Clinical Challenges in an Outbreak of COVID-19 in Wuhan, China: Concerns from Frontiers

Yao Wang 1 · Luwen Wang 1 · Xun Li 1 · Zuojiong Gong 1

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Abstract
Purpose of Review In December 2019, outbreaks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected pneumonia patients were discovered in Wuhan City, Hubei Province, China. With the spread of the epidemic, new cases have been found in other regions of China and abroad. This review summarizes the current coronavirus disease 2019 (COVID-19) transmission pathways, high-risk factors, diagnostic points, pathogenesis, and therapeutic drugs to provide the prevention and treatment theories for COVID-19.

Recent Findings COVID-19 is highly contagious and is transmitted mainly through the respiratory tract. Most patients with SARS-CoV-2 infection have milder symptoms. Some patients will have mild disease in the early stage, suddenly exacerbate later, and eventually die of multiple organ failure caused by cytokine storm. The basis for clinical diagnosis of COVID-19 is not just the detection of viral nucleic acids as the gold standard. The diagnostic accuracy improves when viral nucleic acid test is combined with clinical symptoms, CT results, and biochemical tests. For the treatment of COVID-19, the specific antiviral agents have not been developed, except for symptomatic supportive treatments.

Summary The methods for detecting SARS-CoV-2 infection have become increasingly mature, but specific antiviral drugs for the treatment of COVID-19 have not yet been developed. Treatment must pay attention to the cytokine storm that leads to the seriousness of COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Clinical challenges

Introduction
Since December 2019, many cases of viral pneumonia have been found in Wuhan City, Hubei Province, China. It has been determined that the viral infection is transmitted from human to human, which seriously affects public health safety [1]. The World Health Organization (WHO) has named the new coronavirus that caused the Wuhan pneumonia epidemic for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and declared a pandemic. The new coronavirus-infected disease was named coronavirus disease 2019 (COVID-19).

SARS-CoV-2 belongs to the genus beta coronavirus and has higher homology with severe acute respiratory syndromes-associated coronavirus (SARS-CoV) than with Middle East respiratory syndrome-associated coronavirus (MERS-CoV) [2, 3]. SARS-CoV-2 is distinct from SARS-CoV, but the common outgroup with SARS-CoV is a HPU9-1 coronavirus parasitic to fruit bats [2]. It was recently found that the similarity between SARS-CoV-2 and RaTG13 isolated from Yunnan chrysanthemum bat was 96.2% [4]. Therefore, the natural host of the virus is almost certainly bat. However, during the transmission of SARS-CoV-2 to humans by bats, snakes [5], mink [6], and pangolins may be intermediate hosts. The information about the intermediate host still awaits clarification. It is worth noting that asymptomatic infection may also be a potential way of transmission. Wuhan South China Seafood Market is currently considered...
to be the origin of SARS-CoV-2 [7]. However, it remains unclear if the South China Seafood Market is the sole source of the virus [8]. This review summarizes the current COVID-19 transmission pathways, high-risk factors, diagnostic points, pathogenesis, and therapeutic drugs to provide a plan for the scientific control of COVID-19.

Ways of Transmission

The SARS-CoV-2 transmission routes are mainly direct transmission, aerosol transmission, and contact transmission. The public health information is still that droplets are the main route of transmission. The size of the droplet cores containing SARS-CoV-2 is in the sub-micron to micron range. Sub-micron range droplets necessarily imply aerosol transmission. Larger droplets, as one sees with droplet/contact transmission, are more in the > 10 um range (lots of debate around the exact size of “droplets” that can aerosolize, but most would agree that those < 2 um would certainly fall into that category of aerosolization). SARS-CoV-2 in the droplet core is protected by a protein envelope, which may remain active for a long time. If the droplet is aerosolized and inhaled by humans, it may cause infection. It is also worth noting that SARS-CoV-2 can be detected in the conjunctival sac of COVID-19 patients [9]. Meanwhile, an analysis of 9 pregnant women infected with COVID-19 found that there was no vertical transmission between mothers and infants [10].

Characteristics of High-Risk Warning and Deaths

A study involving 1099 patients in China found that all populations were susceptible to SARS-CoV-2, with an average age of 47.0 years (35.0–58.0). The proportion of patients ≥ 65 yrs. was 153/1011 (15.1%) [1]. Medical staff is also a high-risk group. The peak period for medical staff cases occurred on January 28. Among the 422 medical institutions providing diagnosis and treatment services for patients with COVID-19, a total of 3019 medical staff were infected with the new coronavirus (1716 confirmed cases), of whom 5 died and the crude case fatality rate was 0.3%. There may be infections from non-occupational exposures. These data confirmed that medical staffs were concentrated in Wuhan (64%) and the rest of Hubei (23.3%). The proportion of severe cases diagnosed by medical staff was 17.7% in Wuhan, 10.4% in Hubei, and 7.0% outside Hubei nationwide. On the whole, most cases were mild (85.4%) [11].

The risk of COVID-19 death is mainly related to age, underlying chronic disease, and the time interval from the onset of initial symptoms to dyspnea [12]. The deaths caused by SARS-CoV-2 mainly occur in elderly patients and usually the elderly with underlying diseases [13]. A study of statistical analysis of public case data found that the median time from symptom onset to death was 13.8 days and the median time from hospitalization to death was 8.3 days [14]. The highest crude case fatality rate in the age group ≥ 80 years was 14.8%. For the risk of chronic disease, the cardiovascular mortality rate was 10.5%, diabetes was 7.3%, chronic respiratory disease was 6.3%, hypertension was 6.0%, and cancer was 5.6%. Severe cases accounted for 13.8%, and critical cases (includes both mechanically ventilated patients and anyone admitted to ICU) accounted for 4.7%. The crude case fatality rate in critical cases was 49% [11].

The gold standard for diagnosing COVID-19: Virological Testing or Combined with Computed Tomography (CT)?

WHO has launched the “Clinical management of severe acute respiratory infection when SARS-CoV-2 infection is suspected: Interim Guidance” (referred as “WHO guidelines”) to strengthen outbreak control and patient management [15]. The gold standard for WHO guidelines emphasizes the SARS-CoV-2 nucleic acid testing. However, there were large numbers of suspected patients with clinical symptoms, pulmonary imaging findings, and abnormal routine blood tests, for whom the virological nucleic acid test is negative. Therefore, the National Health and Medical Commission of China issued the “Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 5)” (referred as “Chinese Guideline”) has re-defined the confirmed cases [16].

The patients in other provinces outside Hubei were still divided into “suspected cases” and “confirmed cases.” However, the patients who have no clear epidemiological history but fulfilled 3 of the clinical manifestations, namely, “fever and/or respiratory symptoms,” “imaging characteristics of pneumonia,” and “the total number of white blood cells was normal or decreased, or the lymphocyte count was reduced in the early onset”, could be defined as confirmed cases awaiting verification. The diagnostic criteria for confirmed cases require positive nucleic acid results.

It is particularly noteworthy that for cases in Hubei Province, a new category of “clinically diagnosed cases” has been added. Suspected cases with pneumonia imaging features are defined “clinically diagnosed cases.” The “suspected case” standard is defined as a case that meets the two clinical manifestations of “fever and/or respiratory symptoms” and “normal or reduced white blood cell count in early onset, or decreased lymphocyte count” whether there is epidemiological link. In other words, the diagnostic criteria for suspected cases in Hubei Province have been relaxed. The diagnostic criteria for confirmed cases have not changed.
As a result, the number of confirmed cases in Hubei Province dramatically rose to 14,840 on the second day after the Chinese Guideline being issued (that is, February 13, 2020). In our opinion, nucleic acid testing is no longer the gold standard for the diagnosis of COVID-19 infection. For the huge number of patients with negative nucleic acid testing results, reasonable use of CT and clinical symptoms as a diagnostic basis is more conducive to the prevention and control of COVID-19.

Possible Pathogenesis for COVID-19: Cytokine Storm

The “cytokine storm” was first proposed in 1993 in graft versus host disease (GVHD) [17]. Pro-inflammatory factors include interleukin (IL), chemokines, colony-stimulating factors (CSFs), and tumor necrosis factor (TNF). When the immune system is activated due to infection, drugs, or autoimmune diseases, pro-inflammatory factors are activated and recruit other immune cells to secrete more cytokines, thus forming a positive feedback cycle. A large number of pro-inflammatory factors may be secreted, leading to unlimited positive feedback cycles, eventually resulting in cytokine storm [18]. Once cytokine storm occurs, it can quickly cause single or multiple organ failure and eventually threaten life [18].

The prediction of cytokine storm mainly depends on the detection of elevated inflammatory factors in blood. A retrospective study of 41 SARS-CoV-2 infected patients found that the expressions of IL-2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, TNFα, and other pro-inflammatory factors in plasma were significantly higher in ICU patients than in non-ICU patients [19]. An analysis of the status of cellular immunity and cytokines in 123 COVID-19 patients found that CD4 + T (52.90% vs. 95.24%) and CD8 + T (28.40% vs. 61.90%) were significantly lower in ICU patients than non-ICU patients. T lymphocytes are more likely to be suppressed in the severe patients [20]. The reduction of NK cells in non-ICU patient group was 34.31% and the ICU patient group was 47.62%, indicating that the activity of NK cells was limited to some extent [20]. The IL4, IL10, IL17, and TNF of 21 patients in ICU patient group were all in the normal range. There was no significant difference between ICU and non-ICU patient groups for TNF and IFN levels. The proportion of IL6 in ICU patient group was significantly higher than that in non-ICU patient group (76.19% vs. 30.39%) [20]. These data on inflammatory indicators suggest a cytokine storm in ICU patients, resulting in a worse overall prognosis.

For the specific process of cytokine storm (Fig. 1), SARS-CoV-2 infects lung epithelial cells by binding with ACE2 receptors [21]. Cell death, apoptosis, and pyroptosis occur due to infection-induced production of pro-inflammatory cytokines (IL1β, IL6, IL8) and chemokines (IP10, MCP1) [19, 22]. These factors mediate the early recruitment of monocytes/macrophages in lung and promote the production of a unique set of chemokines by activated macrophages, such as MIG, IP-10, and MCP-1 [19]. These chemokines further recruit neutrophils, monocytes, and T cells into lung tissue [23]. Activated T cells then migrate into the lung tissue and specifically destroy virus-infected lung cells by releasing perforin [19, 23]. It could lead to extensive tissue damage to the lung parenchyma and ARDS [24]. On the other hand, SARS-CoV-2 rapidly activates pathogenic T cells to produce cytokines such as granulocyte-macrophage colony-stimulating factors (GM-CSF) and IL6. GM-CSF will further activate CD14 + CD16+ inflammatory monocytes and produce a larger amount of IL6 and other inflammatory factors [25]. Thereby, it forms a cytokine storm, leading to severe immune damage to the lungs and other organs. In summary, the levels of CD4 + T and CD8 + T are generally low; the level of IL-6 is high in the severe patients. However, the “warning value” of CD4+ T, CD8 + T, and IL-6 still needs a large number of samples to confirm.

The main methods to treat cytokine storm are to eliminate the pathogens and suppress inflammatory responses. Specific drugs against SARS-CoV-2 are still in clinical trials, which will take several months to produce results [26]. Although the application of glucocorticoids can inhibit normal human immunity and delay the removal of coronavirus, for the severe patients caused by cytokine storm, the most commonly used and effective drug to directly reduce cytokine storm is still glucocorticoids [27, 28]. In addition, immunosuppressive agents, such as anti-IL-6 monoclonal antibody, gamma globulin, PPARs inhibitors, and sphingosine phosphate 1 (S1P1) receptors inhibitors, cyclooxygenase (COX) inhibitors, antioxidants, and anti-tumor necrosis factor therapy may be effective against cytokine storm [29, 30]. Although most cases have mild symptoms and good prognosis, cytokine storm is still a hidden danger in the mild patients with COVID-19. Early monitoring and early treatment are the best ways to eliminate this hidden danger.

Development and Evaluation of Antiviral Drugs

The development of vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon treatments, and small-molecule drugs for COVID-19 will take at least months or even years. Therefore, it is recommended to find antiviral drugs with therapeutic potential among the drugs approved in the market for the treatment of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). Nucleoside
analogs such as favipiravir, ribavirin, remdesivir, and galidesivir can block RNA synthesis of various RNA viruses including SARS-CoV-2 through targeted intervention with RNA polymerase [31]. Approved protease inhibitors, including disulfiram, lopinavir, and ritonavir, have activity against MERS-CoV and SARS-CoV [26].

**Favipiravir**

Favipiravir is a guanine analog approved for the treatment of influenza that effectively inhibits RNA viruses such as influenza virus, Ebolavirus, yellow fever virus, chikungunya virus, norovirus, and enterovirus [31]. Favipiravir is a nucleoside antiviral drug, and its mechanism of action has not been fully elucidated. Its target is a viral RNA-dependent RNA polymerase. After oral absorption, the drug is converted into a nucleoside triphosphate of biologically active favipiravir. Its structure is similar to purine, and it can compete with purine for virus RNA polymerase. Favipiravir’s nucleoside triphosphates can also be inserted into the viral RNA chain and induce fatal mutations in the virus [32]. Therefore, mechanistically, favipiravir has potential antiviral effects on various RNA viruses. The steady-state trough concentration of favipiravir is 11.3–22.6 μg/mL. It has been reported that favipiravir has anti-SARS-CoV-2 activity in Vero E6 cells, with an EC50 of 61.88 μM [33].

**Remdesivir**

Remdesivir is a modified prodrug of the adenine nucleoside analog. It has strong in vitro activity and cell permeability and can be more effectively metabolized into active nucleoside triphosphate (NTP). NTP acts as a substrate for RNA polymerase in viral RNA polymerase-guided primer extension, thereby terminating the transcription of RNA strand information [34]. Coronavirus expresses exonuclease in non-structural protein 14, nsp14, and it is conserved across the entire coronavirus family. Nucleoside analogs are incorporated into viral RNA and are excised by coronavirus exonucleases [35]. However, remdesivir is resistant to...
envelope viruses, processes such as glycoprotein translation modification also require a low pH environment, and chloroquine can inhibit a variety of viruses through its pH dependence [44]. For some viruses of the Flaviviridae family, chloroquine can also inhibit the hydrolysis of its proteins and disrupt the viral infection process; chloroquine can also inhibit some non-infectious retroviruses by inhibiting the glycosylation of viral envelope proteins [42]. In addition, the virus needs to attach to cell receptors through mucin to infect cells. ACE-2 was found to be a receptor protein for SARS-CoV and SARS-CoV-2. SARS-CoV-2 enters cells through the ACE-2 receptor. Chloroquine may interfere with the virus. The binding of mucin to cellular ACE-2 receptor protein exerts an inhibitory effect on the virus [45]. In addition to its direct antiviral effect, chloroquine can also regulate immune activity and inhibit inflammatory reactions associated with viral infections [46]. Therefore, it is often used in clinical practice to treat immune system diseases such as rheumatoid arthritis. Immune system diseases often have overexpression of inflammatory cytokines. Chloroquine inhibits the inflammatory response by reducing the expression of inflammatory cytokines such as TNF-α. This may have a positive effect on the activation of the immune system and the severe inflammatory response accompanied by the viral infection [42]. Chloroquine may also be used to treat lung damage caused by viral infection by inhibiting cell autophagy [47].

**Hydroxychloroquine**

The difference between hydroxychloroquine and chloroquine is that an ethyl group in chloroquine is replaced by a hydroxyethyl group in hydroxychloroquine [48]. The therapeutic effect is similar, but the side effects are significantly reduced compared with chloroquine. Therefore, hydroxychloroquine is widely used as an immunosuppressive agent in the treatment of rheumatic diseases [48]. By observing the electrocardiogram of 84 COVID-19 patients who took oral hydroxychloroquine and azithromycin for 5 days, it was found that most of the patients who received hydroxychloroquine and azithromycin showed an extended QT interval. Moreover, the severity of other underlying diseases and SARS-CoV-2 infection may aggravate this situation [49].

**Respiratory Support Therapy**

Some patients with COVID-19 can progress rapidly to acute respiratory distress syndrome (ARDS) [16, 50]. Among them, severe hypoxemia is a common clinical manifestation of such patients and usually requires respiratory support treatment in the intensive care unit [51]. Patients with severe COVID-19 need individualized respiratory support technology based on the degree of hypoxia in the patient. For patients with mild to
moderate hypoxia, nasal catheters, masks, nasal high-flow oxygen therapy, and non-invasive ventilation can be preferred for non-invasive ventilation. Self-pronation can also ameliorate blood oxygenation and is a low-tech intervention that can prevent the need for more invasive methods of oxygen delivery. Awake pronation is also used in ICU and other inpatient populations, but it has saved many an emergency department (ED) patient from going on the vent. Non-invasive ventilation, invasive mechanical ventilation, and external membrane oxygenation (ECMO) can be selected for moderate to severe hypoxia. Severe COVID-19 requires mechanical ventilation in the event of severe hypoxemia and respiratory distress. Clinical studies on MERS-CoV, SARS-CoV, and influenza have shown that non-invasive ventilation has a higher failure rate in such patients [15]. Delayed intubation can increase patient mortality [52]. Compared with SARS-CoV, the progression of respiratory failure in COVID-19 patients is slower. Some patients with severe respiratory failure can still be successfully treated with non-invasive ventilation. It is recommended to use non-invasive ventilation as much as possible. When patients with impaired consciousness level, upper airway obstruction, deterioration of oxygenation, or deterioration of ventilation status [53], invasive artificial airway invasive ventilation should be established immediately.

Prevention and Control of Nosocomial Infection

An analysis of data from 138 SARS-CoV-2 cases found that 40 medical staff (29%) and 17 hospitalized patients (12.3%) had nosocomial infection in the hospital. In the infected medical staff, 31 worked in the general ward, 7 in the emergency department, and 2 in the intensive care unit [54]. The invading power of the virus from “super communicators” cannot be underestimated. In addition, patients with heart disease and diabetes have a low ability to defend themselves against infections. As mentioned above, the best way to prevent nosocomial infection in hospitals is to establish and implement a strict disinfection and isolation system, including airway management, quarantine measures, and disposal of excreta.

Conclusions

COVID-19 is highly contagious and is transmitted mainly through the respiratory tract. Most patients with SARS-CoV-2 infection have milder symptoms. Some patients will have mild disease in the early stage, suddenly exacerbate later, and eventually die of multiple organ failure, which must get worldwide attention. It is worth noting that some asymptomatic patients are also potential sources of infection. The diagnostic criteria for cytokine storm caused by SARS-CoV-2 need to be further studied. The diagnosis of COVID-19 relies on the detection of viral nucleic acids as the gold standard. However, diagnostic accuracy is better when combined with clinical symptoms, CT results, and biochemical tests. At present, for the treatment of COVID-19, no specific antiviral agents have been developed, except for symptomatic supportive treatments. Therefore, based on the present information, the strategies for the prevention and treatment of COVID-19 need be further studied.

Authors’ Contribution Zuojiong Gong made substantial contributions to the study concept and design. Yao Wang wrote the manuscript draft. Yao Wang, Luwen Wang, and Xun Li collected the references. Zuojiong Gong made substantial revisions to the manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

Ethical Approval Not required.

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