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Review Article

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), in the Era of Highly Drug-Resistant Bacteria

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Abstract

Coronaviruses (nCoV) or SARS-CoV-2 is RNA positive-strand viruses, belong to the genus betacoronavirus and has high mutation rate in the family Coronaviridae. The aim of this review paper was to have a useful idea about the disease (COVID-19), caused by the SARS-CoV-2, the transmission ways, prevention in this early stage and the options of treatment in the era of multi-drug resistant bacteria.

Keywords: *COVID-19; Coronaviruses; SARS-CoV-2; Outbreak; Multi-Drug Resistant organism (MDRO)*

Introduction

Coronavirus, a particles with irregularly-shaped ~60 - 220 nm in diameter, with an outer envelope behavior distinctive, 'club-shaped' peplomers (~20 nm long 10 nm at wide distal end) these viruses belong to the family Coronaviridae. The name "Coronavirus" is derived from the Latin corona, meaning crown or halo. The Viruses of the family Coronaviridae like coronaviruses possess a single strand, positive-sense RNA genome ranging from 26 - 32 kilobases in length [1]. Coronaviruses have been identified in several avian hosts [2,3] as well as in various mammals, including camels, bats, masked palm civets, mice, dogs, and cats. Novel mammalian coronaviruses are now regularly identified. Among the several coronaviruses that are pathogenic to humans, most are associated with mild clinical symptoms [1] with two notable exceptions: severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), betacoronavirus that emerged in Guangdong, southern China, in November, 2002 [4] and resulted in more than 8000 human infections and 774 deaths in 37 countries during 2002-03 [5] and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), which was first detected in Saudi Arabia in 2012 [6] and was responsible for 2494 cases of infection and 858 death since September, 2012, including 38 deaths following a single introduction into South Korea [7,8]. In late December, 2019, several patients with viral pneumonia were found to be epidemiologically associated with the seafood market in Wuhan, in the Hubei province of China where a number of animals such as birds and rabbits were also on sale before the outbreak. The new viruses provisionally named 2019 novel coronavirus (2019-nCoV). On Jan 28, 2020, China has reported more than 5900 confirmed and more than 9000 suspected cases of 2019-nCoV infection across 33 Chinese provinces. Now a day (COVID-19 or SARS-CoV-2) has been reported in all continents and in the most of countries, human-to-human transmission has been confirmed and more than one million infected case, 50000 death, actually the number of infected individual and the number of death change for higher every hour in the world and the curve change every minute.

Outbreak

End of December 2019, patients presenting with unknown cause of pneumonia were reported in Wuhan, China. Subsequently, a novel coronavirus was identified as the causative pathogen, temporary named 2019 novel coronavirus (2019-nCoV) [9,10] January 26, 2020, more than 5900 confirmed cases and more than 9000 suspected cases of 2019-nCoV. Most of people living in or visiting Wuhan and

human-to-human transmission has been confirmed. Since that time the nouvelle coronavirus was called by several names (nouveau coronavirus (2019-nCoV), (coronavirus infectious diseases COVID-19), (human coronavirus hCoV-19) and (sever acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According the lancet, sever acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the appropriate name of the new coronavirus caused the last pandemic, this name was giving by the international committee on taxonomy of viruses to facilitate good practice and scientific exchange [11]. (SARS-CoV-2), is a positive-sense single-stranded RNA virus. It is contagious in humans and is the cause of the ongoing pandemic of coronavirus disease 2019 (COVID-19) that has been designated a Public Health Emergency of International Concern by the World Health Organization (WHO). SARS-CoV-2 has close genetic similarity to Betacoronaviruses, suggesting it emerged from a bat-borne virus. An intermediate animal reservoir such as a pangolin is also thought to be involved in its introduction to humans [12]. From a taxonomic perspective, SARS-CoV-2 is classified as a strain of the species Severe acute respiratory syndrome-related coronavirus (SARSr-CoV) [13].

In china, from eight patients, samples from Bronchoalveolar lavage fluids or throat swabs were cultured by inoculated into the Special-pathogen-free human airway epithelial HAE cells through the apical surfaces. HAE cells were maintained in an air-liquid interface incubated at 37°C. The cells were monitored daily for cytopathic effects by light microscopy and the cell supernatants were collected and the infectious agent was isolates for use in quantitative RT-PCR assays. By using next-generation sequencing, 2019-nCoV was found. The genomic characterization of eight genomes of this novel virus, providing important information on the origins and cell receptor binding of the virus. After virus genome analyzed, sequence alignment of 2019-nCoV with reference sequences was done with Mafft software (version 7.450). On the basis of the genome sequences obtained, a real-time PCR detection assay was developed. PCR primers and probes were designed using Applied Biosystems Primer Express Software (ThermoFisher Scientific, Foster City, CA, USA) on the basis of the sequenced virus genomes. The eight genome sequences obtained from the patients were extremely similar and exhibiting more than 99·98% sequence identity. 2019-nCoV was closely related (with 88% identity) to two bat-derived Severe acute respiratory syndrome (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, but were more distant from SARS-CoV (about 79%) and MERS-CoV (about 50%). Phylogenetic analysis revealed that 2019-nCoV belong to the genus Betacoronavirus, and was genetically distinct from SARS-CoV notably, homology modelling revealed that 2019-nCoV had a similar receptor-binding domain structure to that of SARS-CoV, despite amino acid variation at some key residues [14]. Genomic study showed incontestable difference was founded, a longer spike protein encoded by 2019-nCoV compared to that bat SARS-like coronaviruses, SARS-CoV, and MERS-CoV. The results of the study suggests that 2019-nCoV might use angiotensin-converting enzyme 2 (ACE2) as a cell receptor. However, the authors observed that several key residues responsible for the binding of the SARS-CoV receptor-binding domain to the ACE2 receptor were variable in the 2019-nCoV receptor-binding domain [14]. The SARS-CoV-2 virus is believe to enter the nasal tissues through the ACE2 receptor, this protein is abundant in the nose. Although its function is not clear. By entering the nose through this protein the virus may cause temporary damage to the smell nerves, however this damage appears to get better within one to two weeks after the onset of the diseases. Though further research is needed to confirm. Some study demonstrated that ACE2 is extensively present in human's epithelia of (oral and nasal mucosa, nasopharynx, and lung) which might provide possible routes of entry for the SARS-CoV [15]. (ACE2) is an attached to the outer surface (cell membrane) in the lungs, arteries, heart, kidney and intestines [16]. ACE2 also serves as the entry point into cells for some coronaviruses [17].

Source and modes of transmission

Since a decades CoVs have been defined as a novel respiratory tract virus in the samples collected from the individuals who present symptoms of respiratory tract infection. This is a large family of viruses that are common in many different animal species, including camels, cattle, cats, and bats. Rarely, animal CoVs can infect humans and, as a result, may spread among humans during epidemics such as MERS, SARS, and SARS-CoV-2 [18]. At the onset of major outbreaks caused by CoVs, palm cats have been proposed to be a natural reservoir of Human CoVs for SARS and dromedary camels for MERS [19]. Studies have reported that most of the bat CoVs are the gene source of alpha-CoV and beta-CoVs [19]. Recent study from Guangzhou China, researchers had demonstrated a pangolin sample with a viral nucleic acid sequence "99% identical" to SARS-CoV-2 [20]. However, a study showed that pangolin coronaviruses share only 92% of their whole genomes with SARS-CoV-2 [21]. In contrast the SARS virus responsible for the 2002-2004 outbreak shared 99.8% of its genome with a known civet coronavirus [22]. Now a day the reservoir for SARS-CoV-2 still unknown. The first known infections caused by SARS-CoV-2 strain were discovered in Wuhan, China [23]. The original source of the virus and how transmitted to humans and when became patho-

genic remains unclear [24]. Many workers at the Huanan Seafood Market were found to be infected by the same strain of virus [25]. This observation offer a suggestion that the market could be the first source of the SARS-CoV-2 strain [26]. However, some research showed that visitors may have introduced the virus to the market, which then facilitated rapid spread of the infections [24]. Frequently, human-to-human transmission occurs with close contact with the mucous membranes within a range of about 2 meters (6 ft. 7 in) [27]. The transmission primarily occurs when an infected person coughs, sneezes or talk and through the respiratory droplets produced just as the spread of influenza and other respiratory pathogens.

Infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. Transmission from contaminated surfaces is possible cause of infection. Some studies demonstrated that the virus may persist on plastic and steel for up to three days but does not remain alive on cardboard for more than one day or on copper for more than four hours [28]. The virus was killed by soap. SARS-CoV-2 remained viable in aerosols under experimental conditions for at least three hours [29]. Given the current uncertainty regarding transmission mechanisms, airborne precautions are recommended routinely in some countries and in the setting of certain high-risk procedures in others [30]. Another study showed that Viral RNA has been found in stool from infected people [31]. WHO-China report, fecal-oral transmission did not appear to be a significant factor in the spread of infection [32]. However, an epidemiological model in China suggested that pre-symptomatic may be a source of infections [33]. In recent study they found that the affinity between the receptor ACE2 and SARS-CoV-2 is 10 to 20 time comparing to this of SARS-CoV, which suggest that the transmission, contagiosity and the pathogenicity of SARS-CoV-2 is stronger than this of SARS-CoV.

Incubation and infectivity period

The most of studies demonstrated that the incubation period for COVID-19 is 14 days following exposure, with most cases occurring approximately four to five days after exposure [34]. From study of 1099 patients with COVID-19, the median incubation period was four days (range two to seven days), median incubation period in this study was 5.1 days [35]. Data concerning the Infectivity Period showed that the duration of viral shedding is variable; from study of 21 patients with mild illness (no hypoxia), 90% had repeated negative viral RNA tests on nasopharyngeal swabs by 10 days after the onset of symptoms; with more severe illness, positive test is longer. Another study of 137 patients who have COVID-19, the median duration of viral RNA shedding from oropharyngeal specimens was 20 days (range of 8 to 37 days) [36]. Viral RNA levels appear to be higher in the beginning of the infection compared with the end of illness, which raises the possibility that transmission might be more likely in the earlier stage of infection, but additional data are needed to confirm this hypothesis. Finally, patient clinically recovered from COVID-19 doesn't mean that no longer infection will produce by SARS-CoV-2, patient stay contagious 8 days after recovering, so extend the quarantine 2 weeks is indispensable also for the patients with risqué factors like hypertension, diabetic or cardio vascular diseases, should be extend the quarantine for 37 days.

Illness severity and effect of age

According the Chinese Center for Disease Control and Prevention a report included around 44,500 confirmed infections with an estimation of disease severity [37]: Mild (no or mild pneumonia), Severe disease (e.g. with dyspnea, hypoxia, or > 50% lung involvement on imaging within 24 to 48 hours) and Critical disease (e.g. with respiratory failure, shock or multiorgan dysfunction), 81, 14 and 5% respectively. The overall case fatality rate was 2.3%; no deaths were reported among noncritical cases. Most fatal cases have occurred in patients with advanced age or underlying medical comorbidities (including cardiovascular disease, diabetes mellitus, chronic lung disease, hypertension, and cancer) [37]. In Italy, the median age of patients with infection was 64 years and the estimated fatality case rate was 7.2% in mid-March [38]. In contrast, in South Korea the median age was in the 40s and the estimated case fatality rate in mid-March in was 0.9 percent [39]. All Individuals of any age can acquire (SARS-CoV-2) infection, adults of middle age and older are most commonly affected. Older age was associated with increased mortality, with fatality rate of 8 and 15% among those aged 70 to 79 years and 80 years or older, respectively. In the United States, 80% of deaths occurring in those aged ≥ 65 years. Children's infection appears to be uncommon; it is usually mild, severe cases have been reported [40]. Chinese report showed that only 2% of infections appeared in individuals younger than 20 years old [41], in South Korea, only 6.3% [39]. In a small study of 10 children in China, clinical illness was mild; fever disappeared within 24h, cough, had sore throat, 4 had evidence of pneumonia on CT, and none required oxygen [42]. In France, public health recently

published that the % of death was occurred at 57% of men and 43% of women, according the age the % of death was 0, 1, 6.3, 14.4 and 78.3 at the persons of 0 - 14, 15 - 44, 45 - 64, 65 - 74 and 75 years old and above respectively.

Symptoms of the diseases

Pneumonia appears to be the most frequent serious manifestation of infection, firstly characterized by fever, dry cough, dyspnea, and bilateral infiltrates on chest imaging [43]. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. A study of 138 patients with COVID-19 in Wuhan china describing pneumonia, the most common clinical features at the onset of illness were [45]: fever in 99%, fatigue in 70%, dry cough in 59%, Anorexia in 40%, Myalgia in 35%, Dyspnea in 31% and Sputum production in 27%. Other studies of patients from Wuhan with confirmed COVID-19 have reported a similar range of clinical findings but fever might not be a universal finding. In this study fever was reported in almost all patients, but approximately 20% had a very low grade fever < 38°C [44]. However high fever was noted during the hospitalization in 89% of patients [45]. The authors demonstrated that less common symptoms have included headache, sore throat and rhinorrhea were noted. In addition to respiratory symptoms, gastrointestinal symptoms (e.g. nausea and diarrhea) have also been reported; and in some patients, they may be the presenting complaint [43,44]. In a study of 62 patients with COVID-19 in the Zhejiang province of China, one had pneumonia, two developed dyspnea, and only one warranted mechanical ventilation [46]. Anosmia has been reported as a distinguishing symptom in patients who were eventually diagnosed with COVID-19 and with age under 40 years [47]; those who have been affected also report that sensory loss comes back within seven to 14 days.

Asymptomatic infections

The frequency of asymptomatic infections is unknown and have been described [48]. When COVID-19 was detected among passengers during the outbreak on the cruise ship Diamond Princess, All passengers and staff were screened for SARS-CoV-2, approximately 17% of the travelers on board tested positive were asymptomatic at the time of diagnosis on February 20 [49]. Even patients with asymptomatic infection may have objective clinical abnormalities [50]. Example study of 55 patients with asymptomatic infection identified through contact tracing, 67% had evidence of pneumonia by CT on admission; only two patients' developed hypoxia, and all recovered [50].

Complications

Some patients with mild symptoms may have amelioration after one week. Study of 138 patients hospitalized in Wuhan for pneumonia due to SARS-CoV-2, dyspnea appeared after mostly five days after the first symptoms appeared, and hospital admission occurred after a seven days [51]. The same study demonstrated that acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease, in 20% of patients this complication appeared after a median of eight days and in 12.3% on mechanical ventilation [51]. In Wuhan another study of 201 hospitalized patients with COVID-19 showed that 41% with age greater than 65 years, diabetes mellitus, and hypertension of developed ARDS [52]. Other complications have included arrhythmias, acute cardiac injury, and shock, were reported in 17, 7, and 9 percent, respectively [51]. In the United States, one-third severely ill patients admitted to the ICU are developed cardiomyopathy [53]. According to the WHO, recovery time appears to be around two weeks for mild infections and three to six weeks for severe disease [54]. Community acquired pneumonia, is one of the most fatal complication of COVID-19, study of 205 patients with COVID-19 demonstrated that the highest rates of positive viral RNA tests were reported from bronchoalveolar lavage (95%, 14 of 15 specimens) and sputum (72%, 72 of 104 specimens), compared with oropharyngeal swab (32%, 126 of 398 specimens) [55]. Data from this study suggested that viral RNA levels are higher and more frequently detected in nasal compared with oral specimens. SARS-CoV-2 RNA is detected by reverse-transcription polymerase chain reaction (RT-PCR generally confirms the diagnosis of COVID-19. Serologic tests should be able to identify patients who have either current or previous infection but a negative PCR test. A study showed from 58 patients with clinical, radiographic, and epidemiologic suspicious for COVID-19 but with negative SARS-CoV-2 PCR, an immunoglobulin (IgM) ELISA was positive in 93% [56]. The importance of testing for other pathogens including influenza and bacterial infection was recommended and this is very essential for management decisions.

Clinical suspicion and laboratory diagnosis

The first death due to coronaviruses has been reported after isolation of SARS-CoV from a patient with pneumonia in China. Like SARS CoV and MERS CoV that caused epidemics in the past years, COVID-19 is the cause of this fatal pandemic possible originated from Wuhan China. The first symptoms commonly appeared in COVID-19 are fever, cough and shortness of breath. According the Centers for Disease Control and Prevention (CDC) the possibility of infection caused SARS-CoV-2 we should be considered mainly: -patients with new onset fever and/or respiratory tract symptoms (e.g. cough, dyspnea). Patients with severe lower respiratory tract illness without any clear cause. Individual live in or/ have traveled within the prior 14 days to a location where there is of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Individual has had close contact (six feet approximately two meters) with a confirmed or suspected case of COVID-19 in the prior 14 days. The diagnosis cannot be definitively confirmed without microbiologic testing [57].

According the WHO, to test the presence of COVID-19 from different specimen collected form patient suspected. Nowadays different diagnosis method are implemented:

1. Nucleic acid amplification tests (NAAT).
2. SARS-CoV-2 RNA is detected by reverse-transcription polymerase chain reaction (RT-PCR) [58].
3. Serological testing to detect the presence of antibody anti SARS-CoV-2 (IgG, IgM), the initial sample collected in the first week of illness and the second ideally collected 2 - 4 weeks later [59].
4. Viral culture, virus isolation is not recommended as a routine diagnostic procedure.

Other laboratory findings

In patients with COVID-19, the main finding that the white blood cell count can vary and Leukopenia, leukocytosis, and lymphopenia have been reported and lymphopenia appears most common [60]. High level of Lactate dehydrogenase, ferritin and aminotransferase levels are described. High D-dimer levels and more severe lymphopenia have been associated with mortality [61]. Also recent study demonstrated that decrease in neutrophils counts, hemoglobin and the index values of serum ferritin.

Imaging findings

Chest CT in patients with COVID-19 commonly demonstrates ground-glass opacification with or without consolidative abnormalities, consistent with viral pneumonia, abnormalities are more likely to be bilateral, less findings include pleural thickening, pleural effusion, and lymphadenopathy [62].

Peoples in priority to testes for COVID-19:

1. Hospitalized patients to inform infection control decisions.
2. Individuals with high exposure risk (e.g. recent travel to areas with community transmission, contact with patients with COVID-19, and work in the health care setting).
3. Critically ill patients with unexplained viral pneumonia or respiratory failure.
4. Any individual (including health care workers) with fever or features of a lower respiratory tract illness.
5. Individual with Close contact with confirmed COVID-19 within 14 days.
6. Individuals with fever or features of a lower respiratory tract illness who are also Immunosuppressed, older, or have underlying chronic health conditions.

7. Patients with unexplained fever and features of a lower respiratory tract illness.

8. Outpatients who meet criteria for influenza testing (e.g. fever, cough, and other suggestive respiratory symptoms plus comorbid conditions, such as diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, age > 50 years, immuno-compromising conditions); pregnant women.

9. Testing is for community surveillance [63].

Infection prevention and control (IPC)

The infection control department play a crucial role in the hospital for taking care about the patients with suspected or documented COVID-19 and to prevent the spread of the virus to the other patients and to the healthcare workers. In China, concerning COVID-19 a report of 138 patients with COVID-19 they founded that 43% acquired infection in the hospital setting [64]. Insufficient use of infection control procedures In Washington State resulted to the spread of infection to 81 residents, 34 staff members, and 14 visitors [65]. To prevent and reduce transmission of the infection in the community several measures are recommended:

- Carefully hand washing, Use of hand sanitizer 60 percent alcohol.
- Respiratory hygiene (e.g. covering the cough or sneeze).
- Avoiding touching the eyes, nose, and mouth before washing hand.
- Avoiding crowds and close contact with ill individuals.
- Cleaning and disinfecting objects and surfaces that are frequently touched.

Environmental decontamination

To decrease the spread of COVID-19 virus, environmental infection control procedures should be implemented (guidelines of the CDC and WHO). The importance of environmental disinfection was illustrated in a study from Singapore, in which viral RNA was detected on nearly all surfaces tested (handles, light switches, bed and handrails, interior doors and windows, toilet bowl, sink basin) in the airborne infection isolation room of a patient with symptomatic mild COVID-19 prior to routine cleaning [66]. Since a decades we observe that the most of beautiful touristic city I world especially in Europe suffering from a lack of hygiene, however if we know that the SARS-CoV-2 can persist on plastic surface at room temperature for six days. Various disinfectants (including ethanol at concentrations between 62 and 71 percent) inactivated a number of coronaviruses related to SARS-CoV-2 within one minute.

Treatment options

Lopinavir-ritonavir; Lopinavir-ritonavir appears to have little role in the treatment of SARS-CoV-2 infection. This combined protease inhibitor, which has primarily been used for HIV infection, has *in vitro* activity against the SARS-CoV [67].

Remdesivir is a novel nucleotide analogue that has activity against (SARS-CoV-2) *in vitro* and against those of (SARS and MERS-CoV). Any clinical impact of remdesivir on COVID-19 remains unknown [68].

Hydroxychloroquine/chloroquine and azithromycin

Study published in the International Journal of Antimicrobial Agents describes a trial demonstrated that combination of hydroxychloroquine with Azithromycin gives a 100% viral clearance of SARS-CoV-2 in 6 days [69]. Azithromycin is an Antibiotic from the Macrolide group, it was recorded to have antiviral [70] and anti-inflammatory effects [71]. The reason behind having a significantly improved viral clearance when Azithromycin is added to Hydrochloroquine can purely be due to the action of Azithromycin [72]. For this reason, Azithromycin alone may be sufficient to clear the virus at the initial stage of the disease.

In vitro old study demonstrated that the Chloroquine has strong antiviral effects on SARS-CoV infection of primate cells. This study demonstrated the increase of endosomal pH and the drug appears to interfere with terminal glycosylation of the cellular receptor (ACE 2). This may inhibit the binding of the virus to its receptor on the host cells and inhibit virus entry when the cells are treated with NH4Cl and Chloroquine and inhibits the virus spread and stop the infection [73].

Discussion and Recommendations

Two years back in 2018 the 100th anniversary of the deadly pandemic in human history. In 1918 - 1919, pandemic caused by the virus H1N1 influenza appeared around the globe and produced an estimated 50 - 100 million deaths associated with unexpected clinical and epidemiological features [74]. The descendants of this virus still as endemic influenza viruses and cause significant mortality each year. It is appear that our ability to expected influenza pandemics still not greater than it was a century ago, numerous scientific advances provide an important works include development of vaccines against antigenically of both current and future influenza viruses for limiting their severe disease and death. Improve diagnosis and treatment of influenza-associated pneumonia and improve effective prevention and control measures still a major's issue to defend the influenza pandemic like actual pandemic caused by SARS-CoV-2. In 2012 MERS-hCoV with 99% sequence similarity to the surface spike protein of human SARS-CoV which have been isolated in China from (*Paguma larvata*), a cat-like mammal closely related to the mongoose. Like SARS-CoV, MERS-CoV is a zoonotic virus transmitted from animals to humans. Bats are the likely natural reservoir of MERS-CoV, and two mutations appeared to play critical roles in the eventual bat-to-human transmission of MERS-CoV [75]. Dromedary camels are believed to be an important reservoir host of MERS-CoV and they appear to be the only animal host responsible for human infections [76]. MERS-hCoV was spread in Saudi Arabia then transmitted to for more than 27 countries in the world. The virus called Middle East respiratory syndrome caused more than 2500 infection and 900 death around (35%) mortality. In late 2019, a novel coronavirus, now designated SARS-CoV-2, was identified as the cause of an outbreak of acute respiratory illness in Wuhan, a city in China. On 11 February 2020, the World Health Organization (WHO) announced a name for the new coronavirus disease COVID-19 and lately on March 11 declared the COVID-19 outbreak a global pandemic. However within 3 month from December 31 to March 31, 2020 more than 900000 total infected cases and 45000 death worldwide, which mean 5% mortality, the question raised here why this % is more in some country Italy around 12%, Spain 9%, France around 7% and in china the origin of the outbreak stopped at maximum 4.5%. Also, this % different by age. One study demonstrated the difference of mortality between Italy and China with different age (0 - 69), (70 - 79) and (80 and above) the % of mortality was (3, 3), (2, 7) and (20, 15) respectively. This difference perhaps explain by the high % of population who has more than 70 years old in Italy 37.6% in Italy comparing to 11.9% in china. As the pandemic caused by H1N1 virus of 1918 - 1919 was spread very fast, we observe the same for the SARS-CoV-2 caused actual fatal pandemic with high reproduction rate (1:3.28) [77]. There is a lot of information concerning the SARS-CoV-2, must be elucidated like the host, the origin of the first case, the exact sequences viral, the mechanism of viral pathogenicity of this virus and the role of the receptors in this mechanism. Also, as the SARS-COV in 2003 and MERS-COV since 2012 no vaccine was produced and no any specific medication was discovered tell today [78] however we will be able to find one for SARS-CoV-2? Which belong to the same family and has 99% identity to SARS-CoV. On the other hand the discussion about the treatment of covid-19, several studies propose certain antiviral as Lopinavir-ritonavir which appears to have a role in the treatment of SARS-CoV-2 infection. This combined protease inhibitor, which has primarily been used for HIV infection, has *in vitro* activity against the SARS-CoV [67]. However, HIV and SARS-CoV-2 have distinct proteases, bringing into question the target specificity and usefulness of such drugs in treating COVID-19. Another anti-viral Remdesivir; is a novel nucleotide analogue that has activity against (SARS-CoV-2) in vitro and against those of (SARS and MERS-CoV). Any clinical impact of remdesivir on COVID-19 remains unknown [68]. Study showed that Hydroxychloroquine/Chloroquine and Azithromycin combination demonstrated an excellent therapeutic activity against COVID-19. Until now there is cautious optimism that (hydroxy) Chloroquine may have prophylactic and/or therapeutic effects against COVID-19. A trial in this study demonstrated that this combination produced 100% viral clearance of SARS-CoV-2 in 6 days [69], however, the effects of azithromycin alone were not assessed. Recent study propose new finding about the pathology of the SARS-CoV-2 on the hemoglobin , firstly the image of ground glass opacity (GGO) appear on the chest x-ray at critical patient with low hemoglobin, second by viral experiments, they found that the viral proteins can bind to porphyrin, attack hemes and attack hemoglobin.

The question about the reinfection of patient after recovery, study published in physician's first watch by David G. Fairchild in the issue: April 13 2020, in this study they found that the level of antibodies to SARS-CoV-2 in patient after recovery widely varied, a proportion of

patients infected would recover without developing high titer of virus specific antibodies how these patients recovered without the help of antibodies and whether they were at risk of reinfection.

My question now that how the scientist will be react if new mutation more severe than SARS-CoV-2 produced with the presence of all difficulty in all the country to face this pandemic. Another problem more serious the presence of bacteria resistant to the most of antibiotic in the market in all of the health facility and in all of the globe called multi-drug, extensive and pan drug resistant organism (MDR, XDR and PANDR). The WHO published the listed bacteria in question and requested in priority to find some molecule of antibiotic anti these bacteria. Our question concerning the patients of COVID-19 who hospitalized for community acquired pneumonia, here there is an even larger threat suspicion behind the current outbreak, one that is already killing hundreds of thousands of people around the world and that will complicate the care of many Covid-19 patients. This is the hidden threat from antibiotic resistance bacteria like *Acinetobacter baumannii* that are not killed by standard antibiotics [80]. Regrettable, actually, the pipeline of drugs to manage these deadly infections is nearly dry. The so-called superbugs that cause these infections grow strongly in hospitals and medical facilities, putting all patients in high risqué and increase the morbidity and mortality rate. Even thought, antibiotic resistance never getting our attention in the same way that SARS-CoV-2 has and antibiotic-resistant bacteria present a growing global menace. I think to prove this fact a good studies should be realized to know exactly the cause real of mortality during the hospitalized patients with COVID-19 during this outbreak. My advice, for the actual pandemic is; stopping the pandemic by stopping the spread of the virus through direct contact between the patients and carrier and those who are healthy from the illness. For the future, the governments in all the countries and the united nation health agencies requested to set the highest annual budget for scientific and medical research for the development of diagnostic and therapeutic means and means of protection against various menace; viral, bacterial or toxic that may sweep the world in any time. The haut authority in all the country around the globe should seriously working to create special ministry that aware of a systematic program to teach people different methods of hygiene from firstly personal hygiene to reach the cleanliness streets and beautiful and touristic cities so that we can limit the spread of deadly firsts. Finally, and as we come together to fight today's Covid-19 pandemic, we should also look how to protect from the next one. We cannot be careless, and we cannot be satisfied, especially about antibiotic resistance bugs. We must put measures in place to ensure that we have the antibiotics we need today and in the future. The time to act is now.

Conclusion

SARS-CoV-2 as new coronavirus remains mysterious and need more studies to be explorer in term of its origin, rapidity of spread, physiopathology (Acute respiratory distress syndrome), or/and attack the hemoglobin which lead to (less hemoglobin to carry oxygen and carbon dioxide). Up today there is no specific medication or vaccine could be active against COVID-19. Concerning the different antiviral (Lopinavir-ritonavir) and anti-plasmodium (Chloroquine and hydroxy-Chloroquine) treatment there is contradictory scientific studies concerning their activity on the treatment of COVID-19 The question about the reinfection of patient after recovery, study published in (physician's first watch by David G. Fairchild in the issue: April 13 2020) found that the level of antibodies to SARS-CoV-2 in patient after recovery widely varied, a proportion of patients infected would recover without developing high titer of virus specific antibodies how these patients recovered without the help of antibodies and whether they were at risk of reinfection. Finally, the serious illness appeared in children in UK and in FRANCE with a rare syndrome that could be linked to SARS-CoV-2 with reported cases showing abdominal pain, gastrointestinal symptoms and cardiac inflammation. Patients presenting toxic shock syndrome and a typical Kawasaki disease.

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