COVID-19
The...Aftermath?

Michael Burk, MD
Disclosures/COI

• None significant
• When drug reps do bring lunch, I will often eat while heckling them over their terrible marketing data
• Information that is controversial, or has reasonable evidence but is not in most guidelines will have an asterisk (*) unless specified

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Objectives

• A Brief Retrospective – Epi, Spread, and Containment Measures
• Acute Inpatient and Outpatient Management
• Long COVID and Clinical Pearls
• Questions and Troubleshooting
Where Were You?
Back to the Beginning

• A "Wet Market" in Wuhan, China

• Wuhan size: 11 million, 9th most populous, Provincial Capital
  • "The Chicago of China," 7242 people/sq km in central region
  • NYC is 10,716/sq km, ATL is 1416, San Francisco is about 6300

• Province: Hubei, 58.5 million
31 Dec.
Govt in Wuhan confirms treatment of dozens of unknown pneumonia cases
• "No evidence the virus was spread by humans"

20 Jan.
Cases confirmed in Japan, SK, Thailand

23 Jan.
Wuhan Isolated by Chinese Govt

1 Jan.
Chinese state media report first official death

21 Jan.
First confirmed case arrived in Washington State

24 Jan.
Chinese Public Holiday for Lunar New Year 1/24-30/2020
But Wait a Minute...

• How did we go from:
  • An isolated zoonotic to human outbreak on 12/31 with minimal concerns for human-to-human spread

• To:
  • Chinese travel restrictions:
  • Hubei Province Locked down by end of 1/24
  • 13 cities, 46 million people quarantined
  • In 25 DAYS
• Full Disclosure: My wife and I are absolute nerds.
• At least one of three things must wrong with the Chinese data
  • The date of index case reported (growth time)
  • The $R_0$ (was not well estimated at the time, 2.5-7)
  • The current number of cases (we almost certainly knew this)
• The number of cases had to be inaccurate due to the response
• The index case reported at the time was early Dec 2019, we felt that with the data they presented, it had to have been no later than the last two weeks of Nov if it was a single source (one animal-->human)
• At this point I realized there was no way this was getting contained
Emergence of genomic diversity and recurrent mutations in SARS-CoV-2

Lucy van Dorp, a, * Mislav Acman, a, 1 Damien Richard, b, c, 1 Liam P. Shaw, d, 1 Charlotte E. Ford, a Louise Ormond, a Christopher J. Owen, a, Juanita Pang, a, e Cedric C.S. Tan, a Florencia A.T. Boshier, e Arturo Torres Ortiz, a, f and François Balloux a, *

The origin of the regression between sampling dates and ‘root-to-tip’ distances (Fig. S3) provides a cursory point estimate for the time to the MRCA (tMRCA) around late 2019. Using TreeDater (Volz and Frost, 2017), we observe an estimated tMRCA, which corresponds to the start of the COVID-19 epidemic, of 6 October 2019–11 December 2019 (95% CIs) (Fig. S4). These dates for the start of the epidemic are in broad agreement with previous estimates performed on smaller subsets of the COVID-19 genomic data using various computational methods (Table 1), though they should still be taken with some caution. Indeed, the sheer size of the dataset precludes the use of some of the more sophisticated inference methods available.
Real Background and Timeline

- First confirmed Chinese case 1 Dec 2019
- 26-27 Dec: Multiple cases present to Wuhan Central Hospital
  - Dr. Zhang Jixian worked the SARS epidemic
  - Recognized when multiple pts presented with sx and CTs
  - Reported to hospital and Chinese CDC
- 30 Dec: First coordinated Chinese internal response, including gag order for medical staff
  - 31 Dec: First public messaging from Wuhan Municipal Health Commission
- 30 Jan 2020: WHO Concern
- 11 Mar 2020: WHO Pandemic
Comparing Early and Recent Variants

- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV02)
  - Originally 2019 novel coronavirus (#2019-nCOV) or (#HCoV-19)
  - Positive sense SSRNA, binds ACE2 Receptor

- Original and Beta Variants
  - Median $R_0$ without mitigation: 5.7 (3.8-8.9)
    - Initial reports: 2.2-2.7
  - Incubation: 4.2 days
    - Sx to hospitalization: 5.5 days, Sx to death: 16.1 days

- Delta and Omicron Variants
  - Delta estimated $R_0$ with mitigation: 5.08 (3.2-8)
  - Omicron BA.1 estimated $R_0$: 8.2
  - Omicron BA.2 estimated $R_0$: 12
  - Incubation: 2-4 days
    - Less data on time to hospitalization and time to death
Epi and Spread

Jan/Feb 2020 Containment Recs

- Up to days of stability on hard surfaces at room temp/humidity
- Reported as airborne transmission with small and large droplet sizes
  - Confirmed with high-speed cameras and laser imaging with computer modelling
- Level 3 biocontainment with full contact, N95, and eye protection with decontamination areas were recommended
- Negative airflow for rooms/hospitals
- Universal Masking
- Aggressive testing with contact tracing on a scale and speed not seen since WWII
Epi and Spread

• 2022 Best Practices:
  • PPE: N95 or better, Airborne and full contact precautions, eye protection
  • Negative airflow and/or high ventilation, separate ward ideal
  • Surgical masks not adequate for protection, but better than none
  • Vaccination to reduce harm, nosocomial spread
But before we talk about treatment...
A Quick Question

For the rest of the talk, it would be the most helpful to me if you would spend more time on:

A. Acute inpatient management
B. Acute outpatient management
C. Long COVID management and pearls
D. Q&A
Results Slide
Perhaps the most important slide...

- Where can I get reliable information with so many potential conflicts?
  - https://opencriticalcare.org/covid-dashboard/
Nirmatrelvir with ritonavir (Paxlovid)

Nirmatrelvir with ritonavir, named Paxlovid by its manufacturer, is a novel antiviral medication that has shown promise in clinical trials for prevention.

Convalescent plasma in non-hospitalized patients

Convalescent plasma has been investigated as a potential therapy for outpatients with mild-

Ivermectin for Treatment or Prevention of COVID-19

Ivermectin is an anti-parasitic agent that has been investigated for anti-viral treatment of patients.
Acute Inpatient Management
The Graveyard of Therapeutics

- Statins
- Azithromycin
- Hydroxychloroquine
- Most early Ab therapies
- Famotidine
- Melatonin
- Convalescent plasma
- Remdesivir (Inpatient)*

- Vitamin D supplementation
- Therapeutic anticoagulation (empiric)
- Colchicine
- ACE-I
- Empiric antibiotics
- ASA
- TPA
- Ivermectin
- Favipiravir
- Bleach (IV)
- UV light (Endotracheal)
Current Inpatient Recommendations

• Here's the problem with almost all of these recs
  • They're going to change, probably considerably, year over year.
  • Some have changed (slightly) since I started work on this presentation
  • Everybody wants to do a study; nobody wants to be academically rigorous

• Severity and risk matter

• But where are my vignettes!?!?
Inpatient Recommendations

• Criteria for inpatient therapy
  • Hypoxia requiring supplemental O2 (88% or lower)
  • Any other reasonable admission criteria, especially if felt due to COVID

• Once an inpatient, treatment depends on severity* and risk factors
  • Mild – 6L of supplemental O2 or less
  • Moderate – Requiring greater than 6L or rapidly decompensating
  • Severe – Intubated or nearing intubation on admission
Inpatient Recommendations - Mild

- Supplemental O2 – Goal saturation 88% -94%
- Dexamethasone – at 94% - or – worse than usual if on O2 at baseline
  - 6mg IV or PO daily x 10 days
  - ~4.8% ARR, 16.4% RRR, NNT: ~21, for mortality in all comers needing O2
- Awake proning – MORE is BETTER*
  - 6% ARR, 14% RRR for intubation, Mortality a wash at 28 days
  - But the supplement..... Mexico with by far highest mean prone at 9hrs/day
- DVT Prophylaxis – Regular*
- Supportive and Symptomatic Care
- CRP testing – is it actually mild?
Inpatient Recommendations - Mild

3.5 Investigation of heterogeneity between trials

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<th>Standard care Events</th>
<th>Standard care Total</th>
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<td>0.68</td>
<td>1.26</td>
<td>2.5</td>
<td>4.4</td>
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Fixed effect model
Random effects model
Heterogeneity: $i^2 = 0\%$ (0\%; 69\%)

Figure S3: Forest plot with mixed effects linear model with group as a fixed effect and country as a random effect on intubation or death (primary outcome) at Day 28. Median and mean durations of prone positioning sessions in hours
Inpatient Recommendations - Moderate

• Reminder – more than 6L, rapid worsening, *Elevated CRP (10mg/L)
• O2, Dexamethasone, Awake proning, Supportive care

AND

• Immunomodulation with Baricitinib
  • 4mg PO daily x14 days or until DC
• CPAP preferred to High Flow Nasal Oxygen (Vapotherm, etc)
  • ARR of 8% for intubation or mortality at 8cm vs HFNO at 50L, HFNO not different than conventional O2
• Avoid: Non-rebreathers may cause worsening atelectasis and are not titratable
Inpatient Recommendations - Severe

• A note about ARDS
  • Technically, you don't have to be intubated to have a diagnosis of ARDS
  • Definition likely to be updated in next 1-2 years, but for now...
  • P:F ratio less than 200 on PEEP or CPAP of 8cm = ARDS
Baricitinib or Tocilizumab
- ARDSNET settings for ventilator
- If P:F Ratio less than 150, proning 16hrs down/8hrs up
- DEXA-ARDS Study* - (Lancet Resp Med 2020)
  - Released prior to COVID, evaluated all ARDS, viral, bacterial, etc.
  - 20mg Dexamethasone for 5 days, 10mg Dexamethasone for 5 days, vs placebo
  - Mortality reduction of 15% ARR (15.3% vs 21%) at 60 days
  - No difference in nosocomial infections
- Low threshold for empiric antibiotics and ECMO consultation
- Supportive care...and time
Acute Outpatient Management
Current Outpatient Recommendations

• Vaccinate, Vaccinate, Vaccinate

• For acute therapy, we break it down:
  • Healthy
  • Risk factors
  • Immunocompromised/High risk
Acute Outpatient Recommendations

• For the healthy, non-hypoxic, without risk factors
  • Symptomatic treatment
  • Awake proning
  • If history of mild asthma with more symptoms, consider inhaled corticosteroid inhaler
Acute Outpatient Recommendations

- For those with risk factors
  - CAD/HTN/DM/COPD/Cancer/Detectable HIV/TB/Pregnancy/CKD III
  - Immunosuppresion (regardless of reason) or poor functional status
- Symptomatic treatment AND
  - Nirmatrelvir/ritonavir (Paxlovid) BID for 5 days* OR Remdesivir 3-5 days
  - Bebtelovimab is the only Mab that has activity with Omicron BA.2, but is reduced
  - Third line, only for non-pregnant adults: Molnupiravir BID for 5 days
- If hypoxic (94%, or needing to increase baseline O2)
  - Dexamethasone 6mg daily for 10 days
Additional Outpatient Recommendations

• For the immunocompromised or true allergy to vaccine
• Pre-exposure prophylaxis criteria
  • At least moderate immunocompromised state from disease or therapy
  • No response/inadequate response to vaccines
• Tixagevimab-cilgavimab (Evusheld)
  • Not as effective with new variants
  • No data on how long it will be effective for, EUA estimates 3-6 months but will provide further guidance
Long COVID – Where Do We Go From Here?
Long COVID Evidence and Pearls*

• Long COVID can cause profound and prolonged morbidity
• If you think of COVID as a vascular disease that enters through the nares/lungs, this model fits well
• Acute disease severity is suggestive, but not always indicative, of long COVID severity
• We are learning a lot about what happens and a bit about how it happens, but therapeutics are generally limited in evidence
• It will take years to decades for us to fully understand how this is going to affect pulmonary and other organ systems*
So, Do We Know Anything Useful?
Long COVID Evidence and Pearls*

- Occurrence – 52% with symptoms 29 days after onset
- 50% of mild COVID cases have sequelae
  - Smell or taste aberrations and cough most common
- There is an increased risk of new onset dementia in those over 70
- It can affect essentially any organ system
- It can trigger autoimmune disease
- It can cause or worsen asthma
How I approach long COVID*

• Step 1: Be a good physician – people have often avoided care
  • Do a reasonable workup, correlation does not have to be causation
• Step 2: If you can exclude deadly and dangerous etiologies...
  • Try symptomatic support and a bit of time if improving, however slowly
• Step 3: If it's not getting better, we're happy to help
• I used to get early PFTs (30 days post hospital discharge) and if normal, methacholine/bronchoprovocation

• I found a lot of asthma, but it was weird (more in a moment)

• Finally – you get a brief vignette (de-identified and shared with permission)
### Spirometry

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<th>(BTPS)</th>
<th>PRED Ref</th>
<th>LLN-4ULN</th>
<th>Pre % Ref</th>
<th>Post % Ref</th>
<th>% Chg</th>
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<tr>
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### Lung Volumes

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### Diffusing Capacity

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<td>(2.3 - 2.8)</td>
<td>2.30</td>
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**Interpretation:**

**PET Interpretation**

- Effort: Adequate tracing and effort, volume-time tracing plateaus for greater than 1 second which is adequate.

**SPIROMETRY:**

- There is no obstruction. The response to bronchodilators is not significant based on a change in FEV1 or FVC less than 200ml and 12%.

**STATIC LUNG VOLUMES:**

- There is severe restrictive lung disease based on total lung capacity less than 45% predicted.

**DIFFUSING CAPACITY:**

- There is a mild reduction diffusing capacity based on a DLCO greater than 60% but below the lower limit of normal. Note that the value for diffusing capacity is not corrected for hemoglobin and that anemia may decrease while polycythemia may increase the reported value.

**PRIOR TEST RESULTS:**

- No prior test results are available for comparison.

**CONCLUSION:**

- There is no obstruction. The response of bronchodilators is not significant. There is severe restrictive lung disease. There is a mild reduction diffusing capacity.

Restrictive lung disease may be related to pulmonary fibrosis, sarcoidosis, obesity, an interstitial lung disease, drug induced lung disease, neuromuscular weakness or pneumoniosis. The decreased diffusing capacity may reflect loss of pulmonary capillary surface area or anemia. Causes include pulmonary fibrosis, pulmonary vascular disease, emphysema, CHF, or pneumonitis.
### Spirometry

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<td>(3.5 - 5.5)</td>
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<tr>
<td>FEV1</td>
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<td>3.52</td>
<td>(2.7 - 4.4)</td>
<td>3.26</td>
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<td>FEV1/FVC</td>
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<td>99</td>
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### Interpretation:

**PFT Interpretation**

Effort: Note, patient had difficulty with following instructions during his spirometry. Although the loops appear to be of poor quality based on notes from our respiratory therapist, these are probably actually valid.

**SPirometry:**

Normal spirometry. The response to bronchodilators is not significant based on a change in FEV1 or FVC less than 200ml and 12%.

**Prior Test Results:**

Compared to prior test in [redacted], patient has had a profound improvement in FEV1 and FVC.

**Conclusion:**

Normal study. The response bronchodilators is not significant.
How I Approach Post COVID Cough/Dyspnea*

- I don't get a baseline PFT sooner than 30 days post discharge, it will be terrible
- I don't repeat CXR for at least 3 months if pt is not worse
  - It will show "pneumonia", and someone will try to give them C diff with antibiotics
  - I expect persistent CXR changes for 3 months, minimal residual up to 6mo
- Everyone with persistent symptoms gets 3 months of an ICS/LABA w/o proof of actual obstruction – it helps
  - Half of them stop prior to follow up and are better, the rest need more workup
- 1 month/3 months/6 months/12 months
So Where Do We Go From Here?
Q&A
Sources


• Liu Y, Rocklöv J. The reproductive number of the delta variant of SARS-COV-2 is far higher compared to the ancestral SARS-COV-2 virus. Journal of Travel Medicine. 2021;28(7). doi:10.1093/jtm/taab124

• Esterman PA. Omicron Ba.2 is about 1.4 times more infectious than BA.1. the basic reproduction number (R0) for BA.1 is about 8.2, making R0 for BA.2 about 12. this makes it pretty close to measles, the most contagious disease we know about. Twitter. https://twitter.com/profesterman/status/1501794498225262595. Published March 10, 2022. Accessed May 26, 2022.


Sources


