Good morning. First, I hope everyone has a relaxing and safe Labor Day weekend.

Today's Briefing is focused on the 4 articles published online in JAMA a few days ago on steroids. These articles and the impact of the RECOVERY dexamethasone trial brought up a theme I have tried to articulate in several editorials in the Daily Briefing. So, I hope you will take the time to read my comments below and feel free to respond. I added I thought an interesting article from Indiana on the infection fatality ratio among noninstitutional persons.

Ed

VII editorial and comments on steroids: The efforts of the clinical trial groups to initiate and conduct of high-quality trials in the midst of a pandemic is challenging at best. The UK has had a long-standing commitment to large rapid randomized trials. The US in general has preferred smaller and more complex trials. In mid-March researchers in the UK began a randomized evaluation of Covid-19 therapies, known as RECOVERY, that involved almost every hospital in the nation. The goal was to conduct large, rapid, and simple randomized trials to define standard treatment. Some 12,000 patients were quickly randomized — that is, assigned by chance to receive different treatments [they focused on 6 trials] — and within 100 days of the effort's start, researchers made three major discoveries that transformed Covid-19 care worldwide. They found no benefit from the use of HCQ or lopinavir-ritonavir; however, they found dexamethasone reduce mortality up to 33% in patients who require oxygen. This finding has changed the standard of care which is why trials that were ongoing when the results were released were discontinued (see below). The other strength of the British effort was to incorporate research as part of everyday clinical care in hospitals. They were aided by a common NHS database. They also had a national system of research nurses who could be rapidly deployed. An additional fact worth noting, the RECOVERY effort was inexpensive supported by a grant from Oxford for ~2.8 million.

Despite these recent studies many clinically important questions remain. What is the optimal dosing of steroids? Should corticosteroid administration be individualized, with initiation, dosing, and duration guided by clinical response or biomarkers, such as C-reactive protein and LDH? Does inflammation rebound after discontinuing of steroids observed in some patients require tapering them to improve outcomes? Should remdesivir or other potentially active therapeutics (? convalescent plasma) be administered with corticosteroids?

The history of medicine has many examples of promising therapies that have later proven to be ineffective and sometimes harmful which is why we need well designed clinical trials. In our haste to do something, we have delayed finding answers that we need. Now almost 6 months into the pandemic we have only a small minority enrolled in robust clinical trials in the US. We have published only a few breakthrough studies on treatments. Even the most important US study to date showed that remdesivir could reduce time to recovery but had too few patients enrolled to demonstrate a statistically significant reduction in mortality. Many studies around the world including the studies reviewed below were unable to enroll an adequate sample size and therefore were underpowered. The reason the studies below did not reach enrollment was the significant impact of the RECOVERY Dexamethasone trial results. The RECOVERY trials are an example of how science can advance and is critical in the midst of a pandemic. What we have seen are numerous underpowered RCTs and/or observational trials. The fractured nature of our health care system means that multiple different institutions are working in silos trying to ramp up their own trials and competing for patients rather than collaborating.

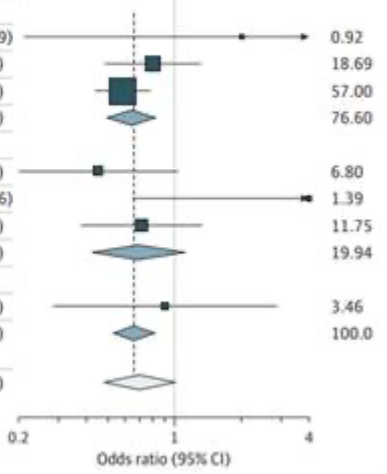
What the UK has done is not beyond what we can do in the US. We have health networks, especially if combined, with comprehensive patient data on a meaningfully large scale. The trials required established research infrastructure, dedicated study teams, and clinical equipoise that was often absent during the pandemic. By demonstration of the ability of networks to quickly launch and complete randomized trials, even during an unprecedented clinical burden; from the willingness of networks to collaborate and join forces to conduct important clinical trials more rapidly; and from the high level of coordination and data sharing facilitated by organizations like WHO and UK, this will lead to more definitively and efficiently answers to important clinical and research questions in the treatment of COVID-19. With these efforts and with rigorous evidence comes better treatments, reduced morbidity, and mortality. In summary we need to awaken our nation's clinical research excellence.

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19 A Meta-analysis
JAMA published online September 2, 2020
Prospective meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The trials were conducted in 12 countries from February 26, 2020, to June 9, 2020, and the date of final follow-up was July 6, 2020. Pooled data were aggregated from the individual trials, overall, and in predefined subgroups. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool.

Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients). The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; $P < .001$ based on a fixed-effect meta-analysis). Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



Effect of Hydrocortisone on Mortality and Organ Support in Patients with Severe COVID-19 The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

JAMA published online September 2, 2020

Between March 9 and June 17, 2020, 614 adult patients with suspected or confirmed COVID-19 were enrolled and randomized within at least 1 domain following admission to an intensive care unit (ICU) for respiratory or cardiovascular organ support at 121 sites in 8 countries. Of these, 403 were randomized to open-label interventions within the corticosteroid domain. The corticosteroid domain randomized participants to a fixed 7-day course of intravenous hydrocortisone (50 mg or 100 mg every 6 hours) (n = 143), a shock-dependent course (50 mg every 6 hours when shock was clinically evident) (n = 152), or no hydrocortisone (n = 108). Enrollment was halted after results from RECOVERY were released. The primary end point was organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who died were assigned –1 day. The primary analysis was a bayesian cumulative logistic model that included all patients enrolled with severe COVID-19, adjusting for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility. Superiority was defined as the posterior probability of an odds ratio greater than 1 (threshold for trial conclusion of superiority >99%). The bayesian model found that fixed-dose hydrocortisone (93% probability), as well as shock-dependent hydrocortisone (80% probability), were both likely superior to no hydrocortisone, but data were insufficient to confirm a single optimal regimen. In addition, the probabilities did not meet the prespecified probabilities to define success, but trends in terms of outcomes were positive for hydrocortisone, but enrollment was halted after results from RECOVERY were released.

Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients with Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 The CoDEX Randomized Clinical Trial

JAMA published online September 2, 2020

The objective of this study was to determine whether intravenous dexamethasone increases the number of ventilator-free days among patients with COVID-19–associated ARDS. Secondary outcomes were all-cause mortality at 28 days. Multicenter, randomized, open-label, clinical trial conducted in 41 intensive care units (ICUs) in Brazil. Patients with COVID-19 and moderate to severe ARDS, according to the Berlin definition, were enrolled from April 17 to June 23, 2020. Final follow-up was completed on July 21, 2020. The trial was stopped early following publication of the RECOVERY trial before reaching the planned sample size of 350 patients.

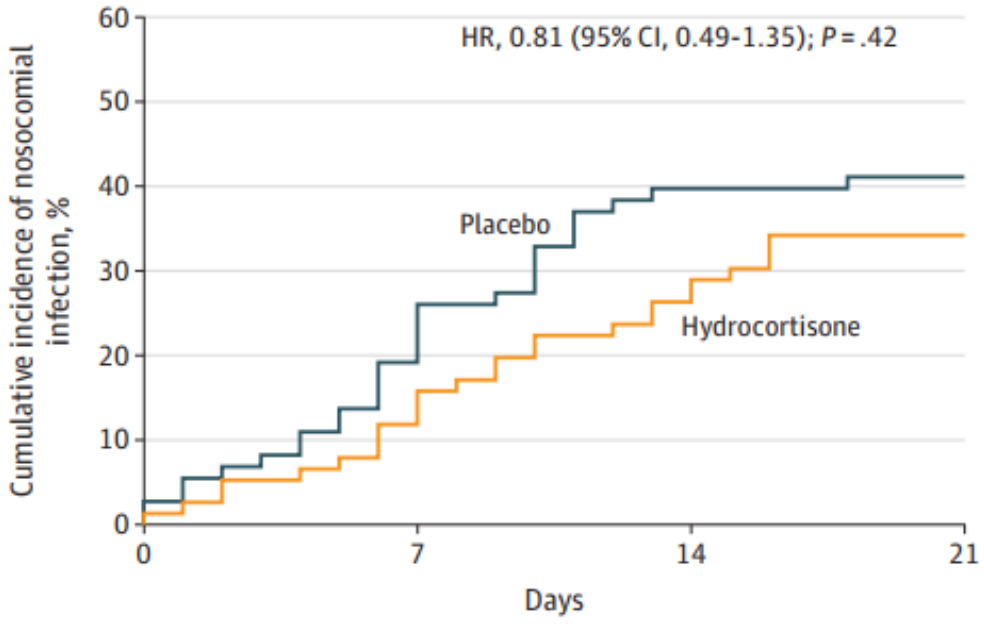
Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; *P* = .04). At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, -1.16; 95% CI, -1.94 to -0.38; *P* = .004). However, there was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days. Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections, 47 (31.1%) vs 42 (28.3%) needed insulin for glucose control [experience with obese diabetic patients has resulted in increased insulin to control glucose], and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events. While 28-day mortality was not significantly different between patients randomized to corticosteroids vs usual care (56.3% vs 61.5%, *P* = .83), stopping the study early when RECOVERY results were announced resulted in a sample size that was underpowered to adequately evaluate the effect of corticosteroids on mortality.

Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19 A Randomized Clinical Trial

JAMA published online September 2, 2020

This study was designed to determine the effect of hydrocortisone on treatment failure on day 21 in critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and acute respiratory failure. This was a multicenter randomized double-blind sequential trial conducted in France, with interim analyses planned every 50 patients. Patients admitted to the intensive care unit (ICU) for COVID-19–related acute respiratory failure were enrolled from March 7 to June 1, 2020, with last follow-up on June 29, 2020. Patients were randomized to receive low-dose hydrocortisone (n = 76) or placebo (n = 73). The primary outcome, treatment failure on day 21, was defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy. Prespecified secondary outcomes included the need for tracheal intubation (among patients not intubated at baseline); cumulative incidences (until day 21) of prone position sessions, extracorporeal membrane oxygenation, and inhaled nitric oxide; PaO2:FIO2 ratio measured daily from day 1 to day 7, then on days 14 and 21; and the proportion of patients with secondary infections during their ICU stay.

The study was stopped after 149 patients (mean age, 62.2 years; 30.2% women; 81.2% mechanically ventilated) were enrolled following the recommendation of the data and safety monitoring board based on publication of the RECOVERY Trial. One hundred forty-eight patients (99.3%) completed the study, and there were 69 treatment failure events, including 11 deaths in the hydrocortisone group and 20 deaths in the placebo group. The primary outcome, treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, –8.6% [95.48% CI, –24.9% to 7.7%]; *P* = .29). Of the 4 prespecified secondary outcomes, none showed a significant difference. No serious adverse events were related to the study treatment. On day 28, 58 patients (38.9%) had at least 1 episode of HAI, 28 of 75 (37.3%) in the hydrocortisone group vs 30 of 73 (41.1%) in the placebo group, for a total of 90 infections (40 vs 50). At least 1 episode of ventilator associated pneumonia occurred in 22 of 75 patients (29.0%) in the hydrocortisone group, vs 20 of 73 patients (27.4%) in the placebo group. The proportions of bacteremia were 6.6% in the hydrocortisone group and 11.0% in the placebo group.



In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study [like the other 2 studies above] was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome.

Infection Fatality Ratios for COVID-19 Among Noninstitutionalized Persons 12 and Older: Results of a Random-Sample Prevalence Study

Ann Intern Med published online September 2, 2020

Because many cases of COVID-19 are asymptomatic, generalizable data on the true number of persons infected are lacking. Mortality rates therefore are calculated from confirmed cases, which overestimates the infection fatality ratio (IFR)

Researchers in Indiana estimated nearly 190,000 cumulative infections from a population-based statewide sample. They calculated a COVID-19 IFR of 0.26% among noninstitutionalized residents aged 12 and older. Infection fatality ratios were higher among those aged 60 and older (1.71%) and non-whites (0.59%). The infection fatality ratio among those aged 65 and older for seasonal influenza, the authors report, is 0.8%. In order of magnitude, the demographic stratified IFR varied most by age, race, ethnicity, and sex. Persons younger than 40 years had an IFR of 0.01%; those aged 60 or older had an IFR of 1.71%. Whites had an IFR of 0.18%; non-Whites had an IFR of 0.59%.

Table. IFR for Coronavirus Disease 2019 Among Noninstitutionalized Persons Aged ≥12 Years in Indiana

Category	Total Deaths, *n*	Mean Age at Death, *y**	Noninstitutionalized Deaths, *n*†	Estimated Noninstitutionalized Infections (95% CI), *n*	Noninstitutionalized IFR (95% CI), %
Age, *y*					
<40	14	32.8	13	108 339 (73 041-142 095)	0.01 (0.01-0.02)
40-59	81	52.4	63	52 917 (33 963-71 546)	0.12 (0.09-0.19)
≥60	1004	79.5	419	24 493 (16 691-33 232)	1.71 (1.28-2.58)
Race					
White	715	78.9	250	141 026 (108 858-171 519)	0.18 (0.15-0.23)
Non-White	384	73.3	245	41 583 (17 630-71 822)	0.59 (0.34-1.41)
Ethnicity					
Hispanic	17	72.9	15	39 783 (10 851-73 317)	0.04 (0.02-0.14)
Non-Hispanic	1082	77.0	480	142 844 (118 830-172 653)	0.34 (0.28-0.41)
Sex					
Male	580	74.9	300	107 891 (64 803-169 979)	0.28 (0.18-0.47)
Female	493	79.5	169	82 096 (53 116-109 200)	0.21 (0.16-0.32)
Total	1099	76.9	495	187 378 (143 881-232 883)	0.26 (0.21-0.35)

IFR = infection fatality ratio.
* Mean age in years at the time of death, among total deaths.
† Excludes deaths among nursing home residents.

Comment: There are several limitations of this study. First, despite random selection and weighting for nonresponse, the potential for response bias remains. Second, imperfections in tests have the potential for false positives, which may bias estimated infections upward. Separately, use of confirmed COVID-19 deaths may undercount the true number of deaths; both issues might result in lower IFRs. Lastly the investigators could not account for disease severity among random-sample participants with positive test results. Despite this the study gives insight into the true IFR which clearly is lower than initial reports in April.