COVID-19 Hot Takes: A look at the latest evidence

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Objectives:

- PCR Testing and Viral Shedding
- Serologic Testing: Abbott IgG Assay
- Review recent evidence from therapeutic trials:
  - Remdesivir
  - Dexamethasone?

PCR testing and Viral Shedding

Objective: To estimate the false-negative rate of SARS-CoV-2 RT-PCR testing by day since exposure

Design: Literature review and pooled analysis

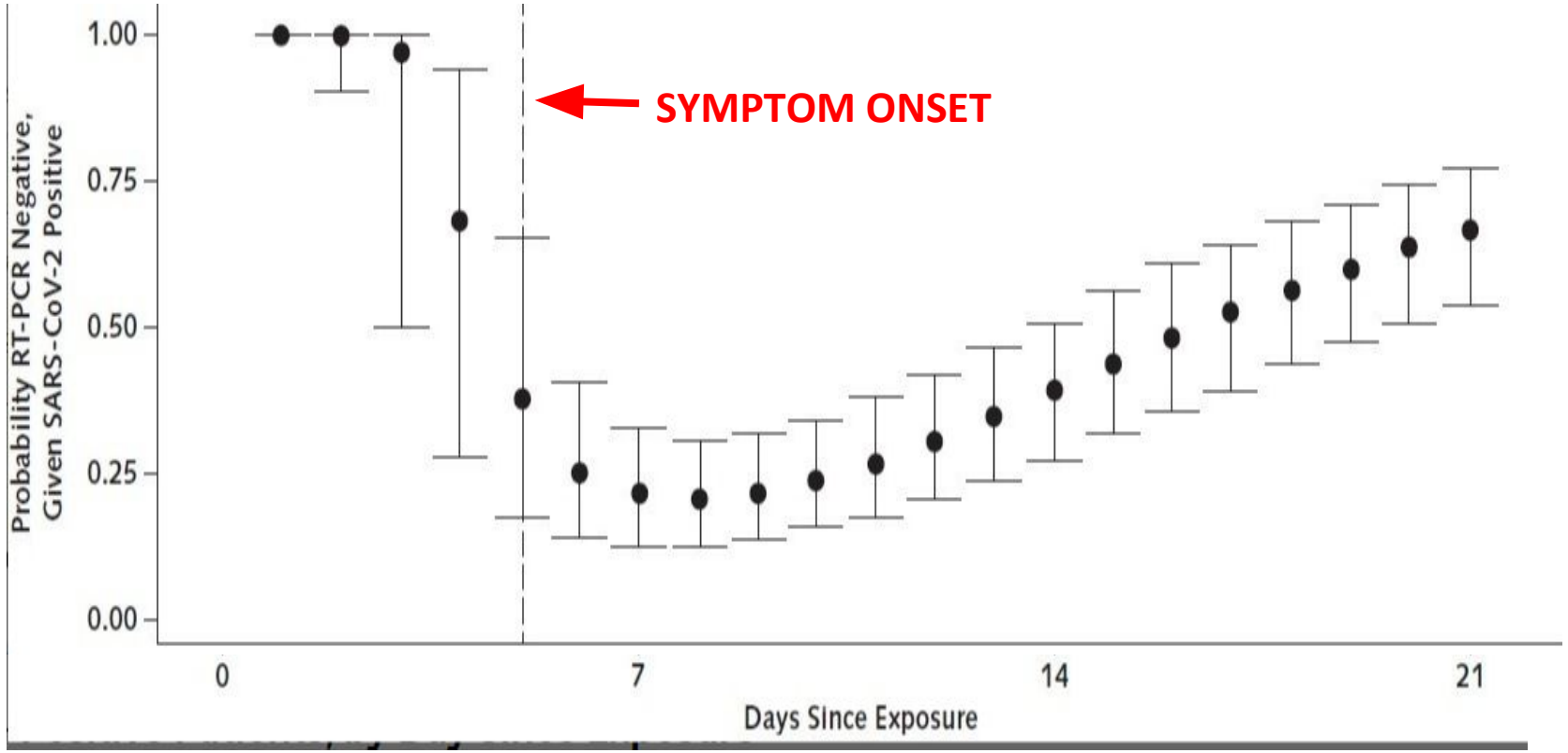
Setting: 7 previously published studies providing data on RT-PCR performance by time since symptom onset on SARS-CoV-2 exposure
Population: Mix of inpatients and outpatients with known SARS-CoV-2 infection (n=1330 swab samples)

PCR testing and Viral Shedding

Annals of Internal Medicine®

Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure FREE

Lauren M. Kucirka, MD, PhDStephen A. Lauer, PhDOliver Laeyendecker, PhD, MBA ... View all authors +



Results:

38% (CI 18%-65%) of patients will be negative on the day of symptom onset

The lowest false negative rate was 20% (CI 12-30%), **8 days after exposure i.e. 3 days after symptom onset**

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Bottom line:

- False negative PCR testing for SARS-CoV-2 is common!
- At best, one in five infected patients will test false negative with RT-PCR swab
- Best time to test is 3 days after symptom onset (8 days after exposure)
- A negative RT-PCR swab needs to be taken in the context of whether the patient has symptoms or not
- Retesting is a valuable strategy
- Conservative infection control policies make sense

Serologic Testing – Abbott SARS-CoV-2 IgG

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Performance Characteristics of the Abbott Architect SARS-CoV-2 IgG Assay and Seroprevalence in Boise, Idaho

Andrew Bryan, Gregory Pepper, Mark H. Wener, Susan L. Fink, Chihiro Morishima, Anu Chaudhary, Keith R. Jerome, Patrick C. Mathias, Alexander L. Greninger

Accepted manuscript, posted online May 7, 2020

NOT an industry funded study

Tested sensitivity in serum of 125 patients following a positive RT-PCR, 689 total serum specimens drawn on sequential days

--> **sensitivity reached 100% at day 17 after symptom onset** and day 13 after PCR positivity

Tested specificity in 1,020 serum specimens collected from Seattle patients PRIOR to SARS-CoV-2 circulation in the US (2018/2019)

--> 1 false positive in 1,020, indicating **specificity 99.90%**

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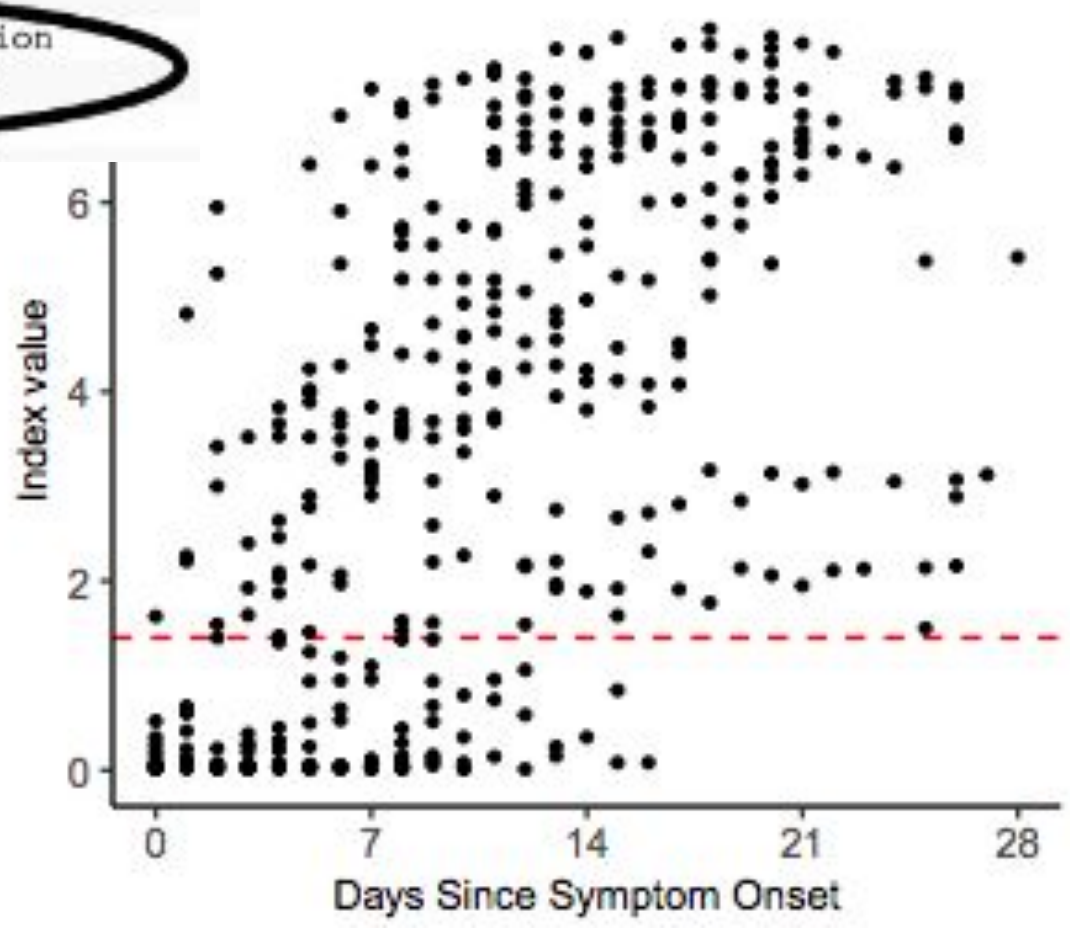
Index (S/C) Value	Interpretation
< 1.4	Negative
>= 1.4	Positive



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Bottom line:

- The Abbott test is very, very specific (low concern for false positives even in a low prevalence area like Alaska)

- Sensitivity of the test is a function of time elapsed since symptom onset and the cut-off used to define a positive test

- A lower cut-off threshold might be useful in certain scenarios even though the sensitivity will be lower, e.g. when you've missed the window for a sensitive RT-PCR swab

Therapeutics - Remdesivir

Background:

- Remdesivir is an anti-viral nucleotide analogue
- Remdesivir has been shown to have activity against SARS and MERS in vitro
- Remdesivir is therefore a potential treatment option for patients hospitalized with Covid-19 infection
- A recent RCT published in the Lancet found no difference in the time to clinical improvement, however this was stopped early due to low enrollment and was underpowered

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Published in NEJM, May 22, 2020

Objective: To assess the efficacy of IV remdesivir in reducing recovery time for adults hospitalized with SARS-CoV-2

Design: Randomized, double-blind, placebo-controlled trial, Intention to treat analysis

Setting: 60 trial sites in the USA (45 sites), Denmark (8), UK (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1) and Singapore (1)

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Population: 1059 hospitalized patients (538 intervention and 521 control) were included in the final analysis, out of 1063 randomized

For inclusion: lab-confirmed infection and one of the following:

- Radiographic infiltrates on CXR
- SpO2 ≤94% on room air
- Requiring supplemental oxygen, mechanical ventilation or ECMO

- Excluded:
  - AST or ALT > 5x ULN
  - Impaired renal function
  - Pregnancy
  - Anticipated discharge/transfer within 72 hours of enrollment

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Intervention:

Remdesivir:

200 mg IV loading dose on day 1, followed by a 100 mg IV maintenance dose on days 2-10, or until hospital discharge or death

Vs.

Placebo

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Primary outcome measure: time to recovery, defined as the first day that the patient fell into the lowest 3 categories on their 8 category ordinal scale:

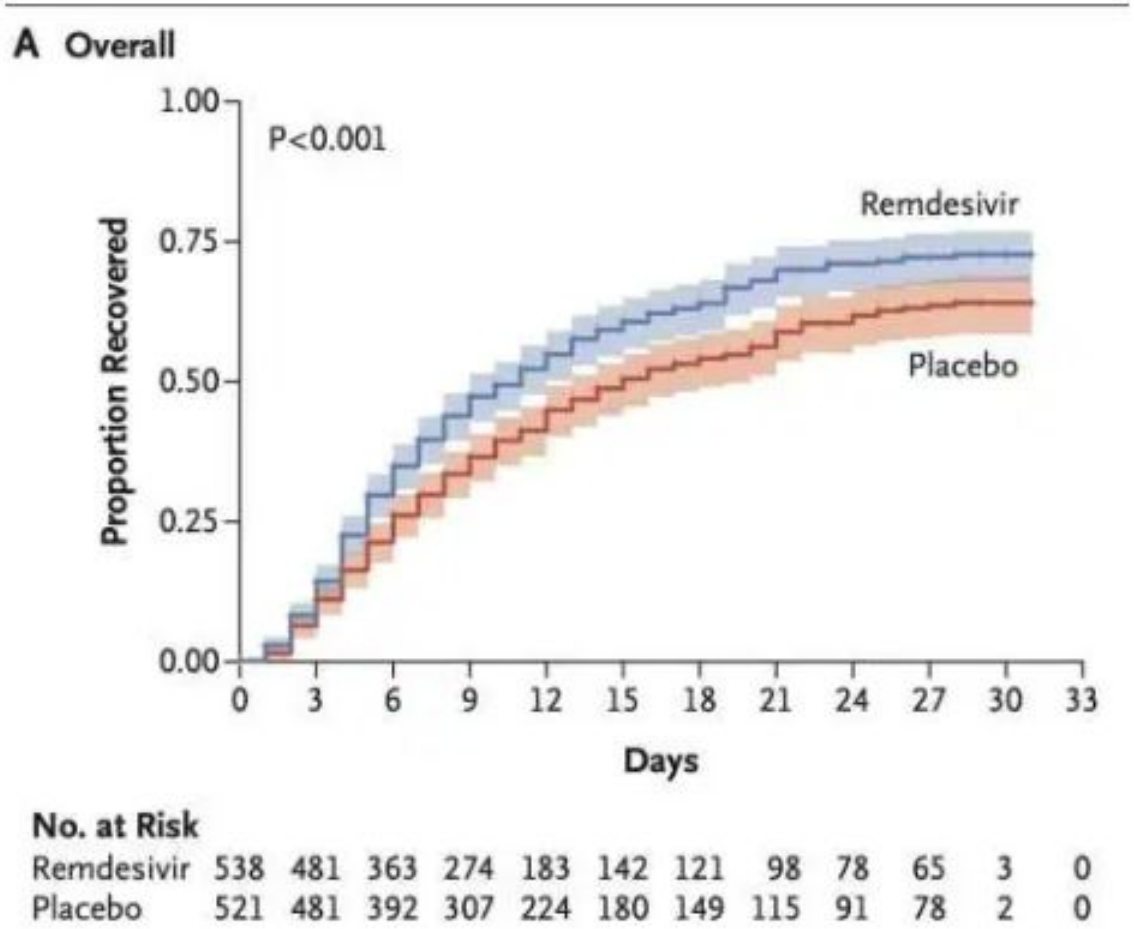
*Image from rebelEM.com

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Results:

Patients in the remdesivir group had **a significantly shorter time to recovery** than patients in the placebo group (median 11 days vs. 15 days, p<0.001, rate ratio for recovery 1.32, CI 1.12-1.55)



Remdesivir: ACTT-1 trial

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Secondary outcomes:

- The **odds of improvement in the ordinal scale score** measured at day 15 were significantly higher in the remdesivir group, when compared with the placebo group
  - odds ratio for improvement, 1.50; 95% CI, 1.18 to 1.91; P=0.001
- **No significant difference in mortality**
  - 32 deaths in remdesivir arm vs. 54 deaths in placebo arm
  - Kaplan-Meier estimate of 14-day mortality was 7.1% for remdesivir vs 11.9% for placebo
  - Hazard ratio for death 0.7 (95% CI, 0.47 to 1.04)
- No difference in patients discontinuing medication due to an **adverse event** between the treatment and control arms

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Limitations:

Changed the primary outcome

No matched placebo in European sites

Study stopped early

External validity

Patients with renal failure excluded w/o GFR criteria for renal failure

Remdesivir: ACTT-1 trial

The NEW ENGLAND JOURNAL of MEDICINE

Bottom line:

Consider remdesivir as an adjunct treatment in hospitalized patients who are SARS-CoV-2 positive

It appears to moderately improve recovery time without serious side effects

30% faster recovery rate could also be important for capacity in overburdened hospitals

Therapeutics - Dexamethasone?

RECOVERY TRIAL (Randomised Evaluation of COVid-19 thERapY)

Oxford University, United Kingdom
Press release (unsubmitted), 6/16/2020

Objective: Assess the impact of multiple different treatments for SARS-CoV-2 on patient mortality

- Lopinavir-Ritonavir (commonly used to treat HIV)
- Low-dose Dexamethasone (IV or PO)
- Azithromycin
- Tocilizumab (IV IL-6 inhibitor)
- Convalescent plasma

Dexamethasone: RECOVERY trial

Design: Randomized, double-blind placebo-controlled platform trial (multiple treatments analyzed simultaneously)

Setting: 175 NHS hospitals in the UK

Patients: >11,500 patients meeting these eligibility criteria:
(i) Hospitalised
(ii) SARS-CoV-2 infection (clinically suspected or laboratory confirmed)
(iii) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

Dexamethasone: RECOVERY trial

Dexamethasone arm: 2104 patients

Control arm: 4321 patients, usual care alone (supplemental O2)

Intervention: 6 mg daily PO or IV x 10 days

There were no substantial side effects seen in the dexamethasone group

On June 8, their oversight committee reviewed preliminary data and stopped the trial because...

Dexamethasone: RECOVERY trial

June 16 Press Release:

Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).

Dexamethasone reduced deaths by 1/3 in ventilated patients, 41% --> 20%

(rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003)

and by 1/5 in other patients receiving oxygen only, 25% --> 20%

(0.80 [0.67 to 0.96]; p=0.0021)

There was no benefit among those patients who did not require respiratory support

(1.22 [0.86 to 1.75]; p=0.14)

Dexamethasone: RECOVERY trial

Possible bottom line:

Dexamethasone ***may*** be an excellent treatment for moderate-severe disease

- NNT of 8 for ventilated patients
- NNT of 25 patients on supplemental oxygen
- Easy to administer
- Inexpensive/accessible

Dexamethasone: RECOVERY trial

Possible bottom line:

Dexamethasone ***may*** be an excellent treatment for moderate-severe disease

- NNT of 8 for ventilated patients
- NNT of 25 patients on supplemental oxygen
- Easy to administer
- Inexpensive/accessible

Limitations:

- NO peer review yet
- Not even any data released
- Baseline characteristics balanced between groups?
- Generalizable?

STAY TUNED...

References

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