Importance of SARS-CoV-2 testing along the curve

Marcos López-Casillas, Ph.D.
Research Program Manager
Puerto Rico Public Health Trust

Assistant Professor
Department of Chemistry
University of Puerto Rico - Humacao

@mlopez@prsciencetrust.org
marcos.lopez11@upr.edu
The concept of ‘flattening the curve’

<table>
<thead>
<tr>
<th>No Intervention</th>
<th>Protective Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal:</strong></td>
<td>Hygiene &amp; Safety Measures</td>
</tr>
<tr>
<td><strong>Community:</strong></td>
<td>Social Distancing</td>
</tr>
<tr>
<td>Monitoring:</td>
<td>Molecular Testing</td>
</tr>
</tbody>
</table>

CUMULATIVE CASES

TIME FROM FIRST CASE

HEALTHCARE SYSTEM CAPACITY

WITH INTERVENTION

NO INTERVENTION
Molecular testing results are the eyes of any intervention

Molecular testing results is the only way to monitor the “no-intervention” and “with intervention” curves.

Molecular testing is the only way to “flatten the curve” with ours eyes wide open, not blindfolded!
Infection progression in a single patient

- **Infection with virus**
  - Incubation period: ≈5 days (99% ≤ 14 days unless asymptomatic) ([Lauer et al. 2020; Li et al. 2020](#))

- **Exposed**
  - Latent period: ≈3 days

- **Infectious**
  - Interval of half-maximum infectiousness: ≈4 days

- **Symptomatic**
  - Diagnosis after ≈5 days

- **Recovery**
  - Mild cases: ≈2 weeks
  - Severe cases: ≈6 weeks

**Case Fatality Rate** (ECDC 2020)
- ≈0.8%-10% (uncorrected)
- **Infected Fatality Rate**
- ≈0.3%-1.3%

Inter-individual variability is substantial and not well characterized. The estimates are parameter fits for population median in China and do not describe this variability ([Li et al. 2020; He et al. 2020](#)).
Molecular testing

- Molecular testing for COVID-19 is achieved by a technique called reverse transcription polymerase chain reaction (RT-PCR).
- This technique is a nucleic acid amplification test (NAT) that detects unique target sequences of the virus that causes COVID-19 (SARS-CoV-2) in respiratory tract specimens.
- The use of this testing has been authorized and reviewed by FDA.
Utility of molecular testing

Infection Symptom onset Symptom relief

RT-PCR diagnostic window

RT-PCR threshold

VIRAL LOAD IN RESPIRATORY SPECIMENS

DAYS FROM SYMPTOM ONSET

MAY VARY FROM PATIENT TO PATIENT

Serological testing (rapid tests)

- It detects IgM & IgG antibodies against SARS-CoV-2 infection in blood, serum or plasma.
- Positive cases with symptoms must be confirmed by RT-PCR.
- Negative cases, specially the ones with symptoms, do not rule out infection.
- Cost is $2-8 dollars per test.
- So far, only one manufacturer has been granted a EUA from FDA. Several others have notified FDA.

Utility of serological testing

-7-14 0 7 14 21 28 35 42

FIRST INFECTION

ANTIBODY TITERS

INCUBATION

FEVER

CLINICAL SYMPTOMS

DAYS AFTER ONSET

-14 -7 0 7 14 21 28 35 42

IgM

IgM + IgG

MAY VARY FROM PATIENT TO PATIENT

Hospitalized patients

- Must be confirmed by RT-PCR
- Their course must be monitored by RT-PCR and other biomarkers
  - Cytokines (IL-6)
  - C-reactive protein – Severe viral infection/viremia/viral sepsis
  - Procalcitonin
  - Other biomarkers depending on clinical approach
Treatment

- None, but convalescent plasma helps a lot!

Research

JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jinxiu Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jiuxin Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD

JAMA. Published online March 27, 2020. doi:10.1001/jama.2020.4783
# Treatment

Table 1. Clinical Characteristics of SARS-CoV-2-Infected Patients Who Received Convalescent Plasma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Smoking</th>
<th>Blood type</th>
<th>Coexisting chronic diseases</th>
<th>Disease presentation and course</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Male</td>
<td>70s</td>
<td>No</td>
<td>B</td>
<td>None</td>
<td>None</td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Male</td>
<td>60s</td>
<td>No</td>
<td>B</td>
<td>Hypertension; mitral</td>
<td>None</td>
<td>Antivirals</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Female</td>
<td>50s</td>
<td>No</td>
<td>B</td>
<td>None</td>
<td>Hypertension; mitral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Female</td>
<td>30s</td>
<td>No</td>
<td>B</td>
<td>Hypertension; mitral</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Male</td>
<td>60s</td>
<td>No</td>
<td>B</td>
<td>Hypertension; mitral</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

- **Estimated incubation period, d**: 1, 7, 3, 7, 15
- **Interval between symptom onset and admission, d**: 2, 4, 2, 2, 3
- **Interval between admission and plasma transfusion, d**: 22, 10, 20, 19, 20
- **Complications prior to plasma transfusion**: Bacterial pneumonia; severe ARDS; MODS, Bacterial pneumonia; fungal pneumonia; severe ARDS; myocardial damage
- **Severe ARDS**
- **Most severe disease classification**: Critical

**Treatments**

- **Steroids**: Methylprednisolone, Methylprednisolone, Methylprednisolone, Methylprednisolone, Methylprednisolone
- **Antivirals**: Lopinavir/ritonavir; interferon alfa-1b; favipiravir, Lopinavir/ritonavir; interferon alfa-1b; favipiravir, Lopinavir/ritonavir; interferon alfa-1b; favipiravir, Lopinavir/ritonavir; interferon alfa-1b; favipiravir

**Abreviations**: ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Estimated incubation period defined as interval between estimated exposure to SARS-CoV-2 and symptom onset.*
C-reactive protein
Procalcitonin
IL-6

All went down after transfusion

<table>
<thead>
<tr>
<th>Table 2. Comparison of Viral Load, Clinical Indexes, and Laboratory Results Before and After Convalescent Plasma Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>Ct value(^c) (viral load proxy)</td>
</tr>
<tr>
<td>On admission to hospital</td>
</tr>
<tr>
<td>Lowest value during hospitalization(^d) (highest viral load)</td>
</tr>
<tr>
<td>Just before plasma transfusion</td>
</tr>
<tr>
<td>Day 1 posttransfusion</td>
</tr>
<tr>
<td>Day 3 posttransfusion</td>
</tr>
<tr>
<td>Day 7 posttransfusion</td>
</tr>
<tr>
<td>Day 12 posttransfusion</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Onset, days before transfusion</td>
</tr>
<tr>
<td>Extubated, days posttransfusion</td>
</tr>
<tr>
<td>ECMO</td>
</tr>
<tr>
<td>Onset, days before transfusion</td>
</tr>
<tr>
<td>Removal, days posttransfusion</td>
</tr>
</tbody>
</table>
Table 2. Comparison of Viral Load, Clinical Indexes, and Laboratory Results Before and After Convalescent Plasma Transfusion

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ct value&lt;sup&gt;c&lt;/sup&gt; (viral load proxy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission to hospital</td>
<td>23.0</td>
<td>19.7</td>
<td>18.9</td>
<td>38.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Lowest value during hospitalization&lt;sup&gt;d&lt;/sup&gt; (highest viral load)</td>
<td>19.2</td>
<td>19.7</td>
<td>18.9</td>
<td>26.6</td>
<td>26.5</td>
</tr>
<tr>
<td>Just before plasma transfusion</td>
<td>28.5</td>
<td>22.0</td>
<td>33.0</td>
<td>26.6</td>
<td>35.9</td>
</tr>
<tr>
<td>Day 1 posttransfusion</td>
<td>30.0</td>
<td>23.7</td>
<td>38.5</td>
<td>28.0</td>
<td>Negative</td>
</tr>
<tr>
<td>Day 3 posttransfusion</td>
<td>34.4</td>
<td>25.0</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Day 7 posttransfusion</td>
<td>38.0</td>
<td>32.0</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Day 12 posttransfusion</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>Remains hospitalized</td>
<td>Remains hospitalized</td>
<td>53</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>Current status as of March 25, 2020</td>
<td>Stable, still receiving mechanical ventilation</td>
<td>Stable, still receiving mechanical ventilation</td>
<td>Discharged home</td>
<td>Discharged home</td>
<td>Discharged home</td>
</tr>
</tbody>
</table>
Is Puerto Rico going to implement convalescent plasma protocols?

- YES!
Are we flattening the curve?

- We are not there yet as we need more testing

WE NEED MORE TESTING AND FASTER

KEY PLAYERS
Laboratorio Clínico Toledo (TAT = 24 h, > 200 test/day)
PR Health Department (TAT = ~24 h, <50 test/day)

Remission to:
Quest Diagnostics (TAT = more than a week!!!)
LabCorp (TAT = more than a week!!!)
Conclusions

- Importance of molecular testing is clear. We need it for all stages of clinical and epidemiological management of the pandemic.
- Molecular testing for detecting SARS-CoV-2 needs to be increased in the Island.
- We need to be cautious with serological testing as it is not a confirmatory tests
- We need a more aggressive approach from the government to try to furnish better laboratory facilities in the PR Health Department
- Social distancing, seems to be working.
- Please stay home as we are NOT THERE YET!
- NOT EVEN CLOSE!
The fastest way of flattening the curve...

STAY AT HOME AND WASH YOUR HANDS!