COVID-19: KEEPING UP WITH A MOVING TARGET Aug 5, 2020 UPDATE



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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 COVID-19 convalescent plasma, remdesivir, and vaccine platforms.

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CME Information

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Learning Objectives

- Describe current data concerning IL-6 inhibition
- Discuss data pertaining to convalescent plasma
- Discuss status of vaccine development







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

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Please see **COVID19.DKBmed.com** for additional resources and educational activities





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Total Global Cases (8/5/20)







High numbers = Greater Likelihood of Infection

The New Hork Times

The Coronavirus Outbreak > Latest Updates Maps and Cases Vaccine Tracker What School May Look Like Economy

LIVE UPDATES Updated 28 minutes ago

Coronavirus Live Updates: Epidemic Is 'Extraordinarily Widespread,' Birx Warns

Dr. Deborah L. Birx said the U.S. had entered a "new phase" in the fight against the virus, and urged people to consider wearing masks at home. With a focus on the coronavirus, other deadly diseases are making a comeback.

RIGHT NOW The World Health Organization said that while progress has been made in treating the virus, there is "no silver bullet" and "might never be."



Dr. Deborah L. Birx during a news conference at the White House last month. Doug Mills/The New York Times

Here's what you need to know:

 Live with someone vulnerable? 'You need to really consider wearing a mask at home,' Birx says. Live with someone vulnerable? 'You need to really consider wearing a mask at home,' Birx says.





COVID Deaths



There are currently 154,785 deaths confirmed to be caused by Covid-19 in the US. With an estimated population of 322m, that equals to about 48 deaths per 100,000 Americans.²

Number of confirmed Covid-19 deaths per 100,000 Americans

Fewer than 5 At least 5 per 100k At least 10 per 100k At least 25 per 100k



Last updated: 3 Aug 6:25am EST

Source: Maps are updated daily at 12am ET using **state-level** and county-level **case** and **death** figures reported from Johns Hopkins University. **State populations** were provided by Johns Hopkins CSSE. ¹Daily increases were found by taking the case and death figures from the timestamp shown above and comparing them to the data from **7 days ago**

²Per capita rates were calculated by taking the case and death tally recorded at the timestamp above and and dividing it by the estimated country population from the 2018 ACS 5-year estimate.

https://www.theguardian.com/world/ng-interactive/2020/jul/15/covid-19-coronavirus-us-map-latest-cases-state-by-state





Treatment



AT THE



Failure of Targeted Anti-IL6 Therapy Tocilizumab

Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia

- COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality
- The study is the first global, randomised, double-blind, placebo-controlled phase III trial investigating Actemra/RoActemra in this setting
- Roche remains committed to continuing the Actemra/RoActemra clinical trial programme in COVID-19 to further explore Actemra/RoActemra in other treatment settings, including in combination with an antiviral

Basel, 29 July - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the phase III COVACTA study of Actemra®/RoActemra® (tocilizumab) did not meet its primary endpoint of improved clinical status in hospitalised adult patients with severe COVID-19 associated pneumonia. In addition, the key secondary endpoints, which included the difference in patient mortality at week four, were not met; however, there was a positive trend in time to hospital discharge in patients treated with Actemra/RoActemra. The COVACTA study did not identify any new safety signals for Actemra/RoActemra. Further analysis of the trial results is needed to fully understand the data. The results will be submitted for publication in a peer-reviewed journal.







"Trippple" Therapy for COVID-19 Remdesivir/Dexamethasone/Convalescent Plasma

- Rationale:
 - Antiviral Antibodies
 - o Anti-inflammatory
- Untested combination
 - \circ Also,
 - No large RCT yet regarding convalescent plasma
 - Rumor: FDA considering moving from eIND to EUA





Convalescent Plasma Treatment

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medRxiv preprint doi: https://doi.org/10.1101/2020.07.29.20162917.this version posted July 30, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy

Michael J. Joyner^{1*}, Stephen A. Klassen¹, Jonathon W. Senefeld¹, Patrick W. Johnson², Rickey E. Carter², Chad C. Wiggins¹, Shmuel Shoham³, Brenda J. Grossman⁴, Jeffrey P. Henderson^{5,6}, James M. Musser^{7,8,9}, Eric Salazar^{7,9}, William R. Hartman¹⁰, Nicole M. Bouvier^{11,12}, Sean T. H. Liu^{11,12}, Liise-anne Pirofski¹³, Sarah E. Baker¹, Noud van Helmond¹⁴, R. Scott Wright^{15,16}, DeLisa Fairweather¹⁷, Katelyn A. Bruno¹⁷, Nigel S. Paneth^{18,19}, and Arturo Casadevall²⁰

 Aggregated patient outcome data from randomized clinical trials, matched control, and case-series studies.



Basis: RCTs, Matched Control Studies (case series)

Table

Table 1 Case Fatality Rates in Hospitalized COVID-19 Patients											
		Convalescent Plasma			Control			Statistics			
Study	Location	Survivor	Non-Survivor	Mortality	Survivor	Non-Survivor	Mortality	OR	Р		
Randomized Clinical Trials (RCT)											
Li et al. ⁷	Wuhan, CHN	43	8	16%	38	12	24%	0.59	0.30		
Gharbharan et al. ⁸	NLD	37	6	14%	32	11	26%	0.47	0.18		
Rasheed et al. ¹⁰	IRQ	20	1	5%	20	8	29%	0.13	0.06		
Fixed Effect Model ^a		100	15	13%	90	31	26%	0.46	0.03		
Matched Controls											
Hegerova et al. ¹¹	Washington, USA	18	2	10%	14	6	30%	0.26	0.13		
Liu et al. ¹⁷	New York, USA	35	5	13%	118	38	24%	0.44	0.11		
Perotti et al. ¹³	Pavia, ITA	43	3	7%	16	7	30%	0.16	0.01		
Abolghasemi et al. ¹⁴	IRN	98	17	15%	56	18	24%	0.54	0.10		
Fixed Effect Model ^b		194	27	12%	204	69	25%	0.41	0.001		
Controlled studies Fixed Eff	fect Model ^c	294	42	13%	294	100	25%	0.43	<0.001		
Case Series											
Salazar et al. ¹⁵	Texas, USA	24	1	4%							
Hartman et al. ¹⁶	Wisconsin, USA	27	4	13%							
Duan et al. ¹⁷	Wuhan, CHN	10	0	0%							
Martinez-Resendez et al. ⁹	Monterrey, MEX	8	0	0%							
Total		69	5	7%							

OR, odds ratio

^a Relative weight (%): Li et al. (49.3), Gharbharan et al. (40.3), Rasheed et al. (10.4).

^b Relative weight (%): Hegerova et al. (9.1), Liu et al. (27.4), Perotti et al. (12.8), Abolghasem et al. (50.7).

^c Relative weight (%): Li et al. (17.8), Gharbharan et al. (14.6), Rasheed et al. (3.8), Hegerova et al. (5.8), Liu et al. (17.5), Perotti et al. (8.2), Abolghasem et al. (32.3).

https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1





Impact of convalescent plasma on mortality



Figure 1. The impact of human convalescent plasma therapy on COVID-19 patient mortality. Forest plot illustrating odds ratios (OR) and 95% confidence intervals for controlled studies and aggregate fixed effect models. Randomized clinical trials including Rasheed et al.¹⁰, Gharbharan et al.⁸, and Li et al.⁷ are represented in orange. Matched controlled studies including Perotti et al.¹³, Hegerova et al.¹¹, Liu et al.¹², and Abolghasemi et al.¹⁴ are represented in blue. Aggregate fixed effect models for each study type are represented by shaded hues. The overall aggregate fixed effect model is represented in teal.

https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1





Convalescent Plasma Benefits?

- ~57% reduction in mortality rate (13%) v. matched-patients receiving standard treatments
 - 25%; OR: 0.43, *P* < 0.001
 - o Meta-regression analysis, no difference
 - Mean or median cohort age
 - Proportion of cohort receiving mechanical ventilation
 - Duration of study follow up did not affect the aggregate OR computed for all controlled studies (all coefficients P> 0.22).
 - The fixed effect OR (OR: 0.44, *P*<0.001) was not different when *outlier* mortality rates from the matched control study by Xia and colleagues were included in analyses (case mortality rate: 2%, control mortality rate: 4%)
 - o Appears therapy beneficial across different countries/health systems
- Limitations: among studies, differences in
 - $\circ~$ Nation of data origin
 - Timing relative to worldwide progression of the pandemic
 - Clinical diagnostic and treatment algorithms
 - o Plasma antibody titer and administration volume
 - Latency between COVID-19 diagnosis and transfusion
 - Duration of follow up after transfusion
- Indication of benefit? Need an RCT, but...





Prevention



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Vaccine Update

Coronavirus Vaccine Tracker

By Jonathan Corum, Denise Grady, Sui-Lee Wee and Carl Zimmer Updated August 3, 2020







NY Times



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

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Do we know how long asymptomatic COVIDpositive people are infectious?







How is convalescent plasma administered? Is it an inpatient transfusion? Do we need to type and cross to receive the plasma?







Are you comfortable with the accelerated vaccine development process? Is there any compromise on the study of the safety of these vaccines?







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