BCM Infectious Disease COVID19 Literature Review Newsletter: WEEK 20
August 10th-14th, 2020

Week 20 Newsletter Prepared by:
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The number of COVID-19 confirmed cases, related deaths, and total tests reported for State and County

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Last Updated</th>
<th>COVID-19 cases in Texas</th>
<th>COVID-19 cases in Harris County</th>
<th>COVID-19 related deaths in Texas</th>
<th>COVID-19 related deaths in Harris County</th>
<th>Total tests performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Texas DSHS a</td>
<td>Aug 9, 2020, 3:20 PM</td>
<td>486,362 (Active cases: 133,008)</td>
<td>84,600 (Active cases: 36,097)</td>
<td>8,459</td>
<td>1,575</td>
<td>4,025,864 Texas</td>
</tr>
<tr>
<td>2. Johns Hopkins b</td>
<td>Aug 10, 2020, 11:34 AM</td>
<td>503,730 (Active cases: 158,885)</td>
<td>85,757</td>
<td>9,165</td>
<td>N/A</td>
<td>4,025,864 Texas</td>
</tr>
</tbody>
</table>

aTexas DSHS daily case count now includes all cases reported publicly by local health departments around the state
bData sources from WHO, CDC, ECDC, NIH, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports.
cData represents total viral tests performed (positive and negative) at private and public labs in Texas. N/A = not available

COVID-19 diagnoses per day in the greater Houston area

Source: County health authorities, Texas DSHS
In the News:
   a. ACTT3 to enroll over 1000 hospitalized adults with COVID-19 at 100 sites in US and abroad

Articles:

Background:
- Case reports and small case series suggest COVID-19 affects cardiovascular system
- Proposed pathophysiologic mechanism: inflammatory plaque rupture, stent thrombosis, cardiac stress due to high cardiac output, endothelitis, myocardial inflammation from infiltration of mononuclear cells

Methods:
- Prospective observational cohort study, University Hospital of Frankfurt
- Patients with +SARS-CoV-2 by RT-PCR, April-June 2020
  - Control: age-matched, sex-matched, normotensive healthy adults (n = 50)
  - Control: age-matched, sex-matched, risk-factor matched adults (n=57)
- Inclusion: minimum of 2 weeks after original diagnosis with resolution of respiratory symptoms and negative RT-PCR
- Exclusion: absolute CI for contrast MR-study, active cardiac symptoms
- Procedures: cardiovascular magnetic resonance (CMR), venous blood sampling (troponin, BNP) in addition to demographic data collected (including endomyocardial biopsy)
  - Median time between positive COVID-19 testing and CMR was 71 days

Results:
- 100 patients recovered from COVID-19 (53% male, median age 49)
  - 67 patients recovered at home, severity ranging from asymptomatic to mild-mod
  - 33 patients were hospitalized, 2 required mechanical ventilation, 8 received steroids
  - All preexisting conditions were similar between patients recovered at home vs hospitalized, as well as between COVID-19 patients and risk-factor-matched controls
- On day of CMR: 17% had atypical chest pain, 20% palpitations, 36% reported ongoing shortness of breath and general exhaustion (*no report of typical angina)
  - Troponin was detectable in 71%, significantly elevated in 5%
- 78% of recovered COVID-19 patients had abnormal CMR findings
  - 73% with raised myocardial native T1 (diffuse fibrosis and/or edema)
  - 60% with raised myocardial native T2 (specific for edema)
  - 32% with myocardial LGE (scarring)
  - 22% with pericardial enhancement
  - 12% with ischemic-type pattern of myocardial LGE
***no difference between home vs hospital recovery for native T2, troponin or BNP, small difference in native T1

- 3 patients with severe CMR findings had endomyocardial biopsy
  - Active lymphocytic inflammation with no evidence of viral genome detected
- Compared to healthy controls and risk factor-matched controls, COVID-19 recovered patients:
  - Lower LV and RV ejection fraction and higher LV volume
  - ROC analysis: Native T1 and T2 had best discriminatory ability to detected COVID-19-related myocardial pathology

**Discussion:**
- COVID-19 sequelae includes cardiac inflammation, larger and prolonged studies are needed
- 78% of recovered COVID-19 patients irrespective of pre-existing conditions, severity or clinical course had abnormal CMR findings
  - Most common abnormality (60%) was myocardial inflammation (abnormal T1 and T2)
  - Volumes and ejection fractions were mildly abnormal
- Limitations: small regional study, several patients were still symptomatic


**Background:**
- COVID-19 can cause severe respiratory disease and viral pneumonia that can become complicated by bacterial and fungal infections
  - These super infections result from the damage of lung tissue, cytokine release, and immune-paralysis caused by viral infection-induced ARDS.
- Invasive pulmonary aspergillosis has been reported post-Influenza viral pneumonia
  - Risk factors include hematologic malignancies, solid-organ transplant recipients, ICU stay, diabetes, COPD, systemic corticosteroids, CKD
- Authors aimed to determine answers to these two questions:
  - Are these same risk factors similar to the risk of developing COVID-19 associated pulmonary aspergillosis (CAPA)?
  - Is isolating *Aspergillus* sp. in respiratory samples always clinically significant in COVID-19 patients?

**Methods:**
- Retrospective observational study of patients with SARS-CoV-2 +PCR with isolation of *Aspergillus* spp. in respiratory samples during a three-month period (March-May 2020). Madrid, Spain, University Hospital La Paz.
- Two commercial tests were used for the diagnosis of COVID-19 in NP swabs and BAL specimens
  - SAR-CoV-2 Realtime PCR Kit (Vircell, Granada, Spain)
  - TaqMan 2019 nCoV Assay Kit v1 (Thermo Fisher, Waltham, MA, USA)
- Sputum, bronchial aspirates, BAL cultures in standard fungal culture media
- *Aspergillus* spp. strains identified by culture characteristics, microscopic morphology, and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF)
  - Susceptibility testing to antifungals was performed by gradient diffusion strips per CLSI methodology
- Galactomannan assays were performed in serum and/or BAL (cut-off index 0.5 for both)
- CAPA cases were classified according to the revised EORTC/MSG criteria (2019) and AspICU algorithm
A confirmed COVID-19 case + ICU stay was considered to have met host criteria

Results:
- 10 patients (80% male, age range 51-76 years) had +PCR for SARS-CoV-2 and *Aspergillus* spp. isolated in respiratory samples
  - Patient has classic risk factors for developing pulmonary aspergillosis
    - E.g., Diabetes, obesity, COPD, male sex, age 65 or older.
  - 4 patients were immunosuppressed
    - E.g., Hematological disease, HIV, Ankylosing spondylitis HLA-B27+ on golimumab
  - 7 patients had ICU stay with mechanical ventilation
  - All patients received corticosteroids as part of their anti-COVID-19 treatment
SARS-CoV-2 detected by PCR on NP swabs in 9 patients, one patient had SARS-CoV-2 PCR+ in bronchial aspirate.

After COVID-19 diagnosis, *Aspergillus* spp. isolates grew on culture from deep respiratory samples.

- 8 bronchial aspirates: time from +PCR median 13 days (range 2-46 days)
Two patients grew mold on consecutive cultures
  - One sputum: 11 days from +PCR
  - One BAL: 9 days from +PCR
- *Aspergillus fumigatus* (9 patients), *Aspergillus nidulans* (1 patient)
  - Strains showed good susceptibility against all tested antifungals
    - Except *A. nidulans* showed poor *in vitro* activity to Amphotericin B
- Galactomannan (GM) was done in 3 patients,
  - One positive in serum = 1.97
  - One positive in BAL = 3.87
  - One positive in BAL = 2.16 (also had GM in serum that was negative = 0.22)
- 7 patients had radiographic chest imaging (XR or CT) showing bilateral basal or interstitial infiltrates, 5 had ground glass opacities
- Signs/Symptoms: 9 patients had cough, fever, dyspnea and/or respiratory insufficiency
- Fungal pneumonia classifications
  - One case – probable fungal pneumonia (EORTC/MSG)
  - 7 cases – putative fungal pneumonia (*AspiCU*)
  - 2 cases – not classified
- COVID-19 treatment:
  - All received hydroxychloroquine, 4 received tocilizumab, 4 received lopinavir/ritonavir
  - 8 received IV antifungals
- Outcomes: 7 died, 2 prolonged ICU stays, only one made it to hospital discharge (survived)

**Conclusions/Limitation:**
- Invasive pulmonary aspergillosis is a clinical entity with high mortality rates and should be considered in COVID-19 patients as a possible consequence of their viral pneumonia.
- This study was limited by a very small sample size, retrospective chart review with inherent bias
- Future studies are needed to better characterize risk factors and diagnostic correlates of CAPA:
  - Does every mold isolated in sputa of COVID patients warrant treatment?
  - Are COVID-19 treatments (e.g., Tocilizumab, systemic corticosteroids) contributing significantly to CAPA?
  - Is there a role for prophylaxis in high-risk and/or severe COVID pneumonia patients?
  - Are patients at risk for CAPA even after recovery from COVID-19? For how long?


**Background:**
- Major risk factors for severe COVID-19 with multiorgan complications include male sex, older age (>65 years), cardiovascular and chronic lung disease, and diabetes. The reasons remain unclear as to why these conditions predispose to severe COVID-19.
- To enter the target cell, SARS-CoV-2 requires the binding of its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor. The entry is additionally facilitated by subsequent priming and cleavage of the spike protein through proteases such as transmembrane serine protease 2 (TPMRSS2) and furin. The ACE2 receptor is mainly expressed in heart, lungs, endothelial cells, kidney, and the gastrointestinal tract, but expression has also been detected in cholangiocytes and hepatocytes.
- No testing has been done so far to determine whether liver fat accumulation or diabetes affects hepatic ACE2 expression. The authors investigated how nonalcoholic fatty liver (NAFL) and diabetes impact ACE2 expression in the human liver.

**Methods:**
- The authors investigated hepatic ACE2 mRNA expression by real-time PCR in surgical liver samples of normal, non diseased tissue from a cohort of 165 individuals (62 women/103 men) of European descent including 31 subjects with type 2 diabetes.

**Results:**
- Hepatic ACE2 mRNA expression was significantly higher in males compared with females \((P = 0.024)\) and higher in older patients \((P = 0.011, r = 0.197)\). Obesity had no link to hepatic ACE2 expression \((P = 0.24, r = 0.092)\). The authors next addressed the impact of liver fat. In their cohort of patients with a wide range of liver fat content, they detected increasing ACE2 expression with increasing fat accumulation \((P = 0.002, r = 0.239)\). This relation remained significant even after adjustment for age, sex, and BMI \((P = 0.0028)\).
- Patients with diabetes had significantly higher ACE2 expression than those without the disease \((P = 0.0085)\). In the 73 patients with available fasting blood samples, neither fasting glucose nor insulin sensitivity was associated with hepatic ACE2 expression \((P = 0.67, r = 0.158, \text{and } P = 0.94, r = 0.009, \text{respectively})\).
- TMPRSS2 had similar associations with sex \((P = 0.048)\) and diabetes \((P = 0.035)\), as well as a positive correlation with liver fat content \((P = 0.0023, r = 0.234)\) but not with age \((P = 0.48)\). In contrast, the authors detected no significant associations between furin expression and sex, diabetes, age, BMI, or liver fat content.

**Conclusion:**
- The authors report upregulated expression of ACE2 in the livers of patients with diabetes, male sex, older age, or NAFL, i.e., situations that predispose to an adverse course of COVID-19. The larger availability of ACE2 and its major cofactor TMPRSS2 most likely fosters viral
penetration into cells and contributes to the susceptibility for hepatic complications in these patients.

- NAFL could play an important role in the development of severe liver damage during infection with SARS-CoV-2 in older population with diabetes.

**Limitation:** In published reports SARS-CoV-2 has been detected in some, but not all, autopsy liver samples of COVID-19 patients. It is still not clear whether SARS-CoV-2 infection affects hepatocytes or cholangiocytes.