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COVID-19 : A BRIEF REVIEW

Microbiology

Manoj Vedpathak Assistant Professor, Department of Microbiology, Dr. VM Govt Medical College, Solapur

Deepak Shinde Assistant Professor, Department of Microbiology, Dr. VM Govt Medical College, Solapur

Nazneen I Malak* Assistant Professor, Department of Microbiology, Government Medical College, Akola.
*Corresponding Author

KEYWORDS

INTRODUCTION

In the month of December 2019, a series of cases resembling viral pneumonia emerged in Wuhan, Hubei, China with majority of patients having visited Huanan seafood market.[1][2] Subsequently, pathogenic gene sequencing confirmed that the infected pathogen was a newer member of Coronaviridae family which was detected by researchers in a patient's bronchoalveolar lavage fluid sample on January 3, 2020.[1][3][4] This new type of coronavirus belonging and to the genus Betacoronavirus and the subgenus Sarbecovirus was named coronavirus disease 2019 (COVID-19) on February 11, 2020.[4][5] The virus entered human beings by crossing the species barrier. Till date the beta-coronaviruses have caused three zoonotic outbreaks namely, SARS CoV (2002-03), MERS-CoV (2012), and SARS-CoV-2.[6]

A highly contagious COVID-19 is commonly associated with fever, cough, and fatigue while in some patients severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS) which can be fatal may develop and even lead to death.[4][6] The COVID-19 pandemic holds great challenges due to the fact that asymptomatic and pre-symptomatic individuals can transmit the virus, and it could be difficult to contained.[7]

Betacoronaviruses express four essential structural proteins, namely the spike (S) glycoprotein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein. S glycoprotein has two subunits: the S1 subunit have the receptor binding domain (RBD) which enables binding to host cell receptors, and the S2 subunit that is important for fusion with the host cell membrane. Among these the S1 subunit is highly immunogenic, and its RBD portion is the main target of neutralizing antibodies.[5]

Detection of SARS-CoV-2 infection relies predominantly on two approaches: nucleic acid testing, which detects viral RNA, and serological testing, which detects antibodies elicited against SARS-CoV2 antigens. However, due to limitations in nucleic acid testing availability and the occurrence of mild or asymptomatic infections, many cases of COVID-19 are not diagnosed. Thus, serological testing, which detects antibodies elicited by SARS-CoV-2 antigens, can play an important role in defining the true prevalence of COVID-19, particularly for subclinical infection.[8][9]

2) Epidemiology

Since the initial report from China, the number of cases increased exponentially due to the rapidity of disease transmission. The first case was reported outside China, in Thailand on January 11 and within months, the disease occupied all the continents except Antarctica. The first case of COVID-19 in India was reported on 30th of January 2020.[10] Based on the current evidences, bats are the most probable original reservoir and pangolins may act as one of intermediate hosts. However, Wuhan Huanan seafood market may not be the only source of SARS-CoV-2.[2]

The spread of the disease among persons with no contact history with Huanan seafood market and infection among healthcare workers indicated person-to-person transmission of the virus mainly via droplets generated from coughing or sneezing or direct contact.[2][10]

Transmissibility is an important factor of an epidemic but the duration for which a patient with COVID-19 remains infective is unclear.[2][10] During the early symptomatic stage of the disease, viral load is highest in the oropharyngeal secretions but the patient can shed the virus even after symptom resolution.[10] The mean or median incubation period of the disease ranges between 5 to 6 days.[10]

3) MORPHOLOGY

Coronaviruses, under an electron microscope appear as round particles with diameter ranging from 60–140 nm and an outer rim studded with 9 to 12 nm long projections resembling the solar corona. The name derived from the Latin word “corona” meaning crown. The virus was first isolated from humans in 1965 and belong to the family Coronaviridae.[10][11]

Genomic analysis revealed that the SARS-CoV-2 genome shares 96.2% sequence similarity to that of the bat coronavirus and less than 80% sequence similarity with SARS-CoV. Thus, researchers classified the SARS-CoV-2 as a member of the genus Betacoronavirus, the subgenus Sarbecovirus and the lineage B.[12]

Coronaviruses are non-segmented, enveloped, positive-sense, single-stranded RNA (ssRNA) viruses having the genome length between 26 to 32 kb which is the largest genome among RNA viruses.[11] The genome consists of 2 flanking untranslated regions (UTRs) with several open reading frames (orfs) and arranged in the order of a noncoding 50-UTR-replicase genes (orf1ab)-structural proteins-accessory proteins–noncoding 30-UTR.[10][11] The coronavirus genome encodes four types of structural proteins namely spike protein (S), envelope protein (E), membrane glycoprotein (M) and nucleocapsid protein (N) and several nonstructural proteins.[11][13] The structural proteins are associated with the envelope and responsible for host infection, membrane fusion, viral assembly, morphogenesis, and release of virus particles, while the nonstructural proteins facilitate viral replication and transcription.[11]

Among these structural proteins, a major target for eliciting antibodies are the S proteins, common among all coronaviruses and therefore, structural and molecular details of S protein and its interactions with cognate receptors would be vital in developing vaccines and antiviral drugs against SARS-CoV-2.[11] The trimeric S proteins are clove-shaped, type-I transmembrane proteins that protrude from the virus envelope and are the key machinery that facilitates virus entry into the host cell. The S proteins have 3 segments: a large ectodomain, a single-pass transmembrane, and an intracellular tail. The ectodomain consist of the S1 subunit, containing a receptor-binding domain (RBD), and the membrane-fusion S2 subunit.(11) Coronaviruses have lower mutation rates than other RNA viruses and high viral replication rates within hosts because of the 3′-to-5′ exoribonuclease activity associated with the nonstructural protein nsp14. This protein has an RNA proofreading function and is also responsible for resistance to RNA mutagens.[12]

4) Pathogenesis

The immunopathology of COVID-19 explains the reaction of immune system against novel coronavirus infection. SARS-CoV-2 infection leads to an uncontrolled inflammatory response, lymphocytopenia, high cytokine levels and increased antibodies. The most prominent observations were depletion of lymphocytes, increased neutrophils, cytokine storm and antibody dependent enhancement. The SARS-CoV-2 virion that attacks ACE2 receptors on type 2 alveolar cells and release the viral genome (RNA) into the cytoplasm of host cell, the RNA further gets translated into structural proteins and then begins to

replicate. The viral particles further undergo transformation in the endoplasmic reticulum-Golgi intermediate compartment and released, then entrapped into vesicles, which on fusion with plasma membrane release the viral particles.[13]

5) Pathological finding

The lung biopsy specimens of one COVID-19 patient at autopsy showed bilateral diffuse alveolar damage with cellular fibro-myxoid exudates. Bilateral pulmonary edema with hyaline membrane formation, reflecting ARDS.[2] The reduced counts of peripheral CD4 and CD8 T cells were found but in a hyperactive status. A report on systemic anatomy at autopsy indicated gray white patchy lesions along with viscous fluid overflow in the lung section and pulmonary fiber bands, reflecting COVID-19 associated inflammatory response characterized by deep airway and alveolar damage.[2]

6) Immune response & Post infection Antibody formation

It is unclear which components of the immune system are most important in fighting SARS-CoV-2 and what levels of antibodies are required to maintain immunity. Most patients seroconvert, or become antibody positive, after 2 weeks of infection.[14] When virus enters the cells, a part of it as antigen is presented on the surface of antigen presentation cells (APC), which is crucial for the body's immune response. Antigen presentation on B and T cells ultimately leads to the production of the typical pattern of IgM and IgG antibodies. [13] Antibodies are detected as early as 6 days after symptom onset and increase steadily over the first 3–4 weeks. Overall, antibodies appear to peak 14–30 days after symptom onset and then slowly decline for 2–3 months. [14]

Researchers have found that these IgM antibodies lasts until week 12, while the IgG antibodies remain long lasting and can provide prolonged protection. These type of virus-specific neutralizing IgG antibodies play major role by regulating the infection at later phase and prevents reinfection in the future. [13] The IgG can be detected after a median of 14 days (IQR 10-18 days) from the onset of symptom during infection. [15] The serological tests to detect the presence of IgG antibodies may provide a more reliable estimation of the prevalence of SARS-CoV-2 past infection in the population, as is likely to persist for a more extended period after cleaning up the viral infection. [15]

Cell-mediated immunity by way of CD4+ or CD8+ T-cells can also be an important indicator of immunity. [16]

7) Clinical presentation

Persons infected with SARS-CoV-2 ranges from asymptomatic infection to severe acute respiratory distress, organ function damage and death. [17][2]

The common symptoms manifested in SARS-CoV-2 infected patients were fever (77.4 –98.6%), cough (59.4 –81.8%), fatigue (38.1 –69.6%), dyspnea (3.2 –55.0%), myalgia (11.1 –34.8%), sputum production (28.2 –56.5%), and headache (6.5 –33.9%). [2] Less common symptoms were diarrhea, nausea, vomiting, hemoptysis, sore throat, rhinorrhea and chest pain. Also in some cases conjunctival congestion was seen. [2] But one of the study mentioned 39.6% confirmed COVID-19 patients had gastrointestinal symptoms, and 10.1% patients presented with gastrointestinal discomfort at onset of disease.[2]

Even though fever, cough, myalgia, or fatigue are common symptoms but they are not unique features of SARS CoV2 because these symptoms are similar to that of other virus‚infected diseases such as influenza.[1][10] On the other hand, few of the patients did not showed fever at onset. Also, few of the patients developed fever after hospitalization and even some serious patients did not have fever.[2]

8) Diagnosis (Radiological, Laboratory diagnosis- Pathological, Biochemical & Microbiological)

Clinical diagnosis can be supported by different Pathological, Biochemical, Radiological and microbiological investigations. Of confirmed COVID19 patients, 5.0–36.2%, 35.3–82.1%, and 9.1–33.7% had thrombocytopenia, lymphopenia, and leukopenia, respectively. In Chen's et al research, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum ferritin, and interleukin-6 (IL6) elevated prominently. [2][18] Also increased levels of D-dimer, lactate dehydrogenase (LDH), creatine kinase (CK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), prolonged prothrombin time was seen in many patients. However, elevated levels of procalcitonin, troponin I and creatinine were uncommon.[2]

CT imaging showed reflection changes of disease and severity. Changes by SARS CoV2 seen on chest computed tomography (CT) are typical which included bilateral patchy shadows, ground-glass opacity, and subsegmental areas of consolidation, sometimes with a rounded morphology and a peripheral lung distribution.[2] Because of high sensitivity, CT Chest becomes more valuable diagnostic method for COVID-19.

Laboratory diagnosis of SARS-CoV-2 infection depends mainly on two approaches: nucleic acid testing, which detects viral RNA and serological testing, which detects antibodies elicited against SARS-CoV2 antigens.[8] Positive result to real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay or high-throughput sequencing for SARS-CoV-2 was consider as laboratory confirmed case with SARS-CoV-2 infection.[2] But confirmation by these molecular testing is difficult in mild clinical form or after long duration of onset of the disease. In such situation serological testing for detection of IgM, IgA and IgG directed against SARS-CoV-2 antigenic sites is promising alternative to assess SARS-Cov-2 infection.[19]

First line of adaptive defense against viral infection is IgM antibodies which are produced by short-lived plasma cells during the early phase of the B cell response, followed by IgG by long term humoral response.[19]Currently different types of serological tests available are Enzyme-Linked Immunosorbent Assay (ELISA), Chemiluminescent Immunoassay (CLIA), Lateral Flow Immunoassay (LFIA) and Immunofluorescent Assay (IFA)[13]. These methods can also provide a semi-quantitative measure of antibody responses that can distinguish between strong and weak responses.[8]

9) Treatment

Treatment strategies for SARS CoV2 patients included oxygen support (nasal cannula, mask oxygen inhalation, non-invasive ventilation, invasive mechanical ventilation), antiviral treatment, empirical antibiotic treatment, corticosteroid, intravenous immunoglobulin therapy, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO).[2]

There is no approved antiviral drugs for treatment of SARS-CoV-2 due to the absence of clinical evidence.[2] In treatment of SARS CoV2 infection oseltamivir, lopinavir and ritonavir were found to be not effective. [2] [20] Some studies found remdesivir and chloroquine were highly effective in the control of SARS-CoV-2 infection in vitro but in current situation according to WHO and joint guidelines by MOHFW, AIIMS and ICMR, Remdesivir, a reserve drug approved under Emergency Use Authorization, should be used only in selective moderate/ severe hospitalized Covid - 19 patients who require supplemental oxygen.[20][21][2] Corticosteroid together with other support care can be consider in severe patients to prevent ARDS development.[2]

10) Prognosis

Many severe patients infected with SARS-CoV-2 had complications, like ARDS, shock, acute renal injury, acute cardiac injury, and secondary infection. Mortality rate of SARS-CoV-2 found to be ranged from 0 to 14.6%.[2]

11) Vaccine – Antibody development

It is very unlikely of spontaneous disappearance of the virus from community and additional outbreaks are expected when the safety measures are breached. Also developing natural acquire immunity through infection in community will take long time and how long it will be protective from re-infection is matter of discussion.[7] The So-called "herd immunity" is reached when >90% of people become immune, so that virus get restricted and use of vaccines will allow us to reach herd immunity more rapidly. [7]

Vaccines can be based on whole viruses (live-attenuated or inactivated), proteins/peptides, RNA, DNA or live cells, viral vectors, nanoparticles or virus-like particles, subunit components.[7]

12) Preventive measures

Even though vaccines are available, until availability of effective vaccines for a large percentage of the global population, public health measures such as isolation, social distancing, and quarantine are must to prevent the spread of the virus. According to WHO recommendation protective measures such as maintaining a distance of at least 1 m between people, avoiding touching of eyes, nose or mouth, practicing frequent hand washing and respiratory hygiene will help to prevent the spread of disease.[10]

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