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Overview of The 2019 Novel Coronavirus (2019-nCoV): The Pathogen of Severe Specific Contagious Pneumonia (SSCP)

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Abstract

In late December 2019 a previous unidentified coronavirus, currently named as the 2019 novel coronavirus (2019-nCoV), emerged from Wuhan, China and resulted in a formidable outbreak in many cities in China and expanding globally, including Thailand, Republic of Korea, Japan, USA, Philippines, Viet Nam, and our country (as of 2/6/2020 at least 25 countries). The disease is officially named as the Severe Specific Contagious Pneumonia (SSCP) in 1/15/2019 and is a notifiable communicable disease of the 5th category by the Taiwan CDC, the Ministry of Health. SSCP is a potential zoonotic disease with low to moderate (estimated 2-5%) mortality rate. Person-to-person transmission may occur through droplet or contact transmission and jeopardized first-line healthcare workers if lack of stringent infection control or no proper personal protective equipment available. Currently, there is no definite treatment for SSCP although some drugs are under investigation. To promptly identify patients and prevent further spreading, physicians should be aware of travel or contact history for patients with compatible symptoms

Keywords: Coronavirus, Outbreak, Pneumonia, Zoonosis

1.Introduction

In late December 2019, an outbreak of a mysterious pneumonia characterized by fever, dry cough, and fatigue, and occasional gastrointestinal symptoms happened in a seafood wholesale wet market, the Huanan Seafood Wholesale Market, in Wuhan, Hubei, China.[1] The initial outbreak was reported in the market in December, 2019 and involved about 66% of the staff there. The market was shut down on Jan. 1, 2020, after the announcement of an epidemiological alert by the local health authority on Dec. 31, 2019. However, in the following month (Jan.) thousands of people in China, including many provinces, (such as Hubei, Zhejiang, Guangdong, Henan, Hunan etc.) and cities (Beijing and Shanghai) were attacked by the rampant spreading of the diseases.[2] Furthermore, the disease was exported to other countries, such as Thailand, Japan, Republic of Korea, Viet Nam, Germany, USA, and Singapore. The first case reported in our country was on Jan 23, 2019. As of Feb. 6, 2020, a total of 28276 confirmed cases with 565 deaths globally were documented by WHO, involving at least 25 countries.[3] The pathogen of the outbreak was later identified as a novel beta-coronavirus, named 2019 novel coronavirus (2019-nCoV) and recalled to our mind the terrible memory of seventeen years ago- the severe acute respiratory syndrome (SARS-2003, caused by another beta-coronavirus).

In 2003, a new coronavirus, the etiology of a mysterious pneumonia, also originated from southeast China, especially Guangdong province, and was named SARS coronavirus that fulfilled the Koch's postulate.[4] The mortality rate caused by the virus was around 10-15%.[5,6] Through the years the medical facilities have been improved, nevertheless, no proper treatment or vaccine is available for the SARS.[6] The emergence of another outbreak in 2012 of novel coronavirus in Middle East shared similar features with the outbreak in 2003.[7] Both were caused by *coronavirus* but the intermediate host for MERS is thought to be the dromedary camel and the mortality can be up to 37%.[5]

The initial clinical manifestations for both SARS and MERS are usually nonspecific except the majority of patients presented with fever and respiratory symptoms. Unprotected hospital staff that exposed to patients' droplets or through contact prone to be infected and nosocomial infections ensue.[1,6] Furthermore, cases associated with travel had been identified for SARS, MERS, and 2019-nCoV.(5,8-11) Because of global transportation and the popularity of tourism, 2019-nCoV is a genuine threat to Taiwan.

2.Virology

Coronavirus virus is an enveloped, negative single strand RNA virus. It belongs to the *Orthocoronavirinae* subfamily, as the name, with the characteristic "crown-like" spikes on their surfaces.[5] Together with SARS-CoV, bat SARS-like CoV, and others, they fall into the genus beta-coronavirus. The SSCP (caused by 2019-nCoV infection) is classified as a fifth-category notifiable communicable disease in Taiwan on Jan. 15, 2019.[12] The genus beta-coronavirus can be divided into several subgroups. The 2019-nCoV, SARS-CoV and bat SARS-like CoV belong to *Sarbecovirus*, while the MERS-CoV *Merbecovirus*.[13] SARS-CoV, MERS-CoV, and 2019-nCoV all cause diseases in humans but each subgroup may have mild different biologic characteristic and virulence.[5-7]

The exact origin, location, and natural reservoir of the 2019-nCoV remain unclear, although it is believed that the virus is zoonotic and bats may be the culprits because of sequence identity to the bat-CoV.[5,13] According to previous studies on the SARS- and MERS-CoV, epidemiological investigations, their natural reservoir is bat while palm civet or raccoon dog may be the intermediate (or susceptible) host for SARS-CoV and the dromedary camel for MERS-CoV.[5,13] A field study for the SARS-CoV on palm civet ruled out the possibility as the natural reservoir (low positive rate), instead, the prevalence of bat coronavirus among wild life is high and it share a certain

sequence identity with the human SARS-CoV.[14] Therefore, bats are considered the natural host reservoir of SARS-like coronavirus.[13] However, the origin or natural host for the 2019-nCoV is not clear, although it might come from a kind of wild life in the wet market.[1] Theoretically, if people contact or eat the reservoir or infected animal, they could be infected. However, to result in large scaled person-to-person transmission as in the past SARS outbreak, the virus must spread efficiently. Initially, the 2019-CoV outbreak was reported as limited person-to-person transmission and a contaminated source from infected or sick wild animals in the wet market may be the common origin.[1,2] But more and more evidences came out with clusters of outbreaks among family confirmed the possibility of person-to-person transmission.[8,10,11,15,16] In addition, the involvement of human angiotensin-converting enzyme 2 (hACE2) as the cellular receptor (like SARS) made droplet transmission to the lower respiratory tract possible.[5,17] Furthermore, contact transmission like SARS is also likely although the survival time in the environment for the 2019-nCoV is not clear at present. Currently, there was no evidence of air-borne transmission. Viral RNAs could be found in nasal discharge, sputum, and sometimes blood or feces. [1,9,10,13,15] But can oral-fecal transmission happen has not yet been confirmed. Once people are infected by the 2019-nCoV, it is believed that, like SARS, there is no infectivity until the onset of symptoms.[15] However, one report describes infection from an asymptomatic contact but the investigation was not solid.[10] The infectious doses for 2019-nCoV is not clear but high viral load up to 10^8 copies/mL in patient's sputum has been reported.[10] The viral load increases initially and still can be detected 12 days after onset of symptoms.[9] Therefore, the infectivity of patients with 2019-nCoV may last for about 2 weeks. However, if infectious viral particles from patients do exist at the later stage requires validation.

3.Epidemiology (Table 1)

The illness onset of the first laboratory-confirmed case of 2019-nCoV infection was on Dec. 1, 2019 in Wuhan, China.[1] Initially, an outbreak involving a local market, the Huanan Seafood Market, with at least 41 people was reported.[1] The local health authority issued an 'epidemiological alert' on Dec. 31, 2019 and the market was shut down on Jan 1, 2020. A total of 59 suspected cases with fever and dry cough were referred to a designated hospital (the Jin Yin-tan Hospital). Of the 59 suspected cases, forty-one patients were confirmed by next-generation sequencing or real-time RT-PCR. Twenty-seven (66%, 27/41) patients had history of Huanan Seafood Market exposure.[1] However, there is a caveat that the first case on Dec. 1 did not show history of Huanan Seafood Market exposure and the subsequent cases started on Dec. 10, nine day later. In the following days, a burst of cases was spreading from Wuhan to the whole Hubei province. Subsequently, many cities and provinces were attacked by this virus. One of the reasons may be due to the heavy transportation load during the Chinese Lunar New Year (on Jan 25) period. The first exported case was into Thailand on Jan. 13, 2020. However, the disease spread rapidly and globally. Not only familial clusters but also outbreaks in ocean liners were reported. As of Feb. 6, 2020, a total of 28,276 confirmed cases with 565 deaths globally were documented by WHO, involving at least 25 countries.[3] The WHO issued an public health emergencies of international concern (PHEIC) alarm on Jan 30, 2020. Many stringent quarantine procedures and fever surveillance were underway. The initial mortality rates for patients in the hospital were estimated to be 11-15%,[1,15] but more recent data were 2-3%. It is very likely that person-to-person transmissions occur via droplets and contact. Nosocomial infections in the healthcare facilities did happen and stress the importance of good infection control.

4.Clinical Manifestations

SSCP has a mean incubation period of 5.2 days (95% confidence interval, 4.1-7.0).[16] The infection is acute without any carrier status. Symptoms usually begin with non-specific syndromes, including fever, dry cough, and fatigue. Multiple systems may be involved, including respiratory (cough, short of breath, sore throat, rhinorrhea, , hemoptysis, and chest pain), gastrointestinal (diarrhea, nausea and vomiting), musculoskeletal (muscle ache) and neurologic (headache or confusion). More common signs and symptoms are fever (83-98%), cough (76-82%), and short of breath (31-55%). There were about 15% with fever, cough, and short of breath.[1,15] Conjunctival injection was not reported in the early series and cases with age under 18 were few. After onset of illness the symptoms are somehow mild and the median time to first hospital admission is 7.0 days (4.0-8.0). But the disease progresses to short of breath (~8 days), acute respiratory distress syndrome (ARDS) (~9 days), and to mechanical ventilation (~10.5 days) in about 39% patients.(1) Patients with fatal disease develop ARDS and worsened in a short period of time and died of multiple organ failure.[1,15] The mortality rate in the early series of hospitalized patients was 11-15%, but the later statistics was 2-3%.[1,15,16,17]

The 2019-nCoV virus may enter the host through respiratory tract or mucosal surfaces (such as conjunctiva). Oral-fecal transmission has not been confirmed. The virus has a preferential tropism to human airway epithelial cells and the cellular receptor, like SARS, is ACE2.[18] However, the pathological changes of the disease and its pathogenesis in human is not clearly elucidated. Theoretically lungs are the major involved organ. Will the virus replicate in other part of the body is not clear.

5.Diagnosis

The SSCP usually presents as an acute viral respiratory tract infection and many differential diagnoses related to common viral pneumonia should be considered, such as influenza, parainfluenza, adenovirus infection, respiratory syncytial virus infection, metapneumovirus infection, and atypical pathogens, such as *mycoplasma pneumoniae* and *clamydophila pneumoniae* infections etc.[1,8] Therefore, it is crucial to trace the travel and exposure history when approaching a suspected patient back from an epidemic area. In addition, commercial respiratory syndromic diagnostic kits that detect multiple etiological agents (such as Filmarray Respiratory Panel) may help timely differential diagnosis.

Laboratory diagnosis for SSCP should be performed in a well-equipped laboratory with up to biosafety level 3 facilities for the viral culture. In Taiwan, SSCP is a fifth-category notifiable communicable disease and should be reported to Taiwan Centers of Disease Control (CDC) within 24 hours. The definitions of reported SSCP include (as of Jan. 31, 2020): 1. Clinical conditions, met any following one (1.1) febrile illness ($\geq$ 38 degrees Celsius) or acute respiratory infection (1.2) clinical, radiological, or pathological evidence of pneumonia. 2. Laboratory conditions, with any of the following: (2.1) clinical specimen (nasopharyngeal swab, sputum, or lower respiratory tract aspirates etc.) that were isolated and identified as 2019-nCoV (2.2) Clinical specimen that show positive by reverse transcription-polymerase chain reaction (RT-PCR) 3. Epidemiologic conditions, with any of the following 14 days before onset of symptoms (3.1) History of travel history from or evidence of contacting patients with fever or respiratory symptoms in the epidemic area of SSCP (currently Hubei, including Wuhan) (3.2) History of travel from or living in other part of mainland China (excluding Hong Kong and Macaw) (3.3) History of contact with probable or confirmed SSCP cases, including health provider, under the same roof, direct contact of the mucus or

body fluid. Once the case fulfills (1) any clinical and epidemiologic condition 3.1 or 3.3 or (2) clinical condition 1.2 and epidemiologic condition 3.2 or (3) any laboratory condition, the patient should be reported to Taiwan CDC within 24 hours. If the first laboratory report is negative but patients' symptoms persist with explainable etiology, a second sample should be examined 24 hours later in case of first negative to rule out false negative result.(Taiwan CDC guideline)

Confirmatory laboratory diagnosis usually rely on a real-time reverse transcription PCR (RT-PCR) assay to detect viral RNA by targeting a consensus RdRp region of pan beta-CoV or other more specific regions (such as E or N region) [1,13,15] Routine laboratory data in the early stage of SSCP epidemic are similar to common viral infection: lymphopenia, prolonged prothrombin time, elevated D-dimer, liver enzymes (alanine aminotransferase), total bilirubin, and lactate dehydrogenase, with worsening data in ICU cases.[1] Leukocytosis may occur if complicated with secondary bacterial infection. Considering patients' and laboratory safety, physicians should carefully evaluate the necessity of frequent blood sampling and conduct aspiration to prevent the risk of unexpected exposure.

6.Treatment

Currently there is no validated treatment for SSCP. The main strategies are symptomatic and supportive care, such as keeping vital signs, maintaining oxygen saturation and blood pressure, and treating complications, such as secondary infections or organs failure.

Because of the potential mortality of SSCP, many investigational treatments are underway:

1. Remdesivir: The experimental drug is a novel nucleotide analogue prodrug in development by Gilead Sciences, Inc.. It is an unapproved anti-viral drug being developed for Ebola and SARS. In a case report on the first case of 2019-nCoV in the United States administering remdesivir for compassionate use on day 11 after illness resulted in decreasing viral loads in nasopharyngeal and oropharyngeal samples and the patient's clinical condition improved.[9] However, randomized controlled trials are needed to determine the safety and efficacy of this drug for treatment of patients with 2019-nCoV infection.
2. Convalescent therapies (plasma from recovered SSCP patients): This strategy had been used to support passive immunization. Based on the studies from MERS, the therapeutic agents with potential benefits include convalescent plasma, interferon-beta/ribavirin combination therapy and lopinavir.(JAC, Yin Mo, Dale Fisher, 2016) However, there are no experience on SSCP and no randomized controlled clinical trials for this management at present.
3. Antiviral drugs: lopinavir/ritonavir and ribavirin had been tried to treat SARS disease with apparent favorable clinical response.[19] *In vitro* antiviral activity against SARS associated coronavirus at 48 hours for lopinavir and ribavirin was demonstrated at concentrations of 4 ug/mL and 50 ug/mL, respectively. A recent report found uncanny similarity of unique insertions in the 2019-nCoV spike protein to HIV-1 gp120 and Gag.[20] Will anti-HIV drugs affect the 2019-nCoV treatment outcome? Further randomized controlled trials in patients with SSCP are mandatory.
4. Vaccine: There is currently no vaccine available for preventing 2019-nCoV infection. The spike protein may serve as a vaccine candidate, but the effect to human requires further evaluation.

7.Prevention

Since there are no standard treatments for SSCP, it is important to avoid infection or further spreading. For general population, travel to epidemic area of SSCP (mainly in China, especially Wuhan, and Hong Kong and Macaw), contact or eating wild animal is dissuaded. For those who had history of travel from epidemic area in recent 14 days, body temperature monitor and self-surveillance for 14 days should be performed. If compatible symptoms developed, designated transportation is recommended to prevent unprotected exposure. For healthcare workers, personal protective equipment should be put on and taken off properly while caring a probable or confirmed patients. Stringent protection procedures should be conducted for high risk procedures (such as endoscopy, Ambu bagging, and endotracheal tube intubation). Once exposed to blood or body fluids of the patient unprotected, the healthcare workers should flush thoroughly the exposure site by water or soap. Afterward, body temperature should be monitored for 14 days. The confirmed case should be isolated (prefer a negative pressure isolation room or, alternatively, a single room with good ventilation). Under the circumstances of symptoms resolved for 24 hours and consecutive two negative results, isolation could be released. Corpses should be burned or buried deep.

Treatments effective against coronavirus include steam and heat. The virus is susceptible to many active ingredients (A. I.), such as sodium hypochlorite (0.1-0.5%), 70% ethyl alcohol, povidone-iodine (1% iodine), chloroxylenol (0.24%), 50% isopropanol., 0.05% benzalkonium chloride, 1% cresol soap, or hydrogen peroxide (0.5-7.0%) etc.[21] According to the WHO recommendations for Ebola virus (RG4) disinfection, the environment with spills of blood or body fluids could be cleaned up with 1:10 dilution of 5.25% household bleach for 10 minutes. For surfaces that may corrode or discolor, the recommendation was careful cleaning to remove visible stains

followed by contact with a 1:100 dilution of 5.25% household bleach for more than 10 minutes.[22]

8.Conclusions

2019-nCoV infection is a zoonotic disease with low to moderate mortality rate. Currently, there is no standard treatment for the disease and supportive treatment was the only strategy. Although many experimental trials are on the way, the best we can do to prevent a rampant outbreak is stringent infection control operation. Clinicians should consider the possibility of 2019-nCoV virus infection in persons with travel or exposure history with compatible incubation period and presenting symptoms. First-line healthcare providers should be highly aware of appropriate infection prevention measures for suspected patients.

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Table 1. Chronological list of 2019-nCoV global outbreak

Year	Date	Event
2019	November ?	Mysterious pneumonia in Wuhan, Hubei, China
	December 1	The first confirmed nCoV case in Wuhan (no Huanan seafood market exposure)
	December 10	The first confirmed nCoV case with Huanan seafood market exposure
	December 31	An epidemiological alert by local agency
2020	January 1	Huanan seafood market shut down
	January 13	The first nCoV case in Thailand (Wuhan history)
	January 15	A notifiable communicable disease (by Taiwan CDC)
	January 21	The first nCoV case in Taiwan (Wuhan history)
	January 30	Public health emergencies of international concern (PHEIC) alarm by WHO
	February 6	28,276 confirmed nCoV cases, 565 deaths, at least 25 countries involved

nCoV: novel coronavirus
CDC: center of disease control
WHO: the World Health Organization