FAZAIA RUTH PFAU MEDICAL COLLEGE

DEPARTMENT OF PATHOLOGY

COVID-19 UPDATE 2020 (Part1)

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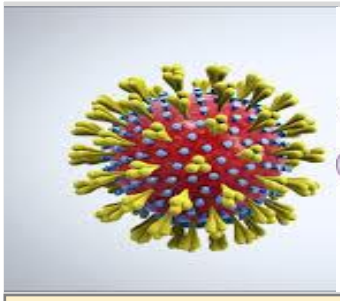
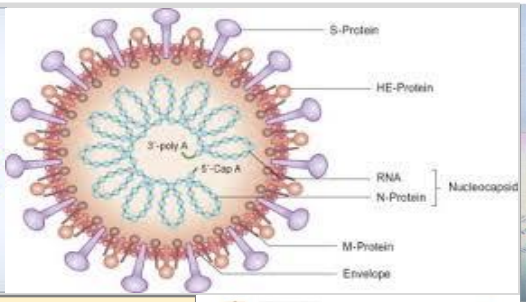
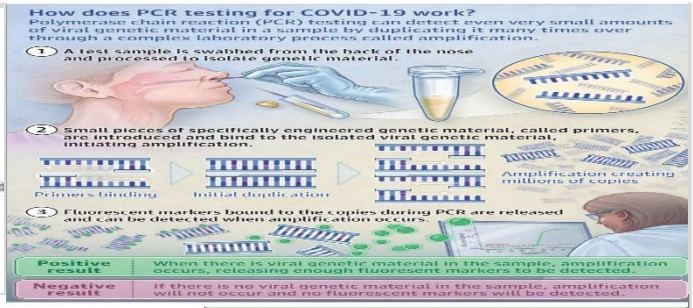






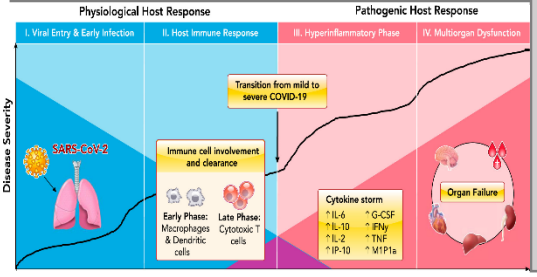
INTRODUCTION/HISTORICAL BACKGROUND

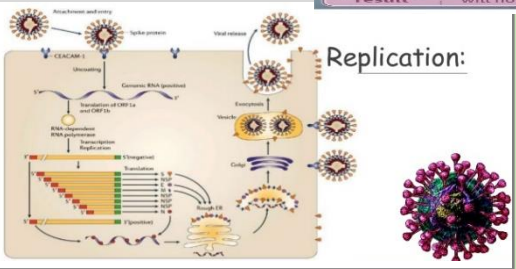
- Corona virus disease COVID-19 is caused by a novel beta-corona virus KNOWN as SARS-CoV-2.
- Corona virus was first identified as a cause of common cold in 1960 which belonged to family of SARS virus.
- The first outbreak of SARS virus occurred in 2003-2004 in China and subsequently it spread to other countries.
- It is a single stranded RNA virus belongs to the family of Coronaviridae.
- There are different species of corona virus (alpha, beta, MER-CoV, SARS-CoV-2) In SARS-COV-2 virus particles have four main structural proteins, Surface spike proteins(S), Membrane proteins (M), Envelope proteins (E) and Nucleocapsid proteins (N).
- Spike protein is responsible for attachment to host AEC2 receptors on various cells.
- Rest of the proteins are responsible for endocytosis, replication and virulence of the organism.
- In December 2019, SARS-COV-2 was first identified as a cause of upper and lower respiratory infection in Wuhan China. It rapidly spread resulting in an epidemic throughout China and gradually to other parts of the world. In March 2020 WHO declared it as Pandemic disease.
- Corona virus has been identified in several avian hosts, as well as in various mammals.
- **Transmission** is from animal to human and then from human to human via aerosols/droplet infection (macro/micro particles),fomites,close contact,,through feces.
- Ro is a measure of transmissibility denoting the theoretical expected number of secondary cases from any given case during the epidemic period of transmission
- An Ro >1 is consistent with sustained outbreak
- Viral particles shown to survive <24h on card board, <72 hrs. on plastic or steel
- Duration of viral shedding from illness onset mean 20 days. Nasopharyngeal viral load peaks within 5 days of symptoms onset followed by decline.
- Viral shedding duration is longer in more severe disease.

PATHOGENESIS/PATHOPHYSIOLOGY

Viral invasion to target hosts receptors. S protein responsible for viral binding and entry into the hosts cells.ACE2 acts as entry receptor for SARS COV2 which is mostly transmissible through large and macro respiratory droplets/particles to upper and lower respiratory tract(mainly nasal ciliated and alveolar epithelial cells).ACE2 also present in other tissues(small intestine, kidneys, heart, thyroid, adipose tissue). Following binding to hosts cell receptors, virus cell membrane fusion enabling entry into cells facilitated by transmembrane serine protease.

- SARS COV2 enters alveolar epithelial cells through ACE2 and surface spike(S) protein mediated by transmembrane serum protease 2(TMPSS2)
- Pulmonary recruitment of macrophages in response to chemokines and cytokines release (early phase)
- Direct viral infection of pulmonary macrophages
- Release of many pro inflammatory cytokines.
- Dendritic cells phagocytose virus in the lungs migrate to secondary lymphoid organs----activate antigen specific T-cells---travel to the lungs and destroy virally infected alveolar cells.
- Increased levels of IL-6, IL-2, IL-7,IL-10.CSF,IFNY,MCPI,TNF pro inflammatory cytokines implicated in cell damage and disease severity.
- Combined TL1 and TL2 response together wit IL -6(mainly) responsible for most of the damage (IL-6>55-80pg/ml) high risks patients.
- Elevation of acute phase reactant proteins (CRP, Ferritin)
- Decrease in lymphocytes and increase in neutrophils. Neutrophil: lymphocyte ratio appears to be useful indicator of prognosis in management.
- Lymphopenia (T cell distribution, exhaustion, TNF-a mediated apoptosis)
- Excessive secretion of proteases and ROS increase---further damage.
- Dysregulated immune response
- Direct infection of immune cells (monocytes and macrophages)
- Elevation of SARS COV-2 specific antibodies (ADE).





CLINICAL Correlation/Complications

STAGES OF DISEASE

- Large majority of confirmed SARS-COV-2 cases are mild to moderate (81%) with 14% progressing to severe illness and 5% critically ill patients developing ARDS, sepsis and multisystem organ failure.
- Most patients are able to generate sufficient immune response leading to viral clearance and resolution of disease.
- Risk factors associated with development of severe disease.

Older age/ Male sex, Hypertension, Cardiovascular disease, Obesity, Diabetes (Raised ACE2 receptors and Neutrophilic dysfunction), COPD, Chronic liver and kidney disease, Malignancy

CLINICAL CLASSIFICATION

Mild cases

- Clinical symptoms are mild (fever 97-98 F), flu like illness, headache, myalgia, fatigue, dry cough, shortness of breath ,GIT symptoms (diarrhea,nausea,vomiting,abdominal pain),,loss of sense of smell No pneumonia manifestation in imaging technique.

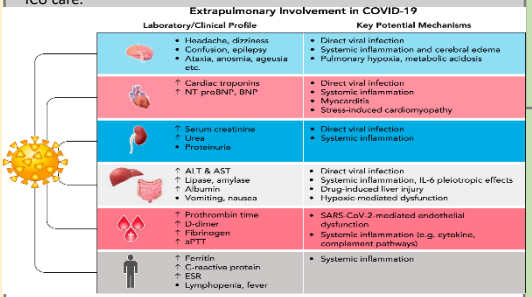
Severe cases

- Patients have high fever and respiratory tract symptoms. Pneumonia manifestations can be seen in imaging. Adult who meet any of the following criteria
- Respiratory rate≥30/minute. Oxygen saturation<92% at rest. Patients with >50% lesions progression in 24-48 hours in lung imaging should be treated as severe cases.

Critical cases

Meeting any of the following criteria

- Occurrence of respiratory failure requiring mechanical ventilation, presence of shock, multiple organ failure, DIC, cardiac symptoms requiring ICU care.



DIAGNOSIS:

TESTING FOR SARS-COV-2 INFECTION.

- **Molecular testing**

Specimens

Nasopharyngeal swab, Oropharyngeal swab, Lower respiratory tract, Saliva, Feces

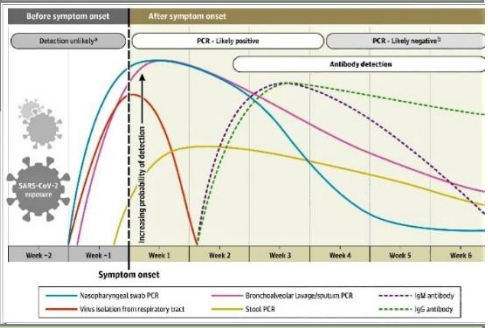
- **Nucleic acid amplification test(NAAT)-RT-PCR**
- Reverse transcriptase polymerase chain reaction (RT-PCR) NAAT remains gold standard for testing SARS COV- 2 virus.
- Test should be done preferably 5-6 days after onset of symptoms.
- Accurate specimen collection methods and timings are important
- Peak of viral shedding appears 3-5 days after the onset of symptoms.
- A single negative test does not rule out COVID 19.Test should be repeated based on high suspicion and clinical presentation of individuals.

ANTIGEN TESTING FOR SARS-COV-2 INFECTION

- Detection of viral antigen which is antigen based less sensitive than RT-PCR
- Advantages low cost and rapid turnover
- Suspected individuals having negative antigen test, NAAT testing/RT-PCR should be performed
- At present limited data to detect viral antigen in asymptomatic individuals

SEROLOGY/ANTIBODY TESTING

- Intended to identify persons with recent or previous SARS-COV-2 infection.
- It may take upto 20 days after onset of symptoms to detect antibody IgM or IgG to SARS-CoV-2
- Not recommended as the sole basis for diagnosing acute infection.
- May be utilized in combination with NAAT and antigen testing to maximize the sensitivity and specificity to detect basic infection (after 2-6 weeks)
- False positive test results may occur due to cross reactivity from antibodies to other corona virus.
- It is currently unclear how long antibodies persist following infection.
- It is at present unclear whether the presence of antibodies provides protective immunity against future infection.
- Serologic testing has usefulness in following situations
- To determine who is eligible to donate convalescent plasma.
- To measure the immune response in SARS-CoV-2 Vaccine studies.
- Estimate the proportion of population exposed to SARS-COV-2.



INDICATORS OF INFLAMMATORY RESPONSE

- Tests of C reactive protein (CRP) , Procalcitonin , Ferritin ,,IL-4,**IL-6**,IL-10,TNF-Y are useful to
- evaluate clinical progress
- Alert for severe/critical illness
- Provide a basis for treatment strategies.
- A rapid and significantly elevated CRP level indicates possibility of secondary infection.
- Expression level of IL-6 greatly involved in severe/critical cases and monitoring of levels helpful to assess disease progression.
- Tests for inflammatory markers should be performed initially and then serially for monitoring

CBC Findings

- Leukopenia
- Lymphopenia (at the beginning of disease-poor prognosis) level decreases with progression of disease.
- Neutrophilia
- Thrombocytopenia (mild to moderate but increased significantly with DIC)

SECONDARY BACTERIAL OR FUNGAL INFECTION

- Severe/critically, ill patients vulnerable to secondary infection
- In suspected secondary lung infection, sputum, tracheal aspirates, bronchoalveolar fluid for bacterial and fungal culture.
- Blood culture in patient with high fever in suspected sepsis or

Laboratory investigations and imaging techniques to be done in RT-PCR Positive cases. Tests need to be repeated as the stage advances to monitor and follow up of the patients.

STAGE	LAB TESTS	RADIOLOGY
MILD	• CBC • CRP • UREA/CREATININE • ALT • LDH • SERUM FERRITIN • PROCALCITONIN D-Dimers	CHEST X-RAY And or CT Scan
MODERATE	• ALL OF THE ABOVE + • ABG's (if dyspnea) • PULSE OXIMETRY	CHEST X-RAY CT-SCAN
SEVERE	• All of the above (In moderate stage) + • CARDIAC MARKERS CK-MB,TROP I(if symptoms are suggestive) Blood & sputum culture	Repeat CHEST X-RAY CT-SCAN Lung ultrasound ECG ECHOCARDIOGRAPHY CARDIAC MRI(may be needed in selective cases)
CRITICAL	• All of the above [in severe stage but cardiac markers (CK-MB,TROP I)are mandatory] + PT,APTT • D-DIMER • SERUM FIBRINOGEN • PLATELET COUNT repeat	All of the above with cardiac symptoms and in elderly patients.