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COMMENTARY

A Quick Summary of the COVID-19 Literature So Far

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Since March 25, two HIV clinical fellows, Eric Meyerowitz, MD, and Aaron Richterman, MD, MPH, have recorded a biweekly deep dive into the most compelling COVID-19 data. Their presentations have become "must-see" TV (or rather, YouTube) for those trying to make sense of all the pandemic-related literature.

Medscape asked them to summarize what they've learned so far, ahead of their next update, scheduled for May 19 .

Below are key takeaways from our fourth update, covering April 23 to May 5, during which more than 3000 COVID-related papers were published on PubMed and another 766 were released in preprint form:

- Remdesivir: A small, underpowered study in China found no difference in 28-day clinical improvement or mortality, in contrast to as-yet unpublished data from a larger NIAID study.
- The benefit of IL-6 inhibitor therapy is unknown; multiple randomized controlled trials (RCTs) are ongoing.
- Early studies suggested that viral RNA was rarely found in the blood. Now viremia/RNAemia with extrapulmonary infection is becoming more characterized, but it's still not clear whether it represents systemic infection with infectious virus.
- It's currently unknown what proportion of patients have a viremic phase of illness.
- The association between thrombosis and COVID-19 is becoming clearer, but the benefit of changing evidence-based anticoagulation strategies is unknown.
- Structural inequities around racism and impoverishment are associated with differential outcomes, and more data are urgently needed.
- Nonpharmaceutical interventions are important for epidemic control and economic recovery.

COVID-19 Therapy Randomized Trials

We summarized the major RCTs on COVID-19 therapeutics for which we have full papers (some in preprint form) (Table 1).

Table 1. Major COVID-19 Randomized Treatment Trials to Date

Ref	Drug Tested	Total N	Outcome	Notes/Limitations
(1)	Lopinavir/ritonavir	199	No difference	Clinical improvement, mortality, and percentage of patients with detectable viral RNA similar; median of 13 days from illness onset to randomization
(2)	Favipiravir versus umifenovir	240	For patients with moderate COVID, favipravir led to faster day 7 clinical recovery and resolution of fevers but no difference in need for mechanical ventilation	Preprint report
(3)	Hydroxychloroquine	150	No difference	Primary outcome of viral clearance at 28 days may not be a good endpoint; randomized late in illness course
(4)	Lopinavir/ritonavir versus umifenovir versus control	86	No difference for primary or secondary outcomes	Randomized 2:2:1; open-label trial with relatively small N; primary endpoint was time to negative RT-PCR, which may not be meaningful
(5)	Remdesivir	237	No difference in primary outcome; trend	Outbreak controlled in Wuhan before

	toward mortality improvement for those started within 10 days of symptom onset	prespecified enrollment goal could be met: underpowered; majority of patients received steroids in this cohort

We also discussed additional therapeutic data from press releases (Table 2).

Table 2. Preliminary Data on COVID-19 Randomized Treatment Trials

Ref	Drug Tested	Total N	Outcome	Notes/Limitations
(1)	Remdesivir	1063	Remdesivir group: 31% faster recovery compared with placebo; trend toward improved mortality	Preliminary report of findings based on press release; formal report pending peer review
(2)	Remdesivir	397	Similar improvement in severe-disease patients who received 5 or 10 days of remdesivir	Industry-sponsored trial (Gilead); no placebo arm
(3)	Tocilizumab	129	Primary outcome was need for mechanical ventilation or death; "*A significantly lower proportion of patients reached the primary outcome in the tocilizumab arm.*"	Open-label study (no placebo); preliminary report of findings based on press release; formal report pending peer review
(4)	Sarilumab	457	"Negative trends" in severe-disease group in phase 2, with "positive trends" in critical group	Industry-sponsored trial (Regeneron/Sanofi); phase 3 trial continuing with sarilumab 400 mg versus placebo in critical group only

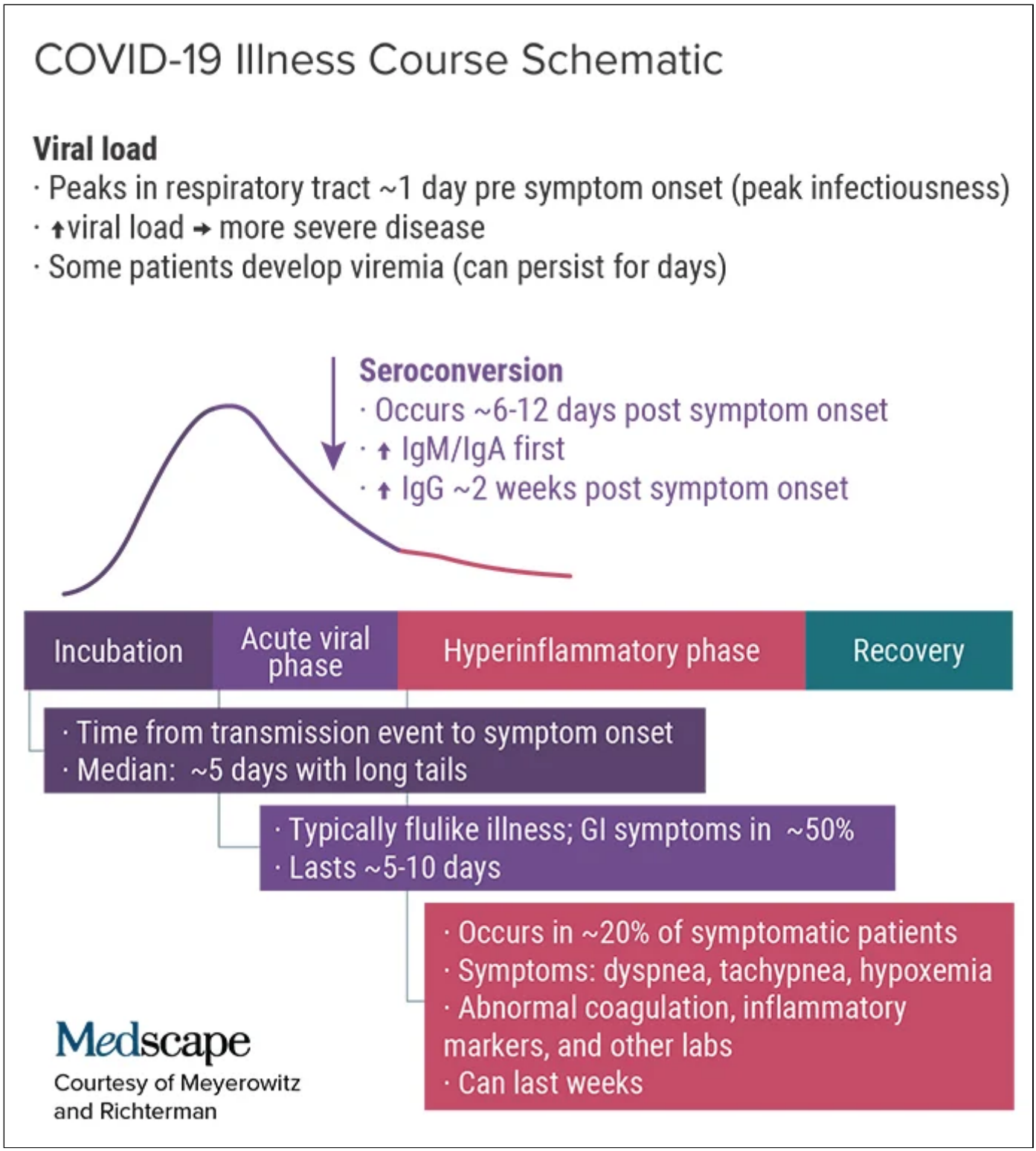
SARS-CoV-2 Transmission

The table below summarizes the key transmission findings.

Table 3. Key Findings in Mode of Transmission

Source	RNA Detected?	Live Virus?	Mode of Transmission and Evidence
Nasopharynx (1)	Yes	Yes	Droplet confirmed Direct contact suspected
Sputum (1) (2)	Yes	Yes	Airborne likely in some circumstances
Saliva (3)	Yes	Yes	Direct contact suspected as above
Stool (4) (5)	Yes	Yes	No evidence fecal-oral to date: Macaques challenged with intragastric SARS-CoV-2 were not infected (however, direct inoculation in oral mucosa suspected)
Blood (6) (7)	Yes	No	No confirmed bloodborne transmissions to date
Conjunctiva (8) (9)	Yes	Yes	Macaques with corneal inoculation develop infection
Vertical	Yes	N/A	Several cases of fetal IgM, 1 case of neonate with RNA at 16 hours (10) (11); additionally, multiple reports of placental infection (12)
Semen/vaginal fluids	Yes		SARS-CoV-2 RNA has been detected in semen, including after recovery (13); most reports have not found virus in vaginal fluids, but there is a signal report with positive vaginal swabs (14)
Urine (15)	Yes	Yes	
Cats (16)	Yes	Yes	Cats can transmit SARS-CoV-2 between each other

The Figure below illustrates what we know about the clinical course of the disease



Here are some key points from our first three presentations that are still valid.

Viral Shedding: Key Points

- Nasopharyngeal viral load peaks around 1 day prior to symptom onset, correlating to peak time of infectiousness.
- Saliva may become an important sampling site for diagnosis.
- SARS-CoV-2 is a descending infection; in later disease, viral loads are higher in the lower respiratory tract (especially in severe/critical illness).
- In mild cases, live virus is isolated up to day 8 after symptom onset.

- There can be prolonged shedding of viral RNA lasting many weeks, particularly after critical illness. Correlation with infectiousness is unknown.
- Studies differ on whether severity of illness correlates with viral load.
- In some cases, viral RNA has also been identified in the stool, blood, conjunctiva, urine, cerebrospinal fluid, and pleural fluid.

SARS-CoV-2 Seroprevalence

- Studies with (near) universal screening of various populations are increasingly available, finding a wide range of asymptomatic people with positive RT-PCR tests.
    - Pregnant women in NYC: 13.5% (87% of total infections)
    - Homeless shelter in Boston: 36% (great majority of infections)
    - Town in Italy: < 1% (41% of total infections)
    - Iceland: < 1% (43% of total infections)
    - Diamond Princess cruise ship: 9% (46% of total infections)
- Varying rates relate to local stage of epidemic, population and sampling, and mitigation strategies in place.
- Some asymptomatic people are likely to be presymptomatic given the variable and sometimes lengthy incubation period.

Viral Entry: Key Points

- ACE2 is an important receptor for viral cellular entry.
- TMPRSS2 primes the S protein and allows for efficient cellular entry.
- An interaction between SARS-CoV-2 and CD147 may facilitate invasion.
- Many unresolved questions remain regarding the exact role of CD147 in viral entry. Does it directly interact with the S protein or is the interaction mediated by CypA and the N protein, as was found for SARS-CoV?

What Else Have We Learned?

Key observations from our first three updates that are still relevant:

- Peak infectiousness is probably 1 day prior to symptom onset.
- In the absence of therapy/vaccine, intermittent social distancing is likely to be needed for years to avoid overwhelming critical care capacity.
- Emerging pathologic correlates of clinical presentations:
    - Multiple mechanisms of cardiac injury
    - Virus can cause systemic infection
    - Viral endotheliitis and possible complement activation as cause of micro/macro thromboses
- Obesity is a risk factor for severity of disease.
- Hypercoagulability is a key feature of the disease.
- Age-based sheltering is unlikely to be effective without social distancing.
- Epidemic control is feasible with contact tracing if minimal delay is achieved.
- Asymptomatic/presymptomatic transmission is substantial.
- The incubation period is highly variable (median, 5 days).

For full details, please see our original presentations—part 1, part 2, and part 3—and be sure to tune in for part 5 on May 19.

Follow Drs Meyerowitz and Richterman on Twitter: @EricMeyerowitz and @AaronRichterman

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