Summary of Major Literature Related to COVID-19 (Week of April 6-12)

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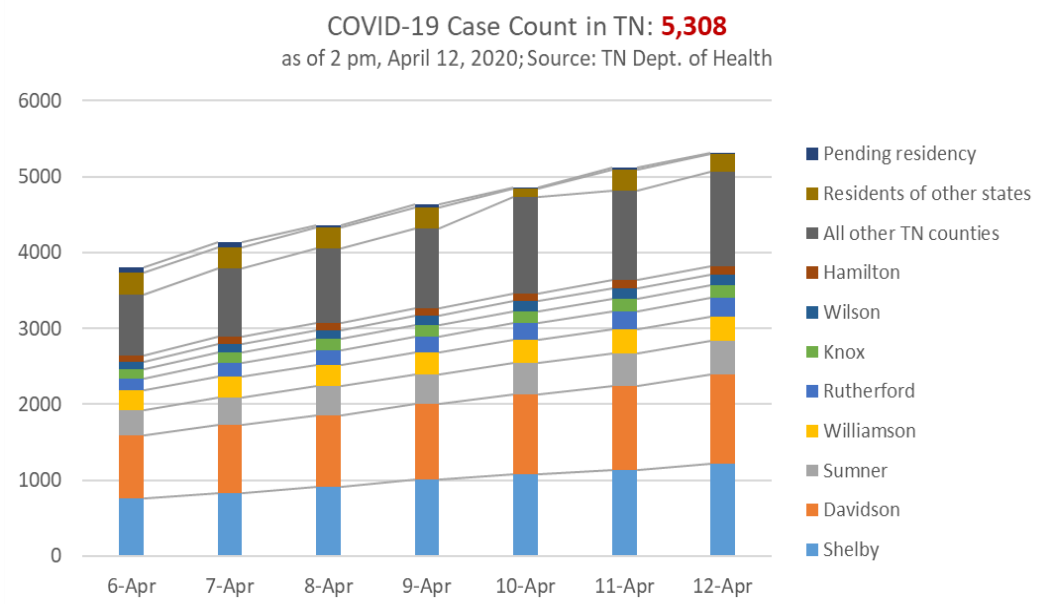
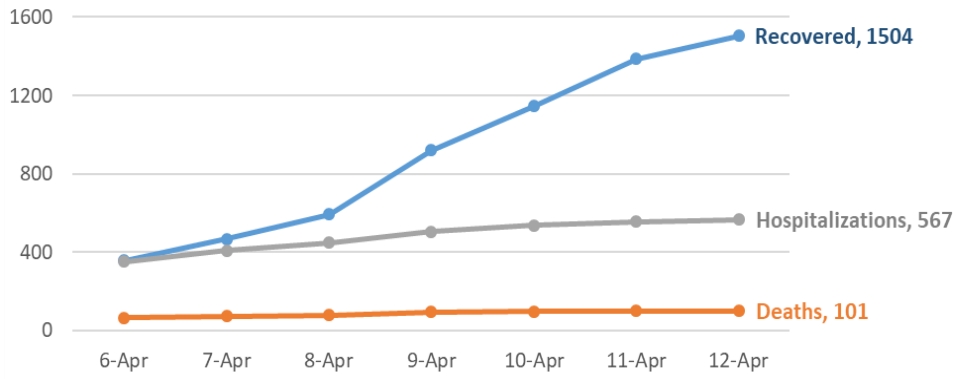
***This is informational and not intended to create variance from VUMC policies/guidance.**

EPIDEMIOLOGY

Statistics - Tennessee and Nashville





- Total tested = 70,599
- Positive rate = 7.5%
- Hospitalized = 567
- **Recovered = 1,504**
- Deaths = 101
- Top three counties:
  - Shelby = 1,215
  - Davidson = 1,178
  - Sumner = 445
- Demographics:

Groups	Cases	%
By sex		
Female	2,740	51.6%
Male	2,464	46.4%
By race/ethnicity		
White	2,504	47.2%
Black	922	17.4%
Hispanic	269	5.1%
Asian	73	1.4%
Other	266	5.0%
Pending	1,274	24%
By age		
0–10	61	1.1%
11–20	248	4.7%
21–30	1,112	20.9%
31–40	851	16.0%
41–50	866	16.3%
51–60	986	18.6%
61–70	665	12.5%
71–80	328	6.2%
80+	178	3.4%

Modeling

1. Vanderbilt Health Policy COVID-19 Modeling for Tennessee. Graves et al. April 10.

- TN epidemic may have started with as few as 10 infected individuals which highlights the significant risk of a second wave of the infection that could be started by just a few infected people
  - Estimated transmission number has declined from each case infecting over 5 new people in mid-March to approximately 1.4 new people as of the week of April 6
- Any lifting of current policies (e.g. Safer at Home, sustained social distancing) must be done carefully, with adequate public health strategies fully operational to ensure the COVID-19 virus does not return to spreading rapidly through our population

2. First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: a modelling impact assessment. Leung. Lancet. April 8.

- Models of transmissibility and severity in four areas of China outside of main outbreak region
- Non-pharmaceutical interventions (e.g. social distancing) effectively and substantially reduced the instantaneous reproduction number (R_t: transmissibility)
- In a simulation study, however, relaxing interventions (allow R_t>1) to when the epidemic size was still small would likely incur both health and economic loss even if aggressive interventions could push the prevalence back

Hospitalizations and ICU

3. **Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020**. Garg, MMWR. April 8**.**

- New COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) established for population-based surveillance in the US (99 counties in 14 states including TN)
- Among 1,482 patients hospitalized, 74.5% were aged ≥50 years, and 54.4% were male.
- The hospitalization rate was 4.6 per 100,000 population (highest (13.8) among adults aged ≥65)
- 89.3% had one or more underlying conditions (hypertension most common)
- Potential racial disparity identified as 18% of residents in catchment population are non-Hispanic black but 33% of hospitalized were black
- Limitation: Only 33% had race/ethnicity data

4. **Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy**. Grasselli, JAMA. April 6**.**

- 82% men, median age 63 (IQR, 56-70), and 68% had ≥1 comorbidity (hypertension most common)
- Median PaO_2/FIO_2 ratio was 160 (IQR, 114-220) requiring high levels of PEEP (median 14 cm H_20)
- 88% required endotracheal intubation and invasive mechanical ventilation
- Overall ICU mortality was 26%; aged ≥70 mortality was 41%
- Limitation: 58% still in ICU as of writing which could underestimate mortality

Children

5. **Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020**. CDC COVID-19 Response Team. April 6.

- Description of 2,572 pediatric U.S. COVID-19 cases, 71% are from New York and New Jersey
- Relatively few children with COVID-19 are hospitalized, and fewer children than adults experience fever, cough, or shortness of breath
- Severe outcomes have been reported in children, including three deaths
- Limitations: incomplete data on symptoms (9%), underlying conditions (13%), hospitalization (33%); testing practices may differ widely in different regions
- See also **Epidemiology and Clinical Features of Coronavirus disease 2019 in Children**. (Review) Choi, Clin Exp Pediatr. April 6**.**
    - COVID-19 infections in children were occurring early in the epidemic in China
    - WHO-China Joint Mission on COVID-19: by Feb 20, 2.4% of cases were children <19 years, of which 2.5% were severely ill and 0.2% were critical

TRANSMISSION/DIAGNOSIS

6. **FDA approves emergency use authorization for Qualitative detection of IgM and IgG antibodies against SARSCoV-2 in serum, plasma**. **Device:** qSARS-CoV-2 IgG/IgM Rapid Test**. Company:** Cellex Inc

- Qualitative test for the detection of IgM and IgG antibodies against SARSCoV-2 in serum and plasma (EDTA or citrate) blood specimens or venipuncture whole blood

- IgM antibodies to SARS-CoV-2 are generally detectable in blood several days after initial infection. IgG antibodies become detectable later. Positive results are indicative of acute or recent infection
- **NIH begins study to quantify undetected cases of coronavirus infection**. April 10.

7. PCR Assays Turned Positive in 25 Discharged COVID-19 Patients. Yuan, Clin Infect Dis. April 8**.**

- 172 patients met criteria for discharge (improvement on chest CT and exhibited two consecutive negative RT-PCR assays) and were monitored at home by RT-PCR detection of COVID-19 with both cloacal swab and nasopharyngeal swab samples
- 25 (14.5%) of discharged patients returned to hospital because of positive RT-PCR results
    - Average time from last negative RT-PCR result to return positive was 7 days
- Implication: 2 negative RT-PCR tests 24 hours apart may not be sufficient for viral clearance evaluation

8. Factors associated with prolonged viral RNA shedding in patients with COVID-19. Xu, Clin Infect Dis. April 9**.**

- 113 symptomatic patients with confirmed infection, divided into two groups: patients with persistent negative viral detection results < 15 days after illness onset (n=37), and patients with prolonged viral RNA shedding ≥15 days after illness onset (n=79)
- Male patients, delayed admission to hospital after illness onset, and invasive mechanical ventilation during hospitalization were associated with prolonged SARS-CoV-2 RNA shedding (RT-PCR from respiratory specimens)
- Implication: hospital admission and treatments should be started as soon as possible
- Limitation: unknown whether shedding of viral RNA correlates with shedding of infectious virus

9. Chest Computed Tomography for Detection of Coronavirus Disease 2019 (COVID-19): Don't Rush the Science. Hope, Ann Intern Med. April 8**.**

- Review of current literature supporting the use of CT for the diagnosis of COVID-19 identified major flaws in study design, incomplete methods, multiple confounding variables, and scant discussion led to premature conclusions regarding the role of CT scan in COVID-19 diagnosis
- American College of Radiology recommends that "CT should not be used to screen for or as a first-line test to diagnose COVID-19"
- This is a cautionary tale from the radiology community about the consequences of rushing the scientific peer review process

10. Stability of SARS-CoV-2 in different environmental conditions. Chin. Lancet Microbe. April 2.

- No infectious virus could be recovered from paper, cloth, or wood (3hr – 2d incubation)
- No infectious virus could be detected from treated smooth surfaces (glass, banknote, stainless steel and plastic) after 4-7 days
- Detectable level of infectious virus could still be present on the outer layer of a surgical mask on day 7 (at 0.1% the original inoculum)
- SARS-CoV-2 was susceptible to standard disinfection methods

CLINICAL MANAGEMENT/SYMPTOMS

11. The use of high-flow nasal oxygen in COVID-19. Lyons, Anaesthesia. April 4**.**

- Current guidelines on the use of high-flow nasal oxygen (HFNO) in COVID-19 treatment are inconsistent, some data suggests use may avoid need for intubation, but also concern for risk of aerosolization of viral particles
- A study in China showed that among 10% of critically ill COVID-19 patients, early use of HFNO and of awake prone positioning has kept the invasive mechanical ventilation rate under 1%

- A previous review study based on nine randomized controlled trials involving 2093 patients with acute hypoxemic respiratory failure of any cause found that use of HFNO resulted in a decreased requirement for tracheal intubation and a lower risk of escalation of oxygen therapy
- Lower mortality has previously been observed in HFNO group than in non-rebreather facemask or non-invasive ventilation group in the treatment of non-hypercapnic acute respiratory failure
- Conclusion: HFNO may be an appropriate therapy for many COVID-19 patients for whom tracheal intubation has not yet become a necessity but for whom low-flow nasal oxygen or facemask oxygen is not providing adequate respiratory support

12. Cardiopulmonary resuscitation after hospital admission with covid-19. Fritz, BMJ. April 6**.**
Covid-19: Doctors are told not to perform CPR on patients in cardiac arrest. Mahase, BMJ. March 29.

- Guidelines on CPR in the acute hospital setting for patients with COVID-19 are conflicting
- Patients who require intubation and ventilation have poor survival rates, and survival after an arrest is likely to be substantially lower, although data are not yet available
- This pandemic has changed the risk-benefit balance for CPR: from "there is no harm in trying" to "there is little benefit to the patient, and potentially significant harm to staff"
- Clinicians, patients, and those close to them should have early discussions about CPR and overall goals of care across all healthcare settings
    - Guidelines https://www.criticalcarenice.org.uk/clinical-guidelines

Neurologic manifestations

13. Neurologic manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther. Baig. April 7**.**
Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. Mao. MedRxiv. Feb 25.

- 214 hospitalized patients with laboratory confirmed COVID-19, 78 (36%) had neurologic manifestations
    - 25% central nervous system (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, epilepsy)
    - 9% peripheral nervous system (hypogeusia, hyposmia, hypopsia, neuralgia)
    - 11% skeletal muscular symptoms
- Patients with more severe disease were more likely to have neurologic symptoms, such as acute cerebrovascular diseases (5.7 vs 0.8%), impaired consciousness (14.8 vs 2.4%), skeletal muscle injury (19.3 vs 4.8%)

TREATMENT/EMERGING DRUG TARGETS

14. Clinical trials on drug repositioning for COVID-19 treatment. Rosa. Rev Panam Salud Publica. April 8**.**

- In the clinicaltrials.gov database, clinical trials involving more than 20 medicines have been identified for the testing of drug repurposing for COVID-19 treatment, including:
    - human immunoglobulin, interferons, chloroquine, hydroxychloroquine, remdesivir
    - arbidol (umifenovir) is approved in Russia and China for treatment of influenza virus infections
    - lopinavir, ritonavir: lopinavir-ritonavir combination is approved for HIV treatment
    - favipiravir, oseltamivir: oseltamivir is used in a clinical trial with combinations with chloroquine and favipiravir, a nucleoside analog that is well-known as a broad-spectrum antiviral drug
    - Carrimyci: a macrolide antibiotic with effects against some gram-positive bacteria and in vitro effects on Mycobacterium tuberculosis.
    - Vitamin C has antioxidant activity, may reduce oxidative stress and inflammation, effects that improve vasopressor synthesis, enhance immune cell function, improve endovascular function

- **See also** **Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 Protease against COVID-19**. Muralidharan, J Biomol Struct Dyn. April 6
- A combination of flu drug oseltamivir with HIV drugs lopinavir and ritonavir has been proposed to control virulence in COVID-19 patients
- CoVs encoded proteinase Mpro has emerged as promising antiviral target because of its major roles in viral replication and self-maturation
- The binding energy of the combination of the three drugs against the SARS-CoV-2 protein is stronger than that of each drug docked against the CoV protein individually

15. Compassionate Use of Remdesivir for Patients with Severe Covid-19. Grein. NEJM, April 10**.**

- Remdesivir were provided on a compassionate-use basis to patients hospitalized with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support
- Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment
- During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated.
- 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation
- **Limitation**: not a clinical trial and no comparable statistics for non-remdesivir treated patients.

16. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Gattinoni. Am J Respir Crit Care Med. Mar 30
Also, see potential mechanisms in **"Less is More" in mechanical ventilation.**

- Lung compliance is a measure of the lung's ability to stretch/expand and typically is reduced in ARDS
- Patients with Covid-19 pneumonia present with atypical form of ARDS
    - Relatively preserved compliance with severe hypoxemia and *hyper*perfusion of gasless tissue
- In patients treated with Continuous Positive Airway Pressure or Non-Invasive Ventilation, who show signs of excessive inspiratory efforts, intubation should be prioritized to avoid excessive intrathoracic negative pressures and self-inflicted lung injury
- High PEEP and prone positioning may help by redistributing perfusion in response to pressure/gravity
- Implication: ventilating these patients is "buying time" with minimum additional damage: the lowest possible PEEP and gentle ventilation

BIOLOGY

17. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Wang. Cell Molec Immunol. April 7**.**

- SARS-CoV-2 could infect T cells through receptor-dependent, S protein-mediated membrane fusion, resulting in lymphocytopenia
- SARS-CoV-2 can infect T cells, but does not replicate, similar to MERS-CoV. Infection could be inhibited by EK1 peptide