COVID-19 PANDEMIC AND PEDIATRICS

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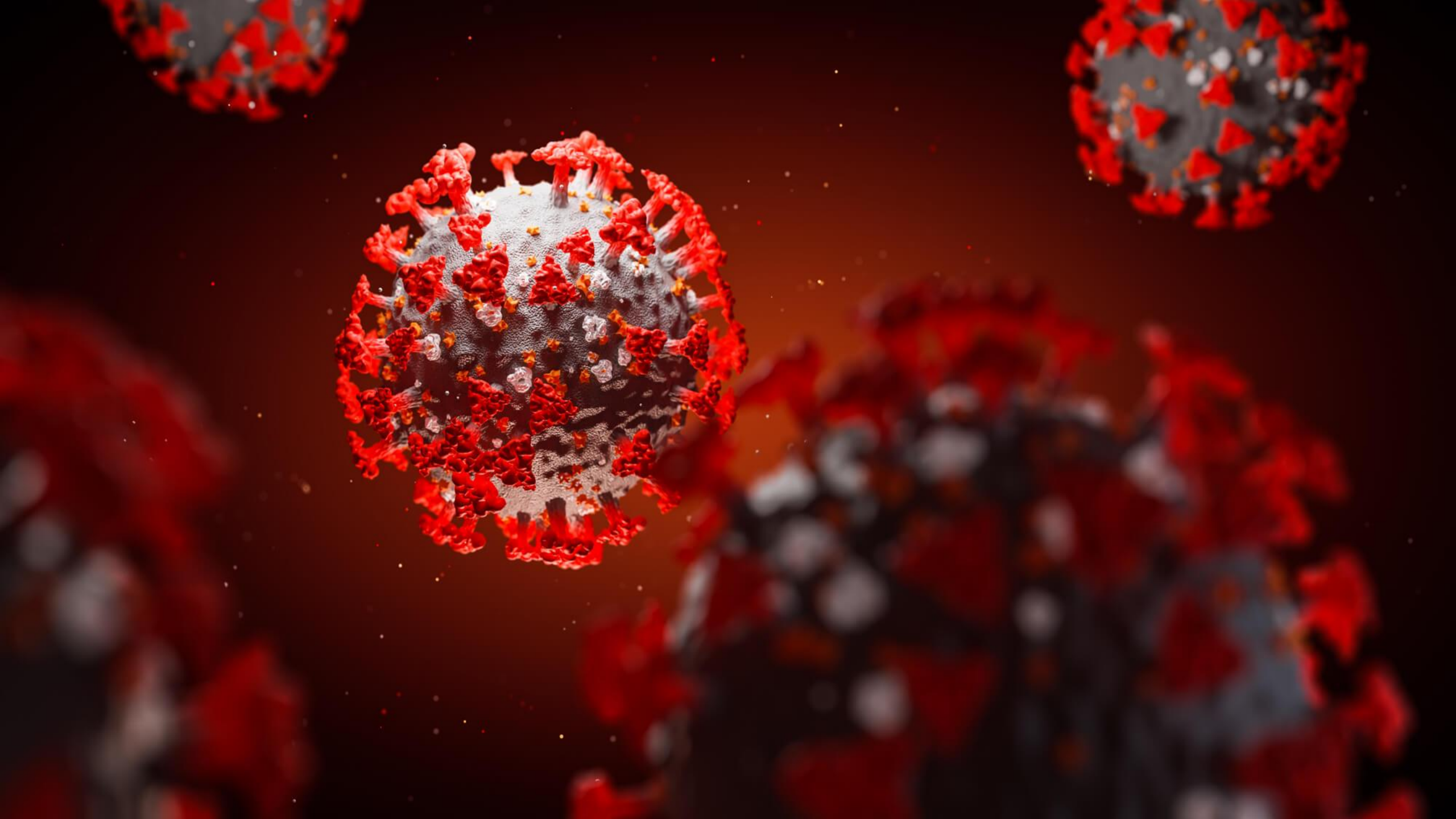


- Corona viruses derive their name from the Latin word “corona” meaning crown.

- The name refers to the unique appearance of the virus under an electron microscope as round particles with a rim of projections resembling the solar corona.

PART 1

EPIDEMIOLOGY OF COVID-19

- Corona virus belongs to the family Corona viridae which is known to produce mild respiratory diseases in humans.
- In recent times, there have been three major corona viruses leading to disease outbreaks:

➢ beginning with the severe acute respiratory syndrome corona virus (SARS–CoV) in 2002,

➢ followed by the Middle East respiratory syndrome coronavirus (MERS–CoV) in 2012,

➢ and now the severe acute respiratory syndrome corona virus 2 (SARS–CoV2)

- In Dec 2019, China reported an outbreak of pneumonia of unknown causes in Wuhan, the capital city of Hubei province. Most of the early cases were epidemiologically linked to the Huanan seafood wholesale market where aquatic animals and live animals were sold
- Using unbiased next-generation sequencing, an unknown betacoronavirus was discovered from lower respiratory tract samples of these patients. Human airway epithelial cells were used to isolate the virus that was named:

2019–novel Coronavirus (2019–nCoV)

- Phylogenetically, the novel coronavirus was found to be more similar to two bat derived coronavirus strains (~88% similarity) than coronaviruses which infect humans including SARS (~79% similarity) and MERS (~50% similarity).

- Based on phylogeny and taxonomy on February 11, 2020, the Coronaviridae study group of the International Committee on Taxonomy of Viruses named the virus as :

SARS–CoV2

- The World Health Organization (WHO) named the resultant disease as:

  Coronavirus disease (COVID-19)

- On March 11, 2020, WHO, after assessing the situation across the globe, declared COVID-19 as a pandemic.

- Outbreak : The increase in the number of cases in a region

- Epidemic : An increase , rapid and sudden transmission of disease in an area , more than expected.

- Pandemic : refers to the persistent transmission of disease at a high level of society between two or more continents.

- Since the initial report from China, the disease spread rapidly, and the number of cases increased exponentially.
- On January 11, the first case was reported outside mainland China in Thailand, and within months, the disease spread to all the continents except Antarctica.

Transmission

Zoonotic transmission initially appeared to be a pausible cause as majority of early cases had a history of exposure to wet markets.

However, by the end of January 2020, the number of people who developed the disease without exposure to the market or another person with respiratory symptoms increased.

The spread of the disease among persons who did not visit Wuhan and among healthcare workers suggested a person-to-person spread of the virus

- The exact mode of transmission of this virus is unknown.
- But, as with other respiratory viruses, droplet borne infection, either directly or indirectly, through fomites is probably the predominant mode of transmission.
- At present, there is no evidence for airborne transmission of the virus.
- Although virus particles have been detected in stool samples of both symptomatic and convalescing patients, the risk of feco-oral transmission is unclear.

DIAGNOSTIC CRITERIA

SUSPECTED OR PROBABLE CASE

- **2 clinical criteria+1 epidemiologic criteria**
- **Clinical** criteria:
- 1-Fever, fatigue , dry cough
- 2-Following chest imaging findings:
- Multiple small patchy shadows and interstitial changes or ground –glass opacities
- Bilateral segmental lung consolidation,especially in the periphery on chest CT
- 3-White blood cells counts are normal or decreased,or with decreased lymphocyte count.

- Epidemiologic criteria:

1- Children with a travel or a history of contacting patient with fever or respiratory symptoms or a history of contacting confirmed or suspected cases infected with SARS-COV-2 within 14 d prior to disease onset.

2-Children who are related with a cluster outbreak, suspected or confirmed cases infected with SARS-COV-2

3-Newborns delivered by suspected or confirmed SARS-COV-2 infected mothers

CONFIRMED CASE

- 1- Throat swab ,sputum, stool or blood samples tested positive for SARS-COV-2 nucleic acid using RT-PCR.

- 2- Genetic sequencing of throat swab, sputum , stool or blood samples being highly homologous with the known SARS-COV-2

- 3- SARS-COV-2 granules being isolated by culture from throat swab, sputum , stool or blood samples

PART 2

PATHOPHISIOLOGY OF SARS-COV-2

MECHANISM OF SARS-COV-2 INVASION INTO HOST CELLS

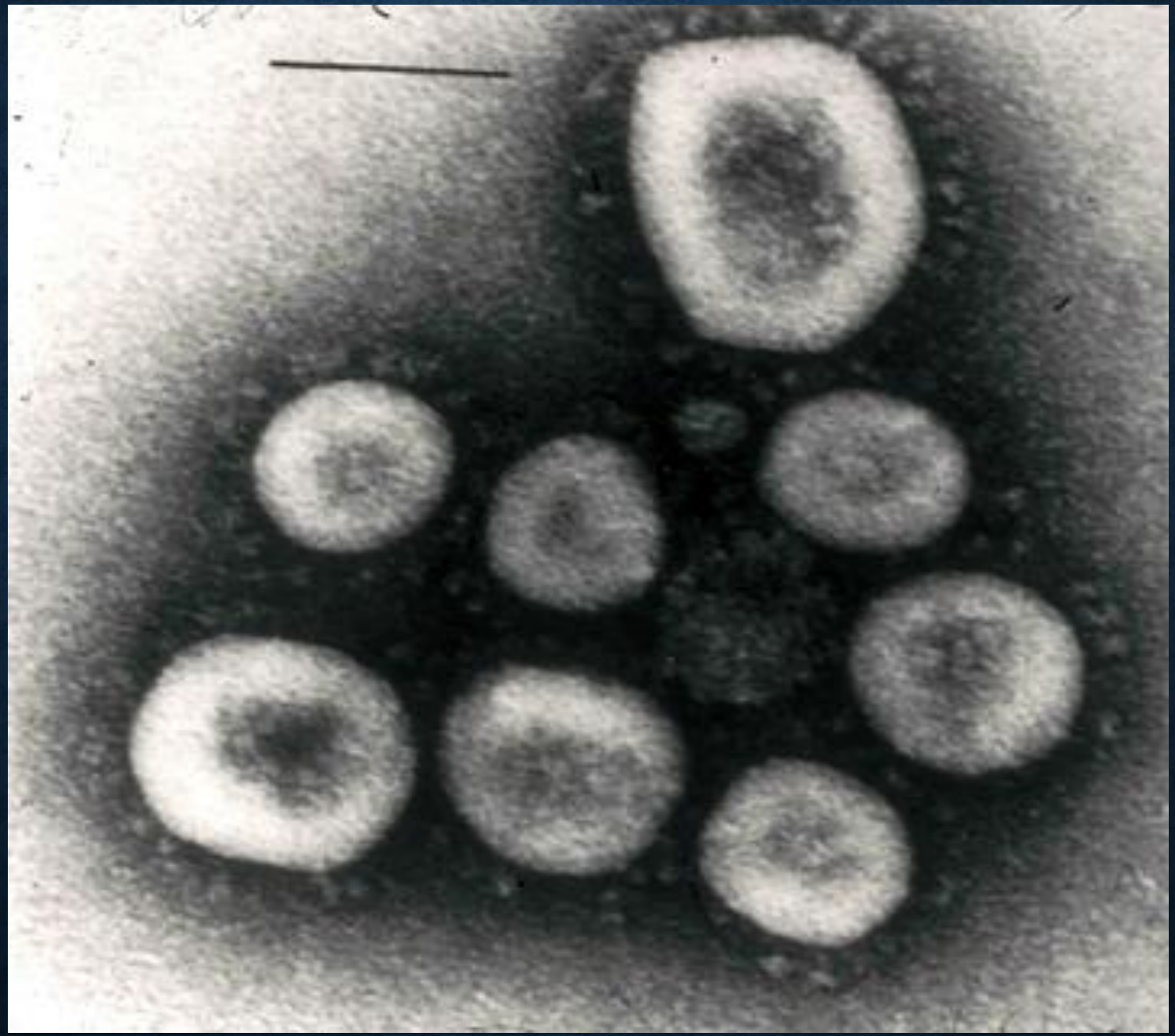
To understand the pathogenic mechanisms of SARSCoV-2 and to discuss the current therapeutic targets :

it is important to describe

the viral structure,

genome,

replication cycle



- CoVs are positive-stranded RNA viruses with a nucleocapsid and envelop
- A SARSCoV-2 virion is approximately 50–200 nm in diameter
- Has a +ssRNA genome of approximately 29.9 kb in length
- The largest known RNA virus with a 5′-cap structure and 3′-poly-A-tail and possess 14 putative open reading frames (ORFs) encoding 27 proteins

- They are divided into four genera:

  α, β, γ, and δ based on their genomic structure

- α and β coronaviruses infect only mammals.
- Human coronaviruses such as 229E and NL63 are responsible for common cold and croup and belong to α coronavirus.
- In contrast, SARS-CoV, (MERS-CoV) and SARS-CoV-2 are classified to β coronaviruses.

The life cycle of the virus with the host consists of the following 5 steps:

attachment

penetration

biosynthesis

maturation

release

- Once viruses bind to host receptors (attachment),

  they enter host cells through endocytosis or membrane fusion (penetration).

- Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication.

- Viral mRNA is used to make viral proteins (biosynthesis).

- Then, new viral particles are made (maturation and released).

- The virion has four structural proteins:

  the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins;

  - the N protein holds the RNA genome,
  - the S, E, and M proteins together create the viral envelope

SPIKE

- Composed of a transmembrane trimetric glycoprotein protruding from the viral surface, which determines the diversity of coronaviruses and host tropism.

- Spike comprises two functional subunits:

  S1 subunit is responsible for binding to the host cell receptor

  S2 subunit is for the fusion of the viral and cellular membranes.

- Angiotensin converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-Co.

- Structural and functional analysis showed that the spike for SARS-CoV-2 also bound to ACE2

- ACE2 expression was high in

  lung, heart, ileum, kidney and bladder

- In lung:

  ACE2 was highly expressed on lung epithelial cells.

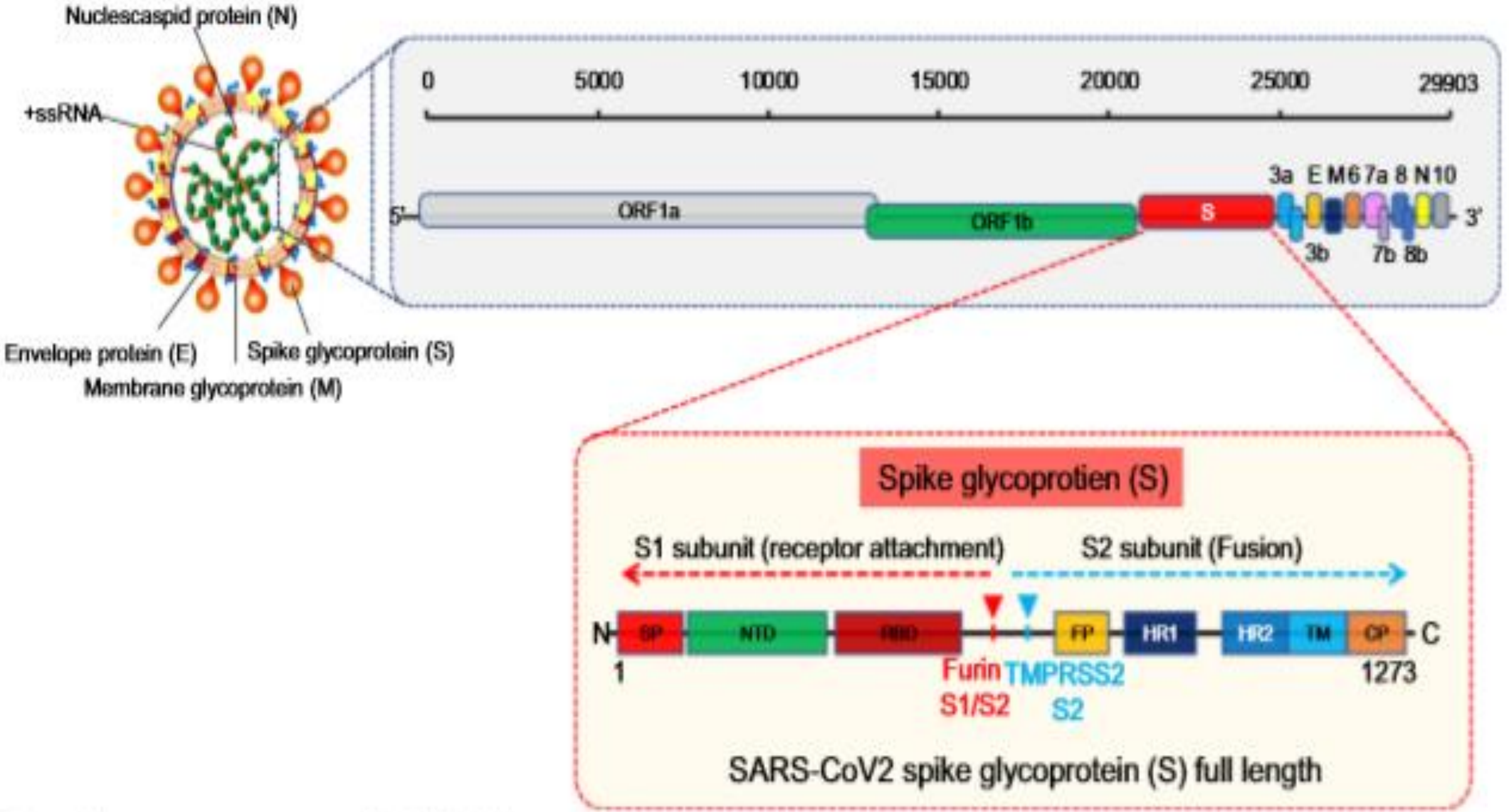
- Following the binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage.
- A two-step sequential protease cleavage to activate spike protein of SARS-CoV and MERS-CoV was proposed as a model, consisting of cleavage at the S1/S2 cleavage site for priming and a cleavage for activation at the S′2 site, a position adjacent to a fusion peptide within the S2 subunit .

- After the cleavage at the S1/S2 cleavage site,

  S1 and S2 subunits remain non-covalently bound and the distal S1 subunit contributes to the stabilization of the membrane-anchored S2 subunit at the prefusion state .

- Subsequent cleavage at the S′2 site presumably activates the spike for membrane fusion via irreversible, conformational changes.

- The coronavirus spike is unusual among viruses because a range of different proteases can cleave and activate it .
- The characteristics unique to SARS-CoV-2 among coronaviruses is the **existence of furin cleavage site (“RPPA” sequence) at the S1/S2 site.**
- The S1/S2 site of SARS-CoV-2 was entirely subjected to cleavage during biosynthesis in a drastic contrast to SARS-CoV spike, which was incorporated into assembly without cleavage .
- Although the S1/S2 site was also subjected to cleavage by other proteases such as transmembrane protease serine 2 (TMPRSS2) and cathepsin L , the ubiquitous expression of furin likely makes this virus very pathogenic.


Nucleocaspid protein (N)
+ssRNA
Envelope protein (E)
Membrane glycoprotein (M)
Spike glycoprotein (S)
0
5000
10000
15000
20000
25000
29903
5'
ORF1a
ORF1b
S
3a
E
M
6
7a
8
N
10
3b
7b
8b
3'
Spike glycoprotien (S)
S1 subunit (receptor attachment)
S2 subunit (Fusion)
N
SP
NTD
RBD
FP
HR1
HR2
TM
CP
C
1
1273
Furin
S1/S2
TMPRSS2
S2
SARS-CoV2 spike glycoprotein (S) full length

HOST RESPONSE TO SARS-COV-2

- Because ACE2 is highly expressed on the apical side of lung epithelial cells in the alveolar space ,

  this virus can likely enter and destroy them.

- This matches with the fact that the early lung injury was often seen in the distal airway.

- 3 main components for innate immunity in the airway :
    1. Epithelial cells,
    2. alveolar macrophages
    3. dendritic cells (DCs)

- DCs reside underneath the epithelium.
- Macrophages are located at the apical side of the epithelium.
- DCs and macrophages serve as innate immune cells to fight against viruses till adaptive immunity is involved.

- **CD4+** and **CD8+** T cells :

  play a critical role.

- CD4+ T cells :

  activate B cells to promote the production of virus-specificAb

- CD8+ T cells :

  can kill viral infected cells.

- Patients with severe diseases:

1.showed lymphopenia, particularly the reduction in peripheral blood T cells .

2.were reported to have increased plasma concentrations of proinflammatory cytokines:

IL-6, IL-10

G-CSF

monocyte chemoattractant protein 1 (MCP1)

macrophage inflammatory protein (MIP)1α

tumor necrosis factor (TNF)-α

The more severe conditions patients → the higher IL-6 levels

- CD4+ and CD8+ T cells were activated in those patients as suggested by higher expression of CD69, CD38 and CD44.
- Higher percentage of checkpoint receptor Tm3+PD-1+ subsets in CD4+ and CD8+ T cells showed that T cells were also exhausted.
- NK group 2 member A (NKG2A), another marker for exhaustion was elevated on CD8+ T cells
- Exhaustion of T cells could have led to the progression of the disease

Another interesting finding was that:

aberrant pathogenic CD4+ T cells with co-expressing IFN-γ and GM-CSF were seen in COVID-19 patients with severe disease.

- GM-CSF production from T cells has been reported as a response to virus infection.

- GM-CSF can help to differentiate innate immune cells and augment T cell function, but it can initiate tissue damage at excess.
- GM-CSF+IFN-γ+ CD4+ T cells :

were previously seen upon strong T cell receptor (TCR) responses in experimental autoimmune encephalomyelitis (EAE) models,

where CD8+ T cells expressing GM-CSF were found at higher percentage and secreted IL-6.

- SARS-CoV infected lung epithelial cells produced IL-8 in addition to IL-6
- IL-8 is a well-known chemoattractant for neutrophils and T cells.
- Infiltration of a large number of inflammatory cells were observed in the lungs from severe COVID-19 patients , and these cells presumably consist of a constellation of innate immune cells and adaptive immune cells.
- Among innate immune cells, we expect the majority to be neutrophils.
- Neutrophils can act as double-edged sword as neutrophils can induce lung injury.

- The majority of the observed infiltrating adaptive immune cells were likely T cells, considering that the significant reduction in circulating T cells was reported.

- CD8+ T cells are primary cytotoxic T cells.

- Severe patients also showed pathological cytotoxic T cells derived from CD4+ T cells.

- These cytotoxic T cells can kill virus but also contribute to lung injury.

- Circulating monocytes respond to GM-CSF released by these pathological T cells.
- CD14+CD16+ inflammatory monocyte subsets, which seldom exist in healthy controls and were also found at significantly higher percentage in COVID-19 patients.
- These inflammatory CD14+CD16+ monocytes had high expression of IL-6, which likely accelerated the progression of systemic inflammatory response.

- An **interesting note** is that :

  ACE2 was significantly expressed on innate lymphoid cells ILC2 and ILC3

- NK cells are a member of ILC1, which constitute a large portion of ILCs in the lung (~95%).

- ILC2 and ILC3 work for mucous homeostasis.
- There is a very limited study of ILC2 and ILC3 in coronavirus infection

- In additionto respiratory symptoms,

thrombosis and **pulmonary embolism** have been observed in severe diseases.

- This is in line with the finding that elevated **d-dimer** and **fibrinogen** levels were observed in severe diseases.

- The function of the endothelium includes:

  promotion of vasodilation, fibrinolysis, and anti-aggregation.

- Endothelium plays a significant role in thrombotic regulation,

hypercoagulable profiles seen in severe diseases likely indicate significant endothelial injury.

- Endothelial cells also express ACE2 .
- Of note, the endothelial cells represent the one third of lung cells.
- Microvascular permeability as a result of the endothelial injury can facilitate viral invasion.

PART3

COVID19 IN PEDIATRICS

- Infants and young children are typically at high risk for admission to hospitals due to respiratory tract infection with viruses as respiratory syncytial virus and influenza virus.

- In contrast, pediatric COVID-19 patients have relatively milder symptoms in general compared to elder patients.

- Because the correlation between the severity of COVID-19 and the amount of viral loads (or the duration of virus-shedding period) , children may have less virus loads even if they get COVID-19.

WHY CHILDREN INFECTED WITH SARS-COVV-2 HAVE LESS SEVERE SYMPTOMS

1- Differences in the immune system:

- Children have a stronger innate immune response

- Higher proportion of total lymphocytes and absolute number of T and B cells , as well as natural killer cells, which might help to fight the virus.

2- lower prevalence in children of the co-morbidities that have been associated with sever disease , such as diabetes,chronic lung,heart and kidney problems or arterial hypertension.

3- Common circulating coronavirus are frequent in this age group,Preexisting immunity and cross-reacting antibodies to SARS-COV-2 may play a protective role.

- Despite the fact that most individuals develop antibodies to common circulation coronaviruses during childhood,infections later in life occur,suggesting waning immunity against coronaviruses and increased susceptibility in adults.

- 4- Children are usually infected by an adult

they are infected by a second or third generation of the virus.

- For SARS and MERS-COV,these following generation have been described to have decreased pathogenicity.

5- Related to ACE2 receptors that are one of the main receptors for the entry of SARS- and SARS-COV-2 into human cells.

It has been postulated that children have less ACE2 receptors with lower affinity compared with adults

less affected by SARS-COV-2

- The interaction between ACE2 concentration and the number and affinity of ACE2 receptor is likely complex and might also be influenced by genetics.

SYMPTOMS AND SEVERITY OF COVID-19

IN CHILDREN

CLINICAL PRESENTATION

The incubation period of SARS-CoV-2 appears to be about the same for children as in adults, at 2-14 days with an average of 6 days.

- Signs or symptoms of COVID-19 in children include:

- Fever
- Fatigue
- Headache
- Myalgia
- Cough
- Nasal congestion or rhinorrhea

- New loss of taste or smell
- Sore throat
- Shortness of breath or difficulty breathing
- Abdominal pain
- Diarrhea
- Nausea or vomiting
- Poor appetite or poor feeding

- Children infected with SARS-CoV-2 may have many of these non-specific symptoms,

- may only have a few (such as only upper respiratory symptoms or only gastrointestinal symptoms),

- or may be asymptomatic.

- The most common symptoms in children are cough and/or fever.

SEVERITY OF ILLNESS IN CHILDREN

- While children infected with SARS-CoV-2 are less likely to develop severe illness compared with adults, children are still at risk of developing severe illness and complications from COVID-19.
- Recent COVID-19 hospitalization surveillance data shows that the rate of hospitalization among children is low (8.0 per 100,000 population) compared with that in adults (164.5 per 100,000 population)

- BUT hospitalization rates in children are increasing.

- While children have lower rates of mechanical ventilation and death than adults, 1 in 3 children hospitalized with COVID-19 in the United States were admitted to the intensive care unit, which is the same in adults.

• Current evidence suggests that children with certain underlying medical conditions and infants (age <1 year)

might be at increased risk for severe illness from SARS-CoV-2 infection.

Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions.

- Children with medical complexity, with genetic, neurologic, metabolic conditions,or with congenital heart disease

at increased risk for severe illness from COVID-19.

- Similar to adults, children with obesity, diabetes, asthma and chronic lung disease, sickle cell disease, or immunosuppression

at increased risk for severe illness from COVID-19.

- Similar to adults, children with severe COVID-19

may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multi-organ system failure.

- Some children with COVID-19 have developed other serious problems like :

intussusception or diabetic ketoacidosis.

THANKS FOR YOUR ATTENTION