Literature RECAP COVID-19

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Theoretical principles

General

- Currently 7 coronaviruses known to infect humans (f.e. SARS-CoV and MERS-CoV)
- Betacoronavirus named SARS-CoV-2 (previously known as 2019-nCoV) can result in COVID-19 disease.
- Animal reservoir likely from bats (intermediate host unclear, possibly pangolins, snakes, and/or turtles)[i]
- Early March: 111 nonsynonymous mutations identified in the outbreak. Today 301 amino acid replacements and 8 deletions documented[ii]. The role of specific subtypes, named the L ('more aggressive', 70%) and S type ('less aggressive', 30%) is controversial [iii] [iv]

Mechanism of action

- Exploits the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry inside the cells[vvi]. ACE2-receptor is expressed in type II alveolar cells in the lungs, but also present in heart, kidneys, intestines, brain and testicles. Recent research demonstrated that the ACE2 is also expressed on the mucosa of oral cavity[vii] These sites are possible targets of COVID-19. It docks on the ACE2 receptor via spike protein[viii] [ix]
- Viral shedding is very high during the first 7 days of symptoms (peak at day 4, 7.11 X 108 RNA copies per throat swab). It also outlasts the end of symptoms and is possibly present before symptoms arise[x]. The longest observed duration of viral shedding in one study was 37 days[xi].
- Possibility of fecal–oral transmission (tested in children, persistently tested positive on rectal swabs even after nasopharyngeal testing was negative)[xii]
- Important role for CD4+ helper T cells, which stimulate B cells to make antibodies against pathogens, in controlling SARS-CoV infection in mice.
- Evidence has been provided on the recruitment of immune cell populations (ASCs, T_{FH} cells and activated $CD4^+$ and $CD8^+$ T cells), together with IgM and IgG SARS-CoV-2-binding antibodies, in the patient's blood before the resolution of symptoms[xiii]
- The innate response is delayed in the elderly and fast in the young immune system[xiv]. The reduced abundance of ACE2 receptors in older adults could leave them less able to cope with SARS-CoV-2 but further research is necessary for this hypothesis.

Contagiousness and viability

- R0 (95% CI) = 2.28 (2.06-2.52) (i.e. reproductive number in order to make a prediction of daily new cases) [xv]
- Remained viable in aerosols for at least 3 hours, with a reduction in infectious titer from $10^{3.5}$ to $10^{2.7}$ $TCID_{50}$ per liter of air (median half-life 1.1-1.2 hours)
- SARS-CoV-2 was stable on plastic (median half-life 6.8 hours) and stainless steel (median half-life 5.6 hours) and viable virus was detected up to 72 hours after application to these surfaces.
- Results indicate that aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed) [xvi]

Aerosol and surface stability of SARS-CoV-2 can last for hours, reproductive number is 2.3

Special groups

- Pregnant women: Currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy.[xvii] Also there is no data suggesting an increased risk of miscarriage or early pregnancy loss in relation to COVID-19. And there is no evidence of the virus in breast milk, general precautions should be taken (i.e. washing hands). Continuous electronic fetal monitoring in labour is currently recommended for all women infected with COVID-19 [xviii]
- Children: In general asymptomatic to mild course of disease, however infected children have a fairly high titre of virus. A total of 6% of the suspected COVID-infections (only 33% is laboratory-confirmed) had severe or critical illness in the Chinese population. Infants had higher rates of serious illness than older children. Extrapolating results to Western countries is questionable due to differences in health baseline [xix].

Children and pregnant women don't have additional health risks, children have a mild disease course but show high viral load.

Epidemiology

- Overall estimated case fatality rate = 0.2% – 6.6%[xx]
- 80% of mortality cases in patients ≥60 years of age[xxi]
- WHO (Report March 18th, with new cases in last 24 hours): 191 127 confirmed (15 123) / 7807 deaths (786) [xxii]
- 48% of hospitalized patients have comorbidity, such as hypertension (30%), diabetes (19%) and coronary heart disease (8%)[xxiii]

Mortality rate of 0.2 – 6.6%, 48% of hospitalized patients have comorbidity.

Current practice

Signs and symptoms

- Incubation period: 2-15 days (mean 5-6 days)
- Common symptoms [xxiv] [xxv]
    - Fever (83-98%) (43.8% of patients had fever at admission, but 88.7% developed fever during hospitalization)
    - Dry cough (67.8%-82%)
    - Dyspnea (33%)
    - Also myalgias (11%), fatigue (38.1%) and sore throat (13.9%), less reported complaints are abdominal pain, headache,

Fever, dry cough and dyspnea are the common symptoms after one week.

Diagnostics

- Sensitivity of the RT-PCR test for COVID-19 has been reported as 66 – 80%. One negative test does not exclude COVID-19! Take timing of testing into consideration.
- Sensitivity of chest CT in suggesting COVID-19 was 97% based on positive RT-PCR results. In patients with negative RT-PCR results, 75% had positive chest CT findings and 48% (36% of total) were considered as highly likely cases. In addition 60% to 93% of cases had initial positive CT consistent with COVID-19 prior (or parallel) to the initial positive RT-PCR results[xxvi]. However another study showed that up to 50% of patients with COVID-19 infection may have a normal CT scan 0 – 2 days after onset of flu-like symptoms. As the disease progresses, crazy paving and consolidation become the dominant CT findings, peaking around 9–13 days followed by slow clearing at approximately 1 month and beyond[xxvii].
- In a hospitalized cohort in China: lymphopenia (70.3%), prolonged prothrombin time (58%), and elevated lactate dehydrogenase (39.9%)[xxviii]. Procalcitionin ≥0.5 ng/mL only in 5.5%[xxix]

Clinical assessment, lab results, RT-PCR and chest CT should be considered in diagnosing COVID-19 infection.

Treatment

- Conservative intravenous fluid strategies are advised when there is no evidence of shock. Aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation[xxx].
- Early empirical antibiotics for possible bacterial pneumonia should be given (according local protocol, in the Netherlands first choice cefuroxime 1500 mg IV 3 times daily or ciprofloxacin 400mg IV 2-3 times daily).
- Caution when using high-flow nasal oxygen, noninvasive ventilation or when using a face mask or supraglottic airway due to risk of dispersion of aerosolized virus in the health care environment, as the seal they generate is usually inferior to that achieved with a correctly placed and inflated cuffed tracheal tube[xxxi].

Generally, it has been suggested that NIV should be avoided due to the risks and high failure rate (76%)[xxxii] [xxxiii]. Therefore consider early invasive ventilation with lung-protective ventilation strategies and periodic prone positioning during mechanical ventilation[xxxiv]. In a CICO situation, use of a scalpel-bougie eFONA technique is advocated to minimise the viral aerosolization risk of high-pressure oxygen insufflation via a small-bore cannula[xxxv].

- Consideration of extracorporeal membrane oxygenation (ECMO).

Conservative fluid strategy combined with early invasive ventilation and empirical antibiotics.

- Chloroquine: highly effective in one in vitro study[xxxvi], additional research follows, preliminary results show that chloroquine is superior to control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening disease course[xxxvii]. At the moment, suggested doses: 500mg PO twice daily during 10 days[xxxviii].
- Remdesivir: highly effective in one in vitro study[xxxix], additional research follows[xl]. At the moment, suggested doses: 200mg IV loading dose, afterwards 100mg IV once a day for 9 days.
- Lopinavir/Ritonavir: recent research (March 18th) shows no benefit beyond standard care in hospitalized adult patients with severe COVID-19[xli]. Additonal research follows. At the moment, suggested doses: 400-100mg PO twice daily during 14 days.

Cloroquine and remdesivir are possibly beneficial, use paracetamol.

- NSAIDs: there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19, this claim is supported by the WHO and European Medicines Agency. Additional research follows. First choice in treatment of symptoms is paracetamol however. [xlii] [xliii]
- ACE-inhibitors: use of ACEI/ARBs could increase ACE2 expression and therefore may increase human SARS-CoV-2 infectivity and severity of illness. However recommendation to discontinue ARBs should not be common practice until confirmation of this hypothesis is as this can result in elevation of BP, which might occur with treatment changes, and carries proven risks[xliv].
- Corticosteroids: are not currently recommended unless indicated for another reason, research shows it can prolong viral shedding time and might exacerbate COVID-19-associated lung injury[xlv].

NSAIDs and ACEI are not proven harmful, corticosteroids could exacerbate associated lung injury.

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