COVID-19: KEEPING UP WITH A MOVING TARGET JUNE 24, 2020 UPDATE

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COVID-19
KEEPING UP WITH A MOVING TARGET

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CME Information

Jointly provided by Postgraduate Institute for Medicine, DKBmed, and the Institute for Johns Hopkins Nursing.

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Name of Faculty or Presenter	Reported Financial Relationship
Paul G. Auwaerter, MD, MBA, FIDSA	Scientific Advisor: DiaSorin, Shionogi Inc. JNJ: Ownership equity

Dr. Auwaerter has indicated that he will be referencing the unlabeled or unapproved use of agents currently being investigated in on-going studies and trials. These include hydroxychloroquine/chloroquine, hydroxychloroquine/chloroquine in combination with azithromycin, lopinavir plus ritonavir, tocilizumab, corticosteroids, and COVID-19 convalescent plasma. All activity, content, and materials have been developed solely by the activity directors, planning committee members, and faculty presenters, and are free of influence from a commercial entity.

CME Information

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COVID19.DKBmed.com

Learning Objectives

- Describe serologic response associated with asymptomatic COVID-19
- Describe features of antibody response in convalescent individuals
- Discuss current data pertaining to steroids in people with COVID-19

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Thank You

This activity is supported by an educational grant from Pfizer, Inc. and in-kind support by DKBmed, LLC.

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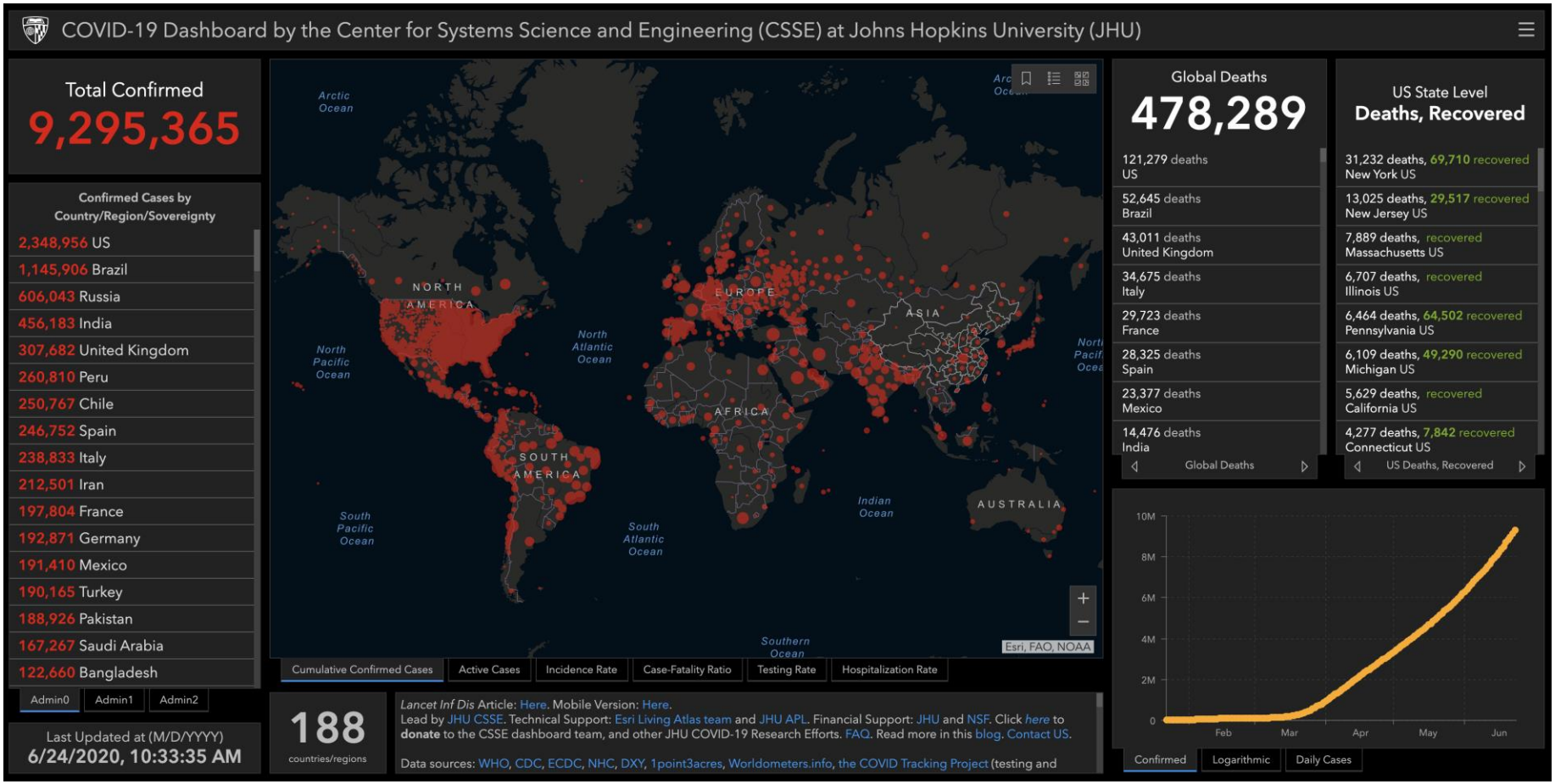
Total Global Cases (6/24/20)



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coronavirus.jhu.edu/map.html

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Antibody Stories

- Surgeon SARS-CoV 2 PCR positive March 2020
  - “Very mild symptoms”
- Felt very lucky
- Four weeks later, decides to get antibody testing
  - SARS CoV-2 IgM: negative
  - SARS CoV-2 IgG: negative
- What does this mean?

Asymptomatic COVID-19

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-0965-6

Check for updates

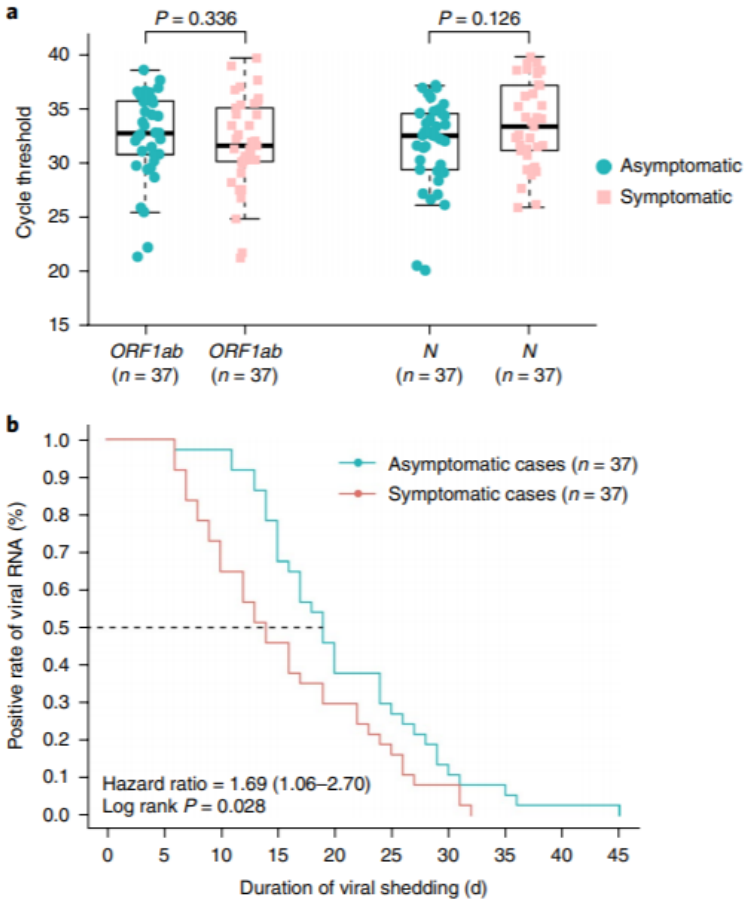
Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

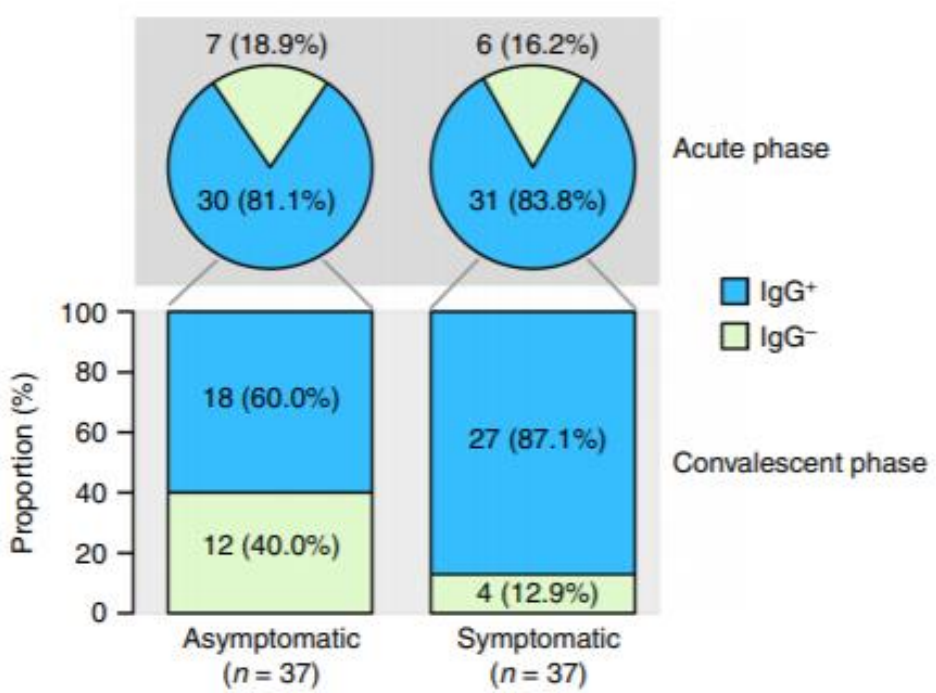
Quan-Xin Long[1,8], Xiao-Jun Tang[2,8], Qiu-Lin Shi[2,8], Qin Li[3,8], Hai-Jun Deng[1,8], Jun Yuan[1], Jie-Li Hu[1], Wei Xu[2], Yong Zhang[2], Fa-Jin Lv[4], Kun Su[3], Fan Zhang[5], Jiang Gong[5], Bo Wu[6], Xia-Mao Liu[7], Jin-Jing Li[7], Jing-Fu Qiu[2]✉, Juan Chen[1]✉ and Ai-Long Huang[1]✉

37 asymptomatic patients –

no symptoms during 14d hospitalization

Asymptomatic COVID-19





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- Conclusions
  - Longer viral shedding, less cytokine generation
  - Less serological responsiveness
    - Asymptomatic 93.3% (28/30) and 81.1% (30/37) had less IgG and neutralizing Abs
      - **In comparison, 96.8% (30/31) and 62.2% (23/37) of symptomatic patients.**
    - 40% asymptomatic → seronegative vs. 12.9% of the symptomatic group during convalescence
    - Protective immunity may not be long-lived

Immunology

Convergent antibody responses to SARS-CoV-2 in convalescent individuals

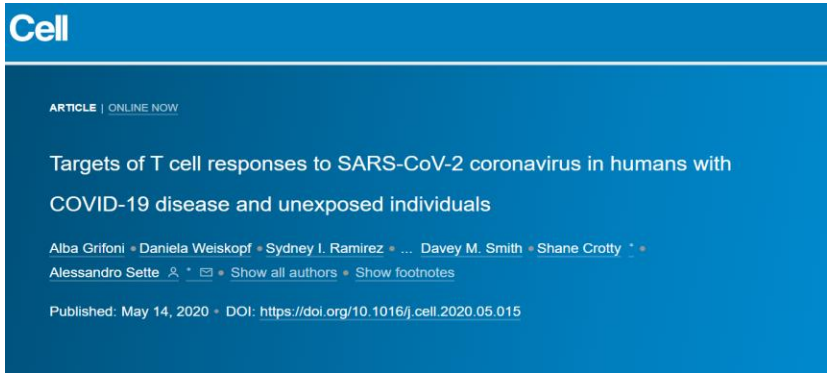
Davide F. Robbiani, Christian Gaebler, [...] Michel C. Nussenzweig

Nature (2020) | Cite this article

211 Altmetric | Metrics

- 149 COVID-19 convalescent individuals, average 39d post-onset
  - pseudovirus neutralizing titers:
  - < 1:50 (33%)
    - < 1:1,000 (79%)
    - > 1:5,000 (1%)
  - Heterogeneous antibody responses (sequencing)
  - Receptor binding domain (RBD) memory B cells with some expanded clones
  - Even with low titers, Abs to 3 distinct epitopes on RBD neutralized
    - At half-maximal inhibitory concentrations (IC_{50} values) at very low levels.
- Conclusion: most don't have high levels of neutralizing antibodies.
  - Rare RBD antibodies may be a good vaccine target to induce.

Immunology



Antibodies may
not be the whole story

- Epitope pools find SARS-CoV-2 specific $CD4^+$ (100%) and $CD8^+$ (95%) T cells in convalescent COVID patients
- T cell responses focused not just on Spike but also other proteins: M, N and other ORFs
- Robust responses by adaptive immune system
  - Additional vaccine focus beyond the spike protein

https://www.cell.com/cell/pdf/S0092-8674(20)30610-3.pdf

COVID-19 Therapeutics

Dexamethasone Trial Arm (RECOVERY Trial)

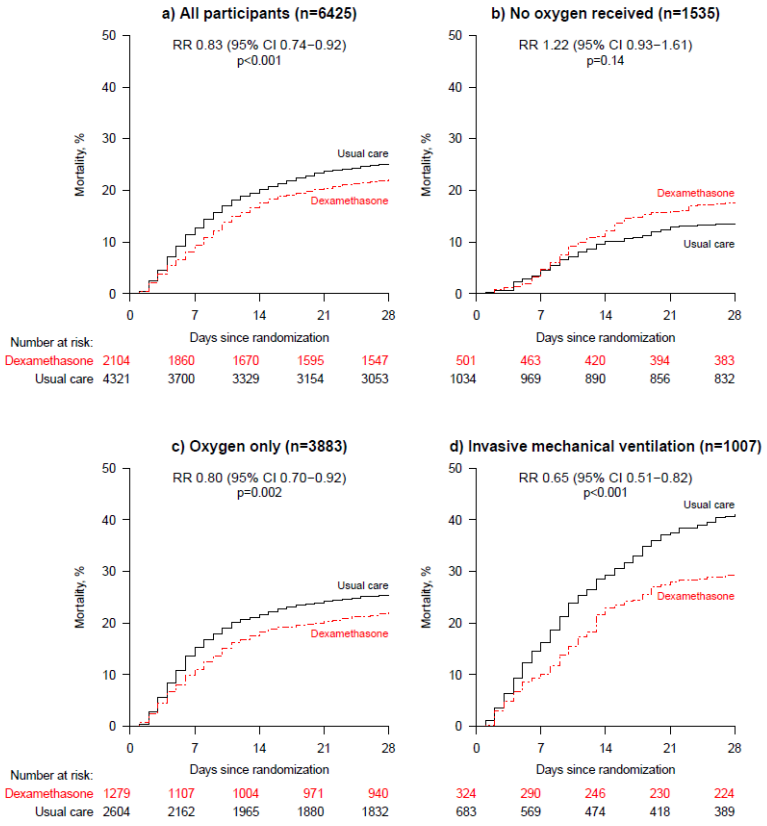
- Target: hyperinflammatory state, trial halted
- UK trial
  - 2104 v. 4321 controls
- NNT avoid 1 death
  - Ventilated patients: 8
    - Mortality rate 40% → 28%
  - On oxygen: 25
    - Mortality rate 25% → 20%
  - No benefit if not on oxygen

RECOVERY -- Dexamethasone

- Conclusion:
  - First drug to show mortality benefit in certain groups
    - On mechanical ventilation or on oxygen
    - Those not on oxygen, trend to more mortality
- Pragmatic, open label trial
  - Higher mortality than U.S.
  - Some with hesitation since steroids with checkered record for ARDS

RECOVERY Dexamethasone arm

Figure 1: 28−day mortality in all patients (panel a) and separately according to level of respiratory support received at randomization (panels b−d)



https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1.full.pdf

Glucocorticoid Treatment

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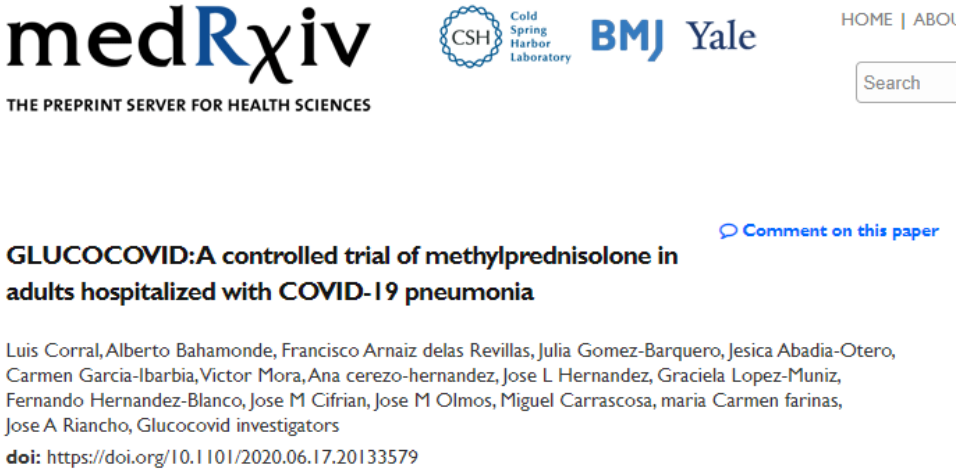
Antiviral Agents

IMPACT OF GLUCOCORTICOID TREATMENT IN SARS-COV-2 INFECTION MORTALITY: A RETROSPECTIVE CONTROLLED COHORT STUDY

Ana Fernández Cruz [MD, PhD], Belén Ruiz-Antorán [MD, PhD], Ana Muñoz Gómez [MD], Aránzazu Sancho López [MD, PhD], Patricia Mills Sánchez [MD], Gustavo Adolfo Centeno Soto [MD, PhD], Silvia Blanco Alonso [MD], Laura Javaloyes Garachana [MD], Amy Galán Gómez [MD], Ángela Valencia Alijo [MD], Javier Gómez Irusta [MD], Concepción Payares-Herrera [MD, PhD], Ignacio Morrás Torre [MD], Enrique Sánchez Chica [MD], Laura Delgado Téllez de Cepeda [Pharm D, PhD], Alejandro Callejas Díaz [MD, PhD], Antonio Ramos Martínez [MD, PhD], Elena Múñez Rubio [MD, PhD], Cristina Avendaño-Solá [MD, PhD]; on behalf of Puerta de Hierro COVID-19 Study Group

- Single center, 463 of 848 hospitalized patients met criteria, Global mortality 15.1%.
- Methyl pred 1 mg/kg/d (steroid pulse not effective)
  - 396 (46.7%) steroids
  - 67 no steroids
- Median time to steroid treatment 10 days (IQR 8-13) from symptom onset
- In-hospital mortality better steroids than in controls
  - 13.9% [55/396] versus 23.9% [16/67], HR 0.51 [0.27-0.96], p= 0.044).
- Steroid treatment reduced mortality by 41.8% relative to no steroid treatment (RRR 0,42 [0.048- 0.65).

Steroids for Severe COVID-19



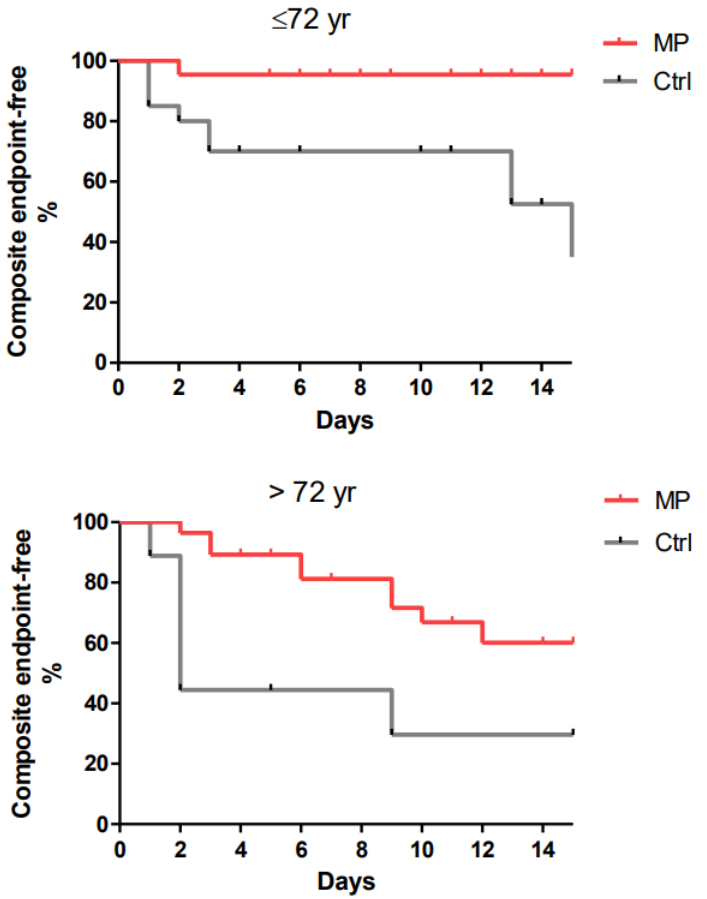
- Open label trial: 85 patients (34, randomized to MP; 22, assigned to MP by clinician preference; 29, control group)
- MP given as 40mg/12h 3 days, then 20mg/12h 3 days
- Composite primary endpoint: death, ICU admission or non-invasive ventilation (NIV)

https://www.medrxiv.org/content/10.1101/2020.06.17.20133579v1

Glucocovid

Kaplan-Meier plots
Probability of NOT reaching primary composite endpoint (ICU admission, need of NIV or death)

Figure 3



Control (grey)
MP (red)

https://www.medrxiv.org/content/10.1101/2020.06.17.20133579v1

Corticosteroids for Severe COVID-19

- MP associated combined risk ratio
  - ITT RR- 0.55 [95% CI 0.33-0.91]; p=0.024)
  - Per-protocol analysis
    - Age ≤ 72 yrs RR 0.11 (0.01-0.83)
    - Age > 72 yr RR 0.61 (0.32-1.17)
    - Following adjustments for age stratification, RR 0.37 (0.19-0.74, p=0.0037)
- Adverse reactions: hyperglycemia
- Conclusion: Some support for RECOVERY Dexamethasone trial findings (press release) with this study, but open label with substantial bias

Hydroxychloroquine Out as an Antiviral for Hospitalized Patients

- Hydroxychloroquine trial arm (RECOVERY trial: preliminary statements/conclusion: no benefit in hospitalized patients
- FDA pulled Emergency Use authorization for both hydroxychloroquine and chloroquine
- Novartis and NIH-sponsored clinical trials halted
  - Including HCQ + azithromycin
  - NIH-sponsored DSMB "…met late Friday and determined that while there was no harm, the study drug was very unlikely to be beneficial to hospitalized patients with COVID-19."

https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine (6/20/20)

To submit your own question, please email QA@dkbmed.com

Is remdesivir being widely used now? Can you comment on how effective it is?

I see percent positive rates being posted by my state government, but don't have guidance on what it means or when I should be concerned. What is the general range of what's considered a "low" or "high" percent positive rate?

I have heard about a new nasopharyngeal swab that can test for both COVID-19 and influenza. Can we expect to see those being used at COVID-19 testing sites moving forward? If so, when?

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- Complete the evaluation on at COVID19.DKBmed.com
- Upon registering and successfully completing the activity evaluation, you will have immediate access to your certificate.

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- Access our resource hub at COVID19.DKBmed.com

To ask your own question to Dr. Auwaerter:

- Email QA@dkbmed.com