Coronavirus Clinical Report 26.4.2020

This report summarizes key points and topics from letters, podcasts, interviews, and web conferences from the past few days by doctors on social media groups established for information sharing during the COVID-19 pandemic, and incorporates relevant information from literature and official updates.

* Medint specializes in gathering medical information from a variety of sources around the world. The information presented is not a medical recommendation.

The report is divided into the following subjects:

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2. **Relevant Studies & Updates**
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10. **Epidemiology**
11. **Oncology**
12. **Pediatrics**
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1. General Information

1.1 - Relevant Links

- **Medtronic** has created a useful guide for hospitals with **ways for minimizing exposure of staff and visitors to COVID-19**.
    - The guide has been implemented in several hospitals across the US. The model is based on a Taiwanese model in which **the hospital areas and staff are divided into specific zones.**
    - The company has created a detailed video explaining the model, compiled a workbook, and had a Webinar held on this issue. For additional information, please contact Procv@medtronic.com.
- **The Greater New York Hospital Association held a webinar** last week on the issue of managing patients in the ICU.
    - The Webinar emphasized the avoidance of intubation, ventilation parameters in COVID-19 patients, in addition to a discussion of the issues of steroid, and anticoagulant therapy.

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2- Relevant Studies & Updates

2.1 - Treatment Updates

- An American Retrospective Study has examined the **outcomes of Hydroxychloroquine** usage in veterans hospitalized with COVID-19. 368 patients were divided into three groups:
    - treatment with Hydroxychloroquine (HC),
    - treatment with Hydroxychloroquine and Azithromycin (HC+AZ)
    - treatment with standard supportive management for COVID-19 (no HC).
    - The study has concluded:
        - **Rates of death in the HC were high as opposed to the no HC - 27.8% and 11.4%, respectively**.
        - **The risk of death from any cause was similar in the HC+AZ and no HC group**, but higher in the HC group.
        - **The risk of ventilation was similar between all groups**.
- **A Chinese Randomized-Control Study** has evaluated the clinical efficacy and safety of **α-Lipoic acid** in addition to standard treatment for critically ill patients with COVID-19.
    - 8 patients were treated with ALA
    - 9 were in the placebo group

    Patients were followed up for 30 days. The following are the key study conclusions:

    - No statistical difference was found regarding SOFA scores between the treatment group and the placebo group.
    - **The all-cause mortality was two-fold higher in the placebo group than in the ALA group**, though a borderline statistical difference was evidenced due to the limited patient number.

2.2 - Assessment of Severity of Disease

- A Chinese retrospective study has created a risk score - **EWAS - Early Warning Score** enabling **early recognition of COVID-19 patients in high-risk of deterioration**.
    - The study included 1,138 mild to moderate COVID-19 patients, cumulative incidences of clinical deterioration were assessed after 14 days. The researchers have shown a match between the observed patients and the scoring technique.
    - **The score includes five parameters:** age, chronic illness, neutrophil to lymphocyte ratio, CRP, and D-dimer.
    - **The score ranges from 0 to 4.5**. According to the score, patients will be divided into 3 risk groups: low-risk, medium-risk, and high risk.

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2.3 - Publications

- **The CDC has added "new loss of taste or smell" as a symptom** on its COVID-19 information page, following numerous reports of COVID-19 patients with this presentation.
    - The president of the British Rhinological Society agrees and adds that COVID-19 should be taken into consideration as a Differential Diagnosis when addressing a patient with these symptoms.
- The NIH has appointed a Panel of experts from many American agencies and organizations with clinical experience. The Panel has published **COVID-19 Treatment Guidelines based on scientific evidence and expert opinion and are rated according to known ratings - strength (A, B, or C) and quality (I, II, or III) of evidence**. The guidelines **will be updated frequently** as published data becomes available. Following are the key recommendations divided into subjects:

    Epidemiology

    - The Panel **does not recommend** the use of any agents for pre-exposure prophylaxis (PrEP) against SARS-CoV-2 or post-exposure prophylaxis (PEP) outside of the setting of a clinical trial (**AIII**).
    - The Panel recommends **no additional laboratory testing** and no specific treatment for subjects with suspected or confirmed asymptomatic or presymptomatic SARS-CoV-2 infection (**AIII**).
    - Currently, **no drug has been proven to be safe and effective for treating COVID-19**.
        - There is insufficient data to recommend either for or against the use of any antiviral or immunomodulatory therapy in patients with COVID-19 who have a mild, moderate, severe, or critical illness (**AIII**).
        - There is insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication (**BIII**).

    Critical Care

    - For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the Panel recommends using N-95 respirators **rather than surgical masks**, in addition to other PPE (**AIII**).
    - Endotracheal intubation for patients with COVID-19 be done by health care providers with extensive airway management experience, if possible (**AIII**).
    - **Intubation should be achieved by video laryngoscopy**, if possible (**CIII**).
    - Norepinephrine should be used as the first-choice vasopressor (**AII**).
    - Dobutamine should be added in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (**BII**).

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- For adults with COVID-19 and **acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends HFNC oxygen over NIPPV** (**BI**).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available (**BIII**).
- For patients who are receiving supplemental oxygen, the Panel recommends **close monitoring for worsening of respiratory status and recommends early intubation** (**AII**).
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS), the Panel recommends using low tidal volume ventilation (**AI**), prone ventilation for 12 to 16 hours per day (**BII**), use of inhaled pulmonary vasodilator in appropriate cases (**CIII**), all according to the patient's need.
- There is insufficient data to recommend either for or against the routine use of ECMO for patients with COVID-19 and refractory hypoxemia (**BIII**).
- The Panel recommends **against the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without ARDS**.
    - In Patients that have developed ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication (**CI**), yet in patients with refractory shock, low-dose corticosteroid therapy is preferred over no corticosteroid therapy (**BII**).

Drug Therapy

- **Except in the context of a clinical trial, the Panel recommends against the use of Hydroxychloroquine plus Azithromycin (AIII), Lopinavir/Ritonavir (AI) or other HIV protease inhibitors (AIII) due to unfavorable outcomes**.
- There is insufficient clinical data to recommend either for or against the use of convalescent plasma or hyperimmune immunoglobulin for the treatment of COVID-19 (**AIII**).
- Except in the context of a clinical trial, the Panel **recommends against the use** of Interferons (**AIII**), because of lack of efficacy in the treatment of SARS and MERS and toxicity as well as Janus kinase inhibitors (Baricitinib) (**AIII**), because of their broad immunosuppressive effect.
- COVID-19 patients who are prescribed ACE inhibitors or ARBs should continue these medications (**AIII**), yet the Panel **recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19** outside of the setting of a clinical trial (**AIII**).
- The guidelines describe indications for treatment with corticosteroids, statins, and NSAIDs for patients who are prescribed these medications.

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In addition, **the guidelines detail about prioritizing patients for diagnostic tests and treatments and management of pregnancy and post-delivery patients**.

3. ICU

- An international group has published a summary of **current guidelines for the ventilatory support for COVID-19 patients**, with a focus on resource-limited settings.
    - In these conditions, **intubation should be avoided when possible**.
    - The article elaborates regarding infrastructure for **ventilatory support in resource-limited countries**, theories regarding the pathophysiology of the disease, and histopathological findings of lungs from patients with COVID-19. Following are key points regarding the management of patients and invasive ventilation:

      Patient Management:

    - Supplemental oxygen is a first essential step for the treatment of severe COVID-19 patients with hypoxemia and should be a primary focus in resource-limited settings where capacity for invasive ventilation is limited.
        - **Oxygen delivery can be increased by using a non-rebreathing mask and prone positioning**.
        - **Hypoxemia as a sole symptom should not be a trigger for intubation**.

      Invasive Ventilation:

    - **Pneumonia due to COVID-19 is different in several aspects from pneumonia due to other causes or from ARDS**.
        - One significant difference is the coexistence of severely affected lung areas adjacent to relatively unaffected areas, those of which **can be damaged from high PEEP**.
    - **Ventilation should be with low TV**, limited to 6mL/k, in particular when the patient is receiving fully controlled ventilation (not pressure support).
        - A higher respiratory rate, up to 35 per minute, should sometimes be accepted to achieve an adequate minute volume.
    - **Use 10cmH20 PEEP** and **limit** to **12cmH20**. Higher PEEP may be considered in several conditions such as:
        - Severe hypoxemia that does not respond to an increase in FiO2 greater than 0.6.
        - High need for vasopressors (high PEEP can help in keeping adequate blood pressure).
        - Certain states of lung lesions due to intubation.

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- **Monitor driving pressure**: although research is limited on this subject, it seems that a high driving pressure is associated with poor patient outcome.
  - The easiest way to achieve a lower driving pressure is to limit the tidal volumes, but this can be done by adequate titration of PEEP, which requires experience.
  - Most COVID-19 patients can be ventilated with a low driving pressure less than 15 cm H20, often as low as 5–7 cmH20.
- **Use prone positioning, which can improve oxygenation and patient outcome in ARDS patients**.
  - The article summarizes important points for the application of this treatment.
- **Set the targets for SpO2 at 88–92%, and set the set CO2 target allowing for hypercapnia accepting an arterial pH as low as 7.2**.

- A Chinese Retrospective Case Series describes **20 patients with severe COVID-19 pneumonia who required tracheal intubation**. Here are some key findings from this series:
  - **Intubation conditions- Performing Ambu mask ventilation is not recommended, full PPE, use of disposable positive pressure headgear system (creates a positive pressure to prevent virus aerosols from entering the headgear. The anesthesiologist who would practice intubation wore the positive pressure headgear after the machine has been worked for 5 min).**
    - **Use of a videolaryngoscope is highly recommended**.
    - To note, none of the 17 anesthesiologists were infected.
  - 90% of patients were over 60.
    - 75% had at least one background disease.
    - Average time until intubation: 10 days.
  - 7 of 20 patients died within a week.
    - Blood gases and lactate levels - before and after intubation- were worse in the deceased.
- **The British Journal of Anaesthesia** has issued guidelines for safe extubation.
  - Pre-extubation: Extubation should ideally take place in a **negative pressure room.** Strategies for supporting respiration after extubation. **Adequate analgesia** and perform oropharyngeal suction to decrease aerosol exposure.
    - Administer **antitussive drugs**, such as Remifentanil, Lidocaine, and Dexmedetomidine, to reduce the risk of coughing.
  - Extubation technique: **Use of 'mask over tube' technique** (see picture)- which allows protection against aerosol exposure by placing a mask attached to a second airway filter.
    - Before performing extubation, **position the patient 30 degrees head up**, and attach a second airway filter to the face mask.

A. Tracheal tube positioned at one corner of the mouth with ties cut.
B. Facemask with airway filter positioned and deflate ETT cuff.

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C. The assistant withdraws the tracheal tube from under the side of the facemask using a two-handed technique to control the tracheal tube.
D. Tracheal tube has been detached and the circuit has been connected to the second airway filter on the facemask.

- Post extubation: Place a surgical mask on the patient once the anaesthetic face mask is no longer required.

4. Pathology

- In a Letter to the Editor from San Paulo, Brazil, they describe the development of a **method of minimal invasion autopsy by using ultrasound (MIA-US**), which allows them to sample tissues with minimal risk for the staff. The group had previously used this method in 2018 during the yellow fever epidemic in San Paulo, and compared the MIA-US results to conventional autopsies. **The following are the main pulmonary findings from 10 COVID-19 patients:**
  - Exudative/proliferative diffuse alveolar damage, with intense epithelial viral cytopathic effects involving alveolar and small airway epithelium.
  - **Small fibrinous thrombi in small pulmonary arterioles in areas of both damaged and more preserved lung parenchyma** in 8 out of 10 cases.
  - Endothelial tumefaction and a large number of pulmonary megakaryocytes in the pulmonary capillaries are other **indicators of activation of the coagulation cascade.**
  - Small fibrinous thrombi were rarely found in the glomeruli and superficial dermal vessels.
  - **Signs of secondary bacterial pneumonia were observed in 6 cases.**
- An article written by NYC Pathologists describes lung and skin pathologies of 5 COVID-19 patients who had respiratory failure, including **three patients with evidence of systemic procoagulant disease with elevated D-dimer levels** and a purpura-type rash. Following are the key results:
  - The pattern of COVID-19 pneumonitis was predominantly a **pauci-inflammatory septal capillary injury** with significant septal capillary mural and luminal fibrin deposition and permeation of the interalveolar septa by neutrophils.
  - **No viral cytopathic changes were observed** and **the diffuse alveolar damage (DAD) with hyaline membranes,** inflammation, and type II pneumocyte hyperplasia, **hallmarks of classic acute respiratory**

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distress syndrome, **were not prominent. Injury in these patients is largely limited to alveolar capillaries - microvascular thrombosis.**

- These pulmonary findings were accompanied by significant **deposits of terminal complement components (MAC)**- C5b-C9, C4d, MBL-MASP 2 in the microvasculature, consistent with sustained systemic activation of the alternative and lectin-based complement pathways.
- **The purpuric skin lesions similarly showed a pauci-inflammatory thrombogenic vasculopathy,** with deposition of C5b-9 and C4d in both grossly involved and normally-appearing skin.

5. ENT

- **New York Head & Neck Society: Tracheostomy Recommendation :**
  - Monitor cuff pressures every 4 hours: All intubated patients should have a Q4-hour cuff pressure check with a goal of approximately 30 cm H_2O, if feasible
    - **Approximately 1-2% increased risk** of tracheal stenosis over prolonged intubations.
    - Pressures higher than 30 cm H_2O can result in pressure necrosis.
  - **Delay timing of tracheostomy up to 21 days** after the onset of symptoms if feasible
    - Decrease viral load in the upper and lower airways
      - Prolonged intubation poses risks
      - **Should be noted that avoiding tracheostomy in patients at high risk of mortality is critical.**
    - **Tracheostomy Technical Guidelines:**
      - Should be performed at bedside in ICU in rooms with negative pressure or a portable high efficiency particulate air (HEPA) filtration system
      - **Minimize aerosolization of the virus**
        - Paralysis to prevent coughing
        - Consider glycopyrrolate to reduce secretions
        - Preoxygenation and cessation of ventilation
        - Utilize of closed suctioning systems
        - Avoid monopolar electrocautery, or harmonic technology
        - Use cold instrumentation when feasible
        - Minimize suctioning and bronchoscopy during the procedure
        - Ensuring the cuff is inflated prior to resuming ventilation
  - Consider percutaneous tracheostomy, a closed **ultrasound-guided** or "cuff-up" apneic technique, avoids opening of the airway **it may be preferential in the setting of active COVID-19**, though current data is limited
  - **To avoid emergency tracheostomy** in high risk patients,
    - Consider endotracheal intubation e.g. video laryngoscope
    - Avoid mask ventilation, such as prolonged open airway manipulation

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    - **During CPR, avoid chest compressions until the airway is secured and the cuff is inflated.**
    - Post-tracheostomy management;
        - Circuit should remain closed as much as possible,
        - Use closed-line suctioning
- **Letter to the Editor** in American Journal of Otolaryngology: Mebird M9pro wireless **otoscope, can be used with a patient's smartphone.**
    - **Can quickly investigate the patient's external auditory canal and tympanic membrane.**
    - Can reduce clinic visits.

6. Neurology

The following are some reports from the past several days regarding neurological manifestations in COVID-19 patients:

- **Miller-Fisher Syndrome:** Two patients presenting, both swabbed positive for COVID-19
    - Negative for COVID-19 in CSF
    - First patient presented five days after fever, the other patient three days after fever and diarrhea.
    - Both patients recovered after two weeks.
- **Meningoencephalitis: A Case Study:** Young, obese woman in Los Angeles
    - Presented with headache, fever, and convulsions without any respiratory distress, stiff neck, and photophobia
    - Lumbar puncture indicated patient had viral meningitis
    - **During hospitalization, she developed encephalopathy with confusion and hallucinations**
        - Treated with anti-epileptic medication and Hydroxychloroquine once tested positive for COVID-19
        - Condition improved after five days
        - **Article mentions that CSF test to confirm presence of COVID-19 has still not been done** (article published nine days after admission)
- **Associated Acute Disseminated Encephalomyelitis (ADEM): Young COVID-19 patient** with atypical presentation:
    - Dysphagia, dysarthria and encephalopathy two days prior to admission
    - Headache and myalgia 11 days prior to admission
    - Pulmonary findings and imaging performed
    - Treated with Hydroxychloroquine, Ceftriaxone and IVIG
        - Authors mention that MS was a possible DD, but unlikely.

7. Cardiology

JAAC: **Systematic Approach to Acute MI patients** during the COVID-19 Pandemic. Following are the key points of the article:

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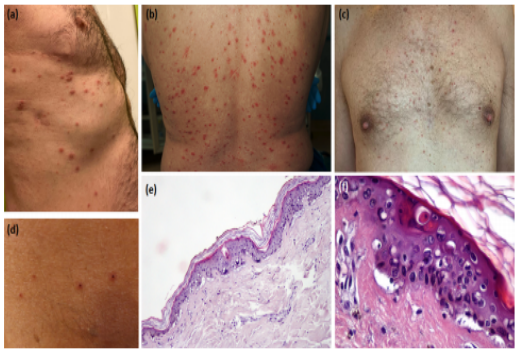
- **Cardiovascular manifestations of COVID-19 are complex** with patients presenting:
    - AMI
    - myocarditis
    - stress cardiomyopathy
    - non-ischemic cardiomyopathy
    - coronary spasm
    - nonspecific myocardial injury
        - The article further emphasizes PPE, role of the ER, cardiac catheterization lab, and regional STEMI systems of care.
    - **Primary PCI remains the standard of care** for STEMI patients at capable hospitals, with PPE, and a dedicated catheterization lab.
    - Otherwise, a **fibrinolysis-based strategy may be considered**

8. Dermatology

Journal of the American Academy of Dermatology (Letter to the Editor): **22 COVID-19 patients in Italy varicella-like papulovesicular exanthem**



- Trunk area always involved (no facial or mucosal involvement)
- **Lesion-onset 3 days on average**
- Lesion-duration 8 days on average
- Lesions scattered in most cases, with either no itching or mild itching.
- **All skin biopsies were consistent with viral infection**

9. Gynecology

Several important case studies published in the past few days on Vertical Transmission:

- Case Study 1: describes a 41-year-old COVID-19 patient with diabetes mellitus who delivered via caesarean section at week 33, due to significant respiratory deterioration.
    - **The neonate was found positive in a PCR test taken 16 hours after birth. No positive IgM or IgG were found,** even 5 days after birth.
    - The neonate required mechanical ventilation for 12 hours, which was replaced by positive pressure ventilation.
    - At 6 days, the baby was presenting with respiratory and coughing difficulties, and needed oxygen support.
- Case Study 2: describes a 22-year-old COVID-19 patient from Iran who delivered via cesarean section at week 30 due to a worsening of her condition and fear of vertical transmission.
    - At birth, amniotic fluid, vaginal specimens, and umbilical cord were taken. Also, baby's nasal and throat cavity tests were taken.
    - **All tests returned negative except amniotic fluid**.

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    - The baby developed fever and was positive in PCR one week after delivery.
- Case Study 3: describes a 25 year old COVID-19 patient who delivered via cesarean section at week 35.
    - **Negative results in tests taken from amniotic fluid, placenta, vaginal discharge, umbilical cord, blood, and breast milk.**
    - The neonate experienced breathing difficulties after birth and was therefore treated with a surfactant and required positive pressure ventilation, but the virus tests returned negative.

10. Epidemiology

Prospective Epidemiological Study in New York City in 1,150 hospitalized patients:

- **22%** who were **critically-ill with COVID-19**
- 82% having at least one underlying condition, most common being hypertension (63%)
- Median age: 62
- 66% men
- **As of April 14th, 2020: the in-hospital mortality was 33%**, with 79% of patients requiring mechanical ventilation.
- The median time to clinical deterioration following hospital admission was 3 days

11. Oncology

- **Cutaneous Lymphoma Recommendations** (JAAD): The article divides patients into 4 groups based on the cutaneous characteristics, the type, and stage of their lymphomas. Below is a summary of the recommendations for the groups:
    - Low Risk Patients: Low-risk therapies that can be utilized at home should be continued for all patients
    - Low/High-Intermediate Risk Patients: **Intermediate-risk therapies may be continued, but dose adjustments may be advised on an individual basis.**
        - The least frequent lab monitoring possible should be performed to limit exposure.
        - Initiation of these therapies may be postponed using low-risk bridge therapies short term.
        - Increasing or initiation of a retinoid or interferon should be considered in cases that necessitate the removal of other high-risk therapies.
    - High Risk Patients: **IV treatment should be considered to extend the intervals between treatments and to reduce access to medical treatment**
        - Romidepsin and Mogamulizumab may be considered on an individual basis with extended intervals and lower doses.
        - **Allogeneic stem cell transplant and treatment with CHOP, Alemtuzumab, Fludarabine are strongly discouraged since they often lead to significant cytopenias that are known risk factors for COVID-19 complications**
- **Recommendations of Head & Neck Cancer Surgery:** French consensus, published in European Annals of Otorhinolaryngology, Head and Neck Diseases.

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Divides patients into three categories, in order to minimize patient exposure while allowing optimal treatment.
    - **Group A**: life-threatening emergencies (e.g. shortness of breath, hemorrhage)
        - Immediate treatment is required.
    - **Group B:** cancers for whom postponing the treatment beyond one month could have a negative prognostic impact for the patient (e.g. squamous cell cancers of the upper aerodigestive tract, aggressive cancers of the salivary glands, aggressive skin cancers.)
        - **If tracheostomy is not required, patient's management should not be delayed.**
        - All necessary investigations and treatments should be performed during a single hospital stay in order to minimize exposure.
    - **Group C:** cancers for which the treatment can be postponed for at least 6 to 8 weeks without any significant prognostic impact (e.g. thyroid cancers, slow-growing cancers of the salivary glands, etc.)
        - Patients should be reassessed after 6 to 8 weeks in order to reconsider a rapid treatment according to the tumor growth velocity and evolution of the COVID-19 pandemic.
- **Letter to the Editor** by Italian physicians on how their centre has dealt with COVID-19 patients. Here are some of the key points from their letter:
    - **All** patients and accompanying caregivers underwent testing.
        - Prior to entering, phone or in-person triage process as well.
    - **All medical personnel tests every ten days, or after exposure to confirmed patients.**
        - Until results are known (6-72 hours), the patient **remains in a separate area.**
    - No changes in the standard management of neutropenic patients at home were introduced, and in particular **no additional prophylaxis.**
    - Patients in febrile aplasia carrying central lines are considered suspicious for COVID-19 at triage.

12. Pediatrics

12.1 Cystic Fibrosis

- Case Study out of Italy: **1-month old baby** diagnosed with CF, family member tested and was positive, baby did not have other symptoms, **did not require medical attention**
- Lancet: Letter to the Editor describes the impact of COVID-19 on CF patients. The authors note that **there has been no apparent effect on CF disease severity.**
    - The authors also note that in some cases with mild COVID-19 symptoms, the cause can **mistakenly be attributed to CF**, and therefore the patient would not have been tested.

12.2 Clinical Findings

A Systematic Review of 1,065 children:

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- **Most** suffer from **only mild symptoms** such as fever, dry cough, fatigue.
    - Some children were asymptomatic.
- Radiology findings include **ground-glass opacities, bronchial thickening.**
- One case of serious illness
- **No cases of death.**

13. Infectious Diseases

A Spanish Study examined five COVID-19 patients who were also carriers of **HIV:**

- Two patients on a protease inhibitor.
- Two patients on an integrase inhibitor.
- 4 of the 5 patients had CD4 levels greater than 400 cells per μL
- Course of Disease:
    - Two patients had upper respiratory tract infections.
    - Three patients had viral pneumonia
        - Two requiring admission to ICU, one requiring invasive and one requiring non-invasive mechanical ventilation
- Treatment: All five patients received boosted-protease inhibitor ART.
    - One patients received a Darunavir-boosted Cobicistat
    - Two patients received Lopinavir-boosted Ritonavir
    - The three patients with pneumonia received antibiotics
- Outcome:
    - Three patients recovered **without the need** for mechanical ventilation.
    - **Four of the five patients have been discharged from the hospital.**
        - One patient remains in ICU (as of publication date), 21 days since admission. On day 13, the patient connected to ECMO and remains on.

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