CORONAVIRIDAE

VIROLOGY, PATHOGENESIS AND COMPLICATIONS IN CHILDREN
CORONAVIRIDAE

- Are members of a family of large, enveloped, positive-sense single-stranded RNA viruses, replicate in cytoplasm of animal host cells.

- Genomes range in length 27 to 32 kb, the largest of any of the RNA viruses.

- Envelope peplomers are solar corona.
GENOMIC ORGANIZATION

- Coronaviruses contain a non-segmented, positive-sense RNA genome of ~30 kb.
- The genome contains a 5’ cap structure along with a 3’ poly (A) tail, allowing it to act as an mRNA for translation of the replicase polyproteins.
- The replicase gene encoding the nonstructural proteins (nsps) occupies two-thirds of the genome, about 20 kb, as opposed to the structural and accessory proteins, which make up only about 10 kb of the viral genome.
CORONAVIRUSES

• Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy.

• They are largely divided into four genera; α, β, γ, and δ based on their genomic structure. α and β coronaviruses infect only mammals.
The organization of the coronavirus genome is:
- 5’-leader-UTR- replicase-S (Spike)
- E (Envelope)
- M (Membrane)
- N (Nucleocapsid)
- 3’ UTR-poly (A) tail
- Accessory genes interspersed within the structural genes at the 3’ end of the genome
GENOMIC ORGANIZATION

- Genome is linear plus -sense ssRNA
  - Capped, Polyadenylated & Infectious.
- Three or four structural proteins:
  - Nucleoprotein (N),
  - Peplomer gp (S),
  - Transmembrane gp (M),
  - Hemaglutinin-esterase (HE).

α-CoVs
- HCoV-229E

β-CoVs
- MHV
- SARS-CoV
- MERS-CoV

γ-CoVs
- IBV
Coronavirus composition

- Spike Glycoprotein (S)
- M-Protein
- Hemagglutinin-esterase dimer (HE)
- Envelope
- RNA and N protein
- E-Protein
HUMAN CORONAVIRUSES

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)
5. MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
6. SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
7. SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)
Several coronaviruses cause fatal systemic diseases in animals:

- Feline infectious peritonitis virus
- Hemagglutinating encephalomyelitis virus
- Infectious bronchitis virus
- Mouse hepatitis virus

It cause economically important diseases in domestic animals.
### Coronaviruses, host ranges and diseases

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>Virus</th>
<th>Host</th>
<th>Diseases (infection sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCoV-229E</td>
<td>human</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TGEV</td>
<td>pig</td>
<td>(X)</td>
</tr>
<tr>
<td></td>
<td>PRCoV</td>
<td>pig</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PEDV</td>
<td>pig</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>FIPV</td>
<td>cat</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>FCoV</td>
<td>cat</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CCoV</td>
<td>dog</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>HCoV-OC43</td>
<td>human</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MHV</td>
<td>mouse</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>RCoV</td>
<td>rat</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>HEV</td>
<td>pig</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BCoV**</td>
<td>cattle</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>IBV</td>
<td>chicken</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TCoV</td>
<td>turkey</td>
<td>X</td>
</tr>
<tr>
<td>4??</td>
<td>SARS-CoV</td>
<td>human</td>
<td>(X)</td>
</tr>
</tbody>
</table>

- Respiratory: X
- Enteric: (X)
- Other: X Systemic, CNS, Eye, GU, CNS, Kidney
## Coronaviruses, host ranges and receptors

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>Virus</th>
<th>Host</th>
<th>Receptor</th>
<th>Co-receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCoV-229E</td>
<td>human</td>
<td>human aminopeptidase N (hAPN)</td>
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</tr>
<tr>
<td></td>
<td>TGEV</td>
<td>pig</td>
<td>porcine APN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRCoV</td>
<td>pig</td>
<td>porcine APN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEDV</td>
<td>pig</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>FIPV</td>
<td>cat</td>
<td>feline APN</td>
<td></td>
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<tr>
<td></td>
<td>FCoV</td>
<td>cat</td>
<td>feline APN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CCoV</td>
<td>dog</td>
<td>canine APN</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>HCoV-OC43</td>
<td>human</td>
<td></td>
<td>9-0AcNA</td>
</tr>
<tr>
<td></td>
<td>MHV</td>
<td>mouse</td>
<td>murine CEACAM1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCoV</td>
<td>rat</td>
<td></td>
<td>9-0AcNA</td>
</tr>
<tr>
<td></td>
<td>HEV</td>
<td>pig</td>
<td></td>
<td>9-0AcNA</td>
</tr>
<tr>
<td></td>
<td>BCoV</td>
<td>cattle</td>
<td></td>
<td>9-0AcNA</td>
</tr>
<tr>
<td>3</td>
<td>IBV</td>
<td>chicken</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCoV</td>
<td>turkey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4??</td>
<td>SARS-CoV</td>
<td>human</td>
<td>Angiotensin-2 (ACE-2)</td>
<td></td>
</tr>
</tbody>
</table>
Coronavirus pathogenesis

Host factors

- They cause more severe disease in neonates, the elderly, and in individuals with underlying illnesses, with a greater incidence of lower respiratory tract infection in these populations.

- The propensity of these viruses to jump between species, to establish infection in a new host

- As bats seem to be a significant reservoir for these viruses, it will be interesting to determine how they seem to avoid clinically evident disease and become persistently infected

- Host immunopathological response
Coronavirus pathogenesis

- Viral factors
  - Viral structural proteins
    - E protein (ion channel)
  - Viral non structural proteins
    - Nsp1, Nsp15
  - Immune evasion
To test the contribution of E protein IC activity in virus pathogenesis, two recombinant mouse–adapted SARS-CoVs, each containing one single amino acid mutation that suppressed ion conductivity, were engineered.

Interestingly, mice infected with viruses displaying E protein IC activity, either with the wild–type E protein sequence or with the revertants that restored ion transport, rapidly lost weight and died. In contrast, mice infected with mutants lacking IC activity, which did not incorporate mutations within E gene during the experiment, recovered from disease and most survived. Knocking down E protein IC activity did not significantly affect virus growth in infected mice but decreased edema accumulation, the major determinant of acute respiratory distress syndrome (ARDS) leading to death.

Levels of inflammasome-activated IL-1β were reduced in the lung airways of the animals infected with viruses lacking E protein IC activity, indicating that E protein IC function is required for inflammasome activation. Reduction of IL-1β was accompanied by diminished amounts of TNF and IL-6 in the absence of E protein ion conductivity. All these key cytokines promote the progression of lung damage and ARDS pathology. In conclusion, E protein IC activity represents a new determinant for SARS-CoV virulence.

Coronavirus nonstructural protein 1: Common and distinct functions in the regulation of host and viral gene expression

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Summary of the biological functions of coronavirus nsp1.

<table>
<thead>
<tr>
<th>Nsp1</th>
<th>Length (amino acids)</th>
<th>Function(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-CoV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGEV</td>
<td>110</td>
<td>• Translation inhibition</td>
<td>• Huang et al., 2011a</td>
</tr>
<tr>
<td>HCoV-229E</td>
<td>110</td>
<td>• Inhibition of reporter gene expression from constitutive and inducible promoters</td>
<td>• Zust et al., 2007; Wang et al., 2010</td>
</tr>
<tr>
<td>HCoV-NL63</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-CoV</td>
<td>Lineage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHV</td>
<td>A</td>
<td>• Induction of cell cycle arrest</td>
<td>• Chen et al., 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inhibition of reporter gene expression from constitutive and inducible promoters</td>
<td>• Zust et al., 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inhibition of type I IFN signaling*</td>
<td>• Lei et al., 2013</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>B</td>
<td>• Inhibition of type I IFN induction and signaling*</td>
<td>• Kamitani et al., 2006; Wathelet et al., 2007; Narayanan et al., 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Translation inhibition*</td>
<td>• Narayanan et al., 2008; Kamitani et al., 2009; Lokugamage et al., 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Induction of host mRNA cleavage</td>
<td>• Kamitani et al., 2009; Huang et al., 2011b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Induction of host mRNA decay*</td>
<td>• Kamitani et al., 2006; Narayanan et al., 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Induction of cytokines and chemokines</td>
<td>• Law et al., 2007; Pfefferle et al., 2011</td>
</tr>
<tr>
<td>Bat CoV:Rm1</td>
<td>B</td>
<td>• Inhibition of host protein synthesis</td>
<td>• Tohya et al., 2009</td>
</tr>
<tr>
<td>Bat CoV:133</td>
<td>C</td>
<td>• Induction of host mRNA decay</td>
<td></td>
</tr>
<tr>
<td>Bat CoV:HKU9-1</td>
<td>D</td>
<td>• Inhibition of type I IFN and IFN-stimulated gene induction</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes function(s) validated in virus infection
Two-pronged strategy of SARS-CoV nsp1 to inhibit host protein synthesis

Nsp1 binds to 40S ribosomal subunit

Translation inhibition

Endonucleolytic mRNA cleavage

Xrn1-mediated mRNA decay

5’ → 3’ decay
Corona nsp1 is a major virulence factor

- The replication of mutant virus, Covs–nsp1, was similar to wild-type Covs in cultured cells, including primary professional antigen-presenting cells, such as dendritic cells and macrophages, but its growth was severely attenuated in vivo, implying that Corona nsp1 is a major virulence factor.
capped mRNAs and within the ribosome loading region of mRNAs carrying picornavirus type I and type II internal ribosome entry sites (IRESes), whereas mRNAs carrying the IRESes of cricket paralysis virus, hepatitis C virus or classical swine fever virus are resistant to nsp1-induced RNA cleavage (Huang et al., 2011b). It has been proposed that the template-dependent nature of SARS-CoV nsp1-induced mRNA cleavage could be due to differences in the requirement of translation initiation factors and mechanism of translation initiation among capped cellular mRNAs and mRNAs with different IRESes (Huang et al., 2011b). However, the exact mechanism underlying the template-dependent mRNA cleavage by SARS-CoV nsp1 still remains to be clarified.

A nuclear magnetic resonance (NMR) structure of the N-terminal region of SARS-CoV nsp1 revealed some unique structural features, including a complex irregular β-barrel fold (Almeida et al., 2007). This study also alluded to the potential role of positively charged residues exposed on the surface of SARS-CoV nsp1 in the mRNA degradation activity of SARS-CoV nsp1 (Almeida et al., 2007). In line with this possibility, a mutated SARS-CoV nsp1, carrying alanine substitution of the charged residues R124 and K125 that are exposed on the surface of nsp1, lacks the mRNA cleavage function but retains the translation inhibition activity, implying the importance of these residues for the mRNA cleavage property of SARS-CoV nsp1 (Lokugamage et al., 2012). The isolation of this cleavage-defective (CD) mutant of SARS-CoV nsp1, nsp1-CD, demonstrates that the translation inhibition function of SARS-CoV nsp1 can be abolished by a mutation in the nsp1 sequence that decreases its affinity for mRNA, without affecting the function of other viral proteins. The results suggest that nsp1 plays a critical role in viral replication and that the CD mutant may serve as a useful tool for studying the interaction between nsp1 and the host cell. The CD mutant may also be useful for investigating the potential use of nsp1 as a therapeutic target for the treatment of viral diseases.

replication of a mutant SARS-CoV, encoding nsp1 with the mutations R124S and K125E, was strongly attenuated in cells with an intact IFN response (Wathelet et al., 2007). Collectively, these studies highlight the role of SARS-CoV nsp1 in regulating the innate immune response during virus infection and also lend further support to the notion that SARS-CoV nsp1 is a potential virulence factor that contributes to viral pathogenesis.

It is worth noting that the nsp1 of bat CoVs belonging to different β-CoV lineages also exhibit functional similarities with SARS-CoV nsp1 (Tohya et al., 2009). Nsp1 of the bat CoV strains, Rm1, 133 and HKU9-1, belonging to β-CoV B, β-CoV C and β-CoV D lineages, respectively, also displayed an ability to inhibit host protein synthesis and promote host mRNA degradation in mammalian cells (Tohya et al., 2009). In addition, expression of these bat CoV nsp1 in trans inhibits the induction of type I IFN and IFN-stimulated genes in cells infected with the IFN-inducing SCoV-mt (Tohya et al., 2009). However, these bat CoV nsp1 had differential inhibitory activities, indicating possible differences in their mechanism of action (Tohya et al., 2009). Nevertheless, the evidence of a conserved biological function among the nsp1 of SARS-CoV and bat CoVs in the β-CoV genus could have potentially significant implications, considering the identification of bats as the natural reservoir of several α-CoVs and β-CoVs, including those closely related to SARS-CoV, and the potential of their virome as the source of emerging human CoVs (Smith and Wang, 2013).
Nsp1 roles in viral life:

1. block host gene expression including the innate immune response genes like type I IFN, ISG15 and ISG56, by inhibiting host protein synthesis and promoting the degradation of host mRNAs in SARS–CoV infected cells.

2. In addition, it also highlights functionally significant correlations between the nsp1 of CoVs belonging to different genera, despite the lack of obvious primary sequence homology with each other, suggesting their evolutionary relatedness and role in the adaptation of CoVs to different host species.
Coronavirus nonstructural protein 15 mediates evasion of dsRNA sensors and limits apoptosis in macrophages

Macrophages are immune cells equipped with multiple double–stranded RNA (dsRNA) sensors designed to detect viral infection and amplify innate antiviral immunity. However, many coronaviruses can infect and propagate in macrophages without activating dsRNA sensors. Here we present a function of murine coronavirus nonstructural protein 15 in preventing detection of viral dsRNA by host sensors. We show that coronaviruses expressing a mutant form of nonstructural protein 15 allow for activation of dsRNA sensors, resulting in an early induction of interferon, rapid apoptosis of macrophages, and a protective immune response in mice. Identifying the strategies used by viruses to evade detection provides us with new approaches for generating vaccines that elicit robust innate immune responses and protective immunity.
The S protein mediates attachment of the virus to the host cell surface receptors and subsequent fusion between the viral and host cell membranes to facilitate viral entry into the host cell.

In some CoVs, the expression of S at the cell membrane can also mediate cell–cell fusion between infected and adjacent, uninfected cells. This formation of giant, multinucleated cells, or syncytia, has been proposed as a strategy to allow direct spreading of the virus between cells, subverting virus–neutralising antibodies.

Prior to the SARS–CoV outbreak, coronaviruses were only thought to cause mild, self-limiting respiratory infections in humans.

Two of these human coronaviruses are α-coronaviruses (HCoV–229E and HCoV–NL63) while the other two are β-coronaviruses (HCoV–OC43 and HCoV–HKU1).

HCoV–229E and HCoV–OC43 were isolated nearly 50 years ago while HCoV–NL63 and HCoV–HKU1 were only recently identified following the SARS–CoV outbreak.

These viruses are endemic in the human populations, causing 15–30% of respiratory tract infections each year.
Human Coronaviruses

- One interesting aspect of these viruses is their differences in tolerance to genetic variability.

- HCoV–229E isolates from around the world have only minimal sequence divergence while HCoV–OC43 isolates from the same location but isolated in different years show significant genetic variability.

- This likely explains the inability of HCoV–229E to cross the species barrier to infect mice while HCoV–OC43 and the closely related bovine coronavirus, BCoV, are capable of infecting mice and several ruminant species.
The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission associated with the seafood market in Wuhan, China. Later it was recognized that human to human transmission played a major role in the subsequent outbreak. The disease caused by this virus was called Coronavirus disease 19 (COVID-19) and a pandemic was declared by the WHO.
SARS-COV-2 PATHOGENESIS

• The study comparing aged and young macaques infected with SARS-CoV showed that aged macaques had more robust proinflammatory responses with worse lung pathology. A similar result was reported using aged and young mice infected with SARS-CoV.

• Severe COVID-19 infection is characterized by a massive proinflammatory response or cytokine storm that results in ARDS and multi-organ dysfunction (MODS). It has been also suggested that inflammatory responses in adults and children are much different.

• Ageing is associated with increasing proinflammatory cytokines that govern neutrophil functions and have been correlated with the severity of ARDS. So far there is no animal model for SARS-CoV-2, but we expect to see a preclinical model in the future.
## CLASSIFICATION OF COVID-19 IN PATIENTS

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>COVID nucleic acid test positive. Without any clinical symptoms and signs and the chest imaging is normal.</td>
</tr>
<tr>
<td>Mild</td>
<td>Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhea).</td>
</tr>
<tr>
<td>Moderate</td>
<td>Pneumonia (frequent fever, cough) with no obvious hypoxemia, chest CT with lesions.</td>
</tr>
<tr>
<td>Severe</td>
<td>Pneumonia with hypoxemia (SpO₂ &lt; 92%)</td>
</tr>
<tr>
<td>Critical</td>
<td>Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury.</td>
</tr>
</tbody>
</table>
COVID-19 IN CHILDREN

• Since the early days of a COVID-19 infection outbreak, it has been thought that pediatric patients were not susceptible to COVID-19.

• However, along with spread of the virus, the number of infected children has gradually increased.

• Males seem to be more susceptible to COVID-19 infection, which is similar to the recent epidemiological studies.

• A higher incidence rate of COVID-19 infection in males and in Asia might be due to the higher expression level of ACE-2.
COVID-19 IN CHILDREN

• Although fever was the most common symptoms at onset of illness in children, it was reported less than in adults.

• Moreover, fever was more prevalent in children aged ≥5 years compared to the patients aged <5 years.

• Diarrhea and vomiting were reported as uncommon symptoms in previous studies of children; however, in one study nearly one third of our patients experiences diarrhea and/or vomiting.

• It has been reported that clinical symptoms in pediatric patients are relatively milder compared with those in adults; however, there are limited data on the epidemiological and clinical patterns of COVID-19 in children.
COVID-19 IN CHILDREN

• COVID-19 can cause symptoms in children in two stages. In the first week, upper and lower respiratory symptoms can occur which has lower severity and prevalence compared to adults.

• But after 2-3 weeks following infection, symptoms of MIS-C or multisystem involvement can occur and COVID-19 should be considered. The most common indication for admission is fever, rash, and respiratory problems.
COVID-19 IN CHILDREN

• multisystem inflammatory syndrome (Similar to adults, children with comorbidities including chronic kidney and lung diseases, malignancies, diabetes, obesity, anemia, immune disorders, heart disease, and congenital malformations are more likely to develop severe conditions from COVID-19).

• Post Covid complications (ex: severe pneumonia)

• Based on the aforementioned, it can be concluded that even with the asymptomatic course of Covid infection in children, complications can be observed and the syndrome of the so-called late Covid, which dictates the need for a thorough examination of these patients and observation in dynamics.
DIAGNOSIS OF COVID-19

• based on:
  • epidemiological history,
  • clinical manifestations
  • some auxiliary examinations, such as nucleic acid detection, CT scan, immune identification technology (Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA)) and blood culture.
The detection of SARS-CoV using RT-qPCR can only achieve a sensitivity of 50%–79%, depending on the protocol used, the sample type, and number of clinical specimens collected. Thus, it is essential to improve the detection rate of RT-qPCR for SARS-CoV-2 infection.

RT-qPCR has some other shortcomings, including certain biological safety hazards brought by the retention and operation of patient samples, cumbersome nucleic acid detection operations, and long waiting time for results.
CT SCANS AND OTHER DIAGNOSTIC METHODS

• For the diagnosis of COVID-19, although RT-qPCR is specific, its false-negative rate cannot be ignored because of the severe consequences of missed diagnosis. So many clinicians proposed CT scans should be one necessary auxiliary diagnostic method because it is more sensitive.

• The sensitivity of SARS-CoV N-based IgG ELISA (94.7%) is significantly higher than that of SARS-CoV S-based IgG ELISA (58.9%), but the sensitivity of SARS-CoV-2 IgG/IgM remains to be studied. Hence, developing other sensitive and specific auxiliary methods is necessary and urgent for the diagnosis of COVID-19.
The Coronavirus Disease 2019 (COVID-19) in Children: A Study in an Iranian Children’s Referral Hospital

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Babak Pourakbari1
Maryam Rostamyan4
Meisam Sharifzadeh Ekbateni3
Hamid Eshaghi10
Mohammad Reza Abdolsalehi4
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Zahra Movahedi6
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Background: Despite the worldwide spread of the coronavirus disease 2019 (COVID-19), the epidemiological and clinical patterns of the COVID-19 infection remain largely unclear, particularly among children. In this study, we explored the epidemiological characteristics, clinical patterns, and laboratory and imaging findings of pediatric patients with COVID-19.

Materials and Methods: From March 7 to March 30, 2020, there were a total of 35 patients who had confirmed COVID-19 infection by laboratory virus nucleic acid test (RT-PCR) assay with throat swab samples or typical chest CT manifestation compatible with COVID-19, in addition to a history of close contact with suspected or confirmed SARS-CoV-2 in family members. Information recorded included demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings and radiologic assessments, severity of disease, treatment, and mortality.

Results: The median age of the patients was 7.5 years (IQR=4–11; range=4 months to 15 years). A total of 63% were male. Cough was present in 80% of the patients, followed by fever (77%), nausea or vomiting (29%), diarrhea (26%), shortness of breath (29%), headache (20%), and myalgia (14%). Lymphopenia was present in 43% of the patients, thrombocytopenia in 9%, neutropenia in 8%, and leucopenia in 26%. We reported severe pneumonia in 40% of the hospitalized patients and 18 (51%) had underlying diseases. Of 35 patients, 11 had positive RT-PCR results (31%). The chest CT images of 24 patients (69%) suggested COVID-19, while their RT-PCR assays from throat swab samples were negative.

Conclusion: This study demonstrates different clinical findings of pediatrics compared to the previous reports of children. Since a high rate of false negative RT-PCR test was observed, early detection of children with COVID-19 infection by CT is conducive to reasonable management and early treatment.

Keywords: COVID-19, children, severe pneumonia, Iran
• Just like SARS-CoV and MERS-CoV, there is currently no clinically proven specific antiviral agent available for SARS-CoV-2 infection.

• The supportive treatment, including oxygen therapy, conservation fluid management, and the use of broad-spectrum antibiotics to cover secondary bacterial infection, remains to be the most important management strategy.

• According to the research on molecular mechanisms of coronavirus infection and the genomic organization of SARS-CoV-2, there are several potential therapeutic targets to repurpose the existing antiviral agents or develop effective interventions against this novel coronavirus.
CURRENT TREATMENT STRATEGIES FOR COVID-19

• **Virally targeted inhibitors**
  • Remdesivir, an adenosine analogue that can target the RNA-dependent RNA polymerase and block viral RNA synthesis, has been a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) infections in cultured cells, and nonhuman primate models.

• **Antibody and plasma therapy**
  • many convalescent patients donating plasma against SARS-CoV-2, just as SARS-CoV
  • the generation of recombinant human monoclonal antibody (mAb) is a fairly straightforward path to neutralize SARS-CoV.
  • CR3022, a SARS coronavirus-specific human monoclonal antibody, can bind potently with the receptor-binding domain(RBD) of SARS-CoV-2 and has the potential to be developed as candidate therapeutics of SARS-CoV-2 infections.
PREVENTION

• Follow basic infectious disease principles
  • Wash your hands regularly. Cover coughs and sneezes with your inner elbow.
  • Avoid touching your eyes, nose, or mouth with your hands.
  • Stay home from work or school if you have a fever.
  • Stay away from people who have signs of a respiratory tract infection, such as runny nose, coughing, and sneezing.

• Vaccines
  • There are several vaccination strategies against SARS-CoV, MERS-CoV and SARS-CoV2 tested in animals, including a live-attenuated virus, viral vectors, inactivated virus, subunit vaccines, recombinant DNA, and proteins vaccines.