Scientific Appraisal of COVID-19 Literature – December 17, 2020 1455

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Article Title: ***Remdesivir for 5 or 10 Days in Patients with Severe Covid-19***

Source: NEJM

Clinical Field: Infectious Disease

Article Type: Clinical Study

Study Type: Non-Randomized Controlled Trial

Patient Group: Hospitalized COVID-19 patients with sat <94% on ambient air

Intervention: Remdesivir aither 5 or 10 days 200 mg x1 and then 100 mgx1

Reviewer	Stefan Jovinge (Dr J).	Vinu Perinjelil
Study Design	Minor Concerns	N/A
Study Design Concerns	Open label randomized trial. No Placebo control. All patients had pos test at least four days before randomization.	** This is an industry funded study, Gilead has developed remdisivir and this article is sponsored by Gilead. - only 44% of the patients in the 10 day completed the full course. treatment groups were not balanced in baseline disease characteristics - did not measure viral load of SAR-CoV-2 as treatment progressed - did not include patients on mechanical ventilation so difficult to assess full scope of benefit in that subset
Main Results	Prim endpoint clinical status on a 7 point scale day 14. Similar improvement in both groups when they were adjusted for inclusion status. Most common side effects	Remdisivir is an RNA polymerase inhibitor and early clinical trials have shown treatment success of this drug in COVID-19 patients. This study is a phase 3, open

	are nausea (9%), worsening of resp failure(8%), elevation of liver enzymes (7%) and constipation (7%). About 2/3 of pats who received 5 day treatment get at least 2 point improvement.	label, randomized and multi-center trial evaluating efficacy and treatment of remdisivir for 5 or 10 days in patients with severe disease. Patients were enrolled at 55 hospitals in the United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan between March 6 and March 26, 2020. Patients were randomly assigned in a 1:1 ratio to receive intravenous treatment withremdesivir for 5 days or 10 days. The randomization was not stratified. All the patients were to receive 200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 or 9 days. Of the 408 patients who were assessed for eligibility, 200 patients were assigned to receive a 5-day course of remdesivir and 197 a 10-day course. In all, 65% of patients who received a 5-day course of remdesivir showed a clinical improvement of at least 2 points on the 7-point ordinal scale at day 14 compared with 54% of patients who received a 10-day course (Table 2). After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a distribution in clinical status at day 14 that was similar to that of patients receiving a 5-day course. The median time to recovery was 10 days among patients in the 5-day group and 11 days among patients in the 10-day group. In multivariate analysis, characteristics associated with shorter time to clinical improvement were an age of less than 65 years, black and white race, a baseline oxygen requirement of low-flow oxygen or ambient air, no use of a biologic

		medication, and enrollment outside Italy. The most common adverse events overall were nausea (10% in the 5-day group vs. 9% in the 10-day group), acute respiratory failure (6% vs. 11%), increased ALT (6% vs. 8%), and constipation (7% in both groups). Better outcomes in patients treated with remdesivir for 5 days than in those treated for 10 days may have several causes. The 10-day group included a significantly higher percentage of patients in the most severe disease categories. No significant difference in efficacy between a 5-day course and a 10-day course of intravenous remdesivir treatment in patients with severe Covid-19 who did not require mechanical ventilation was shown. Supplies that are limited can be conserved with shorter duration of treatment in drugs like remdisivir.
Comments	n=397, The 20 day treatment group had worse clinical status at inclusion. NO CONTROL. Grades: 1: Death 2: Hospitalized, receiving invasive mechanical ventilation or ECMO 3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen 4: Hospitalized, requiring low-flow supplemental oxygen 5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care 6: Hospitalized, not requiring supplemental oxygen or ongoing medical care 7: Not hospitalized	-this study defends the use of remidisivir in the COVID population and strengthens the proof of concept with this drug. however careful evaluation of adverse events especially resp failure (11% in 10 day group) should be considered - report supports better outcomes when initiating remdisivir prior to intubation - only IV preparation/more seriously ill patients being evaluated, so outpatient use for more moderate cases to be developed

Article Title: ***Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China***

Source: JAMA

Clinical Field: Other

Article Type: _____

Study Type: Retrospective Study

Patient Group: Asymptomatic COVID19 patients

Intervention: None

Reviewer	Stefan Jovinge
Study Design	Minor Concerns
Study Design Concerns	This is a retrospective report out of asymtomatic (n=33) and (symptomatic (n=45) patients.
Main Results	The main differences between the groups were (IQR): - Asymtomatic were younger : 37 (26-45) vs 56 (34-63) p<0.001 - Higher proportion women among asymptomatic: 66.7 (31,1) p=0.002 - Duration of viral shedding was shorter: 8 (3- 12) p<0.001 - CT verified lung recovery was shorter 9(6-18) vs 15 (11-18) p=0.003 - Maximum difference CD4/mikrol was lower: 203 (170-304) vs 328 (145-506) - CD4 count during recovery
Comments	The asymptomatic patients had verified lung lesions. There should be an even milder asymptomatic group with different characteristics. No asymtomatic deaths

Article Title: ***Comparison of Estimated Rates of Coronavirus Disease 2019 (COVID-19) in Border Counties in Iowa Without a Stay-at-Home Order and Border Counties in Illinois With a Stay-at-Home Order***

Source: JAMA

Clinical Field: Other

Article Type: Clinical Report

Study Type: Retrospective Study

Patient Group: Population study

Intervention: Stay-at-home order vs no restriction

Reviewer	Stefan Jovinge	Kathrine Ann Kelly-Schuette
Study Design	Well Designed	Minor concerns
Study Design Concerns	Populations well matched (neigboring counties but only difference in vs stay-at-home order was implemented or not.	This analysis includes four states, CO, VA, OH MN. This a brief report that does not describe any variance in each state order or case information
Main Results	There was already an increase of in cases proportional of total cases in IO vs IL; No shutdown vs shutdown) Increases in no-shut down (w=wekk after shut-down order) w1 32.1%, w2 38%, w3 15.2%, w4 17.8%, w5 30.0%, w6 30.4%)	After mandatory stay at home orders observed hospitalizations consistently fell outside of the 95% prediction bands of the projected growth curve. In MN, the projected hospitalizations were 988 and fell to 361, 5 days after the median effective date of the stay at home order. In VA, projected was 2335 to 1048 actual hospitalizations.
Comments	Well-designed observational/epidemiological report evidencing the effect of shutdown.	This article describes predicted cumulative COVID-19 hospitalization data in four states with stay at home orders. Astutely noted is that many factors decreased virus spread. For example, school closing, pandemic awareness and social distancing.

Article Title: ***Remdesivir for the Treatment of Covid-19 - Preliminary Report***

Source: NEJM

Clinical Field: Infectious Disease

Article Type: Clinical Study

Study Type: Proper RCT

Patient Group: Adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection

Intervention: A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo)

Reviewer	Stefan Jovinge
Study Design	Well Designed
Study Design Concerns	_____
Main Results	In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease

	severity). Kaplan-Meier estimates of mortality were 6.7% with Pemdesivir and 11.9% with placebo by day 15 and 11.4% with Remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events: 131 of the 532 patients who received Remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).
Comments	Faster recovery on remdesivir shown in a multicenter RCT. Borderline significance for mortality benefit for Remdesivir.

Article Title: ***Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young***

Source: New England Journal of Medicine

Clinical Field: Infectious Disease

Article Type: _____

Study Type: Case Report

Patient Group: Five patients with Stroke < age of 50

Intervention: _____

Reviewer	Stefan Jovinge
Study Design	N/A
Study Design Concerns	Only a case series of five patients.
Main Results	Five patients, all younger than 50, had a NIHSS score 13-19 and verified by CT to have ischemic stroke were positive for SARS-CoV2 infection. All had complete resolution of thrombus by only anticoagulation.
Comments	Interesting case series: Stroke among younger persons without risk factors, quick resolution of the stroke on ac treatment

Article Title: ***Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates***

Source: New England Journal of Medicine

Clinical Field: Infectious Disease

Article Type: _____

Study Type: Proper RCT

Patient Group: Healthy adults

Intervention: Liquid nanoparticle-formulated mRNA coding fopr Spike protein of SARS-CoV2

Reviewer	Stefan Jovinge
Study Design	Minor Concerns
Study Design Concerns	Small study n(vaccine)=155 and n(placebo)=39
Main Results	Both age groups and vaccines elicited an immunization as evidenced Ab titer that was higher than what was found in convalescent serum. Safe and Two doses of vaccine day 1 and 21 give immunity day 28, higher thatn convalescence serum.
Comments	Two age groups 18-55 and 65-85. Key exclusions: HIV, HCV, HBV, immunocomprimised, autoimmune, pervious verified COVID-19. Pain at the injection site main side effect.

Article Title: ***Clinical Characteristics of Patients With Coronavirus Disease 2019 (COVID-19) Receiving Emergency Medical Services in King County, Washington***

Source: JAMA Network Open

Clinical Field: Infectious Disease

Article Type: Clinical Report

Study Type: Retrospective Study

Patient Group: COVID-19 patients that required EMS (911) and were found to be COVID-19 positive

Intervention: Observational

Reviewer	_____
Study Design	Major Concerns
Study Design Concerns	Small observational study n=147
Main Results	Based on EMS evaluation, 43 of 147 encounters (29.3%) had no symptoms of fever, cough, or shortness of breath. Mortality among the study cohort was 52.4% (65 patients). The Cohort was split by whether the patient was a resident of a long-term facility (LTF) or not. The only characteristics that were significantly different between these cohorts (LTF vs not LTF)were: Age (80.7 vs 71.4), Dementia (16 vs 7), Kidney disease (10.7 vs 1.5) and MOrtality (73.2 vs 35.3)

Comments	Notable is that 1. 1/3 of the patients had no fever. 2. The majority (59.6%) had no fever

Article Title: Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

Source: New England Journal of Medicine

Clinical Field: Infectious Disease

Article Type: Clinical Study

Study Type: Proper RCT

Patient Group: Patients hospitalized with COVID19

Intervention: Remdesivir+Placebo vs Baricitinib

Reviewer	Stefan Jovinge
Study Design	Well Designed
Study Design Concerns	_____
Main Results	A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Overall: Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6) Patients not on ventilator: Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). 28-day mortality: 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09)
Comments	Combination therapy on average a 8 day shorter recovery. The combination therapy trended with borderline significance a lesser mortality at a prize of less serious adverse effects in the combination group.

Article Title: ***Estimated SARS-CoV-2 Seroprevalence in the US as of September 2020***

Source: JAMA Internal Medicine

Clinical Field: Infectious Disease

Article Type: _____

Study Type: Retrospective Study

Patient Group: Population

Intervention: Observational

Reviewer	Stefan Jovinge
Study Design	Minor Concerns
Study Design Concerns	Study based on residual or left over plasma. The estimate will be biased towards people in contact with healthcare. Ab titer as measure of exposure. Some patients have been reported to have either a weak immune response and to be reinfected but also others have been reported to have a T-cell mediated response. Thes could not be detected in the assays performed. Thus, the estimate is an estimate of the people in contact with healthcare rather than the overall population.
Main Results	NY was the state with the highest proportion of detectable serimmunity, around 20%.
Comments	With all its weaknesses still an important read out. It is indicative that we in September 2020 were far from the estimated need of herd immunity to stop the community spread (60-70%). The state with the lowest community immunity was ND with less than 1% seropositivity. Interestingly the first state with confirmed cases, WA had a seropositivity of about 2-5%.

Article Title: ***Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US***

Source: Health Affairs

Clinical Field: Other

Article Type: Clinical Report

Study Type: Retrospective Study

Patient Group: Population

Intervention: Facemask or not

Reviewer	Stefan Jovinge
Study Design	_____

Study Design Concerns	This is a retrospective comparison of states that require facemasks vs those who don't. As it is a real-time experience and support what happens after a governmental order on facemasks and as such as a decision support for politicians it doesn't strictly test the effect of facemasks. In other words it tests the effect of a decision and not the use per se. This study does also not take into account that counties might regulate this in states that don't - these states were accounted as not mandating facemask even if some counties would mandate it.
Main Results	Mandating face mask use in public is associated with a decline in the daily COVID-19 growth rate by 0.9, 1.1, 1.4, 1.7, and 2.0 percentage points in 1-5, 6-10, 11-15, 16-20, and 21 or more days after state face mask orders were signed, respectively. Estimates suggest that as a result of the implementation of these mandates, more than 200,000 COVID-19 cases were averted by May 22, 2020
Comments	Even there are obvious weaknesses in the cleanliness of the face mask use between groups, some don't comply but mostly because some use it while it is not being mandated either because facilities or counties mandate it, despite that the state don't, or that individuals choose to. With all these weaknesses it is reasonable to assume that