Coronaviruses

Subjects: Virology

Contributor: RenÃ© Hage , MacÃ© M. Schuurmans

There are various coronaviruses high and low pathogenicity. The first being associated with a high morbidity and mortality. The SARS-CoV-2 leading to COVID-19 has spread globally and is associated with a high mortality especially in elderly patients and with certain comorbidities (hypertension, obesity, diabetes, etc). Currently there are only limited evidence-based treatment options such as dexamethason, remdesivir, and ICU care. Multiple treatment strategies are being evaluated since the pandemic is still evolving in most countries.

coronavirus
SARS-CoV-2
COVID-19
MERS
SARS
CNI
calcineurine inhibitor
vaccine

1. Introduction

Coronaviruses (CoV) are among the frequent pathogens causing the common cold. They have a single-stranded RNA genome, that is coiled within the virion. In electron microscopy they show spikes protruding from the virion envelope with a crown-like shape, which lead to the name âcoronavirusâ.

They belong to the order of the Nidovirales, and within this order, the coronaviruses have been studied in great detail because of their zoonotic transmission since the 21st century, causing life-threatening infections in humans, their societal and economic impact, unusual features of their pathogenesis, and the complexity of their molecular biology[1]. The coronaviruses are classified into two main subfamilies: the Torovirinae and the Coronavirinae, the latter being subdivided into the genera Alpha-, Beta-, Gamma-, and Deltacoronavirus[1]. The Alpha- and Betacoronaviruses include the seven Coronavirus serotypes, of which there are four (CoV-NL63, -HKU1, -E229, -OC43) with a low pathogenicity, causing mild upper respiratory tract infections. The other three serotypes are highly dangerous viruses, such as the Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) causing SARS, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) causing MERS, and the novel SARS-CoV-2 causing Coronavirus Disease-19 (COVID-19). So far, Gamma- and Deltacoronaviruses have been discovered mostly in avian species[1]. The Gamma- and Deltacoronaviruses cause economically important diseases of livestock, poultry, and laboratory rodents[2].

2. Pathophysiology in Coronaviral Infections

All coronaviruses have a different antigenicity, depending on the spike (S-) protein of the virus. In contrast to influenza viruses, the S-proteins in coronaviruses are very stable. To enter the human cell, coronaviruses use different human cell surface peptidases. Both SARS-CoV and SARS-CoV-2 use the human angiotensin-converting enzyme-2 (ACE-2), which functions as a receptor for the virus. This receptor is widely expressed in a number of organs including pulmonary tissue, as well

as in monocytes and macrophages[3]. Recent studies also demonstrated that both SARS-CoV and SARS-CoV-2 also can use lectins to enter the cell. Moreover, SARS-CoV-2 can use neuropilin-1, which is strongly expressed by endothelial cells and epithelial cells facing the nasal cavity[4][5][6].

Entering the cytoplasm by the receptor, the virus uncoats and starts replicating in the human cell. The exact pathophysiology responsible for the unusually high morbidity and mortality following CoV infections with high pathogenicity, are incompletely understood. Important mechanisms could be the virus-induced direct cytopathic effects, as well as the viral evasion of the host immune system.

3. Morbidity and Mortality of Coronaviruses

The coronaviruses with a low pathogenicity are frequently self-limiting and present with symptoms of the common cold. The highly pathogenic coronaviruses lead to a dysregulated immune system, resulting in an overshooting inflammatory response (cytokine storm), contribute to morbidity and mortality. Mortality rates in MERS, SARS and COVID-19 are around 35%, 9% and 5% of infected individuals, respectively. Nevertheless, the number of infected patients has never been so large as in the current COVID-19 pandemic. The total number of patients suffering from MERS was 2400, from SARS 8300, and from COVID-19 (so far) passes 47 million[7]. MERS spread to 27 countries, SARS to 30 countries and COVID-19 represents currently a global threat of increasing magnitude (currently >190 countries). Symptoms of these highly pathogenic coronaviruses differ depending on the type of coronavirus and host factors.

MERS is a disease predominantly affecting the lower respiratory tract, which in most patients leads to pneumonia. Clinical manifestations are fever, malaise, chills, myalgia, cough, dyspnea, diarrhea, vomiting, and abdominal pain. In severely ill patients dyspnea is severe with acute respiratory failure, renal failure, and shock. As in SARS-CoV-2, there is a high incidence in older patients. Predictors of poor outcome include age above 60 years, male gender, diabetes mellitus, chronic lung disease and chronic renal disease, low albumin level and progressive lymphocytopenia[8]. MERS-CoV infections can be asymptomatic in 12.5â25% of patients[8].

SARS can present with hypoxia, cyanosis, fever, dyspnea and acute respiratory failure. The WHO case definition (2003) includes the following: (1) fever higher than 38 Â°C or history of such in the past 2 days, (2) radiological evidence of new infiltrates consistent with pneumonia, (3) chills, cough, malaise, myalgia, or known history of exposure, and (4) positive test for SARS-CoV by one or more assays.

In SARS patients, neutralizing antibodies are detected 2â3 weeks after the onset of disease, and 90% of patients recover without hospitalization[2]. About 10% of SARS patients develop severe respiratory failure after 5â7 days following infection, with interstitial pneumonia characterized by progressive diffuse alveolar damage.

In COVID-19, most frequent co-morbidities are hypertension, cardiovascular disease, diabetes, and obesity[9]. Age appears to be the strongest predictor of COVID-19 related death. Clinical manifestations of COVID-19 include fever, malaise, headache, myalgia, non-productive cough, dyspnea, nausea, vomiting and diarrhea. Gastrointestinal symptoms can be the first manifestation of COVID-19, especially in patients with immunosuppressive drugs. Olfactory and/or gustatory dysfunctions have been reported in 64% to 80% of patients and are considered typical symptom[10].

COVID-19 can progress to severe organ dysfunction of the heart, brain, lung, liver, kidney, and coagulation system[10], and can lead to myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability[10]. In severe infection, patients may develop acute cerebrovascular disease and encephalitis[10]. Hypercoagulopathy leading to both venous and arterial

thromboembolic events occur in 10% to 25% in hospitalized patients, and in ICU patients with COVID-19 in 31â59%[10]. Approximately 72% of non-surviving COVID-19 patients had hypercoagulopathy[9].

SARS-CoV-2 also can induce vascular damage, and pre-existing endothelial dysfunction combined with the direct assault of SARS-CoV-2 on the vascular system may account for a high mortality of COVID-19 patients[9].

Hospitalized patients with COVID-19 need ICU treatment in approximately 17â35% of patients, most commonly due to hypoxemic respiratory failure requiring intubation and mechanical ventilation[10].

About 4â32% of patients are completely asymptomatic. However, it is unclear which of the following three scenarios are represented in these reports: 1) truly asymptomatic infection by individuals who never develop symptoms, 2) transmission by individuals with very mild symptoms, or 3) transmission by individuals who are asymptomatic at the time of transmission but subsequently develop symptoms[10].

4. Treatment of Coronaviruses

Coronavirus infections of low pathogenicity presenting as common cold required symptomatic treatment, if symptoms are disturbing. For the highly pathogenic coronavirus infections there is an urgent need to develop therapeutic drugs and vaccines. For SARS-CoV-2 infections or COVID-19 there are currently few treatment options besides supportive care in severe cases: Dexamethason (6mg daily) and remdesivir are currently recommended for the treatment of COVID-19, although the evidence for both treatments is still insufficient for a definitive recommendation (duration of treatment and timing of initiation are still subject of investigations). As these the two drugs still are under investigation, research also focuses on other existing drugs with proven effectiveness in other (corona-viral) diseases. Sometimes this is referred to as ârepurposingâ. Using currently approved drugs for other indications reduces time, costs and safety issues. Calcineurin inhibitors (CNI) showing favorable effects in multiple coronaviruses, thereby replacing the âone-drug-for-one-bugâ paradigm. They are well-known, already existing drugs in transplant medicine used for solid organ transplant (SOT) recipients, and are also prescribed in rheumatology, dermatology and ophthalmology. There are a number of other repurposed drugs under investigation and some new drugs being developed and evaluated for COVID-19. Immunoglobulines from previously infected patients are also being evaluated and used to treat these patients.

A number of vaccines are currently under investigation for mass vaccination programmes on a global scale.

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