Special Lecture - 1

COVID-19 : Clinical Features, Diagnosis and Therapy

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At the end of 2019, a series of severe pneumonia cases in Wuhan, China were reported[1]. A novel coronavirus, named as severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*) was detected from the throat swab sample of a patient on January 7th, 2020[2]. The outbreak was declared as Public Health Emergency of International Concern by World Health Organization (WHO) on January 30 and the disease was named as COVID-19 on February 11. After the virus spread rapidly to other countries throughout the world, the epidemic in China has evolved into a pandemic situation. As of mid-June 2020, the number of laboratory-confirmed cases approached eight million with >430.000 deaths, worldwide.

Recent phylogenetic evidence indicates that the origin of *SARS-CoV-2* is *Rhinoloptus spp.* bats, although it is not clear whether an intermediary host exists before switching to humans as a host[3]. In humans, *SARS-CoV-2* is a respiratory pathogen, transmitting from person to person mainly via respiratory droplets in close contacts. During aerosol generating procedures, such as bronchoscopy and endotracheal intubation, airborne transmission also occurs. Droplets can be produced during regular speech as well as various sizes of aerosols by activities like loud speech, singing, crying and shouting. In closed, stagnant air environment these droplets can stay airborne for several minutes and travel as far as 7-8 meters[4 5]. Viability of virus on various surfaces varies from 4 hours on copper, 24 hours on cardboard to 72 hours on plastic and steel[6]. However, transmission through various contaminated surfaces is not thought to be the main mode of virus spread [7]. Additionally, the virus was detected in non-respiratory specimens like stool, but transmission via these ways is also questionable[8]. The fact that the viral load in samples taken from patients immediately after being symptomatic is higher than the later stages of the disease, it is assumed that the infection is more contagious in the early phases of the infection[9]. Although the upper limit of the incubation period is defined as within 14 days after exposure, in real life this window period is much shorter and varies between 4-5 days[10 11].

Clinical features

While most people with COVID-19 develop only mild or moderate disease, approximately 5% of patients may experience respiratory failure requiring intensive care monitoring[12]. The most common form of serious manifestation is pneumonia and these patients present with fever, cough, fatigue, and dyspnea. Moreover, anosmia, upper respiratory system symptoms, headache, abdominal pain, diarrhea, nausea, myalgia can also be seen[13]. The disease tends to be more severe, especially in advanced aged patients with comorbidities such as cardiovascular diseases, hypertension and diabetes[14]. Patients requiring intensive care may

develop acute respiratory distress syndrome (ARDS), septic shock, acute kidney injury and acute cardiac injury. Regarding the pathophysiology of the disease is closely related with endotheliitis, thromboembolic complications not limited to large vessels including pulmonary embolism and acute stroke, but also microvascular thrombotic lesions in various organ systems have been reported [15] [16]. Arrhythmias and hyperinflammatory response including cytokine release syndrome are other severe conditions in some cases. Unlike other respiratory viral pathogens, secondary infections have not commonly been reported in COVID-19. The course and severity of disease differs from adults to children. Although the disease is mostly mild in the latter group, recently a Kawasaki-like multisystem inflammatory syndrome has been reported in children and adolecents[17].

Diagnosis

According to ECDC, case definition can be made with clinical (cough, fever, shortness of breath, sudden onset of anosmia, ageusia or dysgeusia), diagnostic imaging (radiological evidence showing lesions compatible with COVID-19), laboratory (detection of SARS-CoV-2 nucleic acid in a clinical specimen) and epidemiological criteria (at least one of two epidemiological links; close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptom or having been a resident of staff member, in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed)[18]. With these criteria; a **possible case** is defined as any person meeting the clinical criteria; a **probable case** is any person meeting the clinical criteria with an epidemiological link or any person meeting the diagnostic criteria; a **confirmed case** is any person meeting the laboratory criteria. The definite diagnosis is made by detection of SARS-CoV-2 RNA by nucleic acid amplification test and it is recommended to take a respiratory tract sample from patients who meet the diagnostic criteria.

Lower respiratory tract samples such as bronchoalveolar lavage fluid yields higher sensitivity as compared with nasopharyngeal swab samples (93 vs 63%, respectively) for PCR testing [8]. The sensitivity of the test also depends on several factors such as duration of illness, the quality of the sample, the type of specimen. Clinical decisions are crucial in management of suspected patients. Particularly for nasopharyngeal swab testing, since false negative results are likely, a second test within 24-48 hours is recommended. Serological tests which detect antibodies to SARS-CoV-2 in the blood can also be diagnostic especially in the patients who present after 9 - 14 days of illness onset. Sensitivity and specificity values vary for both PCR and antibody tests; therefore, predictive values of the test used while making a diagnosis should be taken into account.

There are some laboratory values supporting the diagnosis in patients with compatible clinical but with negative test results. Laboratory features like lymphopenia, elevated serumlevels of lactate dehydrogenase, ferritin, C-reactive protein, d-dimer, troponin, creatine phosphokinase are associated with worse outcome[19]. Radiological findings may also vary in patients. Most common radiological finding on chest computed tomography (CT) is bilateral, peripheral ground glass opacities with or without consolidation involving the lower lobes consistent with viral pneumonia. Less commonly, pleural thickening, pleural effusion and lymphadenopathy can also be detected. Computed tomography may be normal in early disease and findings may become apparent on average 10-12 days after onset of symptoms.

In a study evaluating correlation of PCR and CT, chest CT had 97% sensitivity, but 25% specificity based on PCR results[20]. A new radiological imaging technology namely dual-energy computed tomography may reveal early systemic microvascular disease[21].

Therapy

There has been no specific, proven, effective treatment against COVID-19, yet. Only a few randomized, controlled trials are available. Supportive care and treatment of complications like ARDS and thromboembolic events are the cornerstones of the treatment. A placebo controlled, randomized trial found that remdesivir shortens the duration of recovery from respiratory tract infection from 15 to 11 days[22].

Chloroquine and hydroxychloroquine used in the treatment of malaria for several decades has been shown to block the entry of the virus into the cell[23]. However, so far no reliable data exist for their use in patients, moreover their potential side effect profiles is a serious concern limiting their widespread use[24].

Routine use of steroids is not recommended. There are several studies about use of antiretroviral drugs (lopinavir/ritonavir), favipiravir (an RNA polymerase inhibitor, which is used for influenza), interferon-alpha and –beta, tocilizumab and sarilumab (monoclonal antibodies against IL-6 receptor), convalescent plasma and hyperimmune immunoglobulins in COVID-19. Current guidelines recommend that these drugs should only be used in a clinical study setting[25, 26].

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