BCM Infectious Disease COVID19 Literature Review Newsletter: WEEK 6
May 4th-May 8th, 2020

The number of COVID-19 confirmed cases, related deaths, and total tests reported for State and County

<table>
<thead>
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<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>
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<tbody>
<tr>
<td>1. Texas DSHS a</td>
<td>May 8, 2020, 12:00 PM</td>
<td>36,609</td>
<td>7,377</td>
<td>1,004</td>
<td>154</td>
<td>477,118 Texas</td>
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<td>461,648 Private Labs</td>
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<td>15,470 Public Labs</td>
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<td>64,530 Harris County</td>
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<tr>
<td>2. Johns Hopkins b</td>
<td>May 8, 2020, 11:32 AM</td>
<td>36,047</td>
<td>7,377</td>
<td>985</td>
<td>N/A</td>
<td>455,162</td>
</tr>
</tbody>
</table>

a DSHS updated the method of reporting COVID-19 cases in Texas on March 24, 2020 to provide the public with more timely information. The DSHS daily case count now includes all cases reported publicly by local health departments around the state.

b Data sources from WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports.

c Data represents total tests from private and public labs in Texas and Harris County, unless otherwise stated. N/A = not available

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COVID-19 in the greater Houston area

Source: County health authorities, Houston Chronicle reporting

**Background:**
- Coagulopathy in severely ill patients with COVID19 appears to be a poor prognostic indicator
  - Association of marked elevations d-dimer with mortality (Tang et al. *see review #3 below*)
- Plan for ongoing updates to these guidelines as more is known

**Laboratory Parameters:**
- **On admission:**
  - Elevated d-dimer 3-4-fold greater than normal may be an indication for admission, even without other evidence of severe disease
  - PT is only modestly prolonged (and may not be reflected in INR) in more critically ill patients
  - Thrombocytopenia is a less consistent predictor of severe disease
  - For all patients presenting with COVID19, recommend measuring d-dimer > PT > platelet count

- **Monitoring:**
  - Unclear role of measuring fibrinogen, but Tang et al. *found DIC developed in 71% of non-survivors compared to 0.6% of survivors*
  - Monitoring of PT, d-dimer, platelet count, and fibrinogen may be helpful for prognostication and anticipated need of additional critical care support

**Management of Coagulopathy:**
- Low molecular weight heparin should be considered for prophylaxis in ALL patients who are admitted with COVID19, unless contraindicated
- Also has anti-inflammatory properties

**Algorithm:**

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**FIGURE 1** Algorithm for the management of coagulopathy in COVID-19 based on simple laboratory markers. **The list of markers is given in decreasing order of importance.** **Performing fibrinogen assays may not be feasible in many laboratories but monitoring the levels can be helpful after patient admission.** **Although a specific cut-off cannot be defined, a three- to four-fold increase in D-dimer values may be considered significant. Any one of the values in this table may be considered significant.**

- **Propose:** use of therapeutic doses of unfractionated heparin to prevent micro- & macro-thrombosis
- **Rationale:**
  - Note lack of bleeding as a typical feature of COVID-19 with DIC
  - Autopsy studies have shown microthrombosis in pulmonary vasculature, which may contribute to right heart strain and contributes to pulmonary dysfunction
  - High fibrinogen levels have been observed in patients with COVID-19 and is associated with:
    - Heparin resistance
    - Thrombosis
  - Higher than anticipated rates of pulmonary embolism have been observed
  - Ease of dosing and management of bleeding over LMWH in renal failure
  - Call for RCT to investigate doses (prophylactic vs therapeutic) and type (LWMH vs unfractionated heparin) of anticoagulation in COVID-19

**Clinical Manifestations:** Multiple case reports and case series have been published regarding clinical manifestations of coagulopathy in COVID-19. You can find some of these below pertaining to the different clinical manifestations

2. **DVT/VTE:** multiple studies have been published with rates of VTE in the ICU from 15-50% (most commonly in the 15-25% range)
3. **Dermatologic findings:** includes findings of typical viral exanthem, vesicular eruption, or urticaria, but also vasculopathy related findings like levido reticularis, red papules resembling chilblains (dubbed “COVID toes”), and peripheral cyanosis

https://doi.org/10.1111/jth.14817

**Background:**
- Severe COVID-19 is commonly complicated with coagulopathy and DIC
- Patients with COVID-19 may be at increased risk due to sepsis, long-term bed rest, and receiving hormone therapy

**Methods:**
- Retrospective review of patients with severe COVID-19 admitted to Tongji Hospital of Huazhong University of Science and Technology in Wuhan from January 1 to February 13, 2020
- Exclusion criteria: bleeding diathesis, hospital stay < 7 days, lack of information about coagulation parameters and medications, and age < 18 years
- COVID-19 diagnosis: based on World Health Organization interim guidance and confirmed by PCR
- Severe COVID-19 definition: Respiratory rate ≥30 breaths/min; arterial oxygen saturation ≤93% at rest; or PaO2/FiO2 ≤ 300 mm Hg

**Results:**
- 449 patients (181 females and 268 males) classified as severe COVID-19 were enrolled
- 272 (60.6%) patients had one or more chronic underlying diseases: hypertension (n = 177, 39.4%), diabetes (n = 93, 20.7%), and heart diseases (n = 41, 9.1%).
- 99 (22.0%) patients received heparin treatment for at least 7 days
  - 94 received LMWH
  - 5 received unfractionated heparin
- By March 13, 315 (70.2%) patients were still survived
- No difference in 28-day mortality between heparin users and nonusers (30.3% vs 29.7%, P = .910).

**Conclusion/Limitations:**
- Effectiveness of anticoagulant therapy for sepsis-associated DIC is controversial
- Several confounding variables including enrollment of patients took place over a 6-week period during which clinical management may have evolved and impacted outcomes, different pharmaceutical treatments
- Selection bias given the retrospective nature of the study


**Background:**
- SARS-CoV-2 patients may experience thrombotic events.
- Studies have reported that clotting variables and platelet counts in COVID-19 patients is suggestive of a hypercoagulation state.
- Aim: determine if changes of clotting variables are dependent on the severity of the disease.

**Methods:**
- Systematic Review
- **Eligibility Criteria:** clinical COVID-19 studies that assessed: d-dimer, platelet counts, prothrombin time, activated partial thromboplastin time, ALT, and AST. Studies had to show COVID-19 infection with severe disease and control group.
- Studies were identified by searching electronic databases by two investigators.
- Disease severity was defined as ARDS, need for mechanical ventilation/ICU treatment, nonsurvivor patients, or severe pneumonia.

**Results:**
- D-dimer: The percentage of patients with elevated D-dimer had high values ranging from 14-46%. Analysis of D-dimer according to disease severity showed increased values of D-dimer in patients with severe vs. non-severe disease (significance was shown in 4/6 studies).
- Platelet Count: Reduced platelet count was detected in 5-18% of the entire population and the impact of disease severity on platelet count was reported in five studies. Platelet reduction was documented in non-survivors compared to survivors.
- Prothrombin Time: Five studies reported changes in PT prolongation, which was detected in 2-11% of the entire population. Analysis of PT according to disease severity found PT prolongation in severe disease and more common in non-survivors with values exceeding 15-16 seconds.
• Activated Partial Thromboplastin Time: Three studies reported changes of aPTT, which was detected in 6-26% on the entire population. Prolongation, as well as shortening, were reported in patients with severe vs. non-severe disease. Prolonged aPTT occurred in non-survivor but need further study.
• ALT: 4/6 studies reported ALT levels exceeding normal values range. ALT increased in 12-31% of patients. Two studies showed a modest increase in case of ARDS or poor survival.
• AST: 4/5 studies reported AST levels exceeding normal value range. AST was increased in 18-62% of patients. Three studies reported AST values according to the disease severity and only two showed a significant increase.

Conclusions/limitations:
• Data suggests low-grade intravascular clotting activation, which is evident in patients with severe disease.
  o This is most consistent with the increase of D-dimer
  o PT, aPTT, and platelet count data are inconclusive
• Future studies are needed to screen for hypercoagulation state and clarify if platelet activation occurs in these patients.
• Limitations: small number of included studies

COVID19 Literature Review Newsletter Volume #17
Pediatric Infectious Disease Fellow: Saki Ikeda, MD
Faculty: Jill Weatherhead, MD
May 6th, 2020


Please see United States Olympic and Paralympic Committee Guidance on Return to Athlete Training and Sport Event Planning. published May 4th, 2020 https://www.teamusa.org/coronavirus

Articles

Background:
• By March 25, Italy had the second highest number of COVID-19 infections worldwide and the greatest number of deaths.
• Children younger than 18 years of age who had COVID-19 composed only 1% of cases
• 11% of pediatric patients were hospitalized and none died.

Method:
Report from the Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) study.
• Cohort of 100 Italian children < 18 years of age with Covid-19 confirmed by RT-PCR
• Period: between March 3 and March 27
Location: 17 pediatric emergency departments in Italy

Findings:
- Median age 3.3 years (CI: 0-17.5)
- In 55% of cases, exposure to SARS-CoV-2 was unknown or outside the child’s family
- 12% of children appeared ill, 54% had temperature above 37.6°C
- Common symptoms were cough (44%), no feeding/difficulty feeding (23%)
- Fever, cough, or shortness of breath in 28/54 (52%) of febrile patients
- 4 patients (1 neonate, 1 infant, and 2 adolescents) had desaturation (SpO2 <95%)
- 9 received respiratory support of which 6 had coexisting condition (11 mo with propionic acidemia, 15 yo with thrombocytopenia & frequent respiratory infection, 12yo with autism, 6yo with CHARGE syndrome & epileptic encephalopathy, 2mo with VSD, and 14 yo with epileptic encephalopathy & tracheotomy).
- Disease classification: 21% were asymptomatic, 58% had mild disease, 19% had moderated disease, 1% had severe disease, and 1% were in critical condition. No deaths.

Discussion:
- Incidence of transmission through apparent exposure to a family cluster lower than in other cohorts (from China and US CDC) possibly due to the late lockdown in Italy
- Fewer patients with moderate-to-severe disease

Limitation:
- Small cohort, the testing criteria for RT-PCR in the EC is unknown (ie why were asymptomatic patients tested), unclear how many of the patients that had emergency visits had RT-PCR testing for SARS-CoV-2


Background: Rapid spread of SARS-CoV-2 in Wuhan, China, prompted heightened surveillance in Shenzhen, China. The resulting data provide a rare opportunity to measure key metrics of disease course, transmission, and the impact of control measures.

Method:
- 391 SARS-CoV-2 cases and 1286 close contacts identified from Jan 14 to Feb 12, 2020 by the Shenzhen Center for Disease Control and Prevention.
- Cases identified by symptomatic surveillance and contact tracing. All close contacts were tested.
- Information including the time from symptom onset to confirmation, isolation, and admission to hospital were collected. Metrics of disease transmission and factors influencing transmission risk were estimated.

Results:
- Symptom-based surveillance: of 379 with a known mode of detection, 292 (77%) were detected by symptom-based surveillance
91% had mild or moderate clinical severity at initial assessment. As of 2/22/2020, 3 cases had died and 225 had recovered (median time to recovery 21 days; 95% CI 20-22).

Cases were confirmed on average 5.5 days after symptoms onset

Cases were isolated on average 4.6 days (95% CI 4.1-5.0) after developing symptoms

- Contact-based surveillance: of 379 with a known mode of detection, 87 (23%) were detected by contact-based surveillance
  - 29% of cases did not have fever and 20% were asymptomatic (By contrast, 258 (88%) of 292 in the symptom-based surveillance group had fever, and only 8 were asymptomatic)
  - Cases were confirmed on average 3.2 days after symptoms onset
  - Cases were isolated on average 2.7 days after developing symptoms

- A larger proportion of symptom-based surveillance cases were male compared to contact based surveillance (161 [55%] of 292 vs 24 [28%] of 87) and aged 20–69 years (266 [91%] of 292 vs 65 [75%] of 87) compared to contact based

- Median incubation period for COVID-19 4-8 days, 95% will develop symptoms within 14 days

- Median time to recovery was 20.8 days, shorter recovery was seen in younger adults and mild disease

- Secondary Attack Rate (overall 6.6%):
  - The household secondary attack rate was 11.2% (95% CI 9.1-13.8), and children were as likely to be infected as adults (infection rate 7.4% in children <10 years similar to population average of 6.6%). NO association of probability of infection and age
  - Household contacts and those travelling with a case were at higher risk of infection (odds ratio 6.27 [95% CI 1.49-26.33] for household contacts and 7.06 [1.43-34.91] for those travelling with a case) than other close contacts.

- The observed reproductive number (R) was 0.4 (95% CI 0.3-0.5), the distribution of individual R values was highly over-dispersed, with a mean serial interval of 6.3 days (95% CI 5.2-7.6).

Conclusion:

- This analysis shows that isolation and contact tracing reduce the time during which cases are infectious in the community, thereby reducing the R.

- Children are at a similar risk of infection to the general population, although less likely to have severe symptoms; hence they should be considered in analyses of transmission and control.

Strength:

- Provides detailed epidemiological information
- Adds knowledge about the transmission and natural history of SARS-CoV-2 on a large primary dataset of cases and close contacts.
- Contacts were all tested with RT-PCR testing.
- Provides important knowledge that contact based surveillance reduced the duration an infected individual transmits in the community by 2 days, which can be helpful for strategic planning.

Limitation:
• The overall impact of isolation and contact tracing is uncertain and highly dependent on the number of asymptomatic cases.
• Not every potential contact is traced.
• Asymptomatic travelers will be missed by symptom-based surveillance and, even if they are tested, some asymptomatic contacts might be missed because of the imperfect sensitivity of the RT-PCR method.

Additional Resources

COVID-19 Literature Review Newsletter Volume #18
Infectious Diseases Fellows: Melanie Goebel, MD and Teena Xu, MD
Faculty: Jill Weatherhead, MD
May 8th, 2020

IN CASE YOU MISSED IT: BCM COVID-19 Grand Rounds (April 30th, 2020)
https://youtu.be/IpyV6DvHgnk

Articles:
1. IDSA guidelines on diagnosis of COVID-19
Published online by IDSA on 5/6/2020

Figure 1. IDSA Algorithm for SARS-CoV-2 Nucleic Acid Testing

- Testing should be prioritized for symptomatic patients first.
- When resources are adequate, testing for selected asymptomatic individuals can also be considered.
Background:
- IDSA panel of ID clinicians and microbiologists agreed on 15 diagnostic recommendations
- Focus on SARS-CoV-2 nucleic acid amplification tests (NAAT)

Recommendations:
- Symptomatic patients
  - **Test all outpatients with suspected COVID (strong recommendation)**
    - Relying solely on clinical judgment for diagnosis leads to over-diagnosis
  - Collect nasopharyngeal (NP), mid-turbinate (MT), or nasal swabs rather than oropharyngeal swabs or saliva alone
    - Compared to NP swabs, saliva had 85% sensitivity in 1 study
    - Oral sampling has lower sensitivity compared to NP, MT, or nasal sampling
    - No studies assess combining specimen types
    - Either patients or healthcare providers may collect nasal and MT swabs
      - Patients should be given clear instructions for self-collection
      - Sensitivity of self-collected tests was similar to provider-collected tests
  - In hospitalized patients, obtain an upper respiratory tract (URT) sample **first**. If negative, and suspicion is high, collect a lower respiratory tract (LRT) sample.
    - URT sensitivity 76%, specificity 100%
    - LRT sensitivity 89%, specificity 100%
    - In intubated patients, tracheal aspirate may be more feasible than BAL
    - Avoid induced sputum
  - Repeat testing **only** if there is intermediate or high clinical suspicion of COVID.
    - Consider a LRT sample 1-2 days after initial testing
    - Diagnostic yield may be impacted by duration of symptoms and site sampled
    - Benefit is lower in low prevalence populations
- Asymptomatic patients
  - Test patients with known or suspected COVID exposure
    - A negative test post-exposure does **not** mean quarantine can be discontinued; a positive test reinforces need for isolation
    - Suggest testing 5-7 days after exposure
  - Test unexposed, hospitalized patients in high prevalence communities (prevalence ≥ 10%)
    - Do not test if community prevalence < 2%
    - Limitation: determining prevalence in the community is difficult
  - **Test immunocompromised patients at time of hospital admission and before immunosuppressive procedures, regardless of COVID exposure (strong recommendation).**
    - Immunosuppressive procedures: chemotherapy, transplant, long acting biologics, immunotherapy, high-dose steroids
    - Test within 48-72 hours before planned treatment/procedure
    - Does not address repeated or prolonged visits for chemo
    - For outpatients with frequent infusion visits, screen regularly for symptoms and exposures
  - Test patients who are undergoing major time-sensitive surgeries or aerosol-generating procedures.
    - Time-sensitive = needs to be done within 3 months
    - Ideally test within 48-72 hours of surgery
    - If positive test, defer non-emergent surgeries
Due to risk for false negative test results, providers at highest risk during surgical procedures should consider wearing PPE at all times

Emergency surgeries should not be delayed for testing

**Limitations**

- Quality of evidence for all recommendations is low to very low
- Only 2 recommendations are strong; all others are conditional
- Recommendations assume availability of diagnostic tests
  - If limited resources: prioritize high-risk, symptomatic patients
- Assumes that performance of standard NAAT methods are comparable across countries
- Does not address serology


**Background:** COVID-19 may increase the risk for thromboembolism. Role of anticoagulation (AC) is unclear.

**Question:** What is the effect of therapeutic AC on in-hospital COVID-19 mortality and major bleeding?

**Methods:**

- Retrospective observational study of lab-confirmed COVID-19 cases hospitalized between March 14th – April 11th, 2020 within the Mount Sinai Health System (NYC)
- Cox proportional hazards model
  - Adjusted for comorbidities, age, sex, ethnicity, BMI, AC use prior to admission, admission date. AC treatment duration was a covariate. Intubation was a time-dependent variable.

**Results:** Total of 2773 patients hospitalized with COVID-19

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<tr>
<th></th>
<th>Therapeutically AC</th>
<th>Not therapeutically AC</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Total patients (n=2,773)</strong></td>
<td>786 (28%)</td>
<td>1987 (72%)</td>
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<tr>
<td>In-hospital mortality</td>
<td>22.5%</td>
<td>22.8%</td>
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<tr>
<td>Survival days, median</td>
<td>21 d</td>
<td>14 d</td>
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<tr>
<td>Major bleeding</td>
<td>24 (3%)</td>
<td>38 (1.9%)</td>
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<table>
<thead>
<tr>
<th>Patients on invasive mechanical ventilation (n=395)</th>
<th>Therapeutically AC</th>
<th>Not therapeutically AC</th>
<th>p-value</th>
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<tbody>
<tr>
<td>In-hospital mortality</td>
<td>234 (29.8%)</td>
<td>161 (8.1%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Survival days, median</td>
<td>29.1%</td>
<td>62.7%</td>
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<td>21 d</td>
<td>9 d</td>
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- Hospitalization duration: 5 d median (IQR 3-8)
- Time from admission to AC: 2 d median (IQR 0-5)
- Duration of AC: 3 d median (IQR 2-7)
- AC patients had higher baseline PT, aPTT, lactate, LDH, ferritin, CRP, D-dimer; difference not observed between intubated groups
- In the multivariate analysis, longer duration of AC was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% CI 0.82-0.89, p<0.001)
- Bleeding more common in intubated patients compared to non-intubated irrespective of AC treatment (7.5% vs 1.35%)
Conclusion:

- In this large cohort of hospitalized COVID-19 patients, in-hospital mortality and major bleeding events were similar between those who received therapeutic AC and those who did not.
- In-hospital mortality was much lower in intubated patients receiving AC at the cost of more bleeding.
- Therapeutic AC may be associated with improved hospital survival times, an effect more pronounced in the mechanically ventilated subgroup.
- Prospective randomized data are needed.

Limitations:

- Retrospective/observational design
- Confounding by indication, unknown indications for AC
- AC strategies were variable

Additional Resources:
3. Rawson et al. Bacterial and fungal co-infections in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. CID. Published on May 2nd, 2020 doi.org/10.1093/cid/ciaa530

Week 6 Newsletter Prepared by:

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