Recent developments in treatment and their consequences for SSA's disability program

November 18, 2020

Paul Auwaerter, MD
Clinical Director, Division of Infectious Diseases
Sherrilyn and Ken Fisher Professor of Medicine
Fisher Center for Environmental Infectious Diseases
Johns Hopkins University School of Medicine
Baltimore, Maryland USA

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Decreasing COVID-19 Mortality
NYC Hospitals, Mortality March – August 2020

Mortality fell from 25.6% → 7.6%

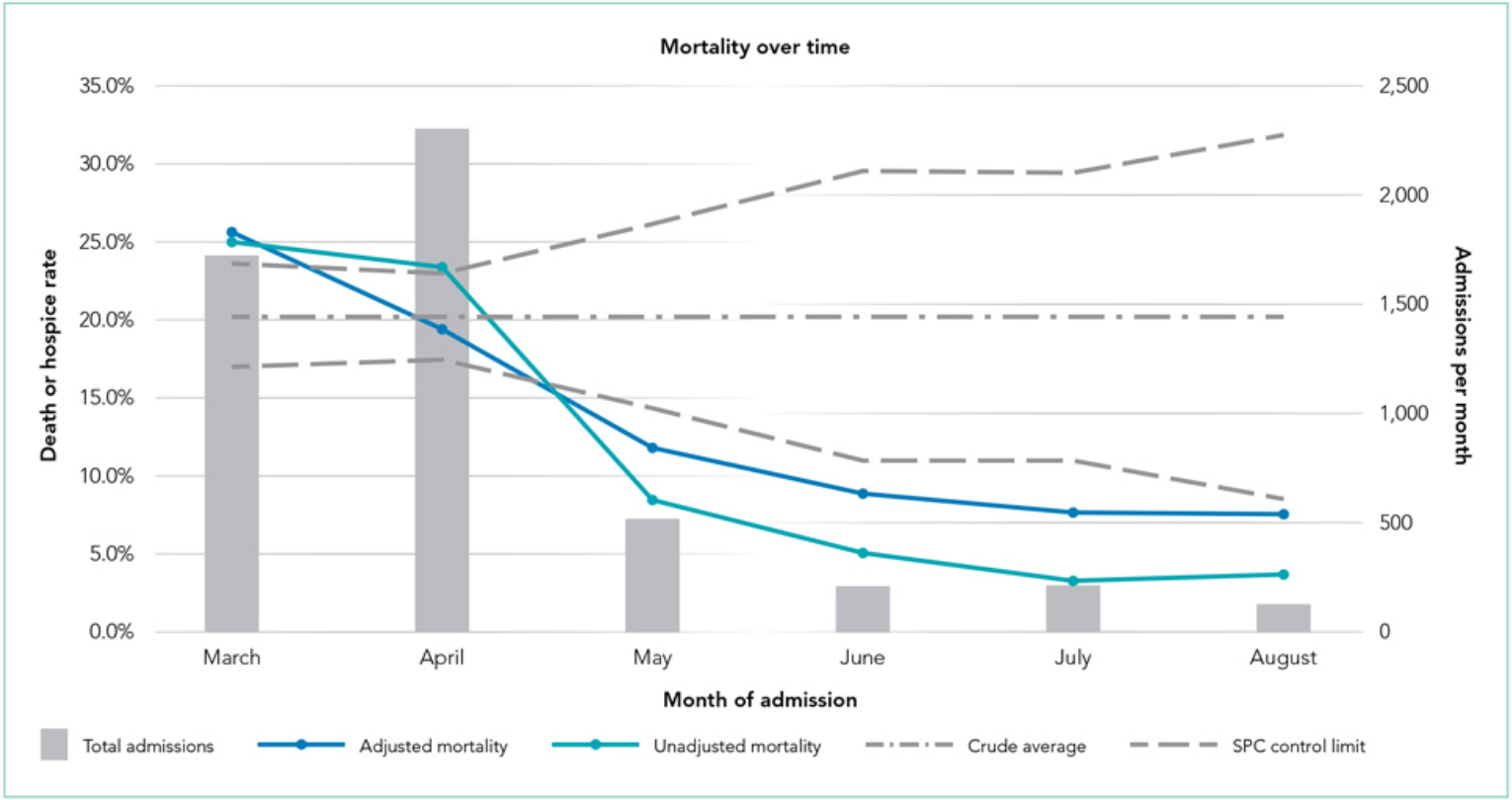

FIG. Adjusted and Unadjusted Mortality or Hospice Rate, by Month of Admission.

Horowitz et al., J Hosp Med Oct 21, 2020

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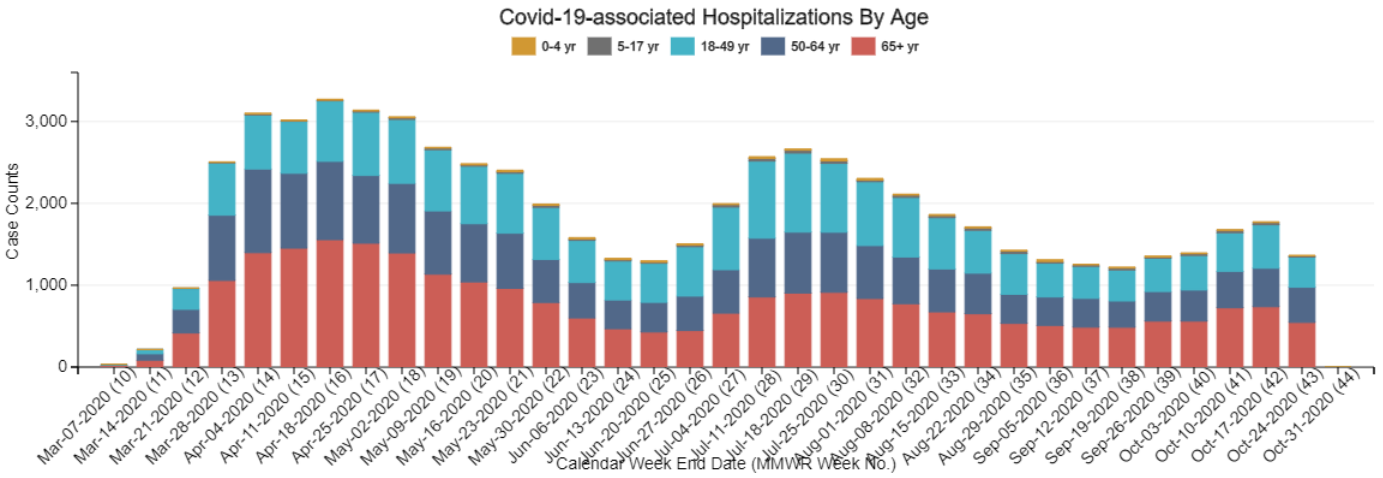
Why declining mortality? Likely many factors

COVID-NET | A Weekly Summary of U.S. COVID-19 Hospitalization Data

COVID-19 Laboratory-Confirmed Hospitalizations
Preliminary data as of Oct 24, 2020



Age	0-4 yr	5-17 yr	18-49 yr	50-64 yr	65+ yr	Total
2020	391	647	19480	18424	26201	65143

The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data are preliminary and subject to change as more data become available. In particular, case counts and rates for recent hospital admissions are subject to lag. As data are received each week, prior case counts and rates are updated accordingly.

CDC data

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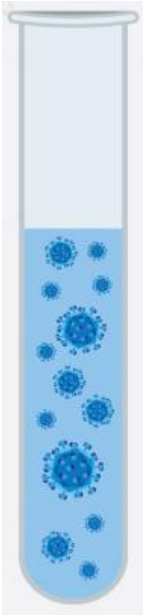
Why declining mortality? Likely many factors

- Shift to younger patients
- Mask wear and social distancing = exposure to lower viral loads
- Less chaos, more experience
  - Patients presenting earlier
  - Proning
  - Ventilator management
- Treatments
  - Dexamethasone (anti-inflammatory): off-label

Antiviral, Immunomodulatory, Antibody-based

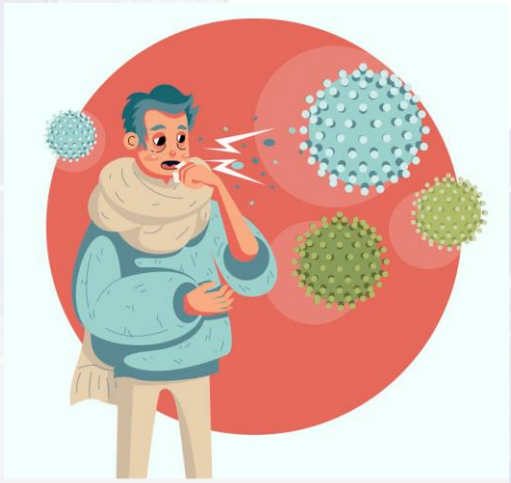
TREATMENT

So much “promise,” So little to show



Hydroxychloroquine
Chloroquine
Ivermectin
Lopinavir/ritonavir

Favipiravir
Baloxivir
Indomethacin
Zinc
Vitamin C



Viral Tissue Culture studies, *in vitro*

Human studies, *in vivo*

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Antivirals: Remdesivir

- ACTT-1 (final report) RDV v. placebo
  - Improved median recovery time
    - 10d v. 15d

    [rate ratio recovery 1.29; 95% CI, 1.12 to 1.49; P<0.001]
  - Mortality trend
    - RDV 6.7% v. 11.9% day 15
    - RDV 11.4% v. 15.2% day 29

    [hazard ratio, 0.73; 95% CI, 0.52 to 1.03]

Beigel, NEJM 2020 (Nov 5); 383:1813-1826

Other Remdesivir Trials

- Overall:
  - No impact on disease
  - None reduce SARS-CoV-2 virus levels
- Solidarity trial: large trial 11,266 (RDV 2750)
  - RDV: no impact on mortality, need for ventilation, length of hospital stay
  - No placebo group, unclear if clinical subgroups benefited
- Unknown whether drug impacts long-term sequelae

WHO, Pan, et al. https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1

Other antivirals under study

- Oral therapy
  - EIDD-2801 (molnupiravir)
  - AT-527

Anti-inflammatories
Dexamethasone Trial Arm (RECOVERY Trial)

- Target: hyperinflammatory state, trial halted
- UK pragmatic trial
  - 2104 v. 4321 controls
- Ventilated patients:
  - Mortality rate 41.4% → 29.3
    rate ratio, 0.64; 95% CI, 0.51-0.81
- On oxygen (not ventilated)
  - Mortality rate 26.2% → 23.3
    rate ratio, 0.82; 95% CI, 0.72-0.94
- No benefit if not on oxygen

NEJM July 17, 2020

Dexamethasone and other corticosteroids

- WHO meta-analysis 1703 patients v. placebo/usual care
  - Dexamethasone, odds ratio mortality 0.64 (95% CI, 0.50-0.82; $P < .001$)
  - Hydrocortisone, odds ratio 0.69 (95% CI, 0.43-1.12; $P = .13$)
- Critically ill patients with lower 28d all cause mortality

JAMA. 2020;324(13):1330-1341

Immunomodulators

Tocilizumab (anti-IL6R)

Unconvincing evidence of benefit

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Enrollment					
No. of sites	68	24	9	67	69
Countries	US	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	3924	126	131	450	389
No. tocilizumab treated	433	60[a]	63	225[b]	194[b]
Clinical severity[c]					
Moderate	No	No	No	No	No
Severe	Yes	Yes	Yes	Yes	Yes
Critical	Yes	No	No	Yes	No
Intervention					
Tocilizumab	Within 2 d of ICU admission	8 mg/kg ×2 Doses, 12 h apart	8 mg/kg ×1, Possible second dose on day 3	8 mg/kg ×1, Possible second dose	8 mg/kg ×1, Possible second dose
Comparator	Usual care	Usual care	Usual care	Usual care plus placebo	Usual care plus placebo
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pao_2:Fio_2 <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)
28- or 30-d mortality, tocilizumab vs comparator, effect size[f]	27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%)	3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)	11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)	19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)	10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)
Trial registration	NCT04343898	NCT04346355	NCT04331808	NCT04320615	NCT04372186

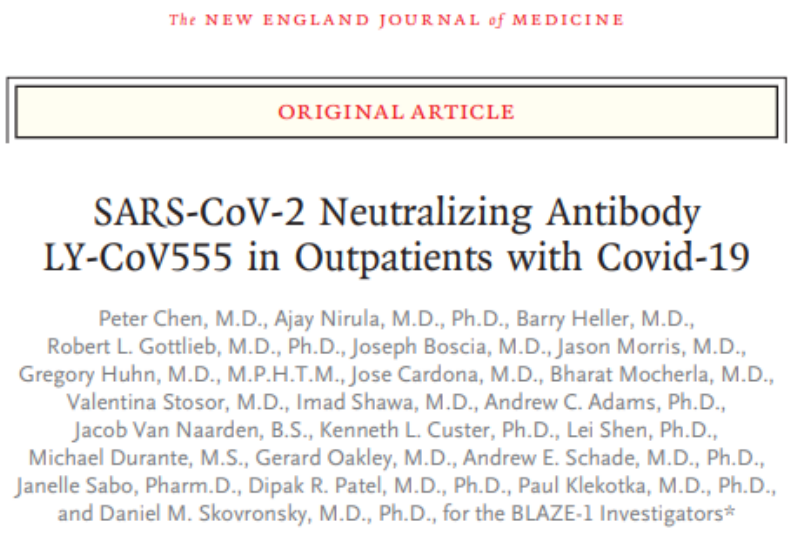
Parr, JAMA Int Med Oct 20, 2020

Convalescent Plasma

- Has FDA EUA approval for hospitalized patients: “may be effective.”
  - Insufficient data due to lack of randomized controlled trials
- Trials ongoing for hospitalized patients, outpatients and prophylaxis

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma (9/2/20)
NIH COVID-19 Treatment Guidelines (10/9/20)

Bamlanivimab FDA EUA (11/10/20)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

BLAZE-1 RCT, interim analysis

Mild/moderate COVID-19

Single dose, 456 non-hospitalized patients

1° endpoint, change viral load d11

NOT met

Approval based on 2° endpoint:

Hospitalization or ED visit at d28

3% vs. 10% placebo

Role: (+) SARS-CoV-2, age ≥ 12, high risk for severe COVID-19

NEJM October 28, 2020

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ELSEVIER

Mayo Clinic Proceedings

Volume 95, Issue 11, November 2020, Pages 2467-2486

Consensus recommendation

Anticoagulation in COVID-19: A Systematic Review, Meta-analysis, and Rapid Guidance From Mayo Clinic

Robert D. McBane II MD [a, b, c], Victor D. Torres Roldan MD [d], Alexander S. Niven MD [e], Rajiv K. Pruthi MBBS [b, f], Pablo Moreno Franco MD [i], Jane A. Linderbaum APRN, CNP [c], Ana I. Casanegra MD, MS [a, c], Lance J. Oyen PharmD, RPh [g], Damon E. Houghton MD, MS [a, c], Ariela L. Marshall MD [b, f], Narith N. Ou PharmD, RPh [g], Jason L. Siegel MD [j], Waldemar E. Wysokinski MD [a, c], Leslie J. Padrnos MD [m], Candido E. Rivera MD [k], Gayle L. Flo APRN, CNP [c], Fadi E. Shamoun MD [n], Scott M. Silvers MD [l] ... M. Hassan Murad MD [d]

- Data mixed, thromboses seen more in ICU patients
- Expert consensus regarding routine prophylaxis against venous thromboembolisms
  - Clinical ward: routine anticoagulation
  - ICU: based on D-dimer levels

REGN-COV2 monoclonal cocktail

- N = 799, placebo-controlled trial, outpatients mild/moderate COVID-19
- Reduced medical visits through d29
  - All: 58% reduction (2.8% v. 6.5%, p=0.024)
  - With 1 risk factor: 72% reduction (p = 0.0065)
- Most benefit in patients without SARS-CoV-2 antibodies present at time of administration
- Few adverse events

https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates (10/28/20)

Treatment Summary

- Trials have focused on acute disease and outcomes relevant survival and hospitalizations
- Dexamethasone with convincing mortality benefit
- Other than survival, unknown if treatments impact long-term health
- Vaccines have >> potential than treatment for avoiding long-term complications