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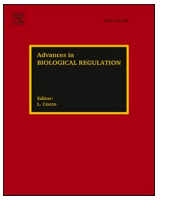

Where are we with understanding of COVID-19?

Shaw M. Akula *, James A. McCubrey

Department of Microbiology & Immunology, Broday School of Medicine, East Carolina University, Greenville, NC, 27834, USA

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ABSTRACT

Coronavirus disease 2019 caused by SARS-CoV-2 originated from China and spread across every corner of the world. The scientific interest on COVID-19 increased after WHO declared it a pandemic in the early February of 2020. In fact, this pandemic has had a worldwide impact on economy, health, and lifestyle like no other in the last 100 years. SARS-CoV-2 belongs to *Coronaviridae* family and causes the deadliest clinical manifestations when compared to other viruses in the family. COVID-19 is an emerging zoonotic disease that has resulted in over 383,000 deaths around the world. Scientists are scrambling for ideas to develop treatment and prevention strategies to thwart the disease condition. In this review, we have attempted to summarize the latest information on the virus, disease, prevention, and treatment strategies. The future looks promising.

1. Introduction

Coronavirus disease 2019 (COVID-19) has resulted in considerable morbidity and mortality globally since December of 2019. The number of COVID-19 infected people around the world has exceded 3 million, and more than 200,000 people have died and this has had a huge impact on human health and economic development (Feng et al., 2020). In less than six months, COVID-19 has managed to spread from a lesser known province of Wuhan in China to almost every country in the world (Sironi et al., 2020). No wonder did the World Health Organization (WHO) declared COVID-19 as a pandemic (Tiwari et al., 2020). The COVID-19 pandemic has managed to expose our poor sanitation/hygiene worldwide; and almost half of the world has been placed in quarantine (El-Hage et al., 2020). In most cases, quarantine has lasted over 45 days.

Severe acute respiratory coronavirus syndrome 2 virus (SARS-CoV-2) causes COVID-19 (Shin, 2020). SARS-CoV-2 is one of the highly pathogenic coronaviruses to emerge and spread in human populations. The International Committee on Taxonomy of Viruses (ICTV) classified SARS-CoV-2 as a member of the *Sarbecovirus* subgenus (genus *Betacoronavirus*) (Zhou et al., 2020; Wilcox, 2020). The animal-human interface is suspected as the primary source of the emerging zoonotic disease, COVID-19 (Malik et al., 2020). Apart from bats, it is too early to rule out the role of intermediate hosts such as snakes, pangolins, turtles, and other wild animals in the origin of SARS-CoV-2 (Tiwari et al., 2020; Tang et al., 2020). SARS-CoV-2 is distantly related to Middle East respiratory syndrome Coronavirus (MERS-CoV) when compared to SARS-CoV (Sironi et al., 2020).

Adults seem to be predominantly affected by COVID-19 (Columbus et al., 2019). The incubation period is about 2–14 days between infection and symptom onset (Singhal, 2020). The most common symptoms are fever, cough, dyspnea, and myalgias and/or fatigue. Interestingly, all cases have shown radiographic evidence of pneumonia (Meo et al., 2020). In this review, we have attempted to summarize the biology of SARS-CoV-2 in COVID-19 pandemic.

* Corresponding author.
E-mail addresses: akulas@ecu.edu (S.M. Akula), mccubreyj@ecu.edu (J.A. McCubrey).

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1.1. Global impact of COVID-19

The lockdown due to COVID-19 has several ramifications to the society. It has resulted in a major financial crisis resulting in the 'Great Recession' (Ruckert and Labonté, 2014). The disproportionate effects of COVID-19 predominantly in underprivileged communities are a reflection of inequality and social exclusion that exist in our society at large (Kim and Bostwick, 2020). It has impacted all forms of education globally. Many countries have managed to switch over to online teaching modes (Sandhu and de Wolf, 2020). However, several other countries struggle with this mode primarily because of lack of infrastructure, guidance, and poverty. Research in general declined sharply because of restricted work times. Layoffs at various levels in the industries is a major concern that is bound to destabilize individuals and families. Last but not the least are the psychological/social problems associated with social distancing. These will have a severe bearing on the future generation.

1.2. SARS-CoV-2

Intermediate hosts have a special role in the transmission of SARS-CoV-2 based on the following evidences: (i) COVID-19 was associated with seafood and wildlife market in Wuhan (Huang et al., 2020); (ii) SARS-CoV-2 is believed to have originated from the bats (Lu et al., 2020); and (iii) Coronaviruses closely related to SARS-CoV-2 have been isolated from Malayan or Sunda pangolins in China (Lam et al, 2020). Genetic analysis has identified 103 commonly circulating strains of SARS-CoV-2; all of which recently shifted to infecting humans (Sen et al., 2020). Based on two single nucleotide polymorphism (SNPs), the strains have been classified into two types: L (T28,144 is in the codon of Leucine) and S (C28,144 is in the codon of Serine) types.

The virus is easily spread by speech droplets airborne from symptomatic and asymptomatic carriers (Stadnytskyi et al., 2020). Risk factors to COVID-19 may include household plumbing, large family cluster, overcrowding, male sex, comorbidities like hypertension, bullous pemphigoid and pemphigus vulgaris patients, cancer patients, renal disease, glutathione deficiency, race, and socioeconomic status (Rodriguez-Lonebear et al., 2020; Ikitimur et al, 2020; Zemlin and Wiese, 2020; Escalera-Antezana et al., 2020; Carugno et al, 2020; Bhargava et al, 2020; Tian et al, 2020; Polonikov, 2020).

SARS-CoV-2 possess a positive sense RNA genome expressing open reading frames that encodes both structural and non-structural proteins (Satarker and Nampoothiri, 2020). The genome length is approximately 29.8 kb (Chen et al., 2020). Like other coronaviruses, SARS-CoV-2 is an enveloped virus. The key structural proteins include spike (S) (Dong et al., 2020a), nucleocapsid (N) (SoRelle et al, 2020), membrane (M) (Hu et al., 2003), and envelope (E) proteins (Tilocca et al, 2020). The envelope is composed of M and E proteins. The fact that the virus is enveloped makes it susceptible to commonly used detergent and ethanol.

The virus entry among the members of *Coronaviridae* family is a highly conserved process that is mediated by the homotrimer and glycosylated S protein (Wrapp et al., 2020; Ou et al., 2020; Millet and Whittaker, 2015). The envelope is studded with 5–7 nm of S protein. Conformational changes to S protein is triggered as soon as receptor binding domain (RBD) within the S1 subunit of S protein interacts with the host cell receptor molecule, angiotensin-converting enzyme 2 (ACE2) (Li, 2016). Receptor binding stabilize the binding by shedding of the S1 subunit and transition of the S2 subunit (Walls et al., 2017). The S2 subunit of S protein facilitates internalization of the virus (Lau et al., 2020). Apart from its role in the virus entry process, it represents a target for antibody-mediated neutralization as it is highly immunogenic; all of which make a good target to design vaccine and therapies.

1.3. Clinical manifestations of SARS-CoV-2 infection

The first manifestation of the SARS-CoV-2 infection are ageusia and anosmia in the patients with COVID-19 infection (Passarelli et al., 2020). The other common manifestations are fever, cough, dyspnea, and myalgias and/or fatigue in COVID-19 patients (Meo et al., 2020). However, it is not limited to the above symptoms alone. The other symptoms may include the following:

(i) Ataxia, headache, dizziness, and loss of consciousness, which suggest a potential for neural involvement (Baig and Sanders, 2020).
(ii) Diarrhea (de Souza et al., 2020).
(iii) Subacute thyroiditis (SAT) (Brancatella et al., 2020).
(iv) Nausea and vomiting (Song et al., 2020).
(v) In severe case, there may be acute respiratory distress syndrome or even multi-organ failure (Li et al., 2020a).
(vi) Skin manifestations like rashes on the back of trunk, and urticaria (Tammaro et al, 2020).

Due to varied symptoms of the disease, it is imperative for the clinician to pay attention while making a diagnosis. According to the current available information, people between the ages of 40 and 60 are more prone to this infection compared to children (Lai et al., 2020).

1.4. Predictors of disease severity

These are some of the commonly used predictors of COVID-19 severity:

(i) COVID-19 patients have higher serum level of inflammatory cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-10) and C-reactive protein. Within COVID-19 patients, serum IL-6 and IL-10 levels are significantly higher in critical group compared to moderate and sever group of patients (Han et al., 2020).
(ii) Lower levels of platelets and albumin means an increase in the severity of COVID-19 pneumonia (Li et al, 2020b).
(iii) Acute or pre-existing renal disease and the need for ventilation at the time of hospitalization are predictors of severe COVID-19 infections (Bhargava et al, 2020).
(iv) Increase in the levels of white blood cells (WBC), neutrophils, D-dimer, fibrinogen (FIB), IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), α-hydroxybutyrate dehydrogenase (HBDH), serum amyloid A (SAA) and a corresponding decrease in the levels of lymphocytes are important risk factors associated with the disease severity (Dong et al, 2020b).

1.5. How to prevent COVID-19?

Prevention of a disease is a challenge when it is declared a pandemic. An elaborate study from China concluded the following key approaches to prevent COVID-19 (Ge et al., 2020):

(i) Identify the source effectively and control the infection: The main source of infection are patients with COVID-19. Medical fraternity must diagnose early, report early, isolate early and start treating the patients early. One other important step is to quarantine those that are suspected of being exposed to the virus or the disease (Khanna et al., 2020).
(ii) Break the transmission cycle: The virus is easily transmitted via aerosol and to lesser extent by feces and urine. The transmission cycle can be halted by following hygienic practices (Berardi et al., 2020; Müller et al., 2020) like washing hands, proposer disposal of nasal secretions, appropriately using hand sanitizers, wearing facial masks, and avoiding physical contacts as much as possible. It is also imperative that the local governments always ensure supply of quality drinking water to households. During times of pandemic, hospitals must strengthen inspection and quality of aerosols and disposal of wastes in their facility.
(iii) Protection of the vulnerable population: The high-risk population includes the aged, pregnant women, patients in emergency, critically ill, with acute cardiovascular and cerebrovascular diseases, with renal disease, on hemodialysis, diabetic, and ailing with cancers (Zimmermann and Curtis, 2020; Filardi and Morano, 2020; Al-Quteimat and Amer, 2020). Medical institutions must pay special attention to the well-being of this population during the pandemic.

1.6. Role of nutritional supplements in management of COVID-19

A pandemic at this level has driven research in identifying nutritional supplements that may have a palliative effect on the outcome of COVID-19 disease. The latest to join the list of potential supplements that may have therapeutic benefits is nicotinamide riboside (NR). NR is supposed to elevate nicotinamide adenine dinucleotide (NAD^+) precursors which is an essential coenzyme for a variety of metabolic pathways (Mehmel et al., 2020).

In general, malnutrition is a risk factor for any infection and SARS-CoV-2 infection is not an exception. Dietary supplements like vitamin A, vitamin C, omega-3 fatty acids, polyphenols and carotenoids exert anti-inflammatory and anti-oxidative properties (Iddir et al., 2020). Supplements like vitamin D may decrease exposure to SARS-CoV-2 by inhibiting expression of ACE-2 (Cui et al., 2019); the known receptor that promotes viral entry (Tseng et al., 2020). Zinc as a supplement is said to enhance both innate and adaptive immunity and thus inhibit SARS-CoV-2 replication (Rahman and Idid, 2020). Again, all these supplements are not without their benefit, but work needs to be done to establish if they can serve as a potential antiviral drug.

1.7. Treatment strategies

The most widely used drugs to treat COVID-19 are chloroquine and hydroxychloroquine (Ibáñez et al, 2020). The other antiviral drugs that are being prescribed to treat COVID-19 are ribavirin (nucleoside analogue) (Falzarano et al., 2013), remdesivir (nucleotide

Table 1
Drugs currently used to treat COVID-19.

DRUG	MODE OF ACTION	ORIGINALLY USED TO TREAT	REFRENCES
Chloroquine/ Hydrochloroquine	Inhibit SARS-CoV-2 entry by changing glycosylation of ACE2 receptor.	Malaria and arthritis.	(Liu et al., 2020; Olofsson et al, 2020; Pahan and Pahan, 2020)
Remdesivir	Inhibition of RNA genome replication.	Ebola.	Mullard (2020)
Lopinavir/ritonavir	Protease inhibition	HIV.	Godfrey et al. (2020)
Favipiravir	A broad spectrum inhibitor of viral RNA polymerase.	Influenza.	(Furuta et al., 2017; Srinivas et al., 2020)
Azithromycin	Interferes with protein synthesis.	Bacterial conjunctivitis.	Diaz et al, 2020
Doxycyclin	Inhibits bacterial protein synthesis.	Antibiotic against gram + and gram – bacteria.	van Velzen et al. (2020)
Ivermectin	Inhibits importin mediated viral import.	Nematode and orthropod parasites.	Choudhary et al. (2020)

analogue that inhibit RNA polymerase) (Morse et al., 2020), lopinavir/ritonavir (protease inhibitor) (Moyle et al., 2013), favipiravir (pyrazinecarboxamide derivative known to inhibit RNA polymerase) (Coomes and Haghbayan, 2020), antibiotics such as azithromycin and doxycycline (Maraj et al, 2020; Farouk and Salman, 2020), and anti-parasite such as ivermectin (Sharun et al., 2020) (see Table 1). Although, several antivirals are being tested in different combinations, there is no definite, specific, and an efficient monotherapy protocol. The major unsolved issues surrounding the treatment regimen of COVID-19 are Lymphocytopenia, excessive inflammation, and cytokine storm. Albeit, it must be kept in mind that work is on to find the magic bullet and time is of the essence.

1.8. Vaccines to prevent COVID-19

The current approach to developing a potent vaccine to counter SARS-CoV-2 infection is by inducing neutralizing antibodies to the S protein of SARS-CoV-2. Several companies are at work in generating a vaccine including Altimmune, BioNTech and Pfizer, GlaxoSmithKline, Heat Biologics, Invio Pharmaceuticals, Moderna, Novavax, Sanofi, and Vaxart. It is not clear how efficient these vaccine candidates may be in terms of providing a long-term immunity for a respiratory tract infection as COVID-19. A review article by Burton and Walker discuss alternate approaches to developing a potent COVID-19 vaccine (Burton and Walker, 2020). Given the short duration of time and the fact that it is an RNA virus capable of mutating rapidly we are not particularly enthusiastic about having a potent and reliable vaccine in the near future.

2. Conclusion

As mentioned earlier, lockdown ensuing this pandemic has destroyed the society economically: people have lost their jobs, businesses closed, drastic changes to education system, and so forth. On the flipside, there has been a dramatic reduction in air pollution (Srivastava et al, 2020), better appreciation for hygienic practices, and a sharp decline in visits to doctors office. Perhaps this pandemic has changed culture-driven behavioral pattern for eternity. We may no longer shake hands, kiss, or hug to greet each other. More importantly, facial masks are here to stay for a long time. Patience is what needs to be practiced. Better prevention and treatment strategies can be developed only when biology of the pathogen is understood.

Declaration of competing interest

We hereby declare that no authors have any conflicts of interest with publication of this manuscript.

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