Aug. 24, 2020

COVID-19 - Convalescent Plasma, Remdesivir Optimal Patient Population and With or Without Dexamethasone, IDSA Guidance on Serologies, and Antigen Tests

Good morning everyone

Today I start with a short commentary on the EUA taken by the FDA on convalescent plasma. It is important to focus clinical trial capacity on the most promising treatments. Faster enrollment is impacted by competing for patients which impacts power and our ability to quickly answer important clinical questions. We must do better. The second article is a recent publication on remdesivir. This trial raises important questions. First the optimal patient population to treat is unclear and what is the relative effect of the drug if given in the presence of dexamethasone or other steroids? The third review is the revise IDSA guidance on serologies. The IDSA panel identified 3 potential uses for serologies: 1) evaluation of patients with clinical suspicion for COVID-19 when molecular diagnostics are negative and at least 2 weeks have passed since symptom onset. 2) assessment of MIS-C, and 3) conducting serosurveillance. The fourth review is the update from CDC on antigen testing for SARS-CoV-2. Antigen tests for SARS-CoV-2 are generally less sensitive than viral tests that detect nucleic acid using PCR. Studies have shown that antigen levels in some patients who have been symptomatic for more than five days may drop below the limit of detection of the test. The last review is another observational trial on famotidine. This was a very small trial and there was no placebo. Nonetheless, I think we should continue to monitor, but we clearly need a RCT.

Have a great day

Ed

Emergency Authorization for Convalescent Plasma

Convalescent plasma has been granted emergency use authorization for treating hospitalized adults with COVID-19, the FDA announced yesterday. This follows a study from the Mayo Clinic that suggested a mortality benefit with convalescent plasma. In 35,000 patients hospitalized with COVID-19, 7-day mortality was 9% in those transfused within 3 days of their diagnosis, and 12% if transfused 4 or more days later. Use of convalescent plasma with higher antibody levels was also associated with lower mortality than plasma with lower antibody levels, with a roughly 35% reduction in overall mortality if given within 3 days.[review last week in the Daily Briefing] The study was <u>not</u> a RCT and has not undergone peer review. Last week, top NIH officials believed the current data were not strong enough to support a EUA.

Comment: The FDA granted EUA despite concerns from scientists at the NIH about the limits of the evidence. Obviously, the science would be stronger if patients had participated in a RCT. We should expand trial networks by running large practical trials like the UK's RECOVERY Trial. Data collection should be limited to the variables most important for measuring whether a treatment is safe and effective. By limiting the data sets this will allow more hospitals to participate without straining healthcare systems. It is important to focus clinical trial capacity on the most promising treatments. Faster enrollment is impacted by competing for patients. There are too many poorly designed trials that take away patients that could be enrolled in better trials. It is time that we collaborate rather than compete for patients to better serve science and our patients. The TMC initiative[if successful] is an example of how communities could cooperate and share data sets to ask and answer critical relevant questions regarding this pandemic in a much shorter period of time.

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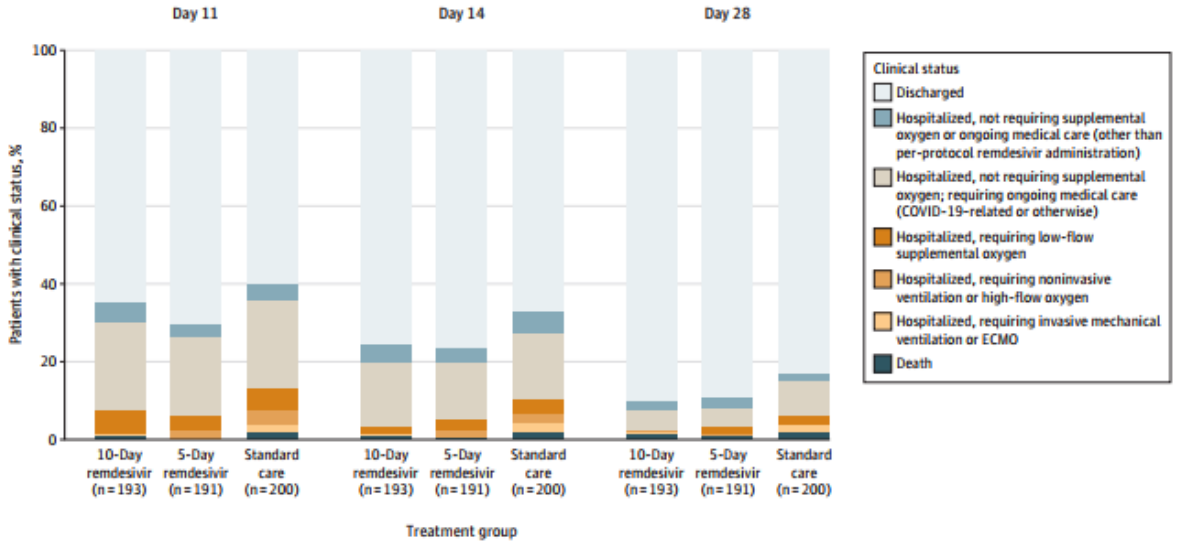
Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19 JAMA published online August 21, 2020 suggested by Murad Aslam

This is an open-label trial of hospitalized patients with confirmed SARS-CoV-2 infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). The primary end point was clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7). Differences between remdesivir treatment groups and standard care were calculated using proportional odds models and expressed as odds ratios.

Median length of treatment was 5 days for patients in the 5-day remdesivir group and 6 days for patients in the 10-day remdesivir group. On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; *P* = .02). The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different (*P* = .18 by Wilcoxon rank sum test). By day 28, 9 patients had died: 2 (1%) in the 5-day remdesivir group, 3 (2%) in the 10-day remdesivir group, and 4 (2%) in the standard care group. Although patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, the difference was of uncertain clinical importance. To further confuse by day 14, both treatment groups were significantly better than standard care. The clinical importance of this finding is uncertain.



Comment: There are now 3 RCTs of remdesivir in hospitalized patients with differing results, raising the question of whether the discrepancies are artifacts of study design choices, including patient populations, or whether the drug is less efficacious than hoped.

ACTT-1 trial was larger and may have been better powered to see small differences. All 3 RCTs required evidence of pulmonary involvement. However, ACTT-1 and the study by Wang [Lancet 2020] recruited patients who required supplemental oxygen or ventilatory support whereas this trial included patients who did not require oxygen (although 15% had deteriorated to the point that oxygen was required between enrollment and study initiation).The benefit observed in ACTT-1 was reported as confined to patients requiring only low-flow supplemental. Thus, it is not immediately clear that the study populations alone are adequately different to explain differences in results across trials. Moreover, it is plausible that antiviral therapy is more efficacious if started sooner, and therefore

targeting moderate rather than severe disease would be a reasonable approach. All 3 RCTs used some variation of an ordinal scale that ranges from recovery through increasing levels of ongoing hospital care to death. This trial measured the primary outcome at study day 11, ACTT-1 and the study by Wang used the scale to assess time to recovery.
OK what does all this mean? [I am not sure] Nonetheless, in aggregate, important questions remain regarding the efficacy of remdesivir. First, the optimal patient population to treat is unclear. Second, the effect on discrete clinical outcomes is unclear. Third, the relative effect of the drug if given in the presence of dexamethasone or other corticosteroids is unclear since this trial started before the RECOVERY trial publication. The trial was not designed to cross-randomize by treatment interactions between remdesivir and steroids. Given remdesivir's cost compared to steroids there is an urgent need to conduct a large RCT to address these uncertainties.

Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Serologic Testing updated August 18, 2020 suggest by Cesar Arias

Current assays use a variety of technologies, measure different classes of immunoglobulin or immunoglobulin combinations and detect antibodies directed against different portions of the virus. Based on available evidence, detection of anti-SARS-CoV-2 antibodies may be useful for confirming the presence of current or past infection in selected situations. The panel identified three potential indications for serologic testing including: 1) evaluation of patients with a high clinical suspicion for COVID-19 when molecular diagnostic testing is negative and at least two weeks have passed since symptom onset; 2) assessment of multisystem inflammatory syndrome in children; and 3) for conducting serosurveillance studies. In general, IgM tests tend to have lower sensitivity to detect past
infection than IgG or total antibody tests. Assays designed to detect and differentiate IgM and IgG in combination, where the detection of either IgM or IgG is used to define a positive test result, and IgA tests tend to have lower specificity to detect past infection compared to IgG only or total antibody tests.

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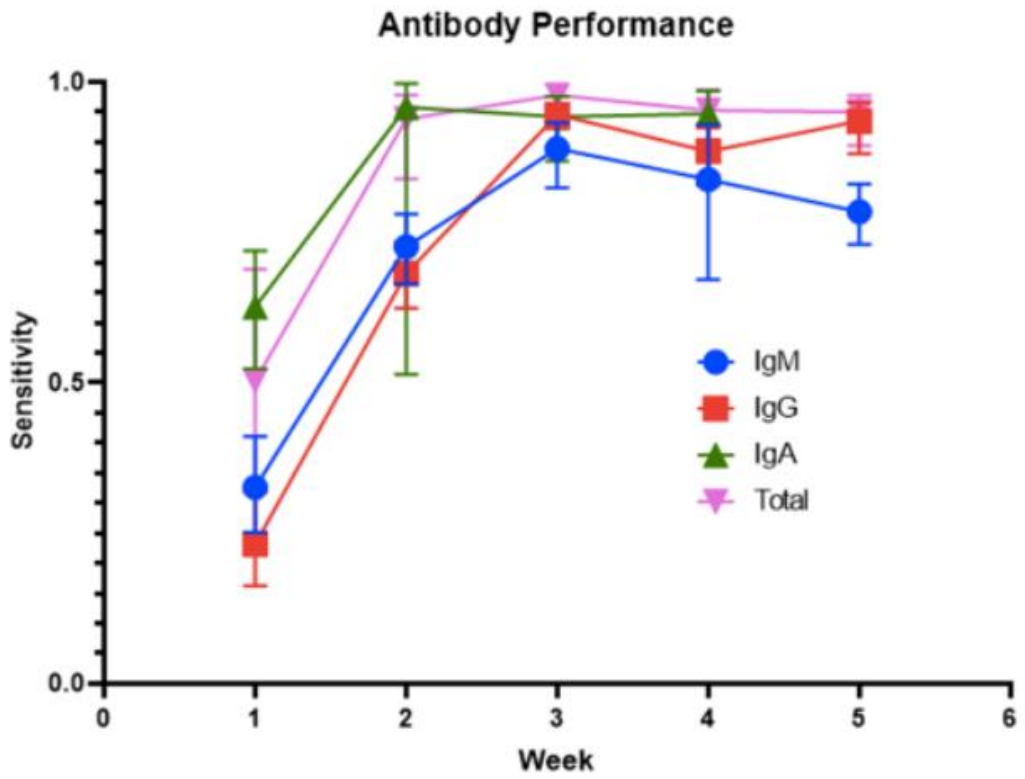

Below are a few highlights:

Recommendation 1: The IDSA panel suggests against using serologic testing to diagnose SARS-CoV-2 infection during the first two weeks (14 days) following symptom onset (conditional recommendation, very low certainty of evidence).

Recommendation 2: When SARS-CoV-2 infection requires laboratory confirmation for clinical or epidemiological purposes, the IDSA panel suggests testing for SARS-CoV-2 IgG or total antibody three to four weeks after symptom onset to detect evidence of past SARS-CoV-2 infection (conditional recommendation, very low certainty of evidence)

Recommendation 3: The IDSA panel makes no recommendation either for or against using IgM antibodies to detect evidence of past SARS-CoV-2 infection (conditional recommendation, very low certainty of evidence)

Recommendation 6: The IDSA panel suggests using IgG antibody to provide evidence of COVID-19 infection in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT testing (weak recommendation, very low certainty of evidence)

Recommendation 7: In pediatric patients with multisystem inflammatory syndrome, the IDSA panel suggests using both IgG antibody and NAAT to provide evidence of current or past COVID-19 infection (strong recommendation, very low certainty of evidence)

CDC Interim Guidance for Rapid Antigen Testing for SARS-CoV-2 August 16, 2020

There are five populations for which SARS-CoV-2 testing with viral tests (i.e., nucleic acid or antigen tests) is appropriate per CDC:

1. Individuals with signs or symptoms consistent with COVID-19

2. Asymptomatic individuals with recent known or suspected exposure to SARS-CoV-2 to control transmission
3. Asymptomatic individuals without known or suspected exposure to SARS-CoV-2 for early identification in special settings
4. Individuals being tested to determine resolution of infection (i.e., test-based strategy for Discontinuation of Transmission-based Precautions, HCP Return to Work, and Discontinuation of Home Isolation), however CDC has moved to a symptoms-based approach for most patients.
5. Individuals being tested for purposes of public health surveillance for SARS-CoV-2

Antigen tests for SARS-CoV-2 are generally less sensitive than viral tests that detect nucleic acid using PCR. Antigen tests, however, are relatively inexpensive and can be used at the point-of-care. The currently authorized devices return results in approximately 15 minutes. Proper interpretation of antigen test results is important for accurate clinical management of patients with suspected COVID-19. The clinical performance of rapid antigen diagnostic tests largely depends on the circumstances in which they are used. Rapid antigen tests are particularly helpful if the person is tested in the early stages of infection with SARS-CoV-2 when viral load is generally highest. There are limited data to guide the use of rapid antigen tests as screening tests on asymptomatic persons to detect or exclude COVID-19.

	RT-PCR Tests	Antigen Tests
Intended Use	Detect current infection	Detect current infection
Analyte Detected	Viral RNA	Viral Antigens
Specimen Type(s)	Nasal Swab, Sputum, Saliva	Nasal Swab
Sensitivity	High	Moderate
Specificity	High	High
Test Complexity	Varies	Relatively easy to use
Authorized for Use at the Point-of-Care	Most devices are not, some devices are	Yes
Turnaround Time	Ranges from 15 minutes to >2 days	Approximately 15 minutes
Cost/Test	Moderate	Low

Comment: Clinicians should understand antigen test performance characteristics in order to recognize potentially false negative or false positive results and to guide patient management. Studies have shown that antigen levels in some patients who have been symptomatic for more than five days may drop below the limit of detection of the test. This may cause the test to return a negative result, while a more sensitive test, such as PCR, may return a positive result. If the patient has all the signature characteristics of SARS-CoV-2 infection and has a negative AG test, repeat testing with traditional PCR should be performed.

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Impact of Famotidime on Clinical Outcomes of Hospitalized COVI-19 Patients **Am** J Gastro published online August 21, 2020

This is a retrospective, propensity-matched observational trial to compare patients hospitalized with COVID-19 who did not receive famotidine versus patients who were treated with famotidine. Patients who received famotidine were younger but did not differ with respect to demographics or comorbidities. Use of famotidine was associated with decrease mortality (OR 0.37, p=0.021) as well as combined death or intubation (OR 0.47, p=0.040). Propensity score matching to adjust for age did not alter the effect on either outcome. In addition, patients who received famotidine had lower levels of severity markers for CRP and PCT, but non-significant mean ferritin levels. Logistic regression analysis demonstrated the famotidine was an independent predictor of both lower mortality and combined death/intubation, while older age, BMI>30 kg/m^2, chronic kidney disease, and higher neutrophil-lymphocyte ratio were all predictors or both adverse outcomes.

Comment: This is a single center retrospective observational trial. Therefore, the results should be interpreted with caution. Freedberg et al(pre-proof Gastroenterology) published a retrospective cohort trial of famotidine vs no famotidine which showed reduced risk for death and intubations.[n=1620] Janowitz (Gut published online) gave high-dose famotidine given as outpatient.[review in Briefing several weeks back] No patients were hospitalized. This was a very small trial and there was no placebo. Bottom line there is insufficient data on the safety and efficacy of famotidine in COVID-19 patients.