Update on Clinical Features and Diagnosis of COVID-19

Nevada State Medical Association

Last month, the Nevada State Medical Association sent out a digest of what was then known about the clinical characteristics, diagnosis and management of COVID-19 (March 20, 2020). This included a review of predominantly online publications from China, many without peer review, but effectively summarizing the clinical experience of Chinese physicians with this novel Coronavirus. This experience of 7 studies was summarized in 3 tables, covering presenting symptoms, laboratory findings, and viral detection in clinical specimens. A syndrome had emerged that featured fever, cough, myalgia, dyspnea, lymphopenia, elevated d-Dimer and elevated LDH. One study identified *Mycoplasma pneumoniae* as the most common coinfection (Zhang et al.). Since then, as the virus has ravaged southern Europe and the coastal states of the U.S., Chicago and New Orleans, a broader clinical experience has been gained. Management has become more sophisticated but remains frustratingly limited. This update will review those extended findings.

**Anosmia & ageusia**

One of the first novel symptoms to be noted by European physicians was that of anosmia and hypogeusia (Vaira, et al.; Gane, Kelly & Hopkins). While these symptoms are not unusual with any respiratory viral illness that causes nasal congestion or rhinorrhea, these cases are occurring in COVID-19 without associated congestion or rhinorrhea. Forty-seven % of COVID-19 patients presenting to Nord Franche-Comté Hospital exhibited anosmia (Klopfenstein et al.). Seventy % of these did not have nasal congestion; they tended to be younger and female in contrast to patients without anosmia. Anosmia was associated with ageusia in 85%. Anosmia appeared first in 12% (Lechien et al.). In retrospect, the phenomenon had been reported in SARS in 2003 as a pure olfactory neuropathy as well (Hwang, 2006). Olfactory sensory neurons do not express two key genes required for CoV-2 entry, ACE2 and TMPRSS2. In contrast however, olfactory epithelial support cells and stem cells express both of these genes, as do cells in the nasal respiratory epithelium (Brann et al.). This would seem to form a basis for olfactory neuropathy in COVID-19. Studies of SARS CoV1 in transgenic mice demonstrated that following infection the highest concentration of virus was initially seen in the olfactory bulb and that this was the pathway into the central nervous system (Gu et al., 2005). Similar observations have been made with other coronaviruses, with the virus taking the path from the olfactory apparatus to the brainstem (Conde et al.).
Neurologic manifestations

Indeed, neurologic manifestations were soon noted after the initial reports of COVID-19 from China. Mao et al. reported that of 214 patients hospitalized in Union Hospital in Wuhan with COVID-19, 36% had one of 3 patterns of neurologic complications: central nervous system (25%), peripheral neurologic (9%) or skeletal muscle disease (11%). Those with severe COVID-19 respiratory disease were more likely to have these complications (45%) than those with mild to moderate disease (30%). Two patients presented with stroke and no other symptom of COVID-19. Their lung lesions were demonstrable only by CT. Most neurologic manifestations occurred early in the illness, i.e. within in 2 days of admission. Cerebrovascular disease included ischemic stroke and cerebrovascular hemorrhage. These cases are not described in any detail, but Tsai et al. (2004, 2005) clearly described the triad of cerebral infarction, polyneuropathy and myopathy with rhabdomyolysis as the leading neurologic complications of SARS. Zhou et al. have now described recovery of SARS CoV2 from the CSF of a patient with COVID-19. From Detroit comes a report of acute necrotizing hemorrhagic encephalopathy in woman in her late 50’s. This is a post viral syndrome seen predominantly in children, especially in East Asia. Influenza A virus, Mycoplasma, and human herpes virus-6 have been the most common causative agents of this syndrome; it is believed that this disease is most likely due to cytokine storm within the brain. Cytokines such as tumor necrosis factor-α, interleukin-1 and interleukin-6 are elevated in the brain in influenza-related cases.

Cytokine storm

Indeed, cytokine storm (or secondary hemophagocytic lymphohistiocytosis) is emerging as a probable major pathogenetic pathway of of COVID-19 (Mehta et al.; P. Conti et al.). Considerable evidence was already at hand that both SARS and MERS morbidity and mortality was attributable to a cytokine storm, characterized by an exuberant response of inflammatory monocyte-macrophages with a florid outpouring of cytokines. Lymphocytes that might have mounted an effective elimination of virus-infected cells, practically disappeared from the scene of battle, in part due to cytokines that induced T cell apoptosis (Channappanavar & Perlman, 2017). Both depletion of monocytes and neutralization of TNF protect mice from SARS CoV1. Cytokine storm in humans has best been described as a complication of chimeric antigen receptor (CAR) T-cell immunotherapy, but is also seen in lupus as a macrophage activation syndrome, and in virus triggered cytokine release. It is not at all clear that these syndromes are all the same, although they are
commonly characterized by high fever, hypertransaminasemia, hyperferritinemia in the thousands, and elevated d-Dimer and IL-6. Severe clinical cytokine storm is typically complicated by renal failure and ARDS.

For these reasons, consideration has been given to treatment of critically ill COVID-19 patients with agents directed against cytokine storm, e.g. tocilizumab (an IL-6 antagonist), ruxolitinib [Jakafi], emapalumab (Gamifant), and anakinra (Kineret), an IL-1 inhibitor. Empalalumab is approved for primary hemophagocytic lymphohistiocytosis and works by binding interferon-γ. Ruxolitinib is a janus kinase inhibitor used for myelofibrosis and polycythemia rubra vera which interferes with cytokine receptors. Several clinical trials of these agents in COVID-19 are currently enrolling. It is not clear what adverse effects on the course of COVID-19 may ensue from interfering with cytokine function. Certainly we know that steroids amplify the peak and duration of viral shedding in both SARS and MERS (Lee et al.; Arabi et al.). It is too soon to leap from theory to therapy without randomized controlled trials (RCT).

**Ophthalmology of COVID-19**

Little has been learned about ophthalmologic manifestations of COVID-19, except that excessive tearing and chemosis occur in 5.2% (Wu et al.) Zhou et al. found redness, itching, discharge, epiphora or chemosis in 6.6% and recovered the virus from 2.5% including 2 without symptoms. Some of these symptoms may be little more than expected complications of mechanical ventilation.

**Cutaneous manifestations**

Dermatologic manifestations of COVID-19 were first highlighted by Italian physicians at Lecco. They excluded any patients who had been placed on new medication and of the remaining 60, 20.4% had rashes: erythematous rashes, generalized urticaria or in one case, vesicles (Recalcati, 2020). Soon after this, Spanish dermatologists reported red maculopapular rashes, urticaria and purpura in COVID-19 from Madrid (Fernandez-Nieto et al.). From 8 dermatology units in Northern Italy came a report of 22 patients with COVID-19 presenting with a vesicular truncal rash mimicking varicella (Marzano et al.). Most significant however have been the more recent reports from Georgia
and California of livedo reticularis (Manalo et al.).

Amy Palle, chief of dermatology at Northwestern, and Esther Freeman of MGH have described a series 40 cases of “COVID-19 toes” or pernio-like nodules on the dorsa of toes.

Cynthia Magro et al. report a small autopsy series from Cornell of severe COVID-19 cases dying of respiratory failure and coagulopathy. Three of the 5 had livedo reticularis or retiform purpura.

Extensive thrombotic microvascular injury was found with deposition of the terminal components of complement, C4 and MASP2 in both alveolar septal capillaries and those of the skin. The pathology was distinct from that of typical
ARDS without the expected diffuse alveolar destruction, edema and hyaline membrane formation, but rather a pauci-cellular terminal lung parenchymal injury with septal capillary damage resembling early reports from Chinese pathologists. The authors cite the analogies of catastrophic antiphospholipid antibody syndrome, atypical hemolytic uremic syndrome, purpura fulminans, which can respond to anti-complement therapy. This pathology fits with the unusual pulmonary physiology of COVID-19, in which compliance is preserved and consolidation is less than in typical ARDS, but hypoxemia seems almost unremediable. The appearance of livedo reticularis, or retiform purpura may be an ominous harbinger of widespread complement-mediated microvascular thrombosis and death.

**Coagulopathy of COVID-19**

In an early Chinese study (Tang et al.), 71% of nonsurvivors of COVID-19 had laboratory evidence of disseminated intravascular coagulation (DIC) in contrast to the 0.6% of survivors with criteria for DIC. One Chinese series described patients who presented with CVA and no other symptoms of COVID-19; these developed soon after. Indeed, COVID-19 is characterized by thrombogenesis rather than the bleeding seen in other viral coagulopathies. Dutch investigators found that despite standard thrombo-prophylaxis, 27% of hospitalized COVID-19 patients developed venous thrombosis, 4% developed arterial thrombosis, and 14% developed pulmonary embolism (Klok et al.). Yan Zhang and his colleagues at Peking Medical College have described 3 patients with multiple infarcts and high titers of anti-phospholipid antibodies, suggesting an additional possible mechanism of microangiopathy in some of these patients. Tang and his colleagues also conducted an observational study of heparin anticoagulation in severely ill patients with COVID-19 in Wuhan and found improved 28 day mortality among those treated, but only at a d-Dimer level more than 6 times the upper limit of normal. More aggressive anticoagulation has been proposed, but only anecdotal reports of using such agents as tPA currently exist.

In a joint webinar between the Chinese Cardiology Association and the American College of Cardiology on March 28, 2020, the Chinese cardiologists described diffuse microvascular thrombi in multiple organs on autopsy review of COVID-19 non-survivors. Absent a published review of this data, it would seem that the cardiomyopathy of COVID-19 may also be a thrombotic microangiopathy due to pathologic complement activation.
Renal Complications of COVID-19

Acute renal failure was a feature of 2-10% of cases of COVID-19 in the original 8 reports of hospitalized patients from China, depending on the proportion of critically ill patients in each series (see “Clinical Characteristics, Diagnosis and Management of COVID-19”, NSMA, March 20, 2020). Four of the studies cited established that patients with pre-existing kidney disease had a 3-fold increase risk of severe COVID-19 illness (Henry & Lippi). Since then, nephrologists from Huazhong University and Shandong University have published postmortem findings in 26 patients dying of COVID-19 (Su et al.). Microscopically, renal injury ranged from diffuse proximal tubular injury and vacuolar degeneration to frank necrosis. There was no interstitial inflammation or hemorrhage. EM demonstrated clusters of coronavirus in tubular epithelium and podocytes with detachment from the glomerular basement membrane. These are sites of known ACE2 receptor concentration. In addition, a second receptor for SARS CoV2, the transmembrane glycoprotein CD147 (Wang et al.), is highly expressed on renal tubular cells. There was endothelial damage and microvascular occlusion in glomerular and peritubular capillaries. However there was no evidence of vasculitis. The ACE2 receptor was found to be upregulated. Antibody to SARS CoV2 was present within tubules. These investigators report that up to 29% of critically ill COVID-19 patients suffer acute renal failure. On clinical review hypoxia, thrombotic angiopathy, and rhabdomyolysis were contributory factors. Pigmented casts accorded with the cases of rhabdomyolysis. New onset proteinuria was often a signal of renal injury. These observations accord with observations on SARS in 2003-2004 in which 7% of patients developed renal failure, often associated with rhabdomyolysis, with a 92% mortality among those with renal failure.

In a clinical series of 701 cases from Tongji Hospital in Wuhan, Cheng et al. reported that 14-15% of cases were admitted with azotemia and 5.1% developed frank acute kidney injury. This was more common in those with an elevated baseline creatinine (12%) than not (4%). Overall mortality was 16.1%, but was 33.7% among those with elevated baseline creatinine. Forty-three % of patients developed proteinuria, and 27% hematuria. Forty-three % of the patients in this study were critically ill, and larger observational studies with fewer critically ill patients have had a much lower rate of AKI. In a separate report of 193 patients from 4 other Hubei hospitals (Li et al.), 33.6% of them being severely ill, 59% had proteinuria, 44% hematuria, and 14% azotemia. By Cox regression analysis, COVID-19 patients that developed AKI had a 5.3-fold greater mortality risk compared to those without AKI.
Recent reports of mild disease and survival of renal (and other solid organ) transplant patients from China, Italy and the U.S. raise the intriguing question of whether targeted immunosuppression may be beneficial (Arpali et al., Bin et al., Fei et al., Gandofini et al., Hsu et al., Kates et al., Seminari et al., Zhu et al.). However most of these cases were managed with attenuation of immunosuppression and were sometimes associated with acute renal failure. Calcineurin inhibitors (CNI), such as cyclosporine, do inhibit hepatitis C virus and coronavirus replication in vitro. So is there a beneficial antiviral effect, as well as a salutary inhibition of cytokine storm due to these drugs? No one is yet ready to use them in other patients with COVID-19, but they may not need to be withdrawn in transplant patients with the disease, and a clinical trial may be justified (Willicombe, Thomas & McAdoo).

**COVID-19 and the Heart**

As noted in our first review of COVID-19, hypertension is the leading comorbidity leading to more severe disease. The potential relationship of this observation and the importance of the ACE2 receptor in viral binding to cells of the lung, kidney, GI tract and heart remains obscure but tantalizing. In addition, pre-existing chronic heart disease is associated with a 5-fold increase in the case-fatality rate (10.5% vs. 2.3%) (Wu & McGoogan). In the SARS epidemic of 2003, cardiovascular disease increased the case fatality rate 12-fold.

More interesting is the effect of SARS CoV2 on the heart. Regardless of pre-existing cardiac disease, patients with critical illness exhibit dysrhythmias (17% of hospitalized and 44% of ICU patients; Wang et al.), heart failure, possibly acute myocardial infarction, and cardiogenic shock. Some of this may be nonspecific, since acute myocardial infarctions are also increased in the setting of influenza. However, in the case of SARS, the virus can be found in the myocardium at autopsy in 35% of cases (Oudit et al., 2009). This myocarditis is dominated by macrophage infiltration. As in COVID-19, these patients have been lymphopenic, and lymphocytes are scarce in tissues. Myocardial infarction has also been described in SARS at autopsy, but we have no such material in COVID-19.

Acute heart failure can be a presenting manifestation of COVID-19 in up to 23% of cases (F. Zhou, Yu, Du et al.). Only half of the patients who develop heart failure have pre-existing hypertension or chronic heart disease. F. Zhou et al. reported that 52% of fatal cases exhibited heart failure and only 2% of the survivors. Non-ST elevation MI may be impossible to diagnose, since up to 33%
of critically ill patients, and 8-17% of hospitalized cases have strikingly and persistently elevated troponin consistent with myocarditis or cardiomyopathy.

This seems to be a COVID-19 cardiomyopathy. In the series of D. Wang et al, this was a hallmark of those who required admission to the ICU. It is not clear how often STEMI occurs in COVID-19. However the vast majority of myocardial injury appears to be without ST changes, and likely a COVID-19 cardiomyopathy. In the series of 187 COVID-19 patients from the cardiology department of Zhongnan Hospital in Wuhan (Guo et al.), 27.8% of hospitalized COVID-19 patients exhibited myocardial injury. The mortality of those without cardiovascular disease (CVD) and normal troponin levels was 7.6%, for those with CVD and normal troponins 13.3%, for those with no pre-existing CVD and elevated troponins 37.5%, and for those with pre-existing CVD and elevated troponins, 69.4%. Troponin levels were closely correlated with C-reactive protein (CRP) and BNP. Rising troponin levels were correlated with malignant arrhythmias, mortality and requiring mechanical ventilation. The potential effect of ACE inhibitors and angiotensin receptor blockers has been puzzling and controversial, but in this observational study, the mortality of those on ACEIs or ARBs was 36.8% vs. 25.6% for those not receiving these drugs (p=0.002). From the cardiology department of another hospital in Wuhan (Shi et al.) comes a series of 416 hospitalized cases, with a myocardial injury rate of 19.7%. These patients were more likely to have hypertension (59.8 vs. 30.5%) and coronary disease (29.3% vs. 10.6%) than those with normal troponins. They were more likely to require mechanical ventilation (68.3% vs. 4.2%). Virtually all complications were more common in these patients than those with normal troponins, including ARDS, electrolyte disorders, acute kidney injury, hypoalbuminemia, and dyscoagulation. Their case fatality rate was 51% as compared to 4.5% in those with normal troponins (p<0.001).

Only one well studied case of COVID-19 “myocarditis” has been reported from China (Hu et al.). This was a 37 year old man admitted with chest pain, dyspnea, cardiomegaly, and hypotension. There were ST elevations in AVF & III, a troponin >10,000, a BNP of 21,025, CKMB 113, and global hypokinesis on echocardiogram with an EF of 27%. His coronary arteriography was normal. His pneumonia was minor. He recovered after treatment with pressors, milrinone, steroids and IV gamma globulin.

Elena Roca et al. described an 87 year old woman in Brescia, Italy, who presented with COVID-19 pneumonia, a troponin I of 5347 (nl <6), and classic findings of takotsubo cardiomyopathy. There is no echocardiographic material in the Chinese series’, so it is unclear how often this might be a feature of
COVID-19 cardiac disease. The clues are tantalizing. Will COVID-19 cardiomyopathy prove to be a viral myocarditis, myocardial injury due to cytokine storm, a takotsubo syndrome, a thrombotic microangiopathy, oxygen supply/demand imbalance or myocardial infarction, or perhaps some combination of these insults? The answer awaits advanced imaging and histopathology.

**The American Experience of COVID-19**

As the Chinese began to report pre-symptomatic transmission of SARS CoV2, the U.S. saw its first confirmed case in Washington state on January 19, 2020. The national response has been characterized by lassitude followed by panic and desperation, as we became the global leader in COVID-19 cases and deaths (Johns Hopkins Coronavirus Resource Center). Our clinical experience to date is summarized in four papers (Arentz et al., Bhatraju et al., Goyal et al., Richardson et al.) summarized in Table I.
Table 1. Clinical Features of COVID-19: U.S. Series

<table>
<thead>
<tr>
<th></th>
<th>Bhatraju** et al. Seattle 24 cases</th>
<th>Arentz et al. Kirkland 21 cases</th>
<th>Goyal et al. New York 393 cases</th>
<th>Richardson et al. New York 5700 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>64</td>
<td>70</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
<td>52%</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td>Obesity or BMI</td>
<td>BMI 33 +/- 7</td>
<td>NR</td>
<td>36%</td>
<td>42%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>NR</td>
<td>NR</td>
<td>50%</td>
<td>57%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>58%</td>
<td>33%</td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td>CVA on admission</td>
<td>8%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>OSA</td>
<td>21%</td>
<td>29%</td>
<td>NR</td>
<td>3%</td>
</tr>
<tr>
<td>Fever on admission</td>
<td>50%</td>
<td>52%</td>
<td>77%*</td>
<td>31%</td>
</tr>
<tr>
<td>Cough</td>
<td>88%</td>
<td>48%</td>
<td>79%</td>
<td>NR</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>88%</td>
<td>76%</td>
<td>57%</td>
<td>NR</td>
</tr>
</tbody>
</table>

*However, on first presenting in ER only 26% had fever.

**Bhatraju et al. also reported 42% had sputum production, 17% had rhinorrhea, 8% sore throat, 8% headache.

The variability in clinical findings and comorbidities resembles that in the Chinese studies. Fever, cough and dyspnea are common presentations, but are not consistently seen. Patients may present with CVA, diarrhea, myalgia or malaise or other features that distract from the diagnosis of COVID-19. As in most of the Chinese series (see our first summary of COVID-19), hypertension was the leading comorbidity overall. Surprisingly, the Washington state cases included no one with a history of travel to a country with known transmission, although Bhatraju et al. reported that 54% had contact with sick persons and 25% were admitted from nursing homes. Seventy-five % had lymphopenia on
admission and all had bilateral pulmonary densities on chest x-ray. None had pleural effusions even on CT. Forty-one % developed hypertransaminasemia and 15%, an elevated troponin. None had a decline in LV function by echocardiogram. No viral or Mycoplasma coinfection was found. Seventy-five % required mechanical ventilation and 71%, vasopressors. The overall mortality of these hospitalized patients was 50%. With a somewhat higher mean age and a large share of patients from a nursing home, the Kirkland, Washington, group saw twice as much cardiomyopathy.

Table 2. Laboratory findings, critical care & mortality: U.S. Cases.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Bhatraju et al., Seattle</th>
<th>Arentz et al., Kirkland</th>
<th>Goyal et al., New York City</th>
<th>Richardson et al., New York</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>75%</td>
<td>67%</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>Elevated transaminase</td>
<td>41%</td>
<td>38%</td>
<td>“many”</td>
<td>58%</td>
</tr>
<tr>
<td>High troponin</td>
<td>15%</td>
<td>33%</td>
<td>NR</td>
<td>23%</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>71%</td>
<td>67%</td>
<td>33%</td>
<td>NR</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>75%</td>
<td>71%</td>
<td>33%</td>
<td>12%*</td>
</tr>
<tr>
<td>Mortality (CFR)</td>
<td>50%</td>
<td>67%</td>
<td>10%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*The case-fatality rate (CFR) among these was 88%, and among those over 65 on mechanical ventilation, 97%.

The 2 Manhattan hospitals from which Goyal et al. reported saw a remarkable rate of diarrhea among their cases, 23.7%, as well as nausea and vomiting (19%), as in some of the Chinese series. The lower rate of vasopressor infusion, mechanical ventilation, and mortality in both New York series suggests that the New Yorkers admitted a larger proportion of moderate cases of COVID-19 than did the Washington physicians. In contrast to the 2 Washington series, Richardson et al. reported a variety of coinfections: non-COVID-19 coronaviruses (16.7%), respiratory syncytial virus (9.5%), parainfluenza virus 3 (7.1%), Chlamydia pneumoniae (4.8%), enterovirus or rhinovirus (4.8%), human metapneumovirus (4.8%) and a rare Mycoplasma or influenza A. Richardson et al. also that mortality rates in hypertensive patients on ACE inhibitors or ARBs were 31-33% as compared to 27% among those not taking these drugs; however there was insufficient power to adjust for other confounding factors.
In the only significant clinical report from California so far, Yan et al. from UCSF reported a strikingly high rate of anosmia and ageusia at presentation among San Francisco patients presenting with COVID-19. Of 58 COVID-19 positive patients among patients with influenza-like illness, 68% had anosmia and 71% loss of taste, whereas 16% and 17% of 203 COVID-19 negative patients had anosmia or ageusia.

**Radiologic Features of COVID-19**

Salehi et al. systematically reviewed reports of radiographic finding in the literature of 919 patients with COVID-19. As is well known by now, bilateral multifocal ground-glass opacities are the hallmark of the disease. They are best seen by CT, which is more sensitive than chest x-ray and often more sensitive than PCR. In addition however, these opacities tend to be peripheral and posterior in distribution, primarily in the lower lobes, infrequently in the right middle lobe. Less commonly septal thickening, bronchiectasis, and pleural thickening are seen. As in SARS, pleural effusion, pericardial effusion, lymphadenopathy, cavitation, and pneumothorax are very uncommon. Progressively over the course of the disease, the number and size of ground-glass opacities increase and may transform into consolidative densities, typically worst at 10 days post onset of symptoms. At this stage the “crazy paving pattern” sign may be seen, as in alveolar proteinosis, lipoid pneumonia, hypersensitivity pneumonitis, graft vs. host disease, Pneumocystis pneumonia, sarcoidosis, and lymphangitic carcinomatosis. If improvement is seen, it begins after 2 weeks.

Harrison Bai at Brown University collaborated with Chinese radiologists to test the performance of American and Chinese radiologists in differentiating COVID-19 from other viral pneumonias by CT in 219 cases of COVID-19 and 205 cases of other viral pneumonia proven by PCR. Using criteria described above, both groups demonstrated a sensitivity of 72-94% and specificity of 88-100%, except for one radiologist with a specificity of only 24%. The most discriminating elements were peripheral distribution, ground glass opacities, and vascular thickening. It seems radiologists can learn, even in the dark.

**Testing for SARS CoV2**

The validation of PCR for detection of the RNA of SARS CoV2 has been very disappointing, as we still do not have defined sensitivity and specificity of the commonly used CDC test. This is further obfuscated by the multiplicity of tests that have since emerged and are in use under FDA EUAs. From an
analytic perspective, the test can detect as few as 5 RNA fragments of the virus in a sample. The European RTR-PCR can detect 3-5 RNA fragments with 95% probability for example (Corman et al.). However, we know that clinically we see false positives as demonstrated by numerous cases that are negative by PCR, positive by CT of the chest and clinical syndrome, who are later positive by PCR (Ai et al.); the delay between evidence of COVID-19 by CT and a positive PCR can be as long as 5 days. We also see cases that are negative at the end of treatment, but then positive on repeat testing, or worse positive at relapse of symptoms. On the other hand, the recovery of the virus as much as 2 days before the onset of symptoms, and the persistence of viral RNA beyond recovery, i.e. 3-6 weeks, speaks to the apparent sensitivity of the test. Some of these discrepancies may have to do with the difference between active infection with live virus, and residual fragments of non-infectious RNA. Specimen handling may impair the test at times. Some of the problem may lie in the anatomic distribution of the virus, which we know is more highly concentrated in bronchoalveolar lavage than in the nasopharynx. Even less virus is found in the oropharynx and anterior of the nose.

The new Abbott test on its ID Now machine for SARS CoV2 IgG antibody has been better validated. Of nearly 1000 pre-COVID-19 serum samples, only 4 were positive, yielding a specificity of >99% (Mark Pandori, pers. comm). This seems to lay to rest concern that we might confuse a positive serology due to endemic coronaviruses (OC43, HKU1, 229E, & NL63) with a diagnosis of past infection due to SARS CoV2. The absence of an IgM component to the Abbott test is disconcerting to some, but since the IgG antibody appears only 2 days after IgM, this should matter very little.
Table 3. Current serologic tests for COVID.
Johns Hopkins Coronavirus Ctr.

<table>
<thead>
<tr>
<th>Type of test</th>
<th>Time to results</th>
<th>What it tells us</th>
<th>What it cannot tell us</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid dx test</td>
<td>10-30 min</td>
<td>Qualitative presence or absence of Ab</td>
<td>Whether the antibody inhibits the virus</td>
</tr>
<tr>
<td>Lateral Flow Assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELISA</td>
<td>2-5 hrs</td>
<td>Quantitative presence or absence of Ab</td>
<td>Whether the antibody inhibits the virus</td>
</tr>
<tr>
<td>Neutralization Assay</td>
<td>3-5 days</td>
<td>This is a test of viral inhibition</td>
<td>It may miss antibodies to viral proteins that are not involved in replication</td>
</tr>
<tr>
<td>Chemiluminescent Assay</td>
<td>1-2 hrs</td>
<td>Quantitative presence or not of antibody</td>
<td>Whether the antibody inhibits the virus</td>
</tr>
</tbody>
</table>

The serologic tests for COVID-19 currently under an FDA Emergency Use Authorization (EUA) are displayed in Table 4. The specificity and sensitivity of each one was provided by the manufacturer in each case, without the transparency or rigorous review that usually accompanies an FDA approval. None of the tests currently authorized under EUA is a neutralization test, although laboratory studies indicate that ELISA antibodies directed against the nucleocapsid and spike proteins and the receptor binding region track well with neutralizing antibody by the plaque reduction neutralization test (Okba et al.). It is neutralizing antibody that should correlate best with protective immunity to the SARS CoV2 virus.
Table 4. Tests approved in the United States under EUA  
Johns Hopkins Coronavirus Center

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Type of Test</th>
<th>Class</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellex</td>
<td>Lateral Flow RDT, POC</td>
<td>IgM, IgG</td>
<td>93.8%</td>
<td>95.6%</td>
</tr>
<tr>
<td>ChemBio</td>
<td>RDT</td>
<td>IgM, IgG</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ortho Clin-Diagnostics</td>
<td>ELISA</td>
<td>IgG</td>
<td>87.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Mt. Sinai Laboratory</td>
<td>ELISA</td>
<td>IgG</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>AutoBio Diagnostics</td>
<td>Lateral Flow RDT</td>
<td>IgM, IgG</td>
<td>95%</td>
<td>99%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>99%</td>
<td></td>
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<tr>
<td>Diasorin</td>
<td>ELISA</td>
<td>IgG</td>
<td>90-97% Early v. Late &gt;15 d.</td>
<td>98%</td>
</tr>
<tr>
<td>BioRad</td>
<td>ELISA</td>
<td>IgM, IgG, IgA</td>
<td>98%</td>
<td>99%</td>
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Resuming Elective Surgery in the Time of COVID-19

A cautionary tale appeared from China in March, when Shaoqing Lei et al. reported a shockingly high postoperative mortality rate in routine surgeries among patients with coincident COVID-19 from 3 hospitals in Wuhan. The median age of their 34 patients was 55. They were asymptomatic when admitted for Cesarean sections, total hip arthroplasties, laparoscopic appendectomies, colectomies or gastrectomy, esophageal resections for cancer, thoracoscopic lobectomies, mastectomy, open reduction and internal fixation of a tibial fracture and a wide variety of other major surgeries in all specialties. Post operatively they developed fever and pneumonia. Forty-four per cent required admission to the ICU and 20% died. All were found to have been incubating COVID-19 in retrospect. They typically became ill 2.5 days post operatively, were dyspneic one week post op and died 16 days post...
Bobin Mi et al. described a 40% postoperative mortality from a 4th hospital in Wuhan in 10 patients admitted with routine fractures requiring open reduction and internal fixation, who also were incubating COVID-19.

In view of these findings, it becomes essential to screen all patients for COVID-19 preoperatively. Obviously, symptomatic patients should have surgery delayed. Since the PCR is less sensitive during the incubation period, it would be prudent to require two negative PCRs for SARS CoV2 twenty-four hours apart prior to elective surgery. As the IgM antibody becomes available, consideration should be given to adding it to the preoperative screen, since it has been shown to increase the sensitivity when combined with the PCR.

**Conclusion**

COVID-19 has provided us with one surprise after another, both fascinating and horrifying as we struggle to care for these very sick patients without the usual compass of published medical literature. You will have noticed that most of the references are not in print and not peer reviewed. The issues surrounding treatment have been complex and changing, but promising therapies are emerging. In our next communication, we will review that present status of management, including convalescent plasma, remdesivir, and other promising drugs.

F. Kevin Murphy, M.D.
May 4, 2020

Update on COVID-19: References
May 3, 2020


Luigi A. Vaira, MD ; G. Salzano, MD; G. Deiana, MD; G. De Riu. Anosmia and Ageusia: Common Findings in COVID-19 Patients. The Laryngoscope DOI: 10.1002/lary.28692.


