Clinical Characteristics, Diagnosis and Management of COVID-19

Introduction

SARS-CoV2 is the 3rd human betacoronavirus to be discovered this century. We were first treated to an epidemic of SARS (Severe acute respiratory syndrome) due to SARS-CoV1 in 2002-2003, which practically disappeared afterward. Then in 2012, Middle Eastern respiratory syndrome (due to MERS-CoV virus) appeared in Saudi Arabia and spread throughout the Middle East, but did not create a pandemic. Prior to this century, the only human coronaviruses known were four alphacoronaviruses that cause about 10% of human respiratory illnesses, which are mild and usually amount to a common cold. Numerous delta- and gammacoronaviruses infect a wide range of animals. SARS and MERS, which are both due to bat viruses, were therefore a surprise. They were passed to humans in each case through a secondary animal, civet cats in Chinese animal markets and camels respectively. SARS-CoV2 is another bat virus that comes to us through pangolins, armadillo-like animals that are prized by the Chinese for their scales. The disease it causes is now called COVID-19.

The first figure from Q. Li, et al., indicates that cases of pneumonia linked to the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China, appeared in December 2019. By January, explosive transmission was occurring in Wuhan and throughout Hubei Province. The Chinese had identified the novel betacoronavirus agent of this pneumonia by January 8, had announced the gene sequence by January 10, and had shared reagent probes and primers with the WHO by January 21.

By comparison with the other 2 betacoronaviruses, this one appears to be more transmissible but with a lower case-fatality rate, i.e. 1-3% vs. 15% for SARS and 37% for MERS. However, this is still 10-30 x higher than the usual case-fatality rate of influenza A.
Clinical Features & Diagnosis

The usual incubation period of COVID-19 is 5-7 days, but in some cases 3 or less, and occasionally more than 14 (fig. 2). It can become transmissible a few days before onset of symptoms and remain transmissible beyond resolution of symptoms. A major unknown is what proportion of infected persons never become symptomatic and whether they are capable of transmitting SARS-CoV2. We will not know this until an IgG antibody test is available for a population-based study. The mean interval between cases has been 3-6 days in China varying between studies.
The most common symptoms have been cough and fever, however there has been some variability in the 8 series reported (Table 1). Most series report 92-98% of patients presenting with fever, however Guan et al. reported that while 89% of patients developed fever, only 44% had fever on admission. Those presenting with fever seemed to be in higher proportion in other studies. Cough was present on admission in 59-82%. A minority of these had a productive cough. Dyspnea was exhibited by 19-55% of patients on admission, but by at least a third in most studies. It was what prompted ICU transfer in most ICU patients. Up to 75% had myalgia or overwhelming fatigue & malaise. A small minority of patients had headache, hemoptysis, vomiting or diarrhea. It is noteworthy that the intestinal epithelial cells bear the ACE2 receptors for the virus and fecal-oral transmission has been suspected.

Dyspnea typically appears at day 7 of illness in both those who survive and those who don’t (Zhou et al.). Those who become critically ill do so about day 12 whether they are going to survive or not. Only 1% of survivors develop acute cardiac injury or acute kidney injury, but 59% of nonsurvivors develop cardiac injury, usually about day 15. Fifty per cent of nonsurvivors develop acute
Table 1. Symptoms of COVID-19 in 6 Chinese Series.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Huang et al Jin Yin-Tan Hospital, Wuhan</th>
<th>Wang et al. Zhongnan Hospital, Wuhan</th>
<th>Zhang et al No. 7 Hospital, Wuhan, 140 cases</th>
<th>Guan et al. 522 hospitals in 30 Provinces 1099 cases</th>
<th>Chen et al. Jin Yin-Tan Hospital 99 cases’ 1/1-1/20</th>
<th>Xu et al. 7 Hospitals Zhejiang 62 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First 41 case prior to Jan 2 Ages 41-61</td>
<td>138 cases Ages 22-92</td>
<td>25-87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>ALL</td>
<td>ICU</td>
<td>ALL</td>
<td>ICU</td>
<td>ICU</td>
<td>ICU</td>
</tr>
<tr>
<td>Fever</td>
<td>98%</td>
<td>100%</td>
<td>99%</td>
<td>100%</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>Cough</td>
<td>76%</td>
<td>85%</td>
<td>59%</td>
<td>58%</td>
<td>75%</td>
<td>85%</td>
</tr>
<tr>
<td>Sputum</td>
<td>28%</td>
<td>38%</td>
<td>27%</td>
<td>22%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
<td>0</td>
<td>7%</td>
<td>8%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>5%</td>
<td>8%</td>
<td>-</td>
<td>-</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>0</td>
<td>10%</td>
<td>17%</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>55%</td>
<td>92%</td>
<td>31%</td>
<td>64%</td>
<td>37%</td>
<td>45%</td>
</tr>
<tr>
<td>Myalgia/Fatigue</td>
<td>44%</td>
<td>54%</td>
<td>70%</td>
<td>81%</td>
<td>75%</td>
<td>74%</td>
</tr>
</tbody>
</table>

*89-92% developed fever but the other 42-45% after admission.

renal failure, also about day 15. The length of stay is about 19-22 days for both survivors and nonsurvivors. The virus is shed throughout that time but ceases about day 21-22 for survivors.
Lymphopenia figures prominently among laboratory findings and all studies found more profound lymphopenia in non-survivors or those admitted to ICU than others (Table 2). The same is true of elevations in D-dimer >1 mcg/L, high troponin I and LDH. So lymphopenia, D-dimer, and elevated LDH have both diagnostic and 

Table 2. Laboratory Findings in Chinese Series

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>63%</td>
<td>(100% in ICU)</td>
<td>75%</td>
<td>83%</td>
<td>35%</td>
<td>42%</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>73%</td>
<td>(100% in ICU)</td>
<td>75%</td>
<td>83%</td>
<td>35%</td>
<td>42%</td>
</tr>
<tr>
<td>Increased CPK</td>
<td>33%</td>
<td>-</td>
<td>7%</td>
<td>14%</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>10%</td>
<td>4%</td>
<td>-</td>
<td>2%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>37%</td>
<td>31%</td>
<td>-</td>
<td>22%</td>
<td>35%</td>
<td>16%</td>
</tr>
<tr>
<td>Increased D-dimer</td>
<td>-</td>
<td>Only increased in ICU pts</td>
<td>43%</td>
<td>46%</td>
<td>36%</td>
<td>-</td>
</tr>
</tbody>
</table>

prognostic value. Acute kidney injury tended to occur only in the critically ill in the ICU. About a third had hypertransaminasemia, which occurred more commonly in the ICU patients.

Procalcitonin was infrequently elevated on admission, and when it rose subsequently, it was a reliable indication of bacterial infection, especially
ventilator associated pneumonia. Accordingly, a rising procalcitonin in these patients was prognostic of death. In the Zhang paper, procalcitonin rose in 23% of non-severe patients and 50% of critically ill; in the Guan paper these were 3.7% and 13.7% respectively. Typically, the median time from dyspnea to intubation was 8-10 days (Wang et al.; Zhou et al.), and the median time from intubation to ventilator associated pneumonia was 8 days (Zhou et al., 2020). In the study of Xu et al., only 11% developed an increased procalcitonin and did so more than 10 days into illness, as you would expect. Sepsis syndrome tended to occur by day 9-10 and ARDS by day 10-12.

SARS-CoV2 was demonstrable in higher quantities in nasopharyngeal swabs than throat swabs (Figure 3) and was present up to 3 weeks after onset of illness (Zhou et al.). The virus is demonstrable in a variety of sites (Table 3). Viremia could be demonstrated by PCR in 15% by Huang, et al., but only 1% by Wang et al. In the one study that looked for coinfection, Mycoplasma pneumonia was found in 8.6% and RSV in 2% (Zhang et al.). Azithromycin may therefore be justified empirically, until Mycoplasma is excluded.

Chest x-rays have sometimes missed the ground glass patchy bilateral pneumonia characteristic of the SARS-CoV2 disease that is more evident on chest CT. According to Wang et al., CT evidence of pneumonia is seen in all of these patients. About 5% of patients have unilateral infiltrates (Wu et al.)
Diagnosis of SARS-CoV-2 infection is of course made by the PCR test now in use. Hospitals may have to wait for 3-5 days for a result at Lab Corp or Quest. In the meantime, the diagnosis may be presumed in a patient with radiographic evidence of pneumonitis, possibly by CT, who has fever, cough, lymphopenia, elevated D-dimer, and elevated LDH in the context of this epidemic. Influenza A can also cause lymphopenia but typically with monocytosis (ratio <2 per Merekoulias et al., 2010). Only Wang et al. described monocytes in COVID-19 patients, and they were not elevated or depressed.
Table 3. Presence of SARS-CoV2 in Clinical Specimens

<table>
<thead>
<tr>
<th></th>
<th>BAL 15</th>
<th>Sputum 104</th>
<th>Nasal 8</th>
<th>Pharyngeal 398</th>
<th>Feces 153</th>
<th>Blood 307</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>96%</td>
<td>72%</td>
<td>63%</td>
<td>32%</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>Ct</td>
<td>31</td>
<td>34</td>
<td>24</td>
<td>32</td>
<td>32</td>
<td>31</td>
</tr>
</tbody>
</table>

The number of specimens tested in each category is indicated in the first row. The % positive is indicated in the second row. The mean cycle threshold (Ct) is indicated in the 3rd row. The Ct is inversely proportional to the quantity of virus present, so the highest quantity of virus was seen in nasal specimens. W.Wang et al. JAMA. Published online March 11, 2020. doi:10.1001/jama.2020.3786

Hypertension leads the comorbidities associated with COVID-19 and in turn with mortality due to the illness across all these studies. In 201 patients hospitalized at Zhongshan Hospital in Shanghai hypertension was seen in 14%, but 27% of those who developed ARDS and 36% of those who died (Wu et al.). One wonders if that has to do with angiotensin converting enzyme displaced from its ACE2 receptor, which is the attachment site for the virus on the apical aspect of type II alveolar cells. Some authors have speculated that ACE inhibitors might be therapeutic. In the Wang study, 21.6% of patients with milder disease managed on the ward had hypertension, whereas 58.3% of those admitted to the ICU were hypertensive (p<0.001). In the case of diabetes, it was 5.9% vs. 22.2% (p=0.009). Cardiovascular disease and COPD were less strongly associated with progression to critical care.

In the Wu study of risk factors for ARDS, age greater than 65 was associated with greater risk of progression to ARDS, as well as a greater risk of death among those with ARDS (Wu et al.). The median age of those without ARDS was 48, among those with ARDS 58.5 (p<0.001). The median age of persons surviving ARDS was 50 and that of those dying with ARDS was 68.5 (p<0.001).
Management of COVID-19

The critical role of N95 masks in the management of these patients is illustrated by the data of Xinghuan Wang et al. (Table 4), who demonstrated that none of 278 doctors and nurses wearing N95 masks in addition to other precautions became infected. However, 10 of 213 doctors and nurses who did not wear masks in Wuhan caring for these patients did become infected. The p value was stunning. A sobering observation is that of Wang et al., who reported that that 12.3 % of their cases were patients hospitalized for other reasons who became infected in the hospital; 29% of their 138 cases were health care workers infected in the hospital.

Table 4. Wuhan Results on N-95 mask use–Publication Pending

<table>
<thead>
<tr>
<th></th>
<th>N-95 Group (N-95, disinfection, hand washing)</th>
<th>Greater patient exposure</th>
<th>0/278 (doctors 56 + nurses 222) infected with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Mask Group (no medical masks, disinfected and clean hands occasionally)</td>
<td>10/213 (doctors 77 + nurses 136) infected by COVID-19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Highly significant p &lt; .0000000000000022</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Xinghuan Wang et al., Association between 2019-nCoV transmission & N95 respirator use. https://doi.org/10.1101/2020.02.18.21881

However, once the patient develops ARDS, that may be different. Wu et al. found that 46% of those treated with steroids for ARDS died as compared to 61.8% of those who did not receive steroids for ARDS (p=0.003). However, this was an observational study and not a randomized controlled trial. Whether you believe that once patients develop ARDS they should receive steroids may depend on whether you believe anyone with ARDS should receive steroids. A meta-analysis of studies of steroids in the treatment of ARDS (Russell et al.) concluded that there is marginal evidence for a favorable impact on mortality and ventilator free days, but that given before ARDS developed, steroids increased the risk of ARDS.

Given the coinfection rate of Mycoplasma pneumoniae in COVID-19, it makes sense to use azithromycin (or doxycycline) until Mycoplasma has been excluded by PCR or antibody testing.
The most promising drug for the treatment of SARS-CoV2 itself is remdesivir. It is a drug with broad antiviral effect against RNA viruses in general and has been proven effective in clinical trials in the Congo against Ebola. In vitro and in animals it has been effective against SARS-CoV1 and MERS-CoV viruses. Gilead has initiated two phase 3 randomized, open label trials across Asia, possibly extending to other countries as the pandemic progresses. The Chinese on their own have initiated clinical trials at multiple centers in Hubei Province.

A compassionate use program is currently being organized. Requests must be submitted by a patient’s treating physician, and the patient must be hospitalized with confirmed COVID-19 with significant clinical manifestations. The supply is currently limited, but Gilead is working to rapidly increase manufacturing and to develop a stockpile for use in pandemics generally. Gilead can be contacted by email through its website.

Chloroquine is known to block SARS-CoV2 virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (M. Wang et al.) and has been suggested as treatment. There is no clinical evidence of its effectiveness in infected patients.

Lopinavir/ritonavir (Kaletra) was associated with a marked reduction in mortality in a retrospective observational study of 44 patients with SARS in 2003, i.e. 2.3% as compared to 15.6% in a matched cohort of 634 (p<0.05). Lopinavir does have some in vitro activity against the SARS-CoV. There is no randomized controlled trial of this drug against SARS-CoV2.

While coronaviruses are sensitive to interferons, nevertheless clinical studies in support of interferon and ribavirin in treatment of MERS are weak and not randomized. Other drugs that show some promise in vitro against betacoronaviruses are arbidol and favipiravir.

**Conclusion**

As Thomas Paine said of our American Revolution, these are months that will try our souls. Facing a highly transmissible viral illness and not a small case-fatality rate in the elderly and compromised, with a shortage of PPE, our courage, dedication and good judgment will be tested. What it means to us to be physicians (and nurses and physician assistants) will be tested. I have no
doubt that as a profession, we will emerge from this crisis in a few months with distinction.

F. Kevin Murphy, MD, for the Washoe County Medical Society

--

References: COVID-19 and the novel coronavirus SARS-CoV2

Due to the urgency of the epidemic of COVID-19, most of these articles were published online, and therefore the DOI is given.


