Coronavirus, COVID-19, SARS

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SARS, COVID-19, 2019-nCoV, SARS-CoV-2

Clinical Setting

SARS-CoV-2 / COVID-19

- **COVID-19 / SARS-CoV-2** (2019-nCoV)
  - SARS-CoV-2: a respiratory coronavirus that emerged in late 2019 from live animal markets in Wuhan, China. Bats are the reservoir species (https://www.biorxiv.org/content/10.1101/2020.03.30.015008v1)(pre-print) Sister virus to the SARS coronavirus (2002-2003) which also emerged from bats. The disease caused by this virus is called COVID-19. **Highly efficient transmission, even when asymptomatic.** Situation is rapidly changing:
    - **US hospitalization rates and patient characteristics** (CDC, MMWR, April 8, 2020)
    - CDC Guidance (3/8/20): HAN No. 429: https://emergency.cdc.gov/han/2020/HAN00429.asp and WHO guidance: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance
    - Evaluation/testing criteria: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html
    - Presentation, patient management: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
    - Prevalence and contagiousness (03/17/20): Science 10.1126/science.abb3221 (2020)
    - Case reports: https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html; WHO global situation dashboard.
  - **Risk of severe disease: All persons, regardless of age, with underlying conditions,** e.g., diabetes, CVD, chronic lung condition (asthma, COPD, emphysema) are at higher risk for severe COVID-19 (MMWR ahead of print, 03/31/20).
- **Prevention measures**
  - **Break transmission pathways!! Do not be complacent!!**
  - Basic precautions (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public)
    - Frequent handwashing (alcohol-based sanitizer and/or soap and water)
    - Sanitize common surfaces
    - **Social distancing** (at least 6 feet / 1.8 meter)
      - **STAY AT HOME** except for essential activities, e.g., food, medicines, healthcare and essential work such as police, fire, sanitation and healthcare.
      - **AVOID CROWDS AND/OR CONGESTED PLACES**
      - **TAKE THIS SERIOUSLY**
      - Self-isolation for 14 days of return from Europe, other CDC level 3 country or area with travel advisory
        - CDC travel advisory for NY, NJ, CT issued 03/28/20.
    - Avoid touching eyes, nose, mouth
    - Respiratory hygiene, i.e., cover nose and mouth when sneezing or coughing
    - If sick, wear a face mask when in presence of others
  - Avoid cruise ships, including river cruises: CDC HAN No. 430 (03/15/20): https://emergency.cdc.gov/han/2020/han00430.asp
- **Mean incubation time is estimated to be ~5 days after exposure** (range 4.1 - 7.0 days, but as short as 36 hours or as long as 14 days). Transmission can occur from an infected person who is asymptomatic (prior to onset of symptoms), although transmission is likely more efficient once symptoms develop.
- **Presentation** (some anecdotal):
  - One week to 10 days prodrome of myalgias, rigors, malaise (bone-tired), cough, confusion (foggy mind), low grade fever, loss of taste. These symptoms may progress to difficulty breathing in the second week. Average 8 days to development of dyspnea and average 9 days to onset of pneumonia/pneumonitis.
  - COVID-19 is not like influenza which is sudden onset and follows a different course of disease
  - Growing evidence for asymptomatic infection (Euro Surveill. 2020 Mar;25(10). doi: 10.2807/1560-7917.ES.2020.25.10.2000180) hence the absolute imperative of effective prevention measures (see Prevention)
- **Patient management** (https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected)
  - **Symptomatic/Mild-Moderate illness**: Stay at home and contact health care provider by phone or electronic means.
  - **Severe symptoms**, e.g., difficulty breathing: seek immediate care
  - **If older (age ≥65 yrs) OR underlying conditions (any age) OR immunocompromised**: contact health care provider early in course of even mild illness
    - Monitor pulse ox (if possible): if drops below 90% at rest, seek care
    - Dyspnea on exertion (difficulty walking from bed to bathroom); Seek Care.
    - Risk factors for poor prognosis: older age, high SOFA score & d-dimer >1mcg/mL (retrospective cohort study, Lancet online ahead of print, 03/11/20)
    - Risk of severe disease at any age if underlying condition (MMWR ahead of print, 03/31/20)
- **Criteria for evaluation and laboratory testing (3/8/20)** (https://emergency.cdc.gov/han/2020/HAN00429.asp)
  - Work with local/state health departments to coordinate testing through public health labs
  - Determine whether patient has signs/symptoms compatible with COVID-19 (fever and acute respiratory illness, e.g., cough, difficulty breathing)
  - Testing priorities are rapidly evolving and may include:
    - Hospitalized patients with signs & symptoms of COVID-19 (in order to inform decisions about infection control)
    - Symptomatic individuals (age ≥65 yrs) and individuals (any age) with underlying chronic conditions (e.g., diabetes, heart diseases, lung disease, kidney disease) or immunocompromised individuals
    - Any person, including HCW, who within 14 days of onset had close contact with a suspect or lab-confirmed COVID-19 patient
    - Any person who has a history of travel to an affected area within 14 days of symptom onset
- **Health care settings**
  - HCWs entering the room with a PUI should use standard precautions, contact precautions, airborne precautions, and eye protection (e.g., goggles or a face shield).
  - Importance of hand hygiene after patient contact and careful surface disinfection, including soles of shoes: see small study (limitation: qualitative, no viral quantitation) of surface and aerosol contamination in 2 Wuhan hospital wards (ICU and general ward) reported in Emerging Infect Dis, pre-print, 04/10/20. 100% positivity from samples of the floor of the hospital pharmacy!
- **Diagnostic Testing**
  - Excellent review of current state of diagnostic testing in Ann Intern Med (04/13/20), doi 10.7326/M20-1301.
  - IDSA primer on serological testing here.
  - CDC interim guidelines: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html
  - **Specimen**: upper respiratory nasopharyngeal (NP) swab preferred (see CDC interim guidelines (above) and JAMA 2020 Mar 11. doi: 10.1001/jama.2020.3786 for yields of different specimen types).
  - **Detailed virologic analysis** of 9 patients without medical co-morbidities and relatively mild (Nature, April 1, 2020):
    - Virus was readily isolated from nasopharyngeal swabs, throat and lung specimens, but not stool, despite high concentrations of viral RNA; no virus was isolated from urine or serum. No virus was isolated from any specimen after 8 days. Viral RNA loads were highest in the early symptomatic period, declining slowly and remained detectable into the second or third week after onset of illness, despite resolution of symptoms.
    - 50% of patients seroconverted by day 7, and 100% by day 14. Seroconversion was not followed by a rapid decline in viral RNA.
  - **Test kits**: The U.S. FDA has issued Emergency Use Application (EUA) letters for a growing list of SARS CoV-2 / COVID-19 diagnostic tests. See FDA for current details: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations

trial with objective endpoints including viral load response is needed.
        - Another small Chinese randomized trial (available as an English abstract only) of 30 patients found no benefit of HCQ 400 mg per day for 5 days compared to placebo control in viral clearance. 1 patient in the HCQ group progressed to severe disease, 3 of 15 HCQ patients and 5 of 15 control patients showed radiographic progression, all of which improved by follow-up. The negative trial in patients with mild disease is underpowered to detect potentially important clinical benefit, particularly in sicker patients. Lack of peer review presentation of primary data are also limitations.
        - Study from Brazil (not peer-reviewed, available as pre-print) comparing 2 dosage regimens of Chloroquine diphosphate, 450 mg bid on day one then 450 mg once daily x 5 days (2.7 gm total dose) compared to 600 mg bid x 10 days (12 gm) for 81 patients with severe COVID-19 illness was terminated early due to toxicity, principally in the higher dose arm: ventricular tachycardia in 2 patients (both higher dose arm), 18% overall with QTc prolongation > 500 msec, and myocarditis. Overall mortality was 13.6%, similar to historical controls and not statistically different for low versus high dose. Only 1 of the 26 patients tested had cleared virus by day 4 on RT-PCR. All patients also received ceftriaxone and azithromycin and 89% received oseltamivir, the latter two of which are known to prolong QTc. Only 40 patients had laboratory confirmed COIVD-19 infection.
        - Randomized, controlled open label trial of 150 adults in China with COVID-19 of varying severity (not peer-reviewed, available as a pre-print) treated with 1,200 mg of HCQ daily for 3 days and 800 mg daily for a total duration of 2-3 weeks found no difference in viral clearance or symptomatic improvement compared to standard-of-care.
        - Retrospective French study of 181 patients with COVID-19 and supplemental oxygen requirement (not peer-reviewed, available as a pre-print) found no difference in death rates, requirement for ICU care, or ARDS for patients treated with HCQ 600 mg once daily compared to patients not treated with HCQ. HCQ was discontinued in 8 patients because of QTc prolongation or first degree atrioventricular block.
        - Retrospective study of 368 patients in US Veterans Administration Hospitals (not peer reviewed, available as a pre-print) treated with HCQ, HCQ+azithromycin, or neither found no benefit to HCQ or HCQ+azithromycin and higher all cause mortality on HCQ patients. Authors conclusions: "These findings highlight the importance of awaiting the results of ongoing prospective, randomized, controlled studies before widespread adoption of these drugs."
        - Note: Chloroquine phosphate (common in aquarium cleaner) is not a substitute. See CDC HAN No. 431 (03/27/20). Serious consequences, including death. Patient education needed.
    - **Remdesivir** (GS 5734) has activity in rodents against beta coronaviruses (Antimicrob Agents Chemother. 2020 Mar 9. pii: AAC.00399-20. doi: 10.1128/AAC.00399-20) available via Expanded Access (Gilead Sciences) or through clinical trials (ClinicalTrials.gov NCT04280705, NCT04257656, NCT04252664, NCT04292899). Summary of preliminary in vitro and clinical evidence of efficacy: Int J Antimicrob Agents ahead-of-print (03/06/20).
        - Cohort study of Remdesivir for compassionate use in 53 patients with severe disease (non-randomized, no control group) found overall improvement in 68% of patients; no data on virologic response (NEJM online publication, April 10, 2020). Authors's conclusion: "Measurement of efficacy will require ongoing randomized, placebo controlled trials of remdesivir therapy."
    - **HIV protease inhibitors:**
        - **Lopinavir/ritonavir**: RCT showed no benefit and nor antiviral effect vs. standard care (N Engl J Med DOI: 10.1056/NEJMoa2001282)(03/18/20). High risk of adverse drug-drug interactions in critically ill patients so should await further trial data. Many drug-drug interactions: see University of Liverpool compilation: https://www.covid19-druginteractions.org/
        - **Darunavir**: no in vitro activity, no evidence of any effect - do not use (https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus)
    - **Immune modulators**, e.g., anti-interleukin drugs.
  - Archive: Insights and concise summary of the situation as of late February published on 28 Feb 2020 in JAMA. Detailed clinical and epidemiologic description of the first 425 cases reported in Wuhan (N Engl J Med 2020 Jan 29 [Epub ahead of print]) with an associated editorial from Fauci et al (N Engl J Med 2020 Feb 28 [Epub ahead of print]).

- Severe Acute Respiratory Syndrome (SARS)(2002-2003).
  - A coronavirus (SARS-CoV), isolated in Spring 2003 (N Engl J Med 348:1953, 2003 & N Engl J Med 348:1967, 2003), emerged from southern China and spread to Beijing, Hong Kong and 32 countries. Bats were a primary reservoir for SARS virus (Proc Natl Acad Sci 102:14040, 2005). Thin section micrograph of SARS virus.
  - Transmission by close contact: effective infection control practices (mask [changed frequently], eye protection, gown, gloves) proved key to stopping transmission in 2003 epidemic. Health care workers accounted for most secondary cases.
  - Therapy tried or evaluated during 2002-2003 outbreak:
    - Ribavirin, baloxavir, neuraminidase inhibitors, lopinavir/ritonavir, and acyclovir are ineffective.
    - Interferon alfa ± steroids used in a small case series. Interferon-beta and mycophenolate mofetil. Pegylated IFN-α effective in monkeys.
    - Low dose steroids alone successful in one Beijing hospital during 2002-2003 outbreak. High dose steroids increased viral load & serious fungal infections.
    - Inhaled nitric oxide improved oxygenation and improved chest x-ray (Clin Infect Dis 39:1531, 2004).
  - HKU1, NL63, 229E, OC43 are human coronaviruses that are detected by some multiplex panels. They are associated with URI and viral pneumonia, but unlike SARS CoV, MERS CoV and SARS-CoV-2, they are not associated with major outbreaks or severe respiratory distress syndrome. SARS-CoV-2 does not appear to cross-react with the URI-associated strains HKU-1, NL63, OC43, and 229E that are detected by multiplex panels such as BioFire FilmArray or Luminex
  - Ref: https://coronavirus.travax.com/library/coronaviruses/events/coronavirus-disease-2019). See also, WHO emergency use listing (EUL) procedure: https://www.who.int/diagnostics_laboratory/EUL/en/

Etiologies

- Coronavirus CoV (SARS-CoV)(2003)
- Coronavirus SARS CoV-2 (COVID-19)

Primary Regimens

- Therapy is predominantly supportive care.
- **There is no drug of proven efficacy** (see U.S. CDC guidance on therapeutic options and Comments (below).
- **Enrollment in a randomized clinical trial, if available, is strongly encouraged**
  - IDSA Guidelines on Treatment and Management of Patients with COVID-19
  - NIH COVID-19 Treatment Guidelines.

Alternative Regimens

- None

Comments

- **SARS-CoV-2 / COVID-19**:
  - Drugs under evaluation, none of proven efficacy.
    - See Summary table of on-going trials compiled by the American Society of Health-Systems Pharmacists.
    - See CDC Guidance on therapeutic options: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
    - Review of treatment options being explored in April 13, 2020 AMA Network
  - See ClinicalTrials.gov (search term = COVID-19) for current status of trials.
    - **Chloroquine or Hydroxychloroquine ± Azithromycin**
      - **Not recommended for out-patient use. If used monitor QTc.**
      - A small, non-randomized French study (available as a pre-print) evaluated hydroxychloroquine (HCQ) 200 mg tid x 10 days for treatment of 26 hospitalized COVID-19 patients. The control arm was 16 COVID-19 patients who declined treatment or who were at another medical center. At day 6 SARS-CoV-2 was undetectable in 70% of those taking HCQ (n=20) vs 12.5% of those not on HCQ (n=16). Addition of azithromycin (500 mg day 1, 250 mg once daily for 4 days, given at provider's discretion to 6 patients to "prevent bacterial infection") might increase potency: HCQ plus azithromycin was associated with 100% viral load undetectable vs 57% with HCQ alone at day 6. However, there are several major limitations and sources of bias in this study: (1) low quality study design, non-randomized, observational; (2) patients in the control group had higher baseline viral loads than those in the HCQ group vs. those in the HCQ/Azithro group; (3) six patients were lost to follow-up in the HCQ arm, including 3 who were transferred to the ICU and one who died, whereas no control patients were lost to follow-up; and (4) no clinical outcomes were reported. Based on this study, it is unclear if HCQ or HCQ plus azithromycin reduces viral loads in patients or results in improved clinical outcomes. Randomized controlled data with clinical outcomes are needed. These drugs are not without adverse effects. QTc prolongation and fatal arrhythmia is a potential side of effect of HCQ, particularly if administered in combination with azithromycin
      - A small, randomized Chinese clinical trial of 62 patients with mild illness (available as a pre-print) comparing HCQ 400 mg per day for 5 days to placebo found that HCQ was associated with a shorter duration of fever and cough, from 3 days to 2 days for each, and radiographic improvement by day 6. There was a statistically non-significant trend for progression to more severe disease in the placebo. Given the small study size, subjective endpoints, and lack of peer-review these results should be considered preliminary and confirmation in an appropriately powered, well-designed clinical

- Other respiratory human coronaviruses (HCOV-229E, OC43, NL63, etc.) implicated as cause of croup, pneumonia, asthma exacerbations, and other respiratory tract infections (RTI) in children (Clin Infect Dis 40:1721, 2005; J Infect Dis 191:492, 2005). Other respiratory human coronaviruses may cause severe disease in HSCT recipients (Blood 115:2088; 2010).
- See also Middle East Respiratory Syndrome (MERS).

Filed under: SARS Coronavirus MERS Corona virus CoV COVID Wuhan

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