COVID-19 UPDATES
April 13, 2020

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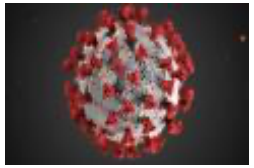
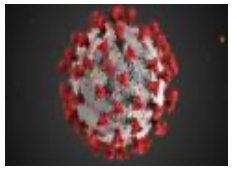
Cherokee Nation Health Services

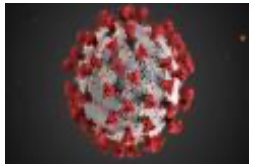


Infection Control: Vaporized Hydrogen Peroxide Gas Plasma Sterilization



- The FDA granted the EUA to Advanced Sterilization Products (ASP) for the STERRAD Sterilization Cycles (STERRAD 100S Cycle, STERRAD NX Standard Cycle, or STERRAD 100NX Express Cycle), which uses vaporized hydrogen peroxide gas plasma sterilization. There are approximately 9,930 STERRAD Sterilization systems in approximately 6,300 hospitals across the U.S. STERRAD 100S Cycle, STERRAD NX Standard Cycle and STERRAD 100NX Express Cycle vary in reprocessing times from 55 minutes, to 28 minutes, and 24 minutes. Each can reprocess approximately 480 respirators per day.

Treatment



Day 1-9 disease is probably viral mediated

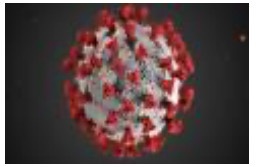
- ACE/ARB: RCT ongoing
- Remdesevir: RCT results pending
- Favipriavir:
  - 1 open label control study in patients without hypoxemia revealed faster viral clearance and radiologic improvement vs Lopinavir/ritonavir (Cai et al Engineering 2020)
- Lopinavir/Ritonavir
  - 1 published RCT did not reveal benefits
- Hydroxychloroquine (HC)
  - 1 open label study of 36 patients showed higher rates of undetectable viral RNA at day 6 that improved with the addition of azithromycin (Gautret et al International Journal of Antimicrobial Agents)
  - 1 randomized trial of 30 adults in Shanghai reported did not show higher rates of viral clearance (Chen et al. Journal of Zheijiang University 2020)
  - 1 unpublished randomized clinical trial reported symptom and radiological improvement as well as lower likelihood of progression in patients without hypoxemia (Chen)

Day 10 onwards disease is probably immune mediated

- IL-6 receptor blockers
  - Tocilizumab, Sarilumab and siltuximab
- Glucocorticoids
  - Not to be used in non critically ill patients unless there is a separate evidence-based indication (CDC)
  - ARDS: Conflicting evidence
- Plasma from convalescent donors (JAMA March 2020)
  - March 24, FDA announced that convalescent plasma may be collected from recovered COVID-19 patients and considered for emergency administration under a single patient emergency Investigational New Drug application for individual patients with life threateningly severe disease but may be used in individual patients outside of clinical trial.*
  - Hyperimmune globulin from convalescent donors

*Complete FDA form 3926) or if urgent call FDA office of Emergency Operations at 1-866-300-4374)

Key Points Related to the Interplay between Covid-19 and the Renin–Angiotensin–Aldosterone System



- ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic

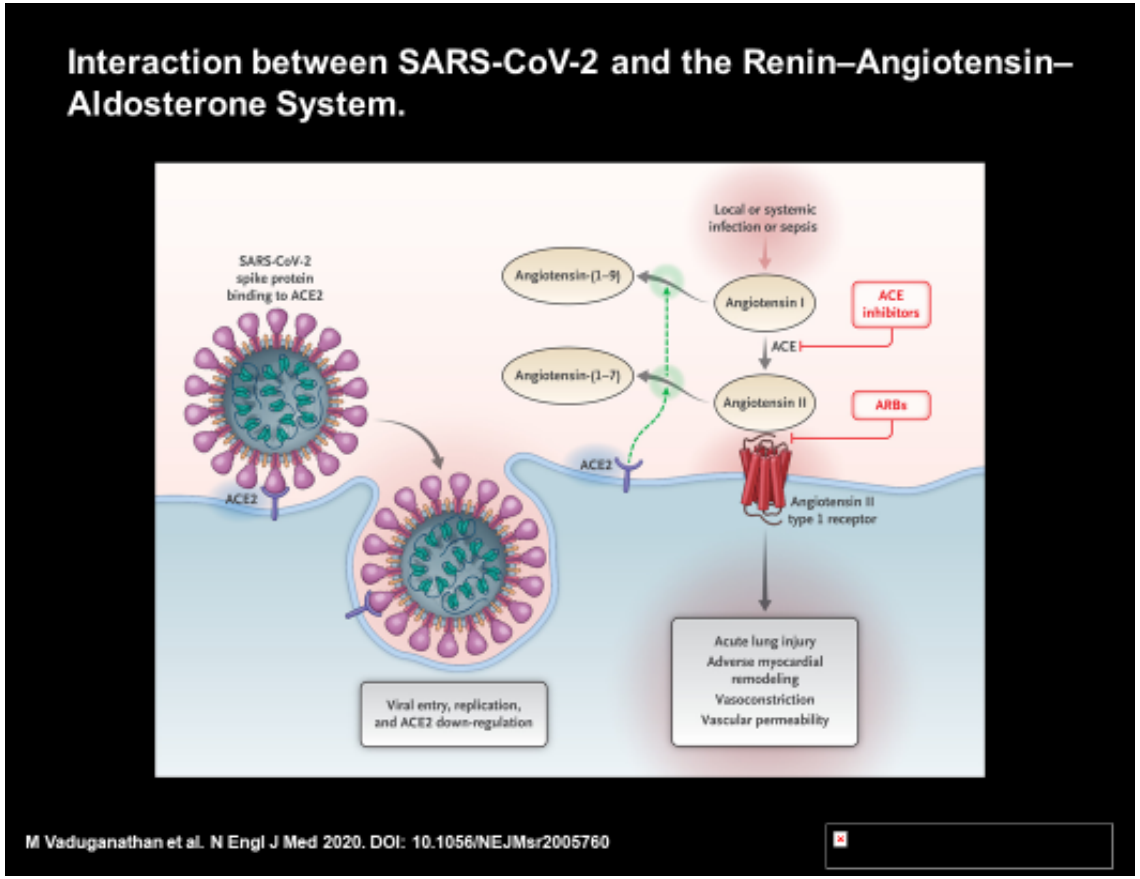
- Select preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with Covid-19

- Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19

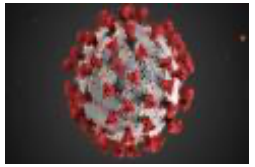
- Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19

- Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes

- Until further data are available, we think that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or with Covid-19



Compassionate Use of Remdesivir for Patients with Severe Covid-19



- Multicenter international study of patients receiving remdesevir between 1/25/2020 and 3/7/2020
- 61 patients with severe COVID-19 (Oxygen saturation <94%), only 53 were analyzed
  - 54% on mechanical ventilation
- Remdesevir administered IV, 200 mg on day 1 and 100 mg on days 2-9
- No control group
- Treatment duration 10 days
- Median follow-up 18 days

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

J Grein et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2007016

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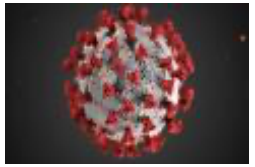

Oxygen-Support Status at Baseline and after Treatment.

No. of Patients in Oxygen-Support Group after Treatment (%)		No. of Patients in Oxygen-Support Group at Baseline (%)			
		Invasive (N=34)	Noninvasive (N=7)	Low-flow oxygen (N=10)	Ambient air (N=2)
Category on ordinal scale →		5	4	3	2
Death	6	6 (18)	1 (14)	0	0
Invasive	5	9 (26)	1 (14)	0	0
Noninvasive	4	3 (9)	0	0	0
Low-flow oxygen	3	0	0	0	0
Ambient air	2	8 (24)	0	0	0
Discharged	1	8 (24)	5 (71)	10 (100)	2 (100)
Improvement		**19 (56)**	**5 (71)**	**10 (100)**	**2 (100)**
↑ Category on ordinal scale					

Figure 1. Oxygen-Support Status at Baseline and after Treatment. For each oxygen-support category, percentages were calculated with the number of patients at baseline as the denominator. Improvement (blue cells), no change (beige) and worsening (gray) in oxygen-support status are shown. Invasive ventilation includes invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or both. Noninvasive ventilation includes nasal high-flow oxygen therapy, noninvasive positive pressure ventilation (NIPPV), or both.

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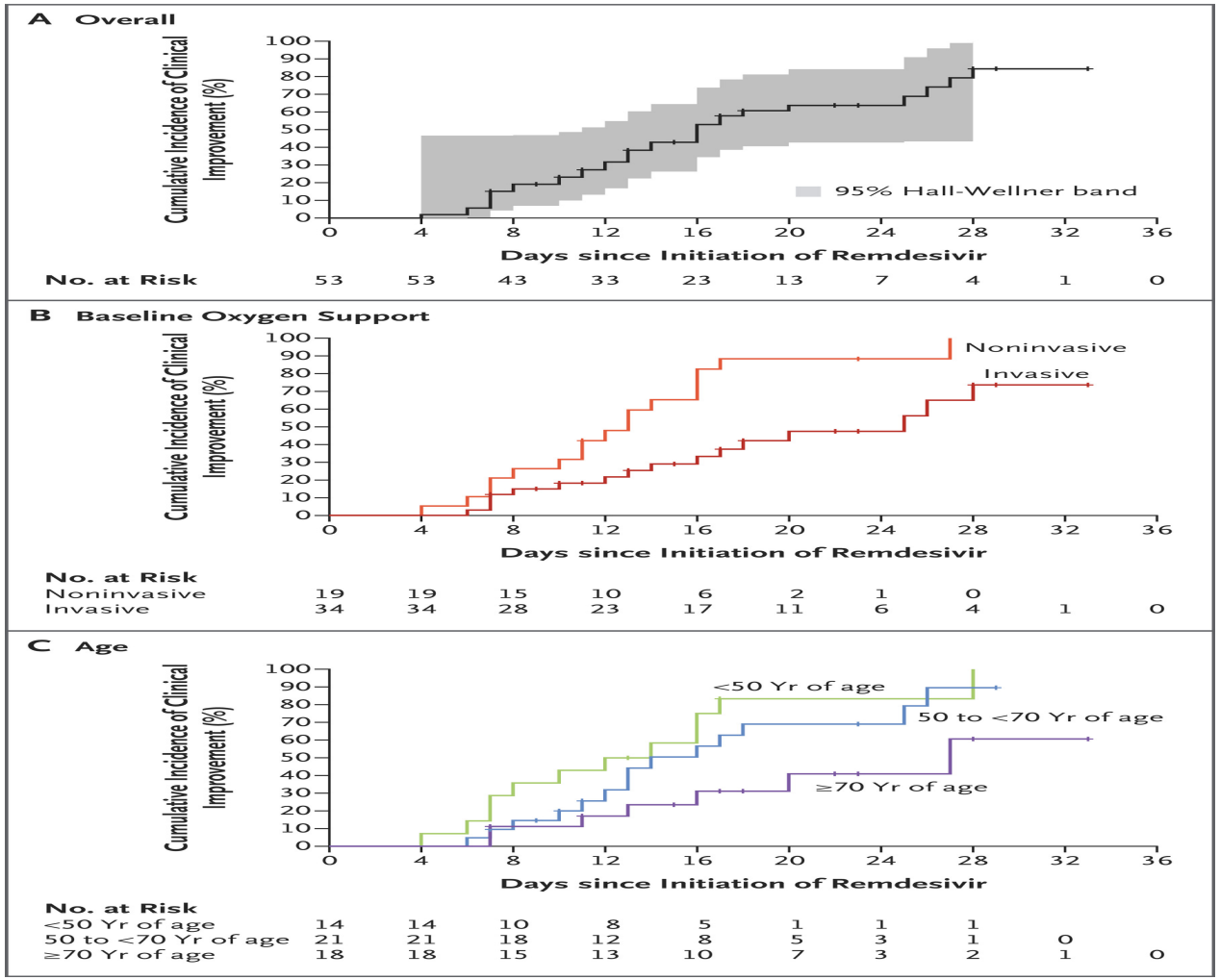

Figure 3. Cumulative Incidence of Clinical Improvement from Baseline to Day 36. Clinical improvement is shown in the full cohort, in the cohort stratified according to ventilation status at baseline, and in the cohort stratified by age.

Conclusions:

"Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy"

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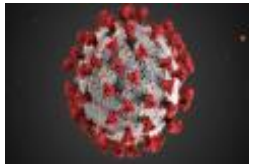
Infectious Disease Society of America COVID-19 treatment Guidelines



- **Recommendation 1**. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)
- **Recommendation 2.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)
- **Recommendation 3.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)
- **Recommendation 4.** Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)
- **Recommendation 5**. Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)
- **Recommendation 6.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)
- **Recommendation 7.** Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)