Unclear Issues Regarding COVID-19

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To know what you know and what you do not know, that is true knowledge

(Confucius)

ABSTRACT

Scientists from all over the world have been intensively working to discover different aspects of Coronavirus disease 2019 (COVID-19) since the first cluster of cases was reported in China. Herein, we aimed to investigate unclear issues related to transmission and pathogenesis of disease as well as accuracy of diagnostic tests and treatment modalities. A literature search on PubMed, Ovid, and EMBASE databases was conducted, and articles pertinent to identified search terms were extracted. A snow-ball search strategy was followed in order to retrieve additional relevant articles. It was reported that viral spread may occur during the asymptomatic phase of infection, and viral load was suggested to be a useful marker to assess disease severity. In contrast to immune response against viral infections, cytotoxic T lymphocytes decline in SARS-CoV-2 infection, which can be partially explained by direct invasion of T lymphocytes or apoptosis activated by SARS-CoV-2. Dysregulation of the urokinase pathway, cleavage of the SARS-CoV-2 Spike protein by FXa and FIIa, and consumption coagulopathy were the proposed mechanisms of the coagulation dysfunction in COVID-19. False-negative rates of reverse transcriptase polymerase chain reaction varied between 3% and 41% across studies. The probability of the positive test was proposed to decrease with the number of days past from symptom onset. Safety issues related to infection spread limit the use of high flow nasal oxygen (HFNO) and continuous positive airway pressure (CPAP) in hypoxic patients. Further studies are required to elucidate the challenging issues, thus enhancing the management of COVID-19 patients.

Keywords: Coronavirus, pathogenesis, transmission, venous thromboembolism

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease mostly effects the lungs caused by a novel betacoronavirus, SARS-CoV-2, which was first described in December 2019, in China, and was later declared as the cause of a pandemic. Despite the similarity of the genetic sequencing of the novel coronavirus with the SARS virus, the management of this unknown disease with non-specific manifestations is still very challenging for the physicians [1]. Patients with COVID-19 present with a variety of incubation period as well as clinical course of the disease. COVID-19 pneumonia may lead to shock and multiple organ failure. In most cases, respiratory failure accounts for the actual cause of death. The estimated global mortality rate is approximately 2%, but it varies according to age [1]. It is important to define the severity of the disease since severe patients experience worse outcomes. Although scientists from all over the world have been trying to unravel the complexity of COVID-19, yet much remains to be learned in regards to pathogenesis of the disease, accuracy of diagnostic tests and treatment modalities. The present review aims to present and discuss the recent literature regarding unclear issues on COVID-19.

Methods

In the present narrative review, an electronic search of the literature on PubMed, Ovid and EMBASE databases was conducted until April 19, 2020 to retrieve relevant systematic reviews, meta-analyses, state of the art articles and randomized trials. The search method composed of Medical Subject Headings (MeSH) search terms "Coronavirus", "Coronavirus Infections",

"Novel coronavirus pneumonia", "COVID", "ARDS", "SARS", "MERS", "Influenza", "Severe Acute Respiratory Syndrome", "SARS-CoV-2". Reference lists of the studies were also checked through to find more studies that are pertinent to our search terms. Articles in languages other than English were excluded.

Pathogenesis

Pathogenesis of COVID-19 infection remains unclear, a variety of potential pathogenic mechanisms including coagulopathy, thrombotic microangiopathy restricted to lungs, endothelial dysfunction, excessive release of pro-inflammatory cytokines are being investigated. The endothelial dysfunction caused by infection activates an excessive thrombin generation and inhibits fibrinolysis, which indicates hypercoagulability [2]. For instance, lung dissection of a deceased patient with COVID-19 pneumonia showed blockage and establishment of small thrombosis in pulmonary microvasculature [3]. Coagulopathy and thrombotic microangiopathy will be discussed in detail below in subsection of 'Coagulation dysfunction and venous thromboembolism in patients with COVID-19'.

SARS-CoV-2 enters target cells with the spike (S) protein engaging angiotensin converting enzyme-2 (ACE2) receptor [4]. The virus will proliferate and cause destruction of the tissues which have high ACE2 expression including lungs, intestines, kidneys when protective immune response is impaired. The major-histocompatibility-complex antigen loci (HLA) seem to be responsible for predisposition to infections. For instance, some murine MHC class II haplotypes are related to predisposition with influenza. HLA-A*11, HLA-B*35, and HLA-DRB1*10 make males vulnerable to H1N1 [5].

During the incubation and early phase of the disease, a specific adaptive immune response may stop SARS-CoV-2 and prevent worsening [6]. The cellular immunity, T lymphocytes are major players in virus clearance after viral infections. Lymphopenia is one of the most prominent characteristics of COVID-19 [7,8,9], and might be explained by the impaired innate and adaptive immune responses. In contrast to the immune response against viral infections, cytotoxic T lymphocytes decline sharply in SARS-CoV-2 infection [10]. A study demonstrated that reduction of CD3+, CD4+ and CD8+ T lymphocytes were related to the course of COVID-19 pneumonia, especially in severe cases [11]. The mechanism of the reduction of T lymphocytes may be a result of the direct assault of SARS-COV-2 or induction of apoptosis by SARCoV-2 like MERS-CoV [12]. In addition, SARS-CoV-2 may modify role of antigen presenting cells, dendritic cells, and cytokines (TNF-alfa and IL-4) which regulate the function of T lymphocytes [13,14]. The immune status differs significantly between severe and non-severe COVID-19 patients [15]. The reduction of T-Cells correlates with disease severity. May here lies the answer of the question of why some patients experience severe disease, while the others show mild symptoms. The complement system is a crucial piece of host defence against infections, has potent pro-inflammatory properties and can aggravate lung injury, and may play a part in COVID-19 pneumonia. Complement activation in the pathogenesis of SARS had been shown before [16], and a recent study revealed that complement C3 was remarkably elevated in serious cases of COVID-19 pneumonia than that in non-serious cases [11].

The cytokine release syndrome (CRS) may play a major role in patients with severe COVID-19 as in ARDS. Pro-inflammatory cytokines that drive progression of the disease including IL2, IL6, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα are reported high in severe COVID-19 patients especially requiring the intensive care unit (ICU) [7]. The pathological characteristics of COVID-19 related ARDS are diffuse alveolar damage with hyaline membrane formation with fibrin deposition and a few multinucleated enlarged cells [17]. A robust immune response and epithelial regeneration is essential for recovery and may lead aberrant wound healing which can cause more severe fibrosis than other causes of ARDS. The function of hyaluronic acid (HA) is insufficient in patients with influenza, therefore, COVID-19 related ARDS has been thought to be associated with HA [18].

Chen et al. [19] demonstrated that the hemoglobin decreases, whereas serum ferritin, erythrocyte sedimentation rate, C-reactive protein (CRP), and lactate dehydrogenase increase significantly in most COVID-19 cases. A molecular study reported genomic structures of the virus interferes with the heme on the 1-beta chain of hemoglobin to seperate the iron as a result forming porphyrin [20]. This inhibits normal metabolic pathway of heme, and cause hemoglobin carry less oxygen. Alveolocapillary units have become inable to transfer carbon dioxide and oxygen.

Coagulation Dysfunction and Venous Thromboembolism in Patients with COVID-19

As clinicians we have to identify the variables that drive mortality early. Considering current data, we have to focus on three important

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points: older age, increased value of D-dimer (>1μg/ml), and presence of co-morbidities [21]. The role of coagulopathy in COVID-19 needs to be clarified. In a previous study, it was suggested that impairment of the urokinase pathway promotes to lung involvement whereas plasminogen activator inhibitor-1 defends against SARS [22]. Moreover, Beri et al. revealed that fibrinolysis activated by plasminogen aggravates inflammation caused by influenza [23]. Abnormal coagulation results are associated with poor prognosis. Disseminated intravascular coagulation (DIC) is common in deceased COVID-19 patients. In a study, D-dimer, fibrin/fibrinogen degradation products (FDP) and fibrinogen levels were higher in patients with COVID-19 than those in healthy controls, while antithrombin level was lower [24]. In addition, levels of D-dimer and FDP in cases with severe COVID-19 were higher than cases with mild disease. A study compared the coagulation parameters between patients with severe pneumonia caused by SARS-CoV2 and non-SARS-CoV2, and also evaluated whether cases with high levels of D-dimer could benefit from anticoagulants [25]. The 28-day mortality was approximately twice fold higher in patients with COVID-19 compared to non-COVID cases. COVID-19 cases had higher platelet counts. The 28-day mortality in COVID-19 patients with D-dimer >3.0 μg/mL, who received anticoagulants were lower than who did not receive and cases with high levels of D-dimer could benefit from anticoagulants. A study from China demonstrated that D-dimer and FDP levels, prothrombin time and activated partial thromboplastin time are significantly higher in deceased patients with COVİD-19 compared to survivors; and 71.4% of non-survivors met the criteria of DIC whereas only 0.6% of survivors did [25].

Development of consumption coagulopathy, especially DIC, may worsen the clinical course in patients with COVID-19. DIC is not so rare in patients with severe SARS-Cov-2 infection, and the rate of DIC in deceased patients was reported 71.4 [26]. Monitoring of coagulation parameters may help to predict deterioration of the disease and establish an accurate therapeutic strategy. Severe COVID-19 can progress to sepsis which also a common cause of DIC, through inflammatory cytokines such as IL-6, IL-8, TNF-α.

Prevalence of venous thromboembolism (VTE) in patients with SARS-CoV-2 infection remains unclear. The incidence of VTE in patients with severe COVID-19 who were admitted to ICUs was found to be 25% in a retrospective study analyzing ultrasound of lower extremity vein [27]. Antiphospholipid antibodies are detected in high titers in antiphospholipid syndrome; however, they can also appear temporarily in critical patients. Zhang et al. [28] described three patients with SARS-CoV-2 infection who had coagulation dysregulation and antiphospholipid antibodies, including anticardiolipin IgA, anti-β2- glycoprotein I IgA, and IgG antibodies, and also intracerebral infarcts.

A post-mortem study reported COVID-19 associated cardiopulmonary changes as follows [29]: The main pulmonary arteries were free of thromboemboli; hyaline membranes consistent with diffuse alveolar damage with mild-to-moderate lymphocytic infiltrates (CD4 immunostain pozitive); fibrin thrombi and megakaryocytes in capillaries and small vessels; cardiomegaly, and right ventricular dilatation. There are nor thrombus in coronary arteries neither lymphocytic infiltrate in myocard suggestive of viral myocarditis. The dominant processes seem to be diffuse alveolar damage, CD4+ mononuclear cell infiltration around occluded small vessels by microthrombi, and pulmonary hemorrhage. Thrombotic microangiopathy is considered restricted to the lungs.

Coagulopathy becomes more prominent on the seventh day of viremia. One theory suggests that anticoagulants could block SARS-CoV-2 replication through inhibiting cleavage of the S protein by FXa and FIIa. Low molecular weight heparins (LMWHs) are suggested in treatment of hospitalized adult patients with COVID-19. The International Society on Thrombosis and Haemostasis (ISTH) recently recommended that all hospitalized COVID-19 patients, even those not in the ICU, should receive standard prophylactic anticoagulation with LMWH in the absence of any contraindications. Early application of anticoagulants is being advocated for better disease course in severe COVID-19, however, it remains unclear whether we should use specific inclusion or exclusion criteria. ISTH has defined a new and earlier phase of sepsis-associated DIC, called "sepsis-induced coagulopathy" (SIC) [30]. Preliminary data from Wuhan suggest that anticoagulation may be beneficial in severe COVID-19 cases with D-dimer levels >6 times the upper limit of normal [31]. On contrary, Harvard Brigham and Women's Hospital guidance suggests initiating prophylactic anticoagulation therapy for all patients with COVID-19 in absence of any contraindications. Oral anticoagulants should be switched to LMWH or unfractionated heparin. However, whether anticoagulants are only useful in patients meeting SIC criteria or with markedly elevated D-dimer but not in unselected patients remains to be unclear. A small case series suggested that dipyridamole could be used, although anticoagulant and antiplatelet agents need further investigation for their therapeutic activities [32].

Viral Transmission

SARS-CoV-2 cause rapid spread [33, 34], even among asymptomatic or minimally symptomatic carriers [35, 36]. A study reported that mean nasopharyngeal swab viral load of severe cases was 60-fold higher than that of mild cases, which suggests that the higher the viral load the more severe the disease [37]. Viral negative conversion seems to occur early in mild cases, a study revealed that 90% of mild group have negative RT-PCR results after 10 days whereas all severe cases yet tested positive over day 10 [37].

Asymptomatic transmission of SARS-CoV-2 may cause challenges for disease control. Presymptomatic transmission can happen through formation of respiratory droplets or indirect transmission. Vocal activities including speech, laughing, singing have been showed to create air particles, and amount of these particles depend on voice loudness [38]. Environmental contamination with SARS-CoV-2 can occur via droplet dispersion or touching with an infected person's contaminated hands [39]. Duration of contagiuous phase while a patient is presymptomatic is still unknown. A study demonstrated that 1-3 days prior to initiation of symptoms, presymptomatic spread exposure occurred [40].

Tranmission and viability of SARS and influenza on surfaces were shown to decrease at higher temperatures. Regard to this, higher temperatures were proposed to may have a protecting impact towards SARS-CoV-2 infection. In a study, it was found that an increase in temperature from 1°C to 9°C, and from 10°C to 19°C was associated with a decrease in case numbers from 24 to 19, and from 18 to 7, respectively [41]. Contrarily, results of another report did not favour the postulation that elevated temperature and UV radiation can decrease the spread of COVID-19 [42]. It was proposed that difference in mortality of SARS-CoV-2 infection among countries could be elucidated by Bacillus Calmette-Guérin (BCG) vaccination status. 55 high income countries with current BCG policy had 0.78±0.40 deaths per million people; contrarily, countries that never had a BCG policy including Italy, Netherlands, Belgium, USA, Lebanon had a higher mortality rate, with 16.39±7.33 deaths per million people [43]. Besides, it is unknown whether BCG vaccination at old age would boost defenses in elderly.

Accuracy of Diagnostic Tests

Test designs vary whether the test detects infection directly (such as the virus itself) or indirectly (such as host antibodies). Countries have used different testing approaches depending on their testing capacities. Current case-fatality rate ranges from 0.6% to 7.2% by region [44-46]. In a couple countries, nation-wide utilization of diagnostic testing became a mainstay of effective confinement approaches. For example, in Germany and South Korea, the case-fatality rates are less than 0.5%, probably because extensive testing revealed a large group of mild cases [47]. Nucleic acid amplification tests are more suitable for diagnosis at the time of symptom onset when viral shedding and transmission risk is highest [48]. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) based assay on respiratory specimens performed in laboratory is the reference standard test for COVID-19 diagnosis. Detection of host-derived antibodies directed against SARS-CoV-2 are crucial for surveillance, determination of SARS-CoV-2 immunity, and potentially for risk assessment of health care workers. The utility of antibody detection assays for diagnosing acute infections is probably limited around the time of symptom onset [48]. Serologic assays might be useful in scenarios in which patients present with late complications of disease, and RT-PCR is false negative due to reduction in viral shedding over time. The Center for Disease Control (CDC) currently recommends priority for testing three groups: hospitalized patients with presentations compatible with COVID-19, other symptomatic persons at risk for poor outcomes, and persons who had close contact with someone with suspected or confirmed COVID-19 within 14 days of illness onset [49]. The CDC does not recommend testing asymptomatic persons.

A nasopharyngeal specimen is the preferred choice for swab-based testing, but samples taken from sputum, endotracheal aspirates, and bronchoalveolar lavage have greater sensitivity than upper respiratory tract specimens [50]. Inadequate sample collection may result false negative. A study identified that the likelihood of a positive RT-PCR test reduces with time following initiation of symptoms, and nasal swabs are better at diagnostic yield than throat swabs [51]. Previous studies have reported rates of false-negative RT-PCR results at symptom onset between 3-41% [52, 53]. Initial sensitivity of RT-PCR to identify SARS-CoV-2 infected patients was found approximately 71% in two different studies [54, 55]. Meanwhile positive test rates were found to be lower for throat samples in comparison with nasal samples (24% vs. 57% respectively) [56]. Likelihood of positivity reduces with time past after initiation of symptoms; the chance of a positive test with nasal swab declines from 94.39% on day 0 to 67.15% by day 10, and there is only a 2.38% chance of a positive test by day 31, (positive rates for throat swabs: 88%, 47.11%, and 1.05% for day 0, 10 and 31 respectively) [51]. Guidelines from the WHO and the European Centre for Disease Control noted that a sole negative result is inadequate to exclude disease. After a patient has had a positive test result, various experts have advised getting minimum 2 negative upper respiratory tract samples, obtained at periods of 24 hours or longer, to document SARS-CoV-2 clearance [57, 58].

Compared with serial nasopharyngeal sampling, chest computed tomography (CT) may be more sensitive than an RT-PCR test at a single time point for the diagnosis of COVID-19 [52-54]. However, CT findings are not completely specific to COVID-19 and do not exclude a co-infection or an alternative diagnosis [59].

Clinical Course

COVID-19 can be divided into three different clinical stages [60]: *Asymptomatic stage* (First 1-2 days): SARS-CoV-2 enters upper airways and binds to epithelial cells. There is local propagation of the virus despite a limited innate immune response. Individuals can spread infection and virus can be detected in the upper airways at this stage. *Conducting airway immune response* (Next few days): The virus moves down through airways, innate immune response is triggered, and the disease clinically manifest. Approximately 80% of the cases, the disease is restricted to this stage and clinical course will be mild. *Respiratory failure and progression to ARDS*: About 20% of the patients will progress to stage 3. The virus reaches the gas exchange units of the lung and develop pulmonary infiltrates.

SARS-CoV-2 exhibited neurotropic features, cases with COVID-19 may have neurological manifestations comprising headache, altered consciousness, and paresthesia [61]. In addition, increasing numbers of cases present with anosmia [62]. SARS-CoV-2 was detected in the brain or cerebrospinal fluid [63]. Neuronal degeneration and intracranial edema was shown in autopsies [64]. Neurologic involvement of coronaviruses manifests in three categories: Viral encephalitis, infectious toxic encephalopathy, and acute cerebrovascular disease [65]. The mechanism of neuroinvasion is still unknown. Possible pathways are proposed: 1. Direct infection injury, 2. Hypoxia injury, 3. Immune injury, 4. ACE2 related injury.

Use of Noninvasive Mechanical Ventilation

HFNO can be used in COVID-19 patients, but infection spread is a real concern in this method. Spread of virus may reduce with putting-on a surgical mask above high flow nasal cannula. CPAP must be first choice of non-invasive ventilation for COVID-19 patients with hypoxemic respiratory failure. CPAP response must be assessed within half an hour, and unless it is adequate, early intubation and invasive mechanical ventilation (IMV) should be applied. CPAP must be continued if clinical findings of the patient are improving, and a trial of weaning CPAP should be considered when oxygen concentration <40% [66]. The peripheral oxygen saturation (SpO_2) monitoring is generally sufficient [66]. Arterial blood gas monitoring is not necessary unless $PaCO_2$ is elevated at presentation. Target level of SpO_2 is 92-96%, and for patients with chronic type II respiratory failure is 88-92% [66]. Bilevel NIV (BiPAP) should be considered for clinical deteriorating patients despite adequate CPAP support or for patients with hypercapnic respiratory failure.

Location of NIV treatment is an important issue in COVID-19 pandemic to be able to protect the healthcare workers (HCWs) because of the high spread rate of the disease. It is recommended that NIV is delivered in a negative pressure room with air exchanges greater than 10 cycles per hour in order to avoid virus spread and to protect HCWs. However, if a negative pressure room is not available because of insufficient number of ICU beds, respiratory intermediate units with opportunity of air exchange (big windows that can be opened periodically making possible to change air at least at a rate of 160L/h) are suggested to deliver respiratory support to entire patients [67]. First recommended interface for NIV is a full-face non-vented mask with expiratory viral filter; after that a helmet preferably with air cushion, a standard face mask must be last choice. A viral/bacterial filter should be placed in the circuit between the mask and the oxygen and exhalation ports and should be changed every 24 hours. An external humidifier should be avoided. Contamination risk of HCWs during NIV is supposed to be low when staff is equipped with proper personal protective equipments which are a FFP3 respirator, double non-sterile gloves, long-sleeved water-resistant gown, goggles or face shield.

Anecdotal observations in field have noted that patients with COVID-19-related respiratory failure respond well to prone positioning with NIV, especially in those who had posterior subplevral dominant opacities in their lung CT. The

care should be taken to avoid ventilator disconnections during proning and the number of staff should be minimalized for turning. Optimal timing and criteria for prone ventilation with NIV is unclear and should be performed on an individualized basis.

Use of Steroids, Nonsteroidal Anti-inflammatory Drugs, and Vitamin C

Current WHO recommendations advise against routine use of prednisolone in the management of COVID-19 [1]. Corticosteroids have shown to be failed against respiratory tract viruses including MERS, SARS, and influenza in various studies, and have serious adverse effects including psychosis, diabetes, avascular necrosis. Corticosteroid which can repress cell-mediated immunity, stimulate the reduction of T lymphocyte, and postpone the virus clearance [68], may worsen the defective function of lymphocytes in patients with SARS-CoV-2. However, a retrospective study reported that application of steroids was attributed to decreased mortality in patients with COVID-19 associated ARDS [69]. Hence, the use of corticosteroids should be careful in severe patients with COVID-19 pneumonia, and the time of corticosteroid prescription merit additional investigation. Although the use of NSAIDs in COVID-19 has also been a controversial issue, it was clarified by WHO that avoiding NSAIDs was not recommended since it was not associated with worse prognosis as previously claimed [1].

Vitamin C has been suggested as a therapeutic option for COVID-19 based on a prospective randomized trial of intravenous vitamin C in patients with sepsis and ARDS [70]. In that trial, there was no difference in the sequential organ failure assessment (SOFA) score and 28-day mortality between the vitamin C and placebo groups. There is no evidence to support use of vitamin C in patients with SARS-CoV-2 infection, however there is an ongoing clinical trial for high-dose vitamin C in China (NCT04264533).

Despite significant progresses achieved globally in the struggle with the COVID-19 pandemic; there are still many conflicting and unclear issues particularly regarding pathogenesis, clinical course, diagnosis and treatment strategies. Further studies are required to elucidate these challenging issues, thus to enhance the management of COVID-19 patients.

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