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Coronavirus (COVID-19): History, Current Knowledge and Pipeline Medications

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Abstract

In spite of being characterised in the 1960s, human coronavirus still needs extensive studying for its better understanding. Since, the start of the new millennium corona viruses had caused pandemic. SARS-CoV and MERS-CoV were the first coronavirus outbreak which has resulted in socioeconomic and psychological losses in the past. The novel corona virus outbreak (COVID-19) needs lesson from our past experience in tackling the devastating situation. The population needs awareness about this novel virus during the current pandemic situation. In this article the author reviews the history of coronaviruses, its lifecycle and genomic structure, current pandemic situation, diagnosis of COVID-19, preventive measures, current medication and pipeline drugs and diagnostic kits.

Keywords: COVID-19; Coronaviruses; Severe Acute Respiratory Syndrome (SARS) Coronavirus; Middle East Respiratory Syndrome (MERS) Coronavirus; Hydroxychloroquine sulfate; Chloroquine phosphate; Favilavir; Remdesivir

History

Tyrell and Bynoe isolated first human coronavirus in the year 1965 from the respiratory tract of a patient with complain of common cold [1]. The virus was named B814. However, the researchers failed to grow the agent in culture media. In a similar study by Hamre and Procknow, the researchers reported similar kind of virus which they named 229E isolated from the samples obtained from medical students with cold [2]. In another study by McIntosh et al. ether sensitive agents of multiple strains were isolated from human respiratory tract [3]. Since they were grown in organ culture, hence were named "OC" [3]. At about the same period of time Almeida and Tyrrel [4] studied organ cultures infected with B814 exploiting electron microscopy and reported particulates of size 80-150 nm resembling infectious bronchitis virus of chickens. Astonishingly both 229E agent identified by Hamre and Procknow and OC virus reported by McIntosh et al. were found to have similar morphology. In the later part of 1960, a group of virologists under the leadership of Tyrell were studying different strains of human and animal viruses which included mouse hepatitis virus, infectious bronchitis virus, transmissible gastroenteritis virus of swine etc. all of them were morphologically same as demonstrated by electron microscopic study. Thus, a new genus of viruses was found which was named CORONA, where the term corona denoted the crown like appearance of the surface in the morphological structure of viruses [5-7]. Further on-going research with advanced serological techniques resulted in bringing new information's about the epidemiology of the coronaviruses. These viruses occur more in the rainy, winter and spring seasons compared to the summer season [8]. Among the different strains of coronaviruses 229E and OC43 were the most extensively studied. However, as per Bradburne and McIntosh et al. B814 and other 3 of the 6 strains of previously studied coronaviruses were related to 229E and OC43 on very few characteristics [9,10]. Upon volunteer inoculation and epidemiological study coronaviruses were found to be associated with a

variety of respiratory illness [2,8,11,12]. The predominant illness was found to be pneumonia in children and young adults [13,14]. They were also associated with chronic bronchitis and asthma in adults and elders [15,16]. Apart from human coronaviruses, the number and epidemiological importance of animal coronaviruses were found to be increasing rapidly. They were found to occur in a number of animal species including mice, rats, cats, dogs, turkeys, chickens, pigs and rabbits. The animal studies were not limited to respiratory tract infections but also included encephalitis, hepatitis, and gastroenteritis [17]. Based on genetic and antigenic studies human and animal coronaviruses where categorised into three broad groups [18] (**Table 1**).

Table 1: Broad category of human and animal coronaviruses.

Category	Coronavirus
Group I (α-CoVs)	229E and other similar viruses
Group II (β-CoVs)	OC43
Group III (γ-CoVs)	Avian infectious bronchitis virus and other related avian viruses

Severe Acute Respiratory Syndrome (SARS) Coronavirus

The SARS coronavirus and new form of the virus emerged from China in the late 2002 and early 2003 and spread throughout the world [19-21]. These viruses grew easily in tissue culture helping in studying the genomic structure of the virus which were found to be sufficiently different from human and animal coronavirus and thus formed a new group of virus similar to viruses cultured from Himalayan palm civets, from which they were presumed to be emerged [22]. During SARS outbreak 29 countries were affected with more than 8000 reported cases and around 770 mortalities [23]. It is still unclear how these viruses entered human population. One theory suggest that Himalayan palm civets acted as a reservoir for these viruses.

Genomic structure of coronavirus

Coronavirus belongs to the order Nidovirales, family Coronaviridae and subfamily Coronavirinae. This subfamily is further divided into alpha, beta, gamma and delta coronaviruses based on phylogenetic clustering. These viruses are made up of enveloped single-stranded RNA genome of size range 26-32 kilobases. The genome contains a 5′ cap structure along with a 3′ poly (A) tail, helping it to act as mRNA for translation of the replicase polyproteins [24]. The 5′ end of the coronavirus genome contains untranslated region and a leader sequence that contains multiple loop structures which assists in RNA transcription and replication. Transcriptional regulatory sequences are also present at the beginning of each structural gene assisting in their expression. The 3′UTR part also contains RNA structures which assists in replication and synthesis of viral RNA. The accessory proteins present in corona virus are non-essential for replication in tissue culture; however, some have shown to play important roles in viral pathogenesis [25].

Virions of coronaviruses are spherical in shape and about 125 nm in diameter as confirmed by cryo-electron microscopic and tomographic technique [26,27]. They have club shape like projections from the surface. Inside the virion envelope there is nucleocapsid which are helically symmetrical common to negative sense RNA virus pathogenesis [24]. The virions four main structural proteins namely the spike, membrane, envelope and nucleocapsid encoded at the 3′ end of the viral genome. A fifth structural protein namely the hemagglutinin esterase is also present in the subset of β-coronaviruses which binds sialic acids on the surface glycoprotein and have acetyl-esterase activity [28]. These activities enhance the S protein-mediated cell entry and virus spread through the mucosa [29].

Life cycle of coronavirus

The life cycle of a coronavirus is subdivided into four phases: (i) entry and attachment (ii) replicase protein expression (iii) replication and transcription (iv) assemble and release. Interaction between the S protein and its receptors marks initial attachment of the virion to the host cell. The interaction between the S protein and receptor is the primary determinant for a coronavirus to infect the host and it also governs the tissue tropism of the virus. Peptidase acts as the cellular receptor for most of the coronaviruses. After the receptor binding the virus gains access to the cytosol of the host cell [30,31]. This process is assisted by the acid dependent proteolytic cleavage of S protein called the cathepsin or another similar protease which is followed by the fusion of the cellular and viral membranes. Two cleavages are formed in the S2 portion of the protein, one is important for separating the receptor binding and fusion domain of S protein [32] and the other is important for exposing the fusion peptide. Most of the fusion occurs within the acidified endosomes however, some coronaviruses may fuse at the plasma membrane site.

The entry and attachment of virion is followed by replicase protein expression in which the translation of the replicase gene occurs within the virion genomic RNA. Two large ORFS namely rep1a and rep1b is encoded by replicase gene which in turn expresses two co-terminal polyproteins namely pp1a and pp1ab. To get both the polyproteins expressed, the virus utilizes a slippery sequence (5′-UUUAAAC-3′) and an RNA pseudoknot which causes the ribosomal frameshifting from the rep1a reading frame into the rep1b ORF [33]. The polyproteins pp1a and pp1ab contain the nsps 1–11 and 1–16, respectively. In pp1ab, nsp11 from pp1a becomes nsp12 following extension of pp1a into pp1b. The nsps gets assembled into the replicase-transcriptase complex (RTC) thus creating an ambient environment for RNA synthesis, and ultimately are responsible for RNA replication and transcription of the sub-genomic RNAs [24].

Assembly and translation occur after the viral RNA synthesis in which both the genomic and sub-genomic RNAs are produced. Sub-genomic RNAs serve as mRNAs for the accessory and structural genes which resides at the downstream of the replicase polyproteins. Both genomic and sub-genomic RNAs are produced through the negative strand intermediates. Finally, coronaviruses are also known for their unique ability to recombine using both homologous and non-homologous recombination [34,35].

S, E, and M viral structure proteins are translated and inserted into the endoplasmic reticulum (ER) following the replication and sub-genomic RNA synthesis. These proteins are capable of moving along the secretory pathway into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [36,37]. There, viral genomes get encapsulated by N protein bud into membranes of the ERGIC which contains the viral structural proteins thus forming mature virions [38]. These virions get transported to the cell surface and gets released by the process of exocytosis.

Human and animal coronavirus disease

Coronaviruses were thought to cause only mild respiratory infection before the outbreak of SARS-CoV. Recent studies suggest that coronaviruses are the cause of 15-30% of the respiratory tract infections in human every year. Infants, elderly and people with underlying illness are more prone to these viruses. HCoV-NL63, a novel coronavirus has been associated with acute laryngotracheitis [39]. Transmission of SARS-CoV only occurred through direct contact with infected individuals after the onset of illness. Thus, the outbreak was largely confined to households and healthcare settings [40], except for few reported cases of superspreading events. SARS-CoV outbreak was controlled in June 2003. SARS-CoV has not returned since then, however in 2012 a novel human coronavirus emerged in the Middle East which was called the Middle East Respiratory Syndrome-CoV (MERS-CoV). It caused highly pathogenic respiratory tract infections in Saudi Arabia and other close countries in the Middle East region [41]. High mortality rate of about 50% were reported during the early stages of the outbreak. However, the outbreak got controlled in 2013, although sporadic cases continued to be reported throughout the rest of the year. In April 2014, there was a sudden rise in the reported cases and deaths prompting fears of mutation being occurred in the virus making them capable of human-to-human transmission. As per the reports of European Center for Disease Prevention and Control a total of 855 cases of MERS-CoV were reported with 333 fatalities by August 2014 [24].

Coronaviruses are capable of causing a variety of diseases in animals like pigs, chickens, cows, cats and dogs causing major loss of economy and livestock. Porcine Epidemic Diarrhea Virus (PEDV) and Transmissible Gastroenteritis Virus (TGEV) causes severe gastroenteritis in piglets, Feline enteric coronavirus (FCoV) causes a mild or asymptomatic infection in domestic cats, Bovine CoV causes respiratory tract infections in cattle, Rat CoV causes respiratory tract infections in rats and Infectious Bronchitis Virus (IBV) cause mild to severe respiratory tract infections in cattle. Murine hepatitis virus (MHV) causes a variety of outcomes in mice, including enteric, respiratory, hepatic and neurologic infections [24].

Pandemic COVID-19 outbreak

The coronavirus disease of 2019 (COVID-19) first appeared in the Wuhan city of Hubei province in China and was declared a global health emergency by World Health Organization on 30th January 2020 [42]. As of 29th March 2020, WHO database confirms 574444 cases of corona globally with 26654 reported deaths from 201 countries [43]. However, this number is subjected to change every second. The most affected countries are Italy with more than 86000 confirmed cases and 9000 deaths, United states with 85000 confirmed cases and 1243 deaths and china with 82000 confirmed cases and 3300 deaths [44,45] (**Figure 1**).

The number of confirmed cases is increasing every day with the availability of rapid testing kits. This pandemic is going to impact severely in the socioeconomic and psychological aspect. COVID-19 is being considered as devastating as World influenza epidemic of 1918.

Elderly people and individuals with history of chronic illness are at higher risk of corona attack and mortality [46]. COVID-19 has a broad clinical spectrum with patients showing only mild and subclinical illness at the early phase of the disease [47,48]. Most of the patients of COVID-19 develops severe acute respiratory disease which requires intensive care and oxygen supplementation.

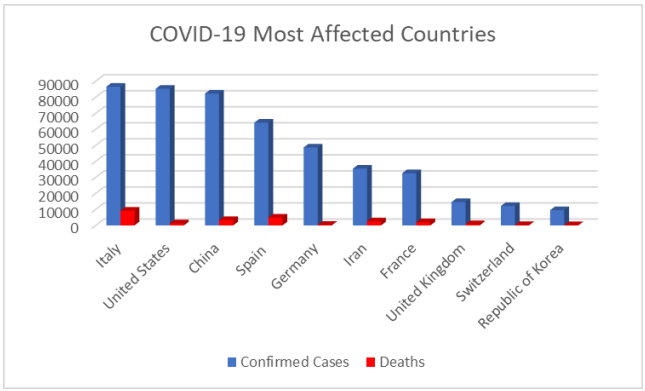

Figure 1: COVID-19 most severely affected countries as per WHO.

The exact transmission mode of this viral disease is not clearly understood however, chances of human to human transmission is suspected [49].

Diagnosis

The common symptoms which are present in a COVID-19 patient includes fever, dry cough, fatigue and shortness of breath. However, some patients may even complain about sore throat, headache, diarrhoea, runny/stuffy nose and body ache. As per recommendations of World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) diagnostic testing for COVID-19 includes tracking the epidemiology and supressing the transmission of the virus. Initial diagnosis includes collecting the testing sample from the upper respiratory tract. Collection of the sample from nasopharyngeal region for swab-based SARS-COV-2 testing is highly recommended. However, alternatively oropharyngeal specimen, Nasal mid-turbinate swab, anterior nares specimen can also be exploited for the diagnosis purpose. CDC also recommends sampling from the lower respiratory tract for patients complaining of cough and sputum [50,51].

Prevention

WHO and CDC released a series of recommendations for the prevention and controlling the spreading of the disease [52,53]. Individuals were suggested:

i. To wash hands regularly with alcohol based handwash or sanitizer or daily using soaps.
ii. Avoid frequent touching of eyes, nose and mouth as they are the most exposed site for catching the infection.
iii. Maintaining social distance of about 1 metre between persons who are coughing or sneezing.
iv. Maintaining respiratory hygiene like covering mouth and nose while sneezing and coughing.
v. Wearing a face mask when in contact with another person
vi. Cleaning and sanitizing home and workplaces.

Current medications and pipeline drugs

Current these is no approved medication for the treatment of COVID-19. However, United States Food and Drug Administration (USFDA) has provided an Emergency Use Authorization (EUA) to hydroxychloroquine sulfate and chloroquine phosphate to be used for patients with COVID-19 [54]. These drugs where conventionally used as antimalarials. Strong clinical data is still required to support the long-term efficacy of both of these drugs in COVID-19. Favilavir, an antiviral drug has been approved by National Medical products Administration of China for the treatment of COVID-19. This drug has shown efficacy in treating the disease with minimal side-effects. Remdesivir, another antiviral has gained attention of many researchers for treating the novel COVID-19 virus due to the similarity of COVID-19 to SARS and MERS viruses. Remdesivir, was previously successfully used in the SARS and MERS outbreak. It was also found effective against Ebola virus. However, more clinical data is needed to support its successful application. Some researchers also suggest supplementation by high doses of Vitamin-C may improve the condition of the patient. Vitamin-C boasts the immunity. But there is no scientific evidence in support of its activity in the treatment of COVID-19. A number of clinical trials are being conducted to develop novel diagnostic technique and medication for the effective treatment of the disease. This review summarizes the current clinical trials which are under way in the United States (**Table 2**) [55].

Table 2: List of clinical trials on coronavirus registered in the United States.

NCT Number	Title	Conditions	Interventions	Sponsors/ Collaborators	Phases	Study Type
NCT04315298	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	COVID-19	Sarilumab	Regeneron Pharmaceuticals/Sanofi	Phase 2/ Phase 3	Interventional
NCT04312997	The Use of PUL-042 Inhalation Solution to Reduce the Severity of COVID-19 in Adults Positive for SARS-CoV-2 Infection	COVID-19	PUL-042 Inhalation Solution	Pulmotect, Inc.	Phase 2	Interventional
NCT04317040	CD24Fc as a Non-antiviral Immunomodulator in COVID-19 Treatment	Severe Coronavirus Disease (COVID-19)	CD24F	OncoImmune, Inc.	Phase 3	Interventional
NCT04318444	Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)	COVID-19, Corona Virus Infection	Hydroxychloroquine	Columbia University	Phase 2/Phase 3	Interventional
NCT04320511	Beaumont Quantitative Lung Function Imaging to Characterize Patients With SARS-COV 2	SARS-COV2, Severe Acute Respiratory Syndrome, COVID-19	CT-V	William Beaumont Hospitals		Observational
NCT04305457	Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19	Coronavirus Infections, Pneumonia, Viral, Acute Respiratory Distress Syndrome	Nitric Oxide	Massachusetts General Hospital/Xijing Hospital/Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico	Phase 2	Interventional
NCT04312009	Losartan for Patients With COVID-19 Requiring Hospitalization	Corona Virus Infection, Acute Respiratory Distress	Losartan	University of Minnesota	Phase 2	Interventional

		Syndrome, SARS-CoV Infection				
NCT04311697	Intravenous Aviptadil for COVID-19 Associated Acute Respiratory Distress	Acute Respiratory Distress Syndrome, Corona Virus Infection	Aviptadil i.v.	NeuroRx, Inc./Relief Therapeutics Holding SA	Phase 2	Interventional
NCT04306393	Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19	Severe Acute Respiratory Syndrome	Nitric Oxide Gas	Massachusetts General Hospital/Xijing Hospital/Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico/Niguarda Hospital	Phase 2	Interventional
NCT04323787	Viral Infection and Respiratory Illness Universal Study [VIRUS]: COVID19 Registry	Coronavirus	observational	Mayo Clinic		Observational
NCT04325672	Convalescent Plasma to Limit Coronavirus Associated Complications	Coronavirus	Convalescent Plasma	Mayo Clinic	Phase 2	Interventional
NCT04323839	PRIORITY (Pregnancy CoRonavIrus Outcomes RegIsTrY)	Pregnancy in COVID-19	Pregnant women under investigation for Coronavirus or diagnosed with COVID-19	University of California, San Francisco/University of California, Los Angeles		Observational
NCT04283461	Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) to Prevent SARS-CoV-2 Infection	Corona Virus Infection	mRNA-1273	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 1	Interventional
NCT04321369	Impact of Swab Site and Sample Collector on Testing Sensitivity for SARS-CoV-2 Virus in Symptomatic Individuals	Respiratory infections	Testing Sensitivity for SARS-CoV-2 Virus in Symptomatic Individuals	Dr. Deneen Vojta/Quest Diagnostics/Bill and Melinda Gates Foundation/UnitedHealth Group		Observational

NCT04292899	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734â„¢) in Participants with Severe Coronavirus Disease (COVID-19)	COVID-19	Remdesivir	Gilead Sciences	Phase 3	Interventional
NCT04280705	Adaptive COVID-19 Treatment Trial (ACTT)	Corona Virus Infection	Remdesivir	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 3	Interventional
NCT04308668	Post-exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	Corona Virus Infection, SARS-CoV Infection	Hydroxychloroquine	University of Minnesota	Phase 3	Interventional

Conclusion

Advancements in coronavirology has taken a giant leap in the recent years. The SARS and MERS epidemic where the reminders about the emergence of novel coronavirus and its potential threat to the human population. The novel coronavirus is significantly similar to the SARS and MERS viruses. But still we do not know much about the possible treatment strategy for this novel virus. They are causing a variety of human and animal veterinary diseases. Future researches are necessary to investigate replication and pathogenesis. COVID-19 outbreak is a setback to our preparation for tackling such pandemic situation. About 30000 people have died of the disease. There is no approved medication for the disease. However, USFDA has provided an Emergency Use Authorization (EUA) to hydroxychloroquine sulfate and chloroquine phosphate to be used for patients with COVID-19. More data are required to support its success in the treatment. A number of researches and clinical trials are being conducted to bring out a possible treatment for the disease. But till date prevention is the best way to tackle this pandemic situation.

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