COVID-19 update
What have we learned?

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Disclosures

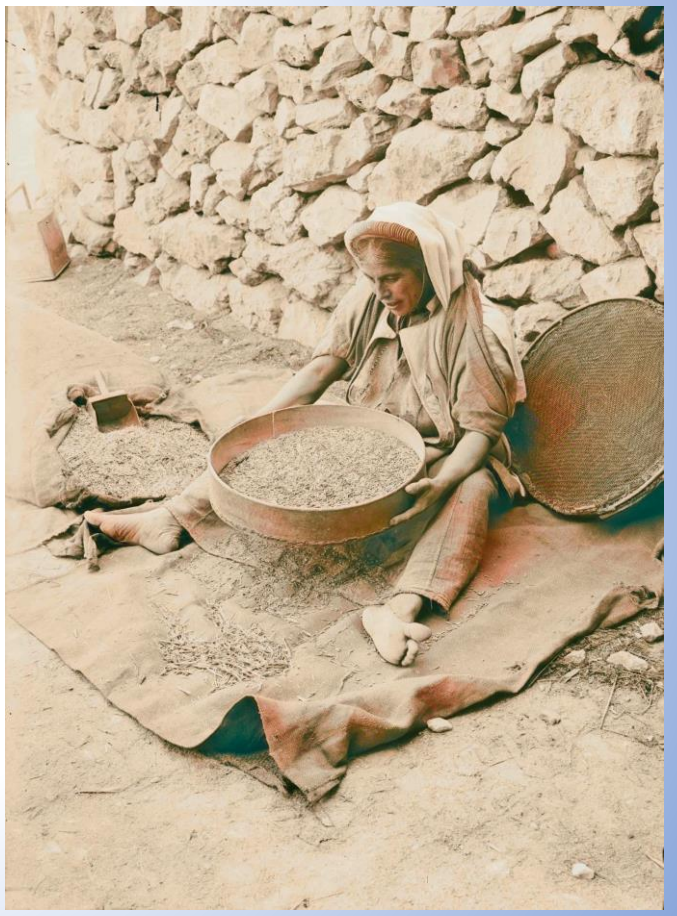
- Gilead
- Esperanza Therapeutics

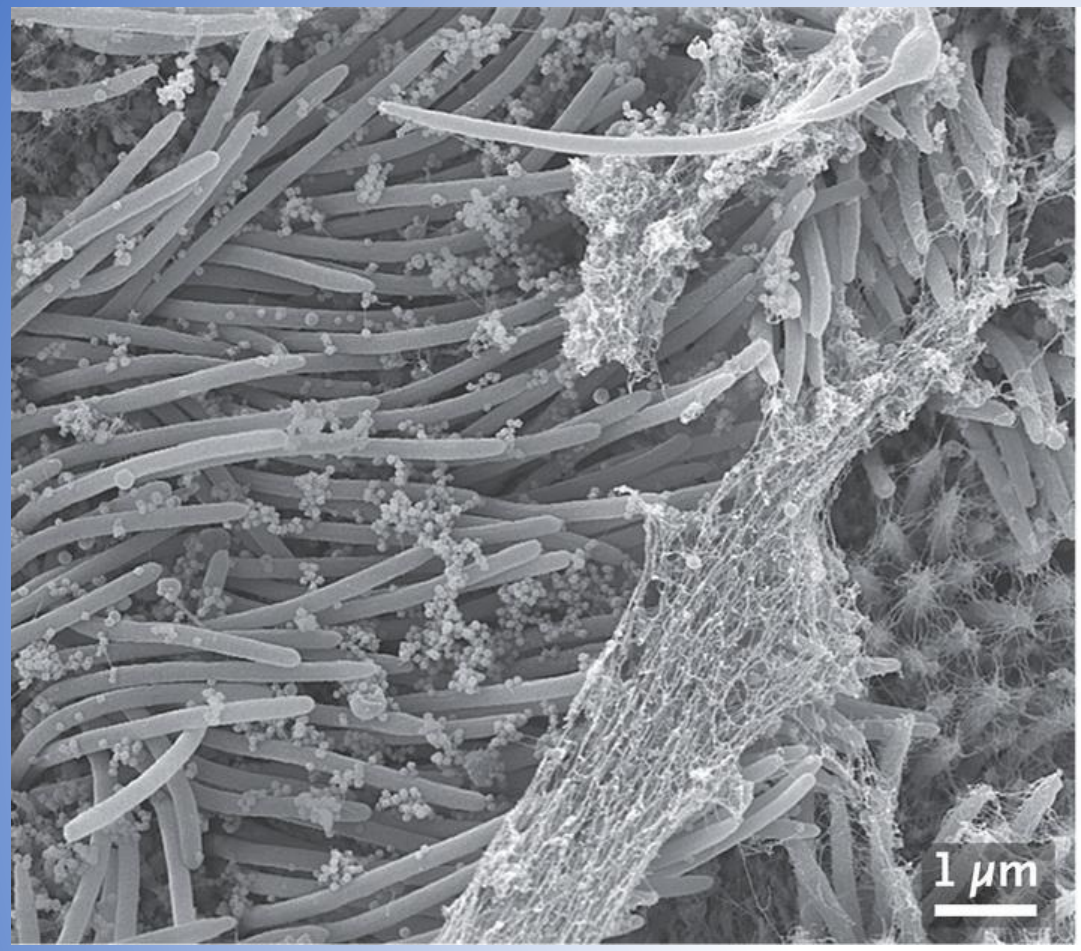
Objectives

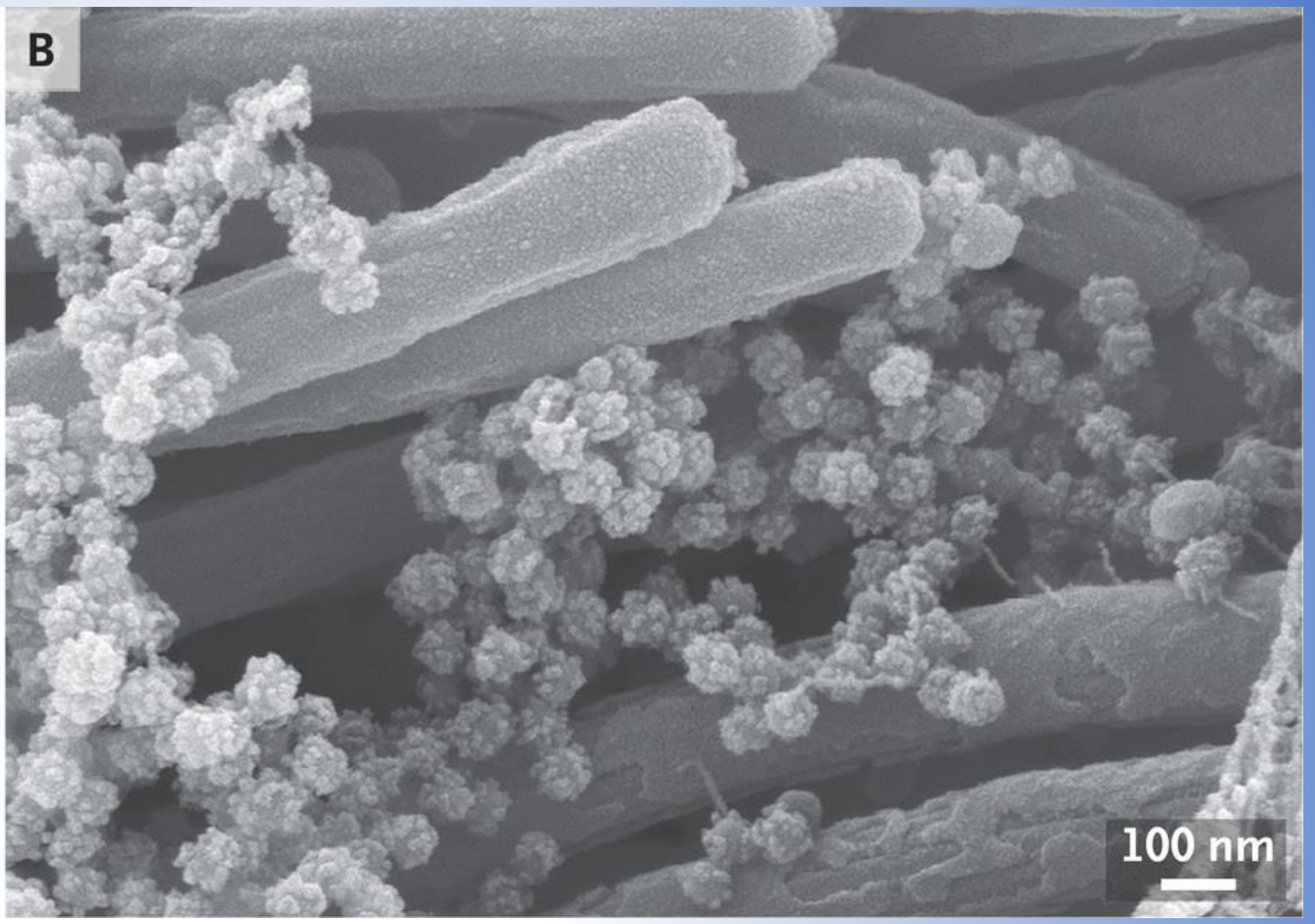
- Review remdesivir data
- Review evidence on convalescent plasma
- Review the IVIG trial at Sharp Healthcare
- Review the Clungene trial at Sharp Healthcare

Sifting through the data

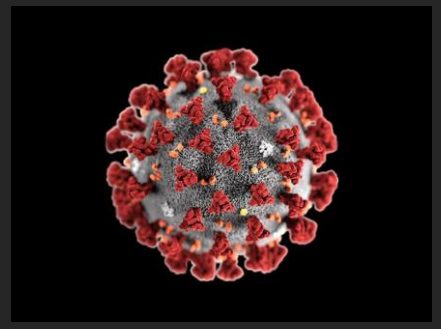
- Trials have been rushed to bring therapeutics to market
- Global spread of the COVID-19 pandemic
- Trials mostly are retrospective with many flaws
- Need for rigorous RCTs and data monitoring boards



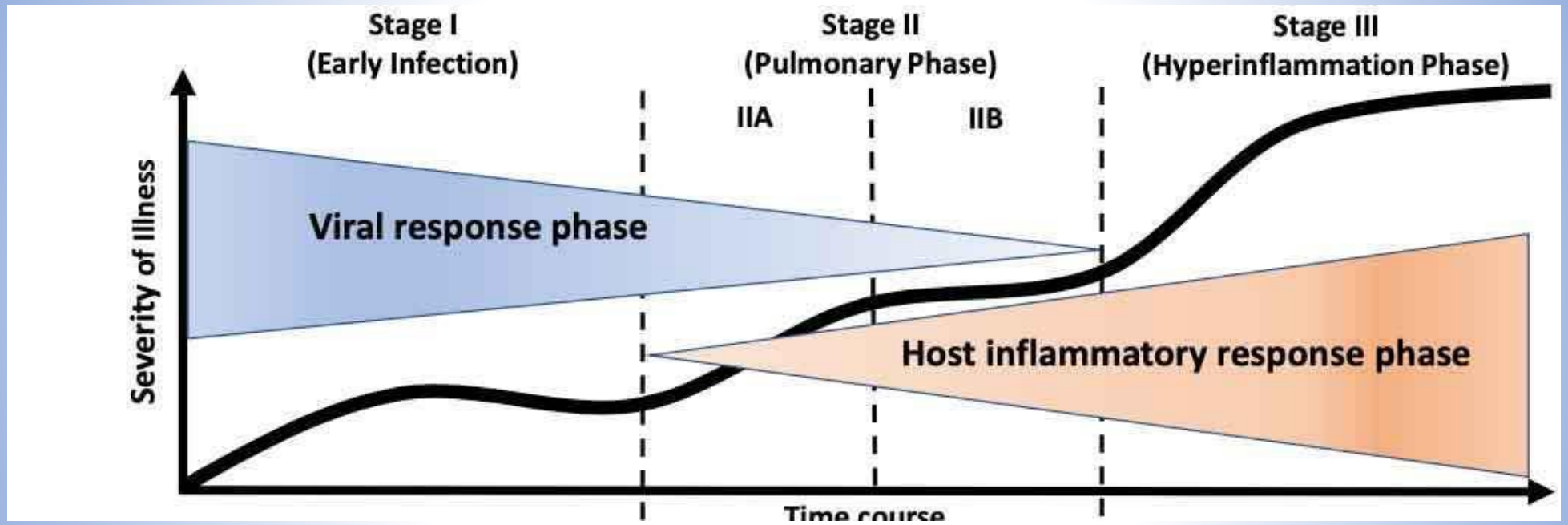




Ehre, N Engl J Med 2020; 383:969
DOI: 10.1056/NEJMicm2023328

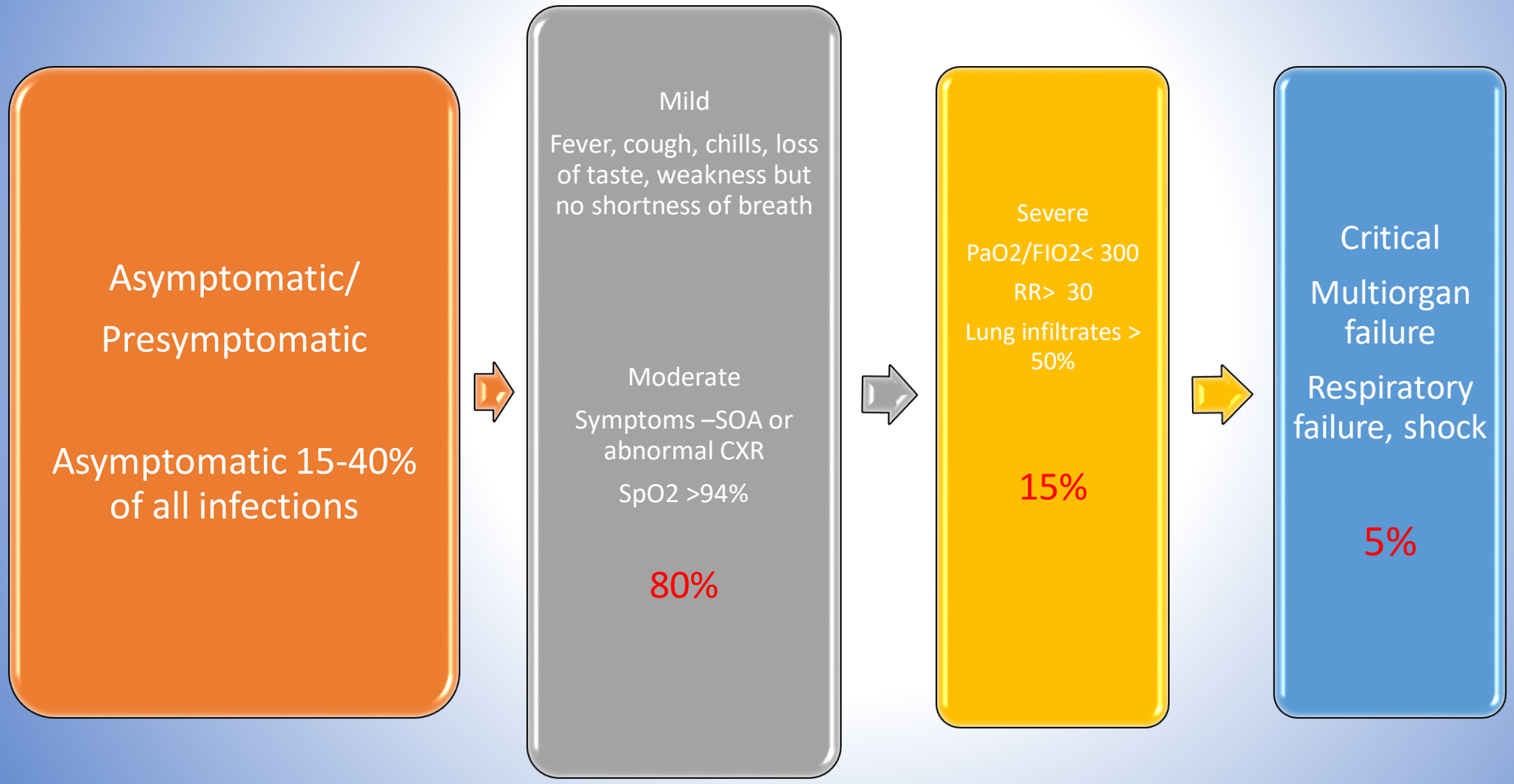


DAY 1-4 (Home) **DAY 4-7 (Medical Floor)** **>1 week (ICU)**

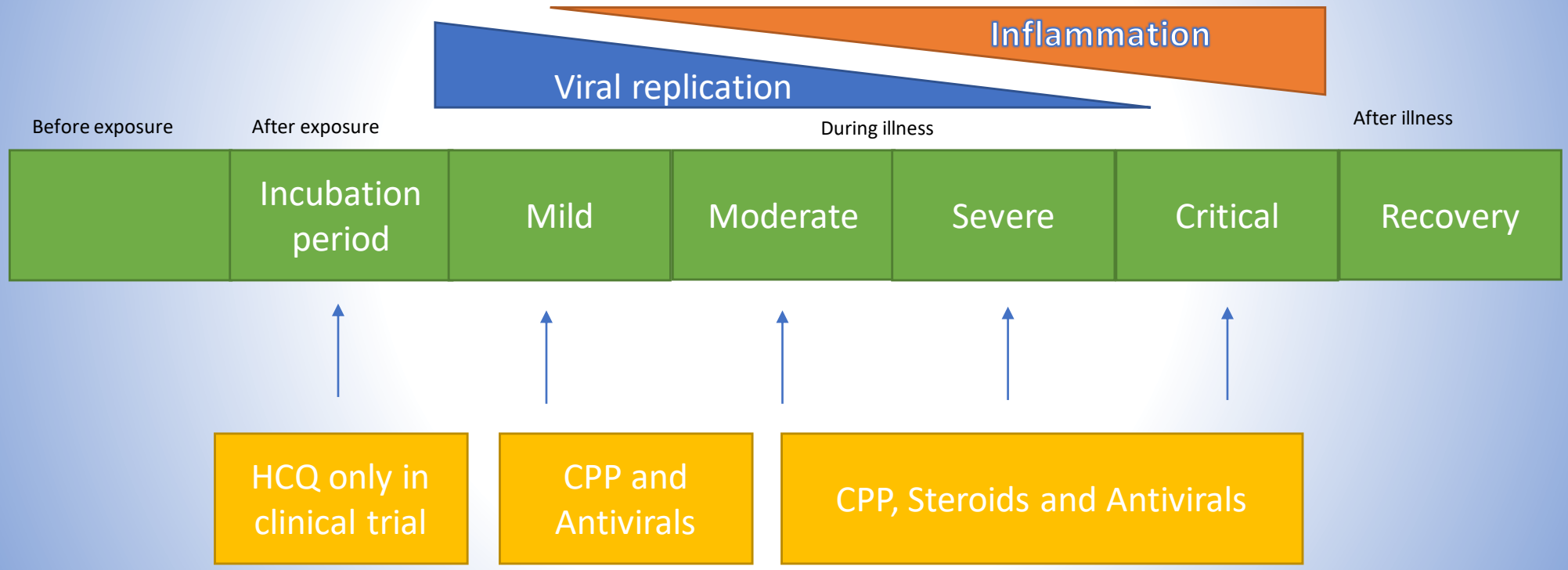


Siddiqu HK, Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical- Therapeutic Staging Proposal. *Journal of Heart and Lung Transplantation.* doi: 10.1016/j.healun.2020.03.012

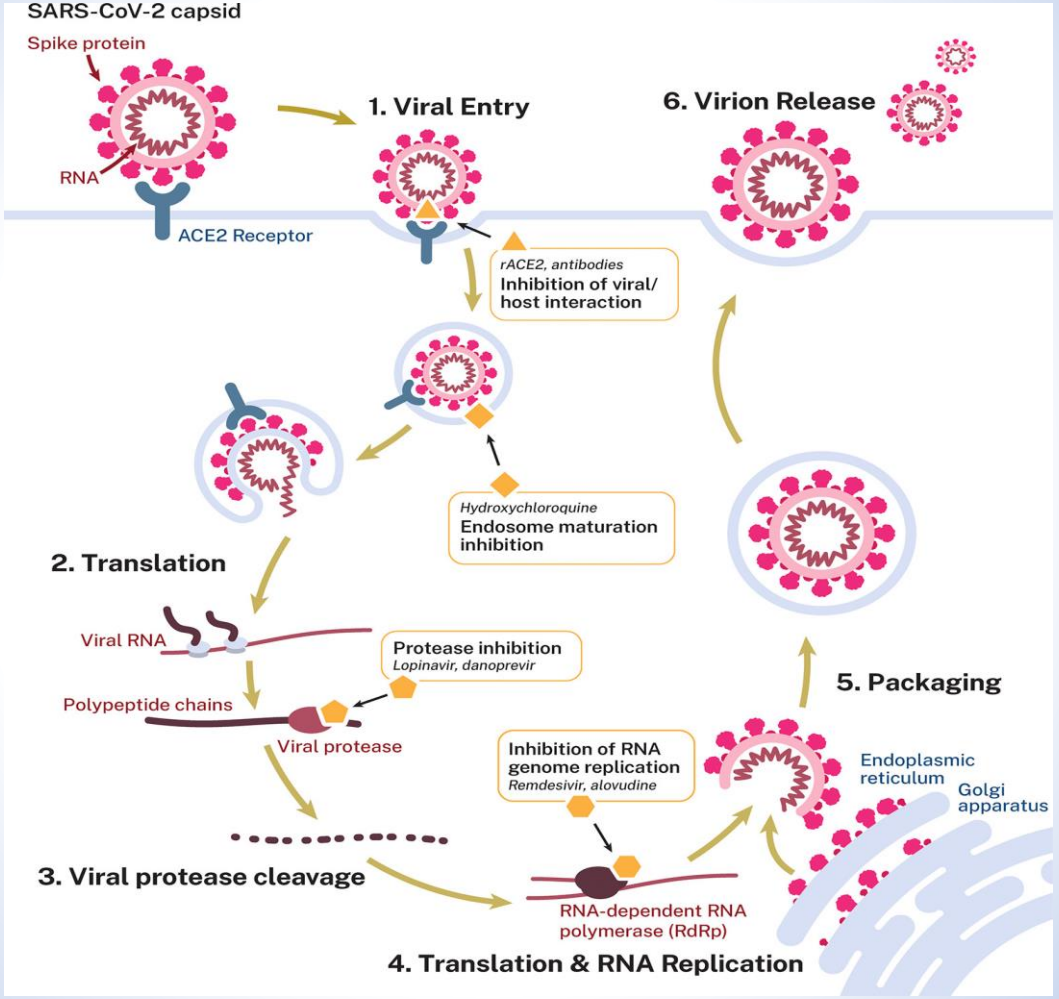
Spectrum of COVID-19



Treatment Targets



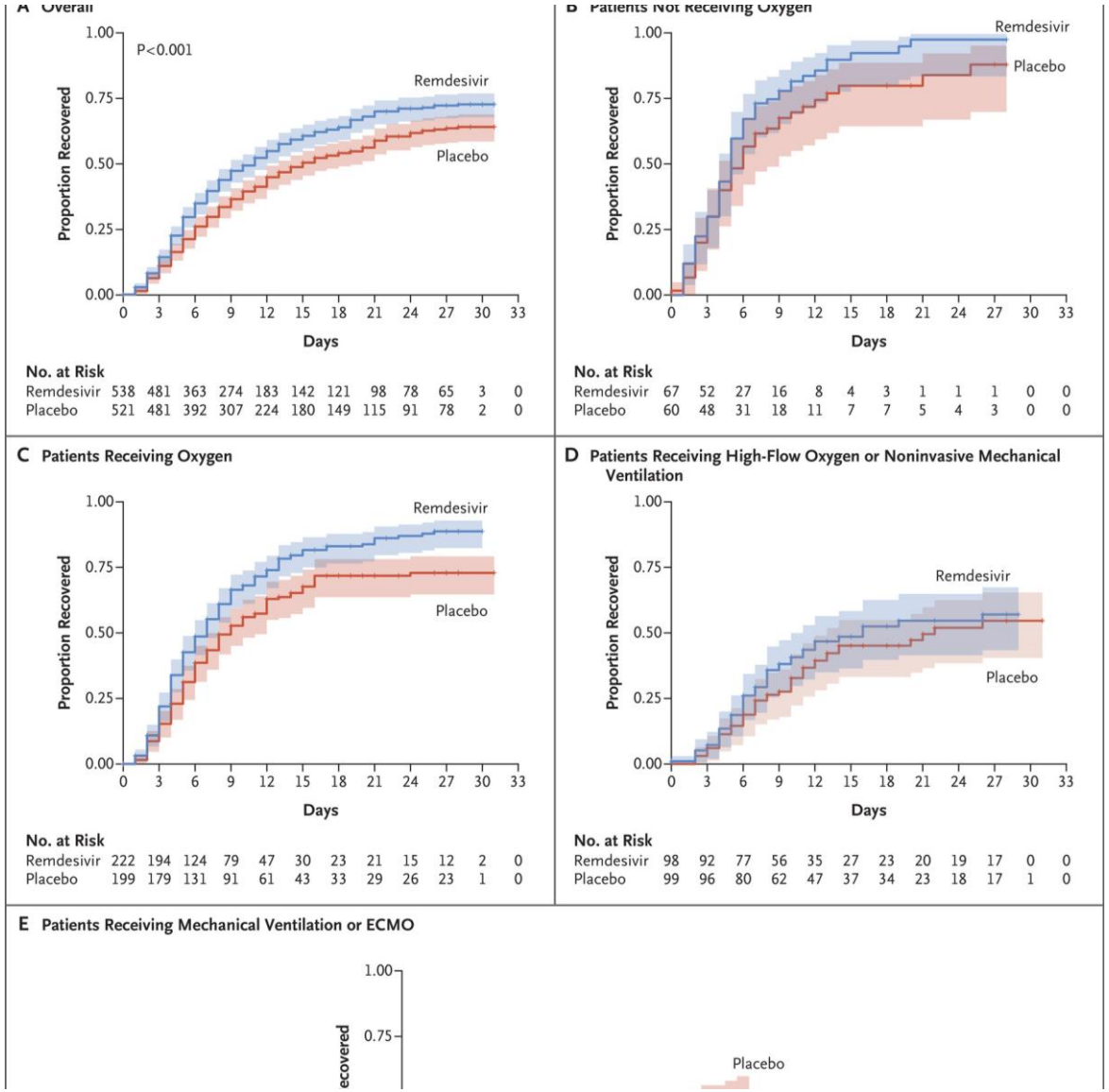
Life cycle of SARS-CoV-2 in host cells



Richard T. Eastman et al. **Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19**
DOI: (10.1021/acscentsci.0c00489)

Remdesivir for the treatment of Covid-19-Preliminary Report (ACTT-1)

- Double-blind, randomized placebo-controlled study of IV remdesivir in adults
- 1:1 study 200 mg loading dose on day 1, followed by 100 mg IV qd for 10 days vs placebo
- 1063 patients
- Primary endpoint: time to recovery
- Secondary endpoint: mortality at day 14



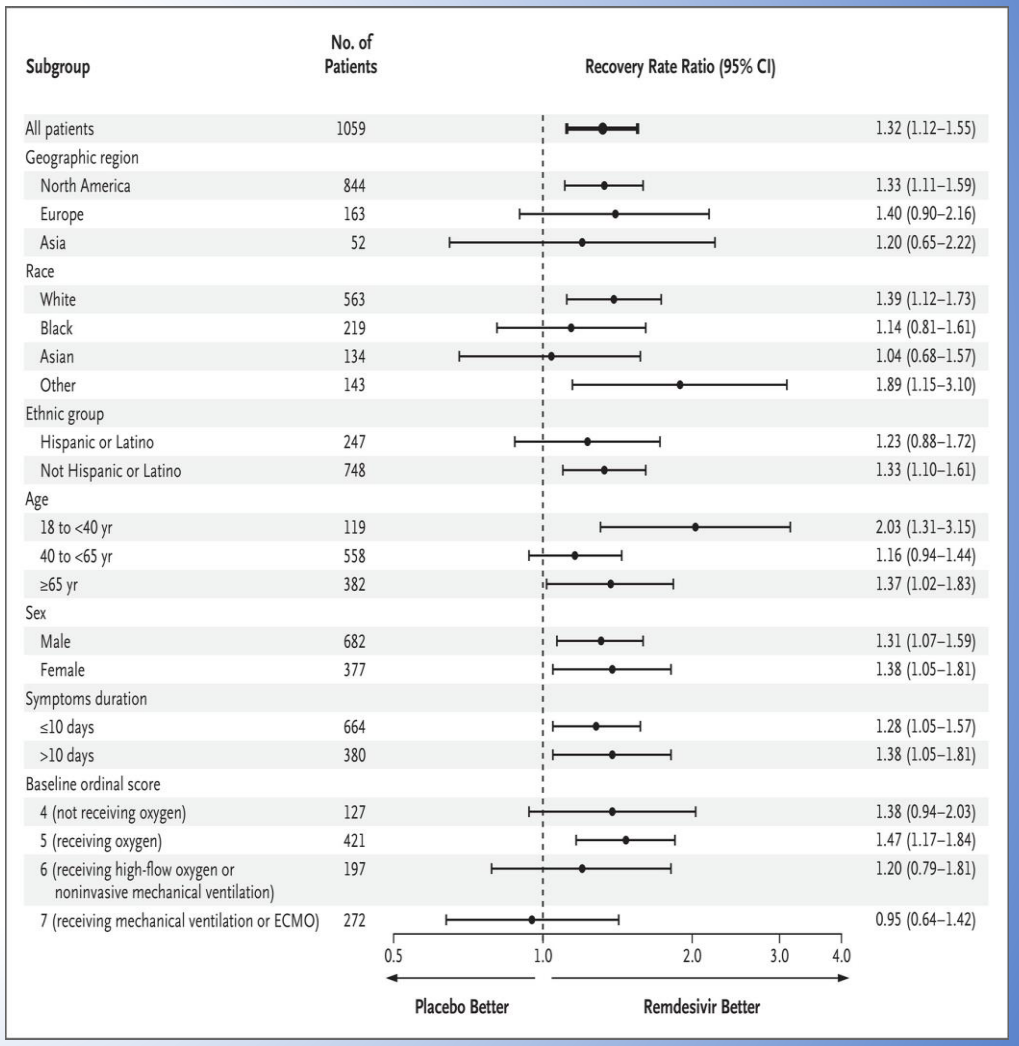
marketed under the name Veklury

Don’t start if LFTs> 5 times normal limit

Antagonism with chloroquine or HCQ

NIH ACTT-1 Result

- Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 with lower respiratory tract infection 11 vs 15 days
- No difference by symptoms onset
- Mortality at 14 days
  - Remdesivir 7.1%
  - Placebo 11.9%
- Serious adverse effects
  - 21.1% vs 27% placebo



Remdesivir for 5 or 10 days in Patients with Covid-19

- Randomized, open Label 5 vs 10 days
- 1:1 study
- 200 mg loading dose on day 1, followed by 100 mg IV daily
- 397 patients
- Primary endpoint: Clinical status day 14 on a 7-point scale
- Secondary endpoints: AEs

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [published online ahead of print, 2020 May 27]. *N Engl J Med*. 2020;NEJMoa2015301. doi:10.1056/NEJMoa2015301

Table 2. Clinical Outcomes According to Remdesivir Treatment Group.

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7. Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)
Clinical improvement — no. of patients (%)			
Day 5	33 (16)	29 (15)	0.2% (−7.0 to 7.5)
Day 7	71 (36)	54 (27)	−5.0% (−14.0 to 4.0)
Day 11	116 (58)	97 (49)	−4.8% (−14.1 to 4.6)
Day 14	129 (64)	107 (54)	−6.5% (−15.7 to 2.8)
Time to recovery (median day of 50% cumulative incidence‡)	10	11	0.81 (0.64 to 1.04)
Recovery — no. of patients (%)			
Day 5	32 (16)	27 (14)	0.1% (−7.0 to 7.1)
Day 7	71 (36)	51 (26)	−6.0% (−14.8 to 2.7)
Day 11	115 (58)	97 (49)	−3.7% (−12.8 to 5.5)
Day 14	129 (64)	106 (54)	−6.3% (−15.4 to 2.8)
Time to modified recovery (median day of 50% cumulative incidence‡)	9	10	0.82 (0.64 to 1.04)
Modified recovery — no. of patients (%)			
Day 5	51 (26)	41 (21)	−2.3% (−10.5 to 5.9)
Day 7	84 (42)	69 (35)	−3.4% (−12.6 to 5.8)
Day 11	128 (64)	106 (54)	−5.7% (−14.6 to 3.2)
Day 14	140 (70)	116 (59)	−6.7% (−15.3 to 1.9)

* Differences are expressed as rate differences, except in the case of time to clinical improvement, time to recovery, and time to modified recovery, for which differences are expressed as hazard ratios; for these time-to-event end points, the hazard ratio and its 95% confidence interval were estimated from a cause-specific proportional-hazards model including treatment and baseline clinical status as covariates. For events at prespecified time points (e.g., days 5, 7, 11, and 14), the difference in the proportion of subjects with an event under evaluation between treatment groups and the 95% confidence interval were estimated from the Mantel–Haenszel proportions adjusted according to baseline clinical status.

† The P value was calculated from a Wilcoxon rank-sum test stratified by baseline clinical status.

‡ Clinical improvement was defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale; recovery was defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7; and modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7. Cumulative incidence functions were calculated for each treatment group for days to the event under evaluation (i.e., clinical improvement, recovery, or modified recovery), with death as the competing risk. Data for patients not achieving the event under evaluation at the last assessment were censored on the day of the last clinical assessment. Patients who died before achieving the event under evaluation were considered to have experienced a competing event.

Limitations:

1. Greater proportion of severe disease in the 10-day group

2. No placebo arm

3. 44% of patients completed therapy in the 10-day group

4. More SAEs were in the 10-day group confounding factor

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [published online ahead of print, 2020 May 27]. *N Engl J Med*. 2020;NEJMoa2015301. doi:10.1056/NEJMoa2015301

Results

- Severe Covid-19 not requiring mechanical ventilation: no significant difference
- Primary end point clinical improvement of 2 points or more by day 14
  - 5-day group: 64%
  - 10-day group: 54%
- Most common AEs:
  - Nausea 9%
  - Worsening respiratory failure 8%
  - Elevated ALT 7%
  - Constipation 7%

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [published online ahead of print, 2020 May 27]. *N Engl J Med*. 2020;NEJMoa2015301. doi:10.1056/NEJMoa2015301

RECOVERY trial

Open label trial
Dexamethasone vs standard of care
1:2 randomization
6 mg (IV or PO) for 10 days or less if discharged sooner
2104 dexamethasone group
4321 usual care

Primary end point: Mortality at 28 days

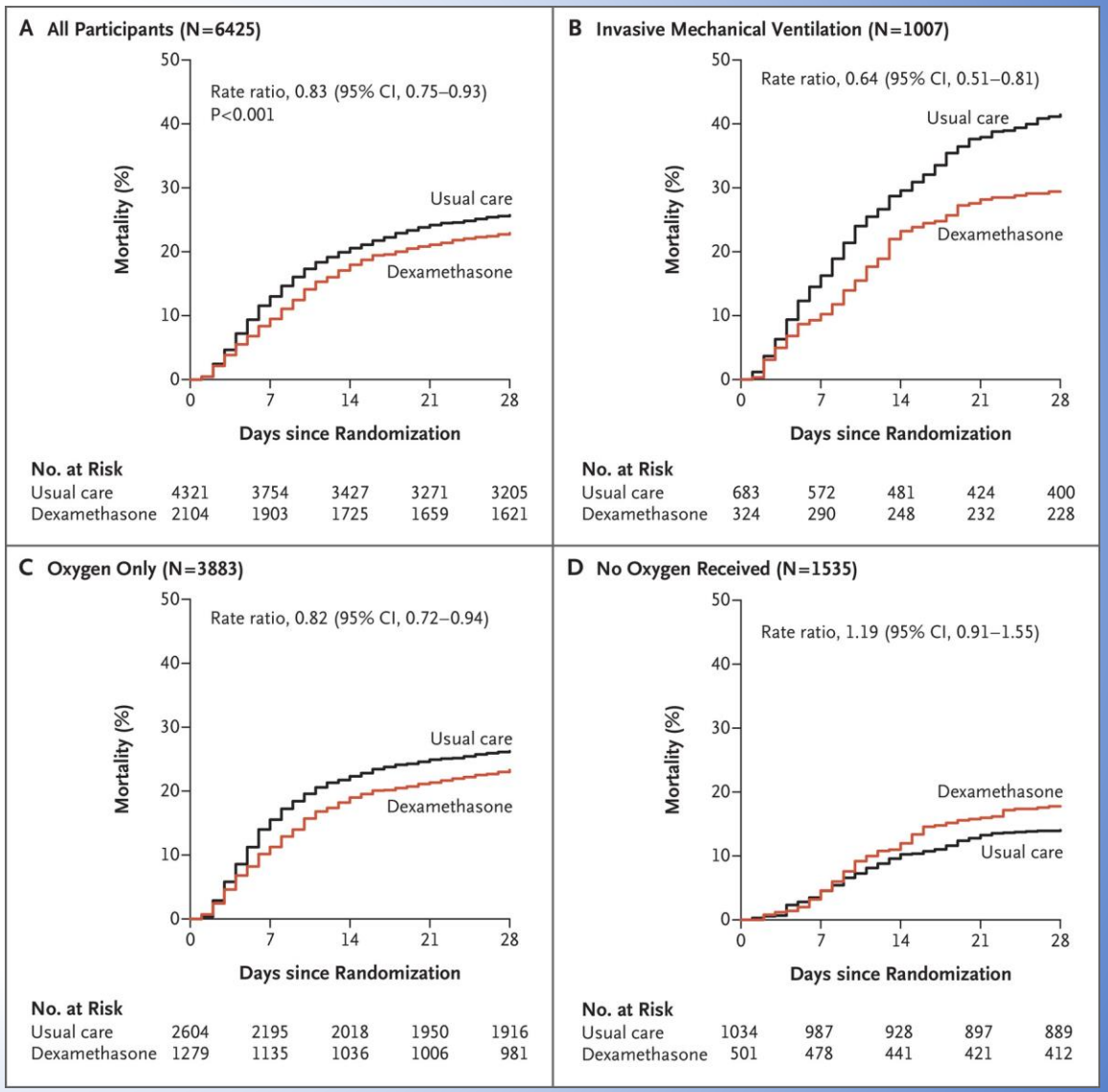
RECOVERY Collaborative Group, Horby P, Lim WS, et al. 2020 Jul 17]. *N Engl J Med*. 2020;NEJMoa2021436. doi:10.1056/NEJMoa2021436

RECOVERY trial Results

Dexamethasone vs usual care mortality rate

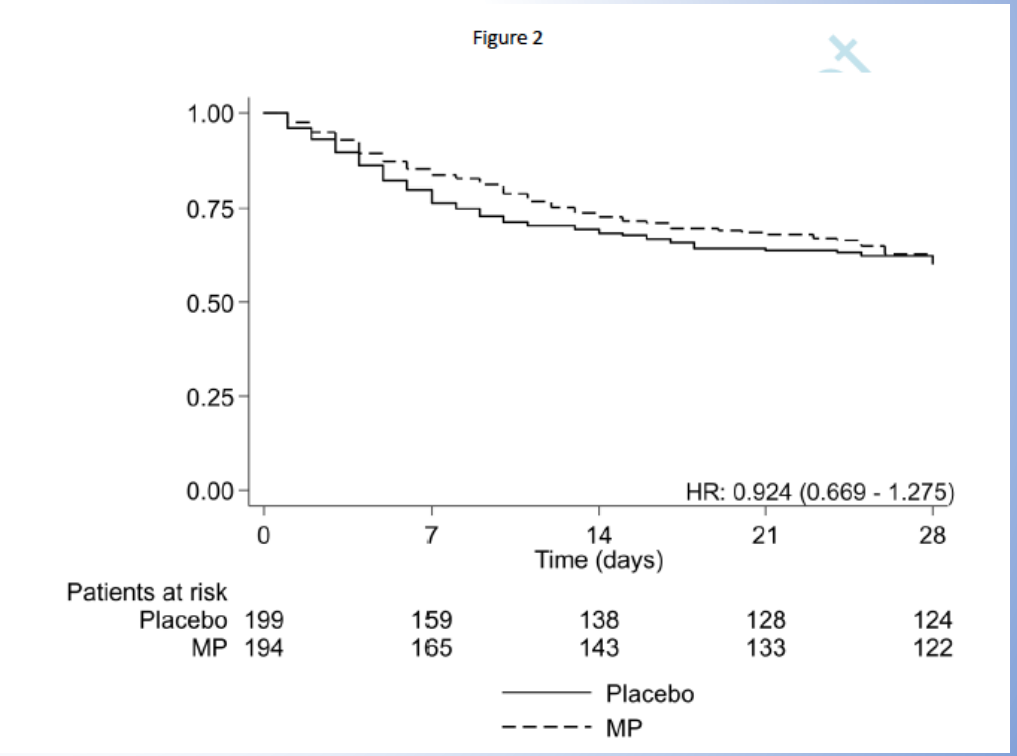
22.9% vs 25.7%

In the dexamethasone group, the incidence of death was lower than usual care (29% vs 41%) in mechanically ventilated patients and among those receiving oxygen without invasive mechanical ventilation (23% vs 26%) but NOT among those who were receiving no respiratory support.



Steroid Debate: The dilemma continues

- Study from Brazil
- Randomized placebo double blinded 1:1
- IV methylprednisolone or placebo 0.5 mg/kg BID for 5 days
- Failed to show a difference in mortality at day 28 after analyzing 393 patients
- Subgroup analysis showed lower mortality in patients > 60 yrs. of age
- Trend for worse outcome with patients < 60 yrs. of age



Jeronimo CMP, Farias MEL, Val FFA, et al.*Clin Infect Dis*. 2020;ciaa1177. doi:10.1093/cid/ciaa1177

Convalescent Plasma Trials

	Li et al. (JAMA 6/2020)	Joyner et al. (Mayo clin Proc 7/2020)	Salazar Et al. (A, J. Path 8/2020)	Perotti et al. (MedRxiv)
N	101	20K	25	46
	28-day mortality No difference	Low adverse events <1% Transfusion reaction or Thromboembolic events 7-day mortality was 13% 15.6% ICU patients 18.3% Vent patients	19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged	30 on CPAP and 7 intubated Weaning from CPAP was obtained in 26/30 patients and 3/7 were extubate

Mayo Expanded Study for Convalescent Plasma

- Observational
- Multicenter 2807 acute care centers in the US
- Not randomized
- 35,322
- Mortality at 7 days 8.7% if transfusion was within 3 days of COVID-19 diagnosis
- Mortality was 11.9% if transfusion was 4 days or more after diagnosis of COVID-19
- Mortality correlated with IgG levels in the transfused plasma

COVID-19 Reinfection

- 1st report of reinfection
- Whole genome sequencing directly performed on two isolates 142 days apart
- Oropharyngeal swabs
- A 33 yr. old man from Hong Kong
  - 1st episode presented with cough and hospitalized from 3/26-4/14
  - Two negative swabs taken 24 hrs. apart
  - In August he tested positive after arrival from Spain via UK

- Yuen, K et al, CID, Sept,2020

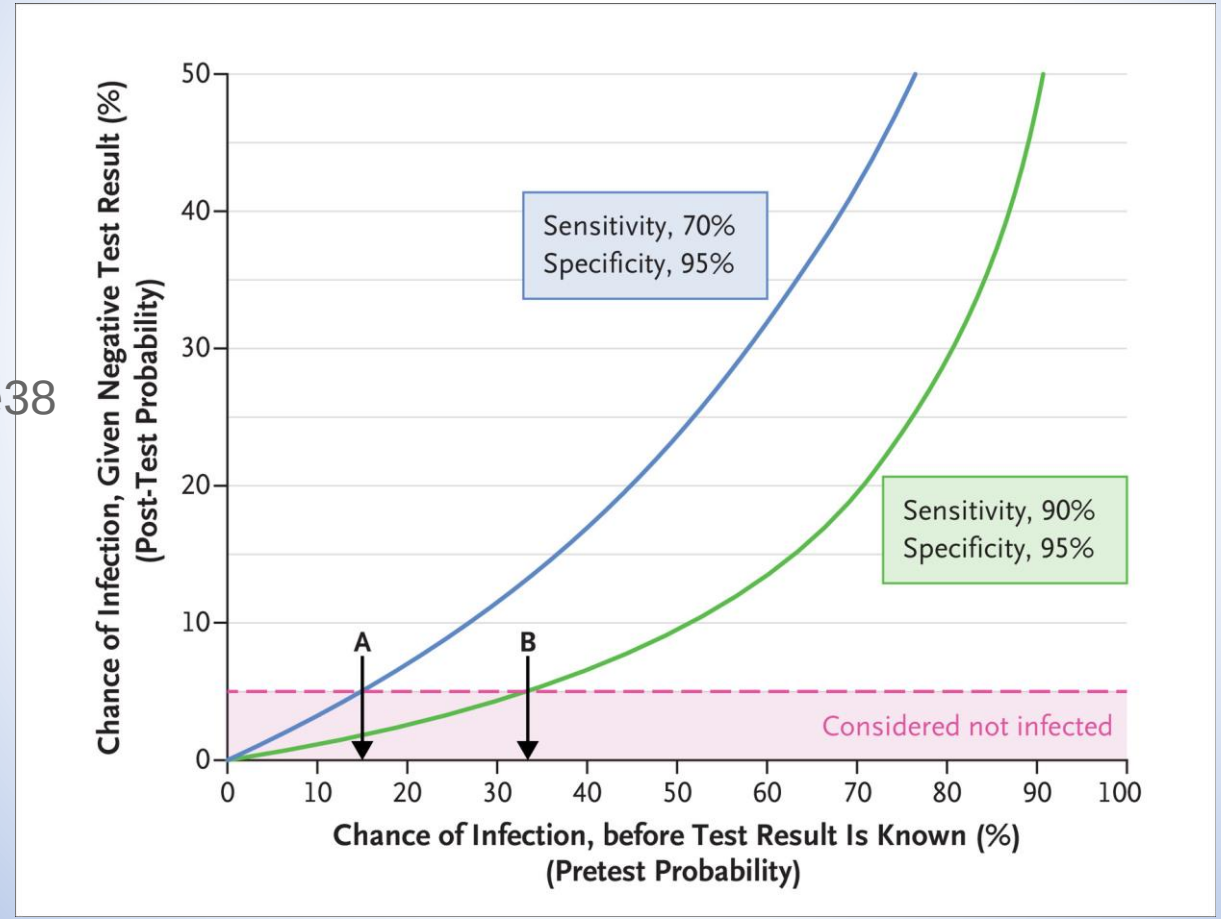
COVID-19 Reinfection

- Evidence for new infection
  - Two clades distinct phylogenetically
  - Elevated CRP and viral load suggestive of new infection
  - Seroconversion 5 days after hospitalization
  - 142 days have passed

- Implications
  - Herd immunity may not be the salvation as reinfection is common for Coronaviruses
  - Role of T cell mediated immunity
  - Mild subsequent infection

COVID-19 testing

Woloshin, S, et al.
N Engl J Med 2020; 383:e38



Humoral Immune response to SARS-CoV-2 In Iceland

- Seroconversion 7-14 days after diagnosis
- Fatality risk can be variable because of unknown denominator
- Study findings
  - 30,576 patients
  - 2 groups of PCR positive tested twice on recovery and 3 months after
  - 6 groups of PCR negative or not tested
  - 6 Assays Pan Ig Anti-N, Pan-Ig Anti-S1-RBD, IgG Anti-N, IgM Anti-N, IgG Anti-S1 and IgA Anti-S1
  - Estimated incidence of Infection 0.9%
  - 0.3% fatality risk, 0.1% if younger than 70 years, 4.4% older than 70 years
  - Over 90% of qPCR-positive persons tested positive with both pan-Ig antibody assays and remained seropositive 120 days after dx with no decrease in antibody levels as detected by two pan-Ig assays.

Risk factors for COVID-19 Antibody Levels

Correlation with higher antibody level

- Age
- Hospitalization
- Male
- BMI
- Clinical severity of illness
- Fever
- Max temp reading
- Cough
- Loss of appetite

Correlate with lower antibody level

- Smokers
- Use of NSAIDS

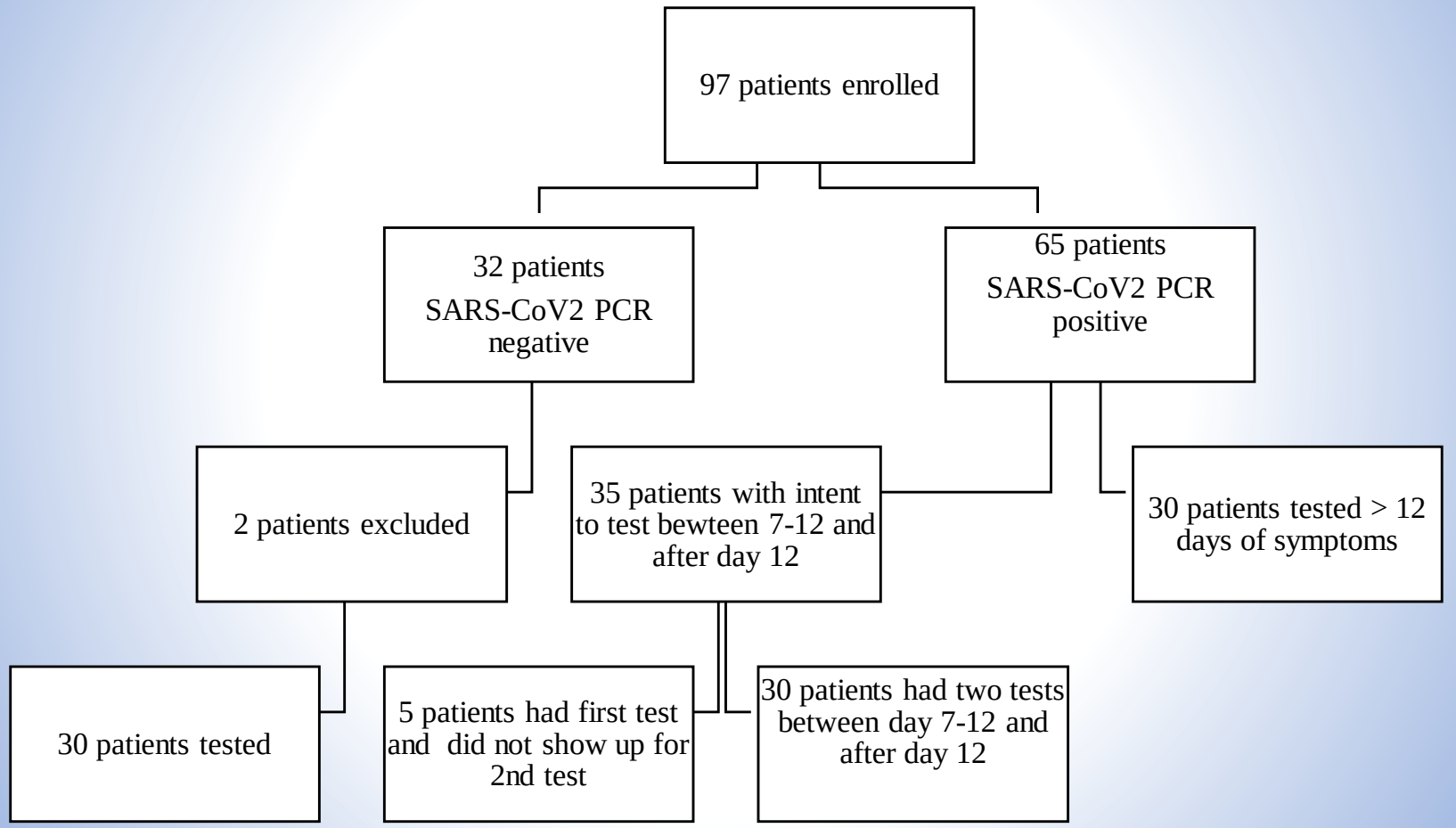
Point of Care Clinical Evaluation of the Clungene® SARS-Cov2 Virus IgG/IgM rapid test cassette with the Cobas® Roche RT-PCR platform in patients with or without COVID-19

- An observational study of 97 patients who were either hospitalized or were in the ER for COVID-19 symptoms
- Two community hospitals in San Diego, California
- IRB approved
- Three arms:
  - Arm A: 35 patients PCR positive tested twice 7-12 days after symptoms onset and after 12 days
  - Arm B: 30 patients PCR positive after 12 days from symptoms onset
  - Arm C: 32 patients with negative PCR tested within 10 days of the result

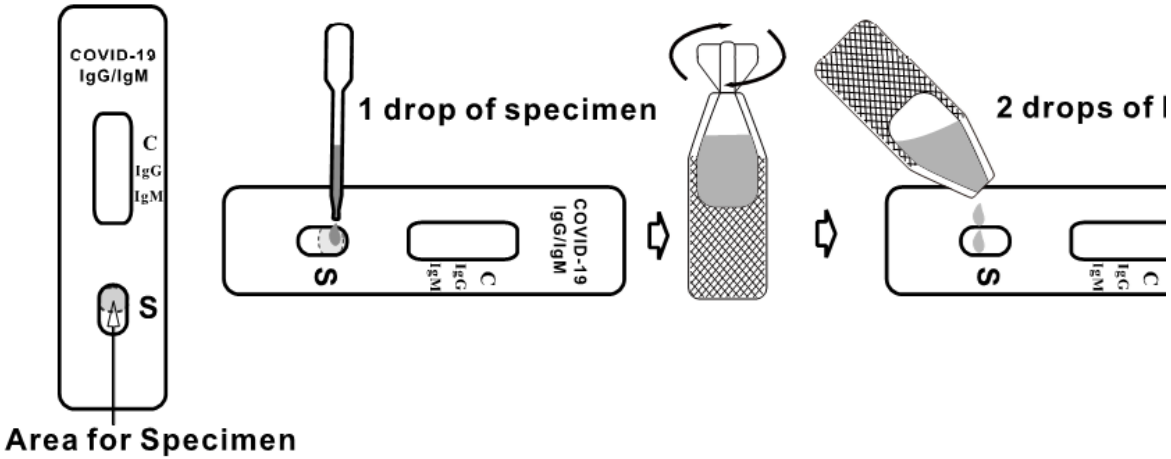
Point of Care Clinical Evaluation of the Clungene® SARS-Cov2 Virus IgG/IgM rapid test cassette with the Cobas® Roche RT-PCR platform in patients with or without COVID-19

- May 2020 and August 2020, 97 patients were enrolled, consented, and tested
- Days from symptom onset were captured from the electronic medical record (EMR) and from asking patients directly
- Symptoms of COVID-19 included fever, weakness, cough, shortness of breath, tiredness, anosmia, and loss of taste.

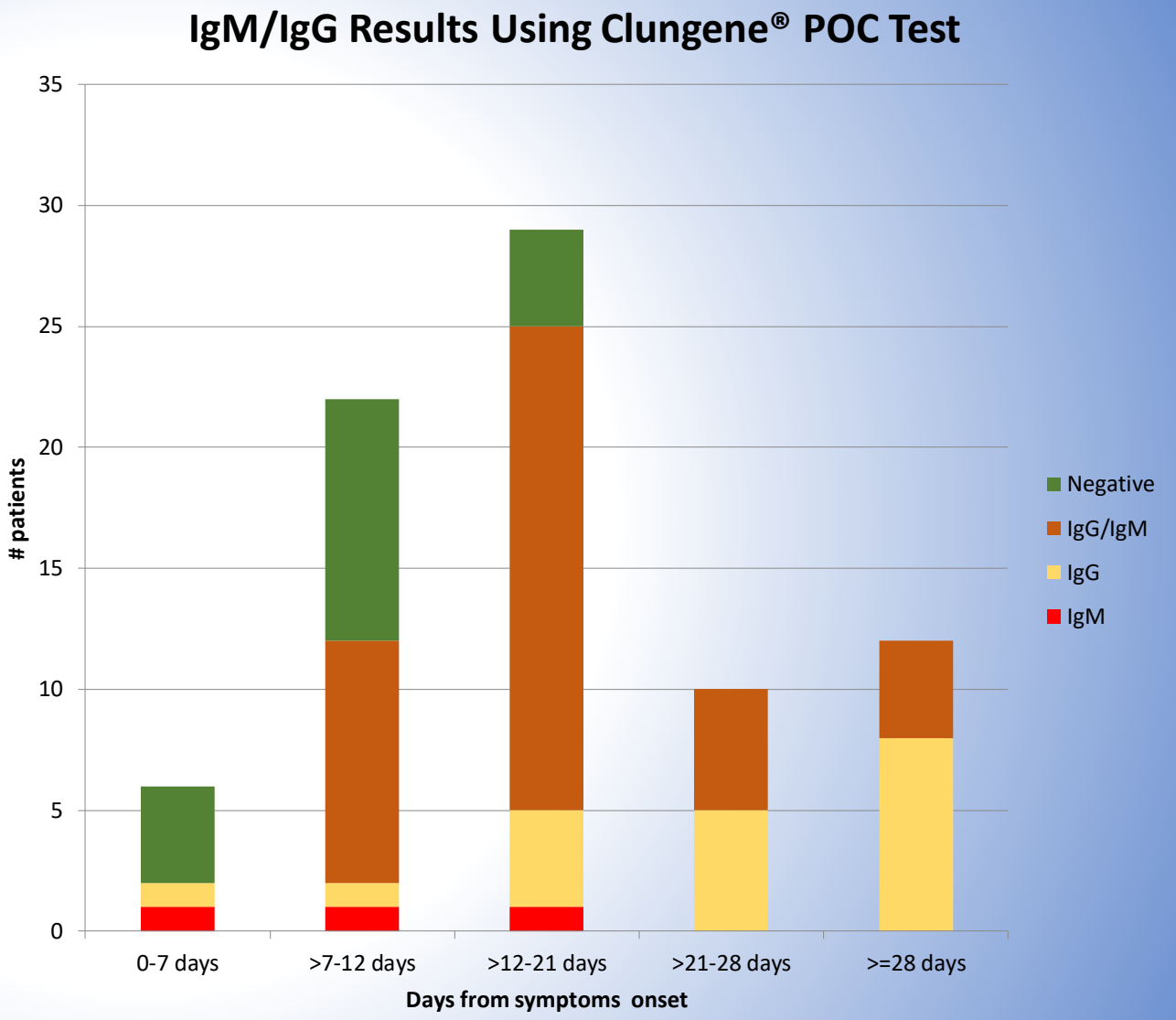
Subjects


97 patients enrolled
32 patients SARS-CoV2 PCR negative
65 patients SARS-CoV2 PCR positive
2 patients excluded
35 patients with intent to test bewteen 7-12 and after day 12
30 patients tested > 12 days of symptoms
30 patients tested
5 patients had first test and did not show up for 2nd test
30 patients had two tests between day 7-12 and after day 12

Methods


COVID-19
IgG/IgM
C
IgG
IgM
S
Area for Specimen
1 drop of specimen
2 drops of
IgM Positive
IgG Positive
IgG/IgM Positive
Negative
Invalid

Results


IgM/IgG Results Using Clungene® POC Test
35
30
25
20
15
10
5
0
patients
0-7 days
>7-12 days
>12-21 days
>21-28 days
>=28 days
Days from symptoms onset
Negative
IgG/IgM
IgG
IgM

Demographics and Laboratory Values in COVID-19 Negative and Positive Patients

Characteristic	Confirmed COVID-19 Negative (n=30)	Confirmed COVID-19 Positive (n=60)	P-Value
Male (N; %)	18 (60%)	37 (61.7%)	0.53
Age (years) (Mean)	60.6	52.2	0.04
Diabetes (N; %)	4 (13.3%)	23 (38.3%)	0.16
Hypertension (N; %)	16 (53.3%)	28 (46.7%)	0.62
Smoker (N; %)	11 (36.7%)	10 (16.7%)	0.06
BMI (kg/m2) (Mean)	30.2	30.6	0.77
CRP (mg/L) (Mean)	27.8	151.1	0.02
Tmax (°C) (Mean)	37.1	37.8	0.000
Ferritin (µg/L) (Mean)	180.2	871.7	0.003

IgG, IgM, and IgG+IgM results based on days from onset of symptoms

DAYS FROM ONSET OF SYMPTOMS	IGG	IGM	IGG+IGM	CONTROL	TOTAL
7-12 Days	4	3	12	16	35
>12 days	25	1	28	6	60
Total	29	4	40	22	95

Clungene® results between day 12 and 70 from

CLUNGENE® RESULT POSITIVE BAND ON EITHER IGG, IGM, OR BOTH	COVID-19 RT-PCR POSITIVE	COVID-19 RT-PCR NEGATIVE	TOTAL
Positive	54	0	54
Control	6	30	36

Conclusion

- Antibody testing for COVID-19 is helpful
- Timing is very essential for interpretation of results
- False negative results more likely early in the disease
- Some patients never seroconvert
- Further research into the immune response for COVID-19 need to be pursued

Limitations

- Small study with one geographic area
- Two methods for collection of blood (venipuncture vs finger prick)
- Patients enrolled had inpatient PCR testing method. Non hospitalized patients with other methods of testing were not included

Intravenous Immunoglobulin (IVIG) Significantly Reduces Respiratory Morbidity in COVID-19 Pneumonia: A Prospective Randomized Trial

- Small open label trial at SGH and SMH
- N=34
- 16 IVIG group three days of IVIG
- 17 standard of treatment (Remdesivir and Plasma were allowed in both arms)
- Patients in the IVIG arm received one dose of solumedrol 40 mg IV methylprednisolone before each IVIG dose for 3 days

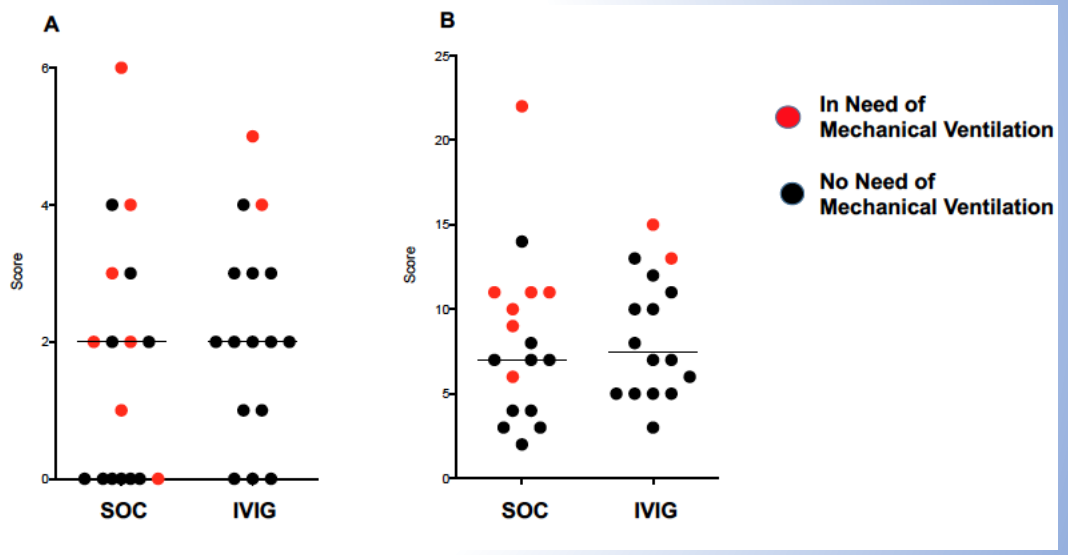
George Sakoulas, Matthew Geriak, Ravina Kullar, Kristina Greenwood, MacKenzie Habib, Anuja Vyas, Mitra Ghafourian, Venkata Naga Kiran Dintyala, Fadi Haddad medRxiv 2020.07.20.20157891; doi: https://doi.org/10.1101/2020.07.20.20157891

Enrolled patient demographics and characteristics

	IVIG (n=16)		SOC (n=17)	
Mean Age (yr)	54		54	
Median Age (yr)	58		51	
Male N (%)	10	(63)	10	(59)
Ethnicity N (%)*				
Hispanic	13	(81)	14	(82)
White	3	(19)	2	(12)
Mean BMI	32.8		34.8	
Admit to Enroll (days) Median (Range)	1.5 (0-8)		1 (0-4)	
Comorbidities N (%)				
Diabetes	6	(38)	6	(35)
Mean HgbA1c (%)	10.1		6.4	
Hypertension	4	(25)	7	(41)
Chronic Kidney Disease	0	(0)	1	(6)
Coronary Artery Disease	1	(6)	0	(0)
Congestive Heart Failure	1	(6)	1	(6)
Asthma/COPD	2	(12)	2	(12)
Current Smoker	1	(6)	1	(6)
Former Smoker	2	(12)	1	(6)
Immunocompromised	1	(6)	0	(0)
Other COVID-19 Therapies N (%)				
Remdesivir	8	(50)	9	(53)
Convalescent Plasma	2	(12)	3	(18)
Any Glucocorticoid Therapy	16**	(100)	10	(59)

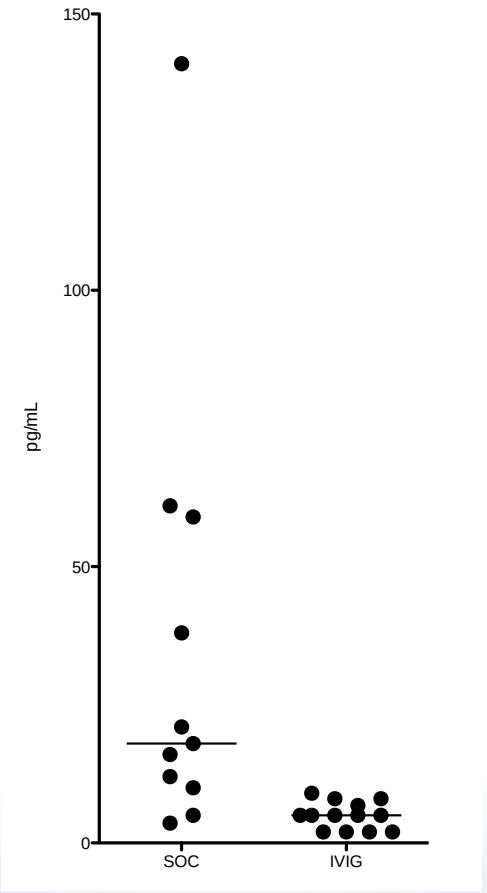
Intravenous Immunoglobulin (IVIG) Significantly Reduces Respiratory Morbidity in COVID-19 Pneumonia: A Prospective Randomized Trial

Distribution of Charlson comorbidity index (A) and APACHE 2 scores (B) of enrolled study subjects in both treatment arms, showing even distribution of chronic illness and acute severity of illness. Horizontal bars denote median values. Red points indicate patients who ultimately required a need for mechanical ventilation.



George Sakoulas, Matthew Geriak, Ravina Kullar, Kristina Greenwood, MacKenzie Habib, Anuja Vyas, Mitra Ghafourian, Venkata Naga Kiran Dintyala, Fadi Haddad medRxiv 2020.07.20.20157891; doi: https://doi.org/10.1101/2020.07.20.20157891

Serum interleukin-6 concentrations of a subset of SOC controls (n=11) and IVIG (n=13) treatment subjects obtained 24-48 hr after enrollment. Median IL-6 18 pg/mL in SOC vs 5 pg/mL in IVIG group are denoted by the horizontal bar (p=0.0012, Mann Whitney u test).



Summary

- COVID-19 pandemic remains a challenging public health crisis
- Race for therapeutics muddled with low quality evidence
- Antibody testing recommended later in the disease process
- Remdesivir has been shown beneficial
- Steroids recommended for moderate to severe COVID-19
- 5 days of Remdesivir is as good as 10 days
- Plasma may be beneficial
- More is needed to prove efficacy of therapeutics

Thanks

- George Sakoulas, MD
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