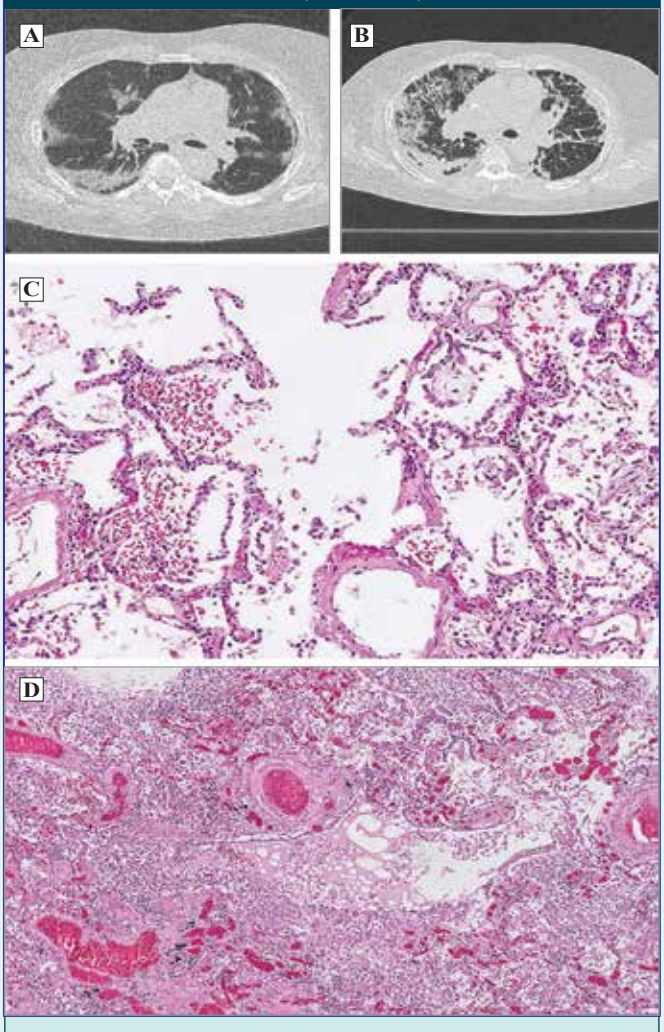
Treatment

Supportive care and respiratory support

Currently, best practices for supportive management of acute hypoxic respiratory failure and ARDS should be followed. Evidence based guideline initiatives have been established by many countries and professional societies, including guidelines that are updated regularly by the National Institutes of Health.

More than 75% of patients hospitalized with COVID-19 require supplemental oxygen therapy. For patients who are unresponsive to conventional oxygen therapy, heated high flow nasal canula oxygen may be administered. For patients requiring invasive mechanical ventilation, lung protective ventilation with low tidal volumes (4 to 8 ml/kg, predicted body weight) and plateau pressure less than 30 mg Hg is recommended. Additionally, prone positioning, a higher

Figure - 3: Radiological and pathological findings of the lung in coronavirus disease 2019 (COVID-19)



A. Transverse thin section computed tomographic scan of a 76 year old man, 5 days after symptom onset, showing subpleural ground glass opacity and consolidation with subpleural sparing.

B. Transverse thin section computed tomographic scan of a 76 year old man, 21 days after symptom onset, showing bilateral and peripheral predominant consolidation, ground glass with reticulation and bronchodilatation.

C. Pathological manifestations of lung tissue in a patient with severe pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) showing interstitial mononuclear inflammatory infiltrates that is dominated by the lymphocytes (magnification, ×10).

D. Pathological manifestations of lung tissue in a patient with severe pneumonia caused by SARS-CoV-2 showing diffuse alveolar damage with edema and fibrine deposition, indicating acute respiratory distress syndrome with early fibrosis (magnification, ×10).

positive end expiratory pressure strategy and short term neuromuscular blockade with cisatracurium or other muscle relaxants may facilitate oxygenation. Although some patients with COVID-19 related respiratory failure have high lung compliance, they are still likely to benefit from lung protective ventilation. Cohorts of patients with ARDS have displayed similar heterogeneity in lung compliance and even patients with greater compliance have shown benefit from lower tidal volume strategies.

The threshold for intubation in COVID-19 related respiratory failure is controversial, because many patients have normal work of breathing but severe hypoxemia. "Earlier" intubation allows time for a more controlled intubation process, which is important given the logistical challenges of moving patients to an airborne isolation room and donning personal protective equipment prior to intubation. However, hypoxemia in the absence of respiratory distress is well tolerated and patients may do well without mechanical ventilation. Earlier intubation thresholds may result in treating some patients with mechanical ventilation unnecessarily and exposing them to additional complications. Currently, insufficient evidence exists to make recommendations regarding earlier vs later intubation.

In observational studies, approximately 8% of hospitalized patients with COVID-19 experience a bacterial or fungal co-infection, but up to 72% are treated with broad spectrum antibiotics. Awaiting further data, it may be prudent to withhold antibacterial drugs in patients with COVID-19 and reserve them for those who present with radiological findings and or inflammatory markers compatible with co-infection or who are immunocompromised and or critically ill.

Targeting the virus and the host response

The following classes of drugs are being evaluated or developed for the management of COVID-19: antivirals (e.g., remdesivir, favipiravir), antibodies (e.g., convalescent plasma, hyperimmune immunoglobulins), anti-inflammatory agents (e.g., dexamethasone, statins), targeted immunomodulatory therapies (e.g., tocilizumab, sarilumab, anakinra, ruxolitinib), anticoagulants (e.g., heparin) and antifibrotics (e.g., tyrosine kinase inhibitors). It is likely that different treatment modalities might have different efficacies at different stages of illness and in different manifestations of disease. Viral inhibition would be expected to be most effective early in infection, while, in hospitalized patients, immunomodulatory agents may be useful to prevent disease progression and anticoagulants may be useful to prevent thromboembolic complications.

More than 200 trials of chloroquine or hydroxychloroquine, compounds that inhibit viral entry and endocytosis of SARS-CoV-2 in vitro and may have beneficial immunomodulatory effects in vivo, have been initiated but early data from clinical trials in hospitalized patients with COVID-19 have not demonstrated clear benefit. A clinical trial of 150 patients in China admitted to the hospital for mild to moderate COVID-19 did not find an effect on negative conversion of SARS-CoV-2 by 28 days (the main outcome measure) when compared with standard of care alone. Two retrospective studies found no effect of hydroxychloroquine on risk of intubation or mortality among patients hospitalized for COVID-19. One of these retrospective multicenter cohort studies compared in hospital mortality between those treated with hydroxychloroquine plus azithromycin (735 patients), hydroxychloroquine alone (271 patients), azithromycin alone (211 patients) and neither drug (221 patients), but reported no differences across the groups. Adverse effects are common, most notably QT prolongation with an increased risk of cardiac complications in an already vulnerable population. These findings do not support off label use of (hydroxy)chloroquine either with or without the coadministration of azithromycin. Randomized clinical trials are ongoing and should provide more guidance.

Most antiviral drugs undergoing clinical testing in patients with COVID-19 are repurposed antiviral agents originally developed against influenza, HIV, Ebola or SARS or MERS. Use of the protease inhibitor lopinavir-ritonavir, which disrupts viral replication in vitro, did not show benefit when compared with standard care in a randomized, controlled, open label trial of 199 hospitalized adult patients with severe COVID-19. Among the RNA dependent RNA polymerase inhibitors, which halt SARS-CoV-2 replication, being evaluated, including ribavirin, favipiravir and remdesivir, the latter seems to be the most promising. The first preliminary results of a double blind, randomized, placebo controlled trial of 1,063 adults hospitalized with COVID-19 and evidence of lower respiratory tract involvement who were randomly assigned to receive intravenous remdesivir or placebo for up to 10 days demonstrated that patients randomized to receive remdesivir had a shorter time to recovery than patients in the placebo group (11 vs 15 days). A separate randomized, open label trial among 397 hospitalized patients with COVID-19 who did not require mechanical ventilation reported that 5 days of treatment with remdesivir was not different than 10 days in terms of clinical status on day 14. The effect of remdesivir on survival remains unknown.

Treatment with plasma obtained from patients who have recovered from viral infections was first reported during the 1918 flu pandemic. A first report of 5 critically ill patients with COVID-19 treated with convalescent plasma containing neutralizing antibody showed improvement in clinical status among all participants, defined as a combination of changes of body temperature, Sequential Organ Failure Assessment Score, partial pressure of oxygen or fraction

of inspired oxygen, viral load, serum antibody titer, routine blood biochemical index, ARDS and ventilatory and extracorporeal membrane oxygenation supports before and after convalescent plasma transfusion status. However, a subsequent multicenter, open label, randomized clinical trial of 103 patients in China with severe COVID-19 found no statistical difference in time to clinical improvement within 28 days among patients randomized to receive convalescent plasma vs standard treatment alone (51.9% vs 43.1%). However, the trial was stopped early because of slowing enrollment, which limited the power to detect a clinically important difference. Alternative approaches being studied include the use of convalescent plasma derived hyperimmune globulin and monoclonal antibodies targeting SARS-CoV-2.

Alternative therapeutic strategies consist of modulating the inflammatory response in patients with COVID-19. Monoclonal antibodies directed against key inflammatory mediators, such as interferon gamma, interleukin 1, interleukin 6 and complement factor 5a, all target the overwhelming inflammatory response following SARS-CoV-2 infection with the goal of preventing organ damage. Of these, the interleukin 6 inhibitors tocilizumab and sarilumab are best studied, with more than a dozen randomized clinical trials underway. Tyrosine kinase inhibitors, such as imatinib, are studied for their potential to prevent pulmonary vascular leakage in individuals with COVID-19.

Studies of corticosteroids for viral pneumonia and ARDS have yielded mixed results. However, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which randomized 2,104 patients with COVID-19 to receive 6 mg daily of dexamethasone for up to 10 days and 4,321 to receive usual care, found that dexamethasone reduced 28 day all cause mortality (21.6% vs 24.6%; age adjusted rate ratio, 0.83 [95% CI, 0.74-0.92]; $P < .001$). The benefit was greatest in patients with symptoms for more than 7 days and patients who required mechanical ventilation. By contrast, there was no benefit and possibility for harm among patients with shorter symptom duration and no supplemental oxygen requirement. A retrospective cohort study of 201 patients in Wuhan China with confirmed COVID-19 pneumonia and ARDS reported that treatment with methylprednisolone was associated with reduced risk of death (hazard ratio, 0.38 [95% CI, 0.20-0.72]).

Thromboembolic prophylaxis with subcutaneous low molecular weight heparin is recommended for all hospitalized patients with COVID-19. Studies are ongoing to assess whether certain patients (e.g., those with elevated D-dimer) benefit from therapeutic anticoagulation.

Prevention

COVID-19 is a potentially preventable disease. The relationship between the intensity of public health action and the control of transmission is clear from the epidemiology of infection around the world. However, because most countries have implemented multiple infection control measures, it is difficult to determine the relative benefit of each. This question is increasingly important because continued interventions will be required until effective vaccines or treatments become available. In general, these interventions can be divided into those consisting of personal actions (e.g., physical distancing, personal hygiene and use of protective equipment), case and contact identification (e.g., test-trace-track-isolate, reactive school or workplace closure), regulatory actions (e.g., governmental limits on sizes of gatherings or business capacity; stay at home orders; proactive school, workplace and public transport closure or restriction; cordon sanitaire or internal border closures) and international border measures (e.g., border closure or enforced quarantine). A key priority is to identify the combination of measures that minimizes societal and economic disruption while adequately controlling infection. Optimal measures may vary between countries based on resource limitations, geography (e.g., island nations and international border measures), population and political factors (e.g., health literacy, trust in government, cultural and linguistic diversity).

Mathematical modeling studies and empirical evidence support that public health interventions, including home quarantine after infection, restricting mass gatherings, travel restrictions, and social distancing, are associated with reduced rates of transmission. Risk of resurgence follows when these interventions are lifted. Other approaches to prevention are likely to emerge in the coming months, including monoclonal antibodies, hyperimmune globulin, and convalscent titer. If proved effective, these approaches could be used in high risk individuals, including health care workers, other essential workers, and older adults (particularly those in nursing homes or long term care facilities).

Conclusions

As of July 1, 2020, more than 10 million people worldwide had been infected with SARS-CoV-2. Many aspects of transmission, infection, and treatment remain unclear. Advances in prevention and effective management of COVID-19 will require basic and clinical investigation and public health and clinical interventions.

References: 1. JAMA, 25 August 2020, Vol. 324, N. 8
2. Eur. J. of Obs. and Gyne. and Repro. Bio., 2020, Vol. 252

Management of post-acute COVID-19 in primary care

Post-acute COVID-19 ("long COVID") seems to be a multisystem disease, sometimes occurring after a relatively mild acute illness. Broadly, such patients can be divided into those who may have serious sequelae (such as thromboembolic complications) and those with a non-specific clinical picture, often dominated by fatigue and breathlessness.

Defining post-acute COVID-19

Post-acute COVID-19 is defined as the one that extends beyond 3 weeks from the onset of first symptoms and chronic COVID-19 is defined as that extends beyond 12 weeks.

How common is it?

Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond 3 weeks and a smaller proportion for months. A recent US study found that only 65% of people had returned to their previous level of health 14 to 21 days after a positive test.

Why are some people affected?

It is not known why some people's recovery is prolonged. Persistent viraemia due to weak or absent antibody response, relapse or reinfection, deconditioning, inflammatory and other immune reactions and mental factors such as post traumatic stress may all contribute. Long term respiratory, musculoskeletal and neuropsychiatric sequelae have been described for other coronaviruses (SARS and MERS) and these have pathophysiological parallels with post-acute COVID-19.

What are the symptoms?

Post-acute COVID-19 symptoms vary widely. Even so called mild COVID-19 may be associated with long term symptoms, most commonly cough, low grade fever and fatigue, all of which may relapse and remit. Other reported symptoms include shortness of breath, chest pain, headache, neurocognitive difficulties, muscle pain and weakness, gastrointestinal upset, rashes, metabolic disruption such as poor control of diabetes, thromboembolic conditions and depression and other mental health conditions.

What tests are required?

Anaemia should be excluded in the breathless patient. Lymphopenia is a feature of severe, acute COVID-19. Elevated biomarkers may include C-reactive protein (for example, acute infection), white cell count (infection or inflammatory response), natriuretic peptides (for example, heart failure), ferritin (inflammation and continuing prothrombotic state), troponin (acute coronary syndrome

"Long COVID" in primary care

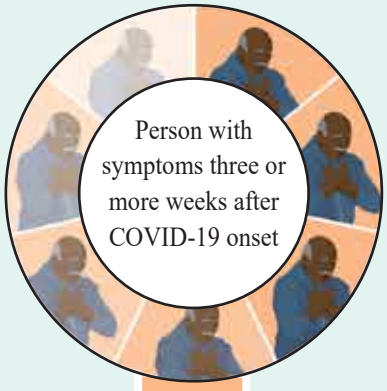
Assessment and initial management of patients with continuing symptoms

Visual summary

This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of COVID-19 that was managed in the community or in a standard hospital ward

An uncertain picture

The long term course of COVID-19 is unknown. However, caution is advised as patients may present atypically and new treatments are likely to emerge



Investigations

Clinical testing is not always needed, but can help to pinpoint causes of continuing symptoms and to exclude conditions like pulmonary embolism or myocarditis. Examples are provided below:

Blood tests

- Full blood count
- Electrolytes
- Liver and renal function
- Troponin
- C-reactive protein
- Creatinine kinase
- D-dimer
- Brain natriuretic peptides
- Ferritin - to assess inflammatory and prothrombotic states

Other investigations

- Chest x ray
- Urine tests
- 12 lead electrocardiogram

Clinical assessment

Full history From date of first symptom

Current symptoms Nature and severity

Examination, for example:

- Temperature
- Heart rate and rhythm
- Blood pressure
- Respiratory examination
- Functional status
- Pulse oximetry
- Clinical testing

If indicated

Managing comorbidities

Many patients have comorbidities including diabetes, hypertension, kidney disease or ischemic heart disease. These need to be managed in conjunction with COVID-19 treatment

Assess comorbidities

Social, financial and cultural support

Prolonged COVID-19 may limit the ability to engage in work and family activities. Patients may have experienced family bereavements as well as job losses and consequent financial stress and food poverty

Social and financial circumstances

Safety netting and referral

The patients should seek medical advice if concerned, for example:

- Worsening breathlessness
- $PaO_2 < 96\%$
- Unexplained chest pain
- New confusion
- Focal weakness

Specialist referral may be indicated, based on clinical findings, for example:

- Respiratory if suspended pulmonary embolism, severe pneumonia
- Cardiology if suspected myocardial infarction, pericarditis, myocarditis or new heart failure
- Neurology if suspected neurovascular or acute neurological event

Pulmonary rehabilitation may be indicated if patient has persistent breathlessness following review

Medical management

- Symptomatic, such as treating fever with paracetamol
- Optimise control of long term conditions
- Listening and empathy
- Consider antibiotics for secondary infections
- Treat specific complications as indicated

Self management

- Daily pulse oximetry
- Attention to general health
- Rest and relaxation
- Self pacing and gradual increase in exercise **if tolerated**
- Set achievable targets

- Diet
- Sleep
- Quitting smoking
- Limiting alcohol
- Limiting caffeine

Mental health

In the consultation

- Continuity of care
- Avoid inappropriate medicalisation
- Longer appointments for patients with complex needs (face to face if needed)

In the community:

- Community linkworker
- Patient peer support groups
- Attached mental health support service
- Cross-sector partnerships with social care community services, faith groups

or myocarditis) and D-dimer (thromboembolic disease). Troponin and D-dimer tests may be false positive, but a negative result can reduce clinical uncertainty.

Supporting recovery from COVID-19

After excluding serious ongoing complications or comorbidities, and until the results of long term follow up studies are available, patients should be managed pragmatically and symptomatically with an emphasis on holistic support while avoiding over investigation. Fever for example, may be treated symptomatically with paracetamol or non steroidal anti inflammatory drugs.

Respiratory symptoms and support

Cough: The British Thoracic Society defines chronic cough as one that persists beyond 8 weeks. Cough seems to be best managed with simple breathing control exercises (Table-1) and medication where indicated (such as proton pump inhibitors if reflux is suspected).

Table-1: Breathing techniques

The patient should sit in a supported position and breathe in and out slowly, preferably in through the nose and out through the mouth, while relaxing the chest and shoulders and allowing the tummy to rise. They should aim for an inspiration to expiration ratio of 1:2. This technique can be used frequently throughout the day, in 5 to 10 minute bursts (or longer if helpful). Other breathing techniques such as diaphragmatic breathing, slow deep breathing, pursed lip breathing, yoga techniques, Buteyko are used in strategies to manage patients' breathing patterns.

Breathlessness: A degree of breathlessness is common after acute COVID-19. Severe breathlessness, which is rare in patients who were not hospitalized, may require urgent referral. Breathlessness tends to improve with breathing exercises. Pulse oximeters may be extremely useful for assessing and monitoring respiratory symptoms after COVID-19 (Table-2).

Table-2: Use of pulse oximetry in post-acute COVID-19

Patients should be provided with a pulse oximeter and an observations diary and given instructions for how to self-monitor. Typically, this would be a daily reading taken on a clean, warm finger without nail polish, after resting for 20 minutes; the device should be left to stabilise and the highest reading obtained should be recorded.

British Thoracic Society guidelines define the target range for oxygen saturation as 94% to 98% and a level of 92% or below as requiring supplementary oxygen (unless the patient is in chronic respiratory failure).

Fatigue: No published research evidence was found on the efficacy of either pharmacological or non-pharmacological interventions on fatigue after COVID-19. Patient resources on fatigue management and guidance for clinicians on return to exercise and graded return to performance for athletes (Table-3) in COVID-19 are currently all based on indirect evidence.

Table-3: The sportsperson returning to exercise (summarised from Stanford-Hall statement)

- After recovery from mild illness: 1 week of low level stretching and strengthening before targeted cardiovascular sessions
- Very mild symptoms: limit activity to slow walking or equivalent. Increase rest periods if symptoms worsen. Avoid high-intensity training
- Persistent symptoms (such as fatigue, cough, breathlessness, fever): limit activity to 60% maximum heart rate until 2 to 3 weeks after symptoms resolve
- Patients who had lymphopenia or required oxygen need respiratory assessment before resuming exercise
- Patients who had cardiac involvement need cardiac assessment before resuming

Cardiopulmonary complications, assessment and management: Perhaps 20% of patients admitted with COVID-19 have clinically significant cardiac involvement. Cardiopulmonary complications include myocarditis, pericarditis, myocardial infarction, dysrhythmias, and pulmonary embolus; they may present several weeks after acute COVID-19. They are commoner in patients with pre-existing cardiovascular disease.

Chest pain: Chest pain is common in post-acute COVID-19. The clinical priority is to separate musculoskeletal and other non specific chest pain (for example, the symptom described by a large patient led survey as "lung burn") from serious cardiovascular conditions.

The older patient: COVID-19 tends to affect older patients more severely. Those who survive are at high risk of sarcopenia, malnutrition, depression and delirium. Post-COVID-19 chronic pain may affect patients of any age but seems to be commoner in elderly patients.

Mental health and wellbeing: Post-acute COVID-19 is often associated with low mood, hopelessness, heightened anxiety and difficulty sleeping. Post-traumatic stress disorder may occur, especially in healthcare workers and others with caring responsibilities.

Reference: BMJ, 2020, V.370, N.3026

Patterns of IgG and IgM antibody response in COVID-19 patients

Coronavirus Disease 2019 (COVID-19), which emerged in Wuhan, China in December 2019 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has become a major global public health concern. Positive detection of SARS-CoV-2 RNA in nasopharyngeal swab samples, sputum samples or bronchoalveolar lavage samples by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) has been used to confirm SARS-CoV-2 infection. Recently, positive detection of IgM and IgG antibodies specific to SARS-CoV-2 has also been recognized as deterministic evidence for confirmed SARS-CoV-2 infection. In the present study, it was investigated that the patterns of antibody response to SARS-CoV-2 in patients with COVID-19, aiming to better clarify the humoral immunological response during SARS-CoV-2 infection.

Patient characteristics: A total of 32 patients with a confirmed diagnosis of COVID-19 were included in a cohort. All were positive for SARS-CoV-2 according to nucleic acid testing by RT-PCR of nasopharyngeal swab, sputum or bronchoalveolar lavage specimens. Patients exhibiting one or more of the following conditions were classified as having severe COVID-19: (a) respiratory distress (≥ 30 breaths/min); (b) oxygen saturation ≤ 93% at rest; (c) arterial partial pressure of oxygen (PaO_2)/fraction of inspiration O_2 (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa); (d) respiratory failure requiring mechanical ventilation; (e) septic shock development or (f) critical organ failure requiring ICU care. Patients not meeting the above criteria were classified as having mild COVID-19. The median age of the 32 patients was 55 years old, and 66.7% of them were male. Among the 32 patients, 18 (56.3%) were severe cases, and 14 (43.7%) were mild cases. The most common symptoms at onset of illness were fever, cough, fatigue, dyspnoea and headache.

Detection of antibodies against SARS-CoV-2: In total, 217 blood specimens were obtained from 32 patients (6.8 blood specimens per patient on average; supplementary materials). A quantum dot immunofluorescence assay was used to semi-quantitatively detect IgM and IgG antibodies. Briefly, serum collected from patients was incubated at 56°C for 30 min and then 80 µl of the diluted serum was added to the well dented on the test chip and was incubated at room temperature for 10 min. During the process, IgM or IgG antibodies in the serum sample reacted with quantum dot nanocrystal conjugated secondary antibodies and purified recombinant SARS-CoV-2 spike (S) protein respectively, which were both coated on a cellulose nitrate membrane. Subsequently, the immunofluorescence signal strength of the sample was analysed by a quantum dot fluorescence detector which emitted a wavelength of

610 nm and excited a wavelength of 365 nm. The quantitative results were expressed in relative vitality units (RU/ml) according to the calibration curve. A value ≥ 10 RU/ml was considered to be a positive result. All serum samples were tested in triplicate and the average of all three relative vitality units was used as the final test result.

Patterns of anti-SARS-CoV-2 IgG and IgM antibodies: Anti SARS-CoV-2 S-specific IgG and IgM antibodies were not detectable in the very early days of infection (from day 0 to day 3). Anti SARS-CoV-2 S-specific IgM antibodies were detectable from day 4 onward; the IgM antibody titres increased over time, peaking at approximately day 20 and then began to decline. The positivity rate of IgM antibody was only 60% with a marked reduction in antibody levels 4 weeks after onset of illness. Anti-SARS-CoV-2 S-specific IgG antibodies were identifiable from day 7 onwards, peaking at approximately day 25. Serum IgG antibodies were still maintained at a high level after 4 weeks of infection.

Comparison of antibody response between mild cases and severe cases: It was further compared the difference in antibody detectability between mild cases and severe cases of COVID-19. Serum IgG antibody levels were not significantly correlated with clinical severity in the early stage of infection. Severe cases of COVID-19 tended to have a more vigorous IgG response against SARS-CoV-2 compared with mild cases. Notably, some patients with mild disease had a robust IgG antibody response from 9 days after symptom onset, while a few mild cases did not generate adequate IgG antibodies (approximately 21.43%).

In summary, it was observed that the IgM antibody response to SARS-CoV-2 occurred earlier and peaked earlier than the IgG antibody response; the IgM antibody response began to decline at week 3 of the illness, while the IgG antibody response persisted and was maintained in patients with COVID-19.

Reference: Emerging Microbes & Infections, 2020, Vol. 9

Clarifying the sweeping consequences of COVID-19 in pregnant women, newborns and children with existing cohorts

The sweeping consequences of the Coronavirus Disease 2019 (COVID-19) pandemic for pregnant women, newborns and children remain uncharted. The greatest outcomes may not be on those with known infections who have dominated the early avalanche of literature. Interactions between humans and viruses evolve over time, judging from previous pandemic histories and it will soon lose the opportunity to understand the current one. This viewpoint suggests that the only way to truly capture the long term consequences of the COVID-19 pandemic for these groups may be in agile reconfiguration of existing large birth cohort studies.

While the broad shapes of pandemics are similar, each has its unique detail. The 2003 severe acute respiratory syndrome coronavirus (SARS-CoV) had higher rates of maternal and neonatal complications and death in younger adults but SARS-CoV-2 is more prevalent and transmissible. Zika virus can be devastating to the fetus, while the relatively few cases of COVID-19 in fetuses, neonates and young children have tended to be mild. However, recent reports of a serious, Kawasaki like illness in young children coincident with the COVID-19 pandemic suggests that its full pediatric story may be yet to emerge. With few pediatric confirmed cases and low rates of severe disease, unknown effects on infants and children at heightened vulnerability in low income countries and an unknown extent of subclinical infection, testing children has been deprioritized and their contribution to COVID-19 epidemiology remains something of a mystery.

To prepare for the inevitable next pandemic, systems designed to help model profiles of transmission, diagnosis, treatment and prevention are needed. It needs to understand the outcome of COVID-19 on pregnant women, infants and children including vulnerable and minority groups. Outcomes must cover those with and without infections, who will both bear the burdens of altered health services, psychosocial stress and economic downturn. It needs evidence to strengthen preventive measures and understand the consequences of infection, chemoprophylaxis, vaccination and treatment. Risks and benefits need to be clarified, including balancing breastfeeding against transmission, physical distancing and mental health. Infection prevention and control strategies must be developed to minimize the spread of COVID-19 in antenatal settings, the household and community. It needs to document common, rare and subtle outcomes over time and the genetic and other contributors to their variations.

Some questions are specific to COVID-19 while others are more generalizable. Examples follow:

True incidence: Rates of asymptomatic, minimally symptomatic and presumptive COVID-19 are unknown; only the numbers of confirmed cases were known. Pregnant women and neonates are the only groups that routinely undergo systematic, universal blood testing. Assuming that the reach of COVID-19 in pregnancy approximates that of the general population, infection rates in this group should mirror the true reach of COVID-19 across all communities and support modeling of population surveillance. Serological testing in pregnancy would also enable study of gestational timing of COVID-19 and modeling the burdens of COVID-19 to pregnant mothers, the fetus, children, families and society.

Mother to child transmission: In utero SARS-CoV-2 transmission findings are not convincing because testing relies on antibody detection and the virus is not detected in amniotic fluid, cord blood, breast milk or neonatal throat swabs. In several reports of maternal infections, the physicians caring for those patients chose cesarean delivery while others chose vaginal delivery, without evidence to guide either choice. Little is known about maternally derived antibodies, including whether this is protective for newborns and for what duration and how long before delivery a mother with a COVID-19 infection can produce sufficient antibody levels to protect a neonate from postnatal exposure.

Breastfeeding recommendations: At present, the US Centers for Disease Control and Prevention recommends considering separation of the mother and infant at delivery, but this recommendation is controversial and must be balanced against the known harms to establishing lactation and bonding, particularly at a time of pandemic associated isolation and stress. If maternal antibodies can protect a neonate, this may permit breastfeeding without prophylaxis, masking or separation.

Long term effects on fetal development and child health: Thus far, the outcome of COVID-19 on women who are vs are not pregnant appears similar. However, perinatal outcomes from a small cohort of women with third trimester infections are insufficient to identify rare events, long term complications or problems that may arise during fetal organogenesis particularly if the pandemic response restricts access to screening of fetal anomalies. It is vital to capture these outcomes before vaccination and antiviral treatments are established or cases disappear. For example, should an antiviral drug become available with adverse pregnancy effects, risks and benefits cannot be balanced in the absence of data from an untreated cohort. A very large birth cohort capable of case cohort analyses could identify rare adverse outcomes over time, including neurodevelopment or immune functioning.

Long term health service outcomes: The international disruption to usual health and other services is extreme. Forced innovations include transitions to telehealth, reduced access to antenatal care and screening unaccompanied deliveries, changes in cesarean delivery use and or early discharge into a socially distanced world. These are seismic, untested and unprecedented health service delivery changes with unknown but possibly profound outcomes. It must not only document but tease out the causality of these wide-reaching systems changes on the care and outcomes of conditions other than COVID-19 itself and their long term economic and psychosocial outcomes.

None of this is possible without an appropriate pregnancy and birth cohort. It would need to be very large, longitudinal, population based and prepared to collect data now. It would need to include appropriate biological samples, requiring innovation in universal capable home self collection of room temperature samples. Advanced and innovative information technology systems would be essential, since physical distancing policies preclude traditional face to face clinical or community research. A well designed, safe, digital platform could replace laborious traditional face to face research assessments of wide ranging psychosocial, phenotypic and functional outcomes (using images and videos) and also provide research support to participants. Removing the need for in person visits, transit time and expense such a program could be more accessible for participants and recruiters.

The value of such a megacohort cannot be doubted. For elderly people, the UK Biobank recently took the unprecedented step of releasing primary care, hospitals and intensive care data for its 500,000 participants to enable research nearly in real time into the mediators and outcomes of COVID-19. This was authorized by the UK Secretary of State. Unfortunately, for pregnancy and early life, attempts to mount such cohorts have failed even in happier times. However, some do exist that are at the right stage of planning, have well established infrastructure and organizational collaboration and are ready to incorporate a focus on COVID-19 with the right government partnerships and support. This would provide a sustainable infrastructure to minimize adverse outcomes associated with the current pandemic for mothers and infants over coming decades, while maximizing knowledge to help address the inevitable pandemics to come.

Reference: JAMA Pediatrics, 10 August 2020

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