Pearls and Best Practices of COVID-19 Inpatient Care

Amiran Baduashvili, MD

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Society of Hospital Medicine

Updates on COVID-19 Management

Amiran Baduashvili, MD
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Agenda

1. Initial assessment and triage of a COVID-19 inpatient
2. Non-pharmaceutical management of the hospitalized patient
3. Pharmaceutical management of COVID-19 hospitalized adult – best practices
4. Ongoing monitoring of the COVID-19 patient and indicators of worsening illness
5. Considerations for discharge of recovering COVID-19 inpatient

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Conflicts of interest – Amiran Baduashvili

Co-investigator

- ORCHID trial – randomized-controlled trial (RTC) comparing hydroxychloroquine to placebo (sponsored by NHLBI, part of PETAL network)
- 6R88-COV-2040 – RTC comparing Sarilumab to placebo (sponsored by Regeneron)
- CINC424J12301 – RTC comparing Ruxolitinib to Placebo (sponsored by Novartis)
- GS-5773 and GS-5774 – single-arm open label trial exploring the role of Remdesivir in treatment of Covid-19
- 10987-COV-2066/2067 – RTC comparing monoclonal antibodies targeting SARS-CoV-2 Spike protein to placebo
- ACTIV-3 – NIH sponsored trial platform, part of Operation Warp Speed.

Financial conflicts

- none

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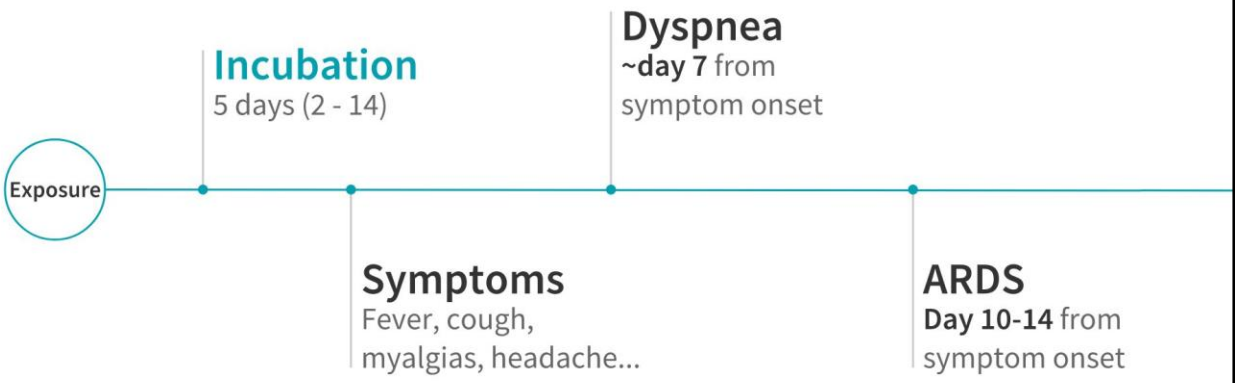
Timeline



Wang D et al, JAMA. 2020, Zhou F et al. Lancet. 2020

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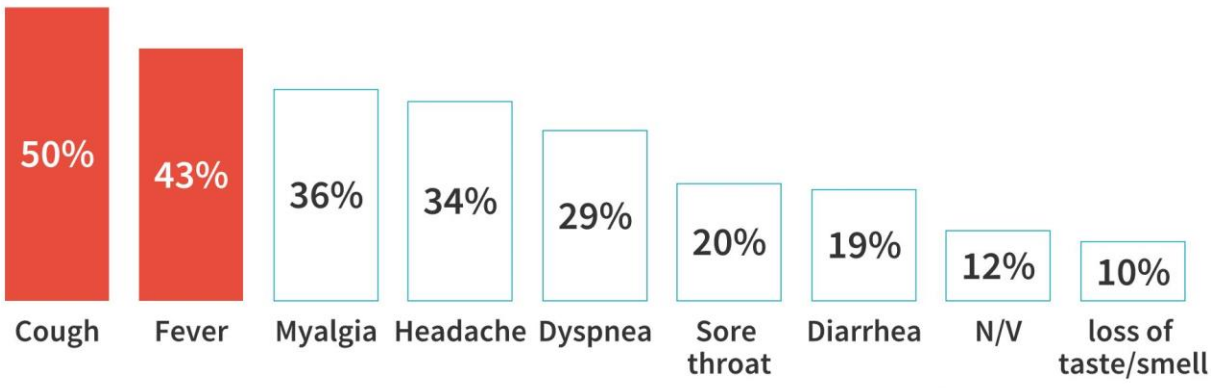
Symptoms

MMWR report, US data. 370,000 confirmed cases



Coronavirus Disease 2019 Case Surveillance - MMWR. 2020;69(24):759

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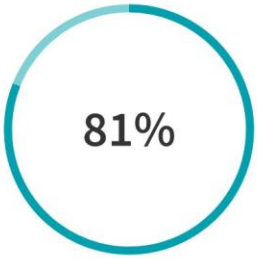
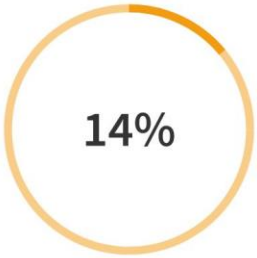
Severity of illness

Chinese CDC data. 44,500 confirmed cases



Mild

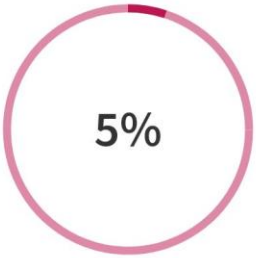
No hypoxia



Severe

Pneumonia

Hypoxia



Critical

Respiratory failure

Shock

Multiorgan dysfunction

Wu Z, McGoogan J, JAMA. 2020;323(13):1239

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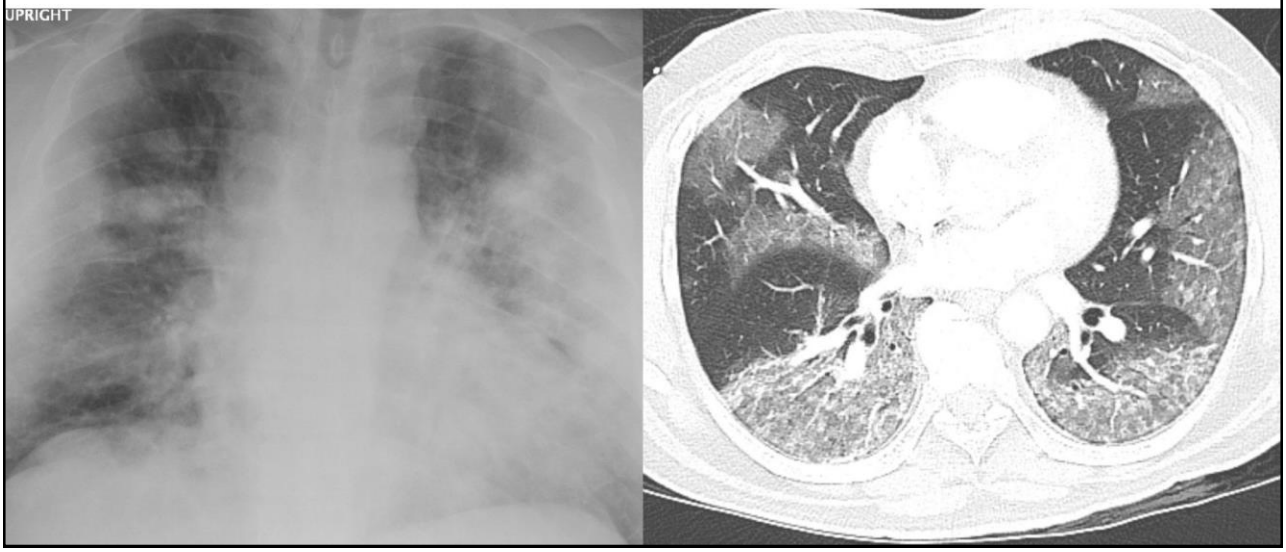
Imaging Findings



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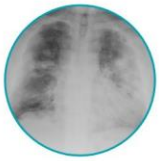
Frequency of imaging abnormalities

1,099 patients with confirmed Covid-19



CXR

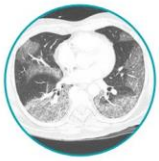
Normal - 41%

Abnormal - 59%

Ground glass - 20%

Local patchy - 28%

Bilateral - 37%



CT scan

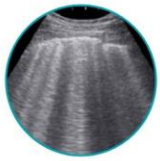
Normal - 14%

Abnormal - 86%

Ground glass - 56%

Local patchy - 41%

Bilateral - 52%



Lung US*

B-lines - 90+%

Subpleural consolidations

Thick/irregular pleura

Guan WJ, et al. N Engl J Med 2020; 382:1708-1720 *separate study, https://doi.org/10.1016/j.ejro.2020.100231

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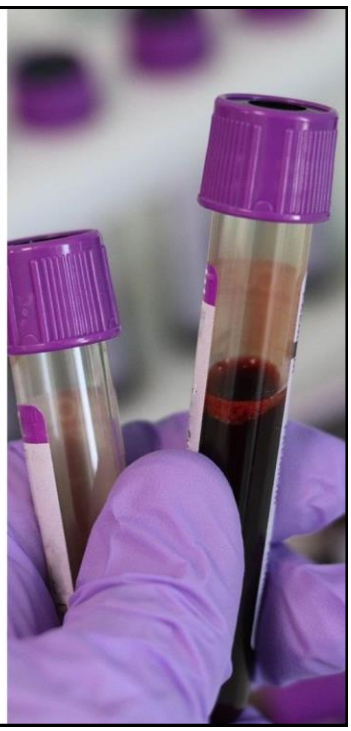
Initial laboratory assessment

- **CBC**
  - Lymphocytes <1.0 is common
  - ↑ WBC - ? bacterial process
- **Basic metabolic panel**
  - Electrolyte abnormalities given GI symptoms
  - Renal function for medication dosing
- **Liver function panel**
  - AST/ALT often mildly elevated in Covid-19
  - ALT > 5xULN may preclude the use of Remdesivir
- **D-dimer**
  - Hypercoagulable state
- **C-reactive protein, Ferritin, LDH**
  - Marker of overall inflammation
  - (?) Role in prognosis
- **Troponin**
  - Subset of patients with myocarditis
- **HIV, HCV**
  - screening



COVID-19 Treatment Guidelines Panel. National Institute of Health. Accessed [Nov 15, 2020]

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Diagnosis

NAAT / PCR based

Rapid antigen

Antibody

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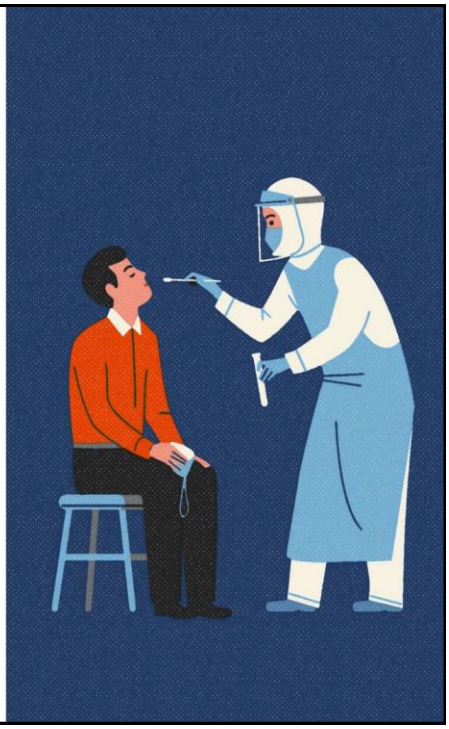
Diagnosis

NAAT/PCR-based assays

- **Sensitivity - 60 to 95%**
  - Variable by **specimen type, symptom duration, assay type**
  - False negatives are possible
  - May need repeat testing if high index of suspicion and tests negative
- **Specificity - 99+%**
  - False positives are exceedingly rare
  - A positive test confirms Covid-19 infection

COVID-19 Treatment Guidelines Panel. National Institute of Health. Accessed [Nov 15, 2020]



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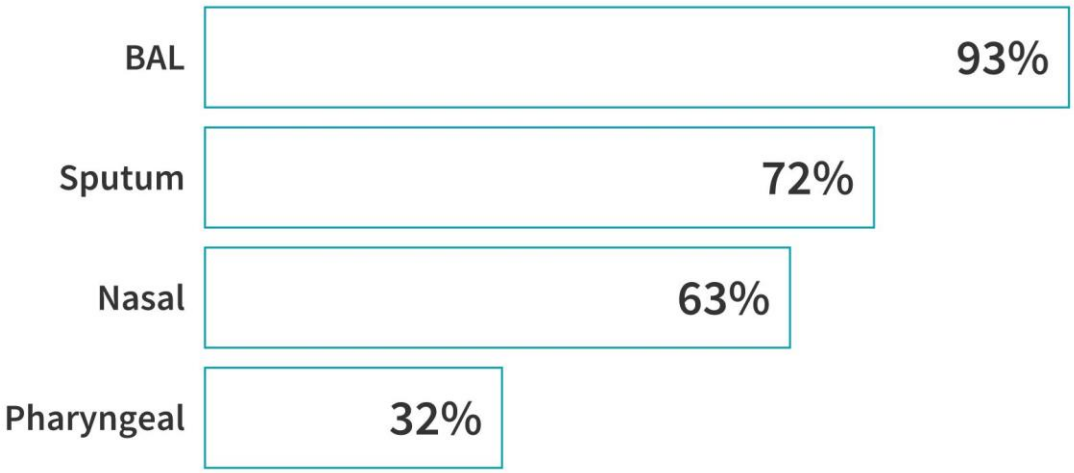
Sensitivity by specimen type



Wang W, et al. JAMA. 2020;323(18):1843-1844

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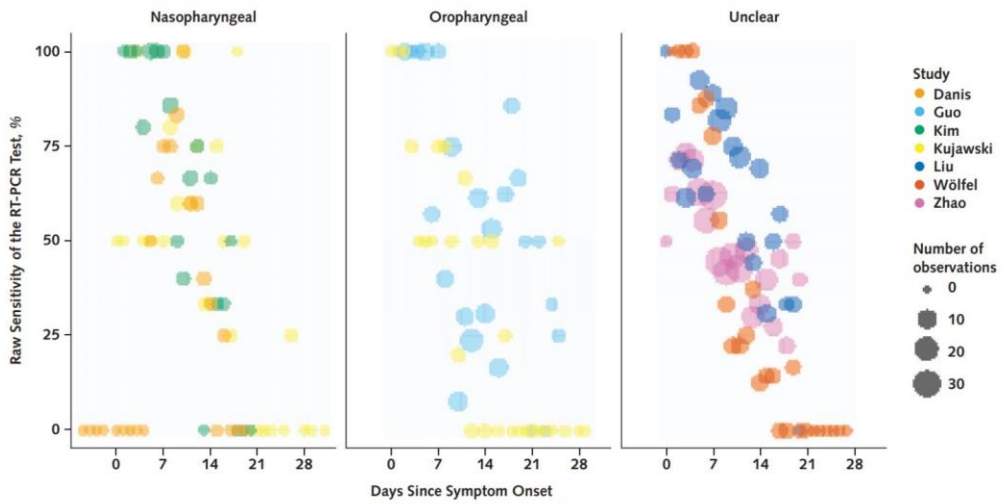
Sensitivity by symptom duration

Kucirka LM, et al. Ann Intern Med. 2020;173:262-267



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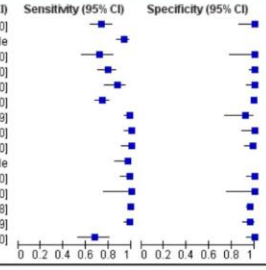
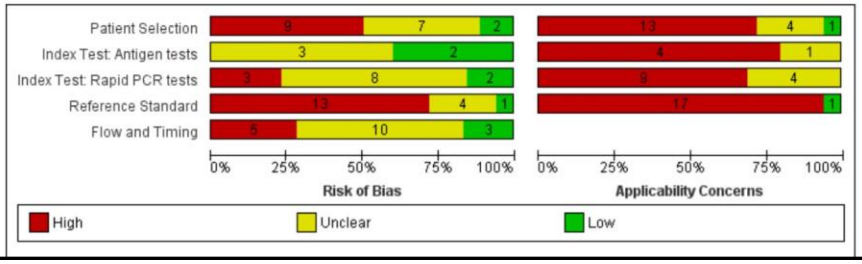
Sensitivity by assay type

Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705

Study	TP	FP	FN	TN	Test	Sample type	Sensitivity (95% CI)	Specificity (95% CI)
Smithgall 2020 [A]	65	0	23	25	Abbott - ID NOW	Mixed	0.74 [0.63, 0.83]	1.00 [0.86, 1.00]
Rhoads 2020	90	0	6	0	Abbott - ID NOW	Mixed	0.94 [0.87, 0.98]	Not estimable
Mitchell 2020	33	0	13	15	Abbott - ID NOW	NP	0.72 [0.57, 0.84]	1.00 [0.78, 1.00]
Moore 2020	94	0	25	79	Abbott - ID NOW	NP	0.79 [0.71, 0.86]	1.00 [0.95, 1.00]
Zhen 2020 [A]	50	0	7	50	Abbott - ID NOW	NP	0.88 [0.76, 0.95]	1.00 [0.93, 1.00]
Harrington 2020	139	2	47	336	Abbott - ID NOW	Nasal	0.75 [0.68, 0.81]	0.99 [0.98, 1.00]
Smithgall 2020 [B]	87	2	1	23	Cepheid - Xpert Xpress	Mixed	0.99 [0.94, 1.00]	0.92 [0.74, 0.99]
Wolters 2020	58	0	0	30	Cepheid - Xpert Xpress	Mixed	1.00 [0.94, 1.00]	1.00 [0.88, 1.00]
Moran 2020	42	1	0	60	Cepheid - Xpert Xpress	Mixed	1.00 [0.92, 1.00]	0.98 [0.91, 1.00]
Broder 2020	34	0	1	0	Cepheid - Xpert Xpress	NP	0.97 [0.85, 1.00]	Not estimable
Zhen 2020 [B]	57	0	1	50	Cepheid - Xpert Xpress	NP	0.98 [0.91, 1.00]	1.00 [0.93, 1.00]
Lieberman 2020	13	0	0	13	Cepheid - Xpert Xpress	NP	1.00 [0.75, 1.00]	1.00 [0.75, 1.00]
Loeffelholz 2020	219	11	1	250	Cepheid - Xpert Xpress (RUO)	Mixed	1.00 [0.97, 1.00]	0.96 [0.93, 0.98]
Assennato 2020	87	3	1	81	DRW - SAMBA II	NP + OP	0.99 [0.94, 1.00]	0.96 [0.90, 0.99]
Hogan 2020	34	0	16	50	Mesa Biotech - Accula	NP	0.68 [0.53, 0.80]	1.00 [0.93, 1.00]





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Summary

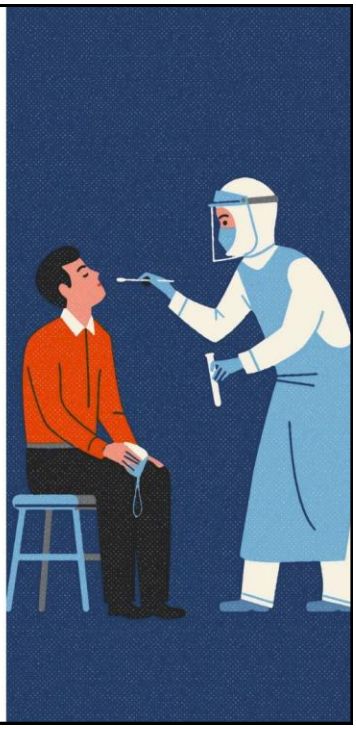
NAAT/PCR-based assays - **SENSITIVITY**

- lower respiratory specimen > upper respiratory
- 0-7 days of symptoms > 14-21 days
- Variable by assay type - ask your lab
- Negative PCR in patients with high index of suspicion

  Obtain lower respiratory specimen when possible and if lab can test it

  OR repeat nasopharyngeal PCR

  Maintain isolation precautions



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Rapid antigen tests

Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705

- More variability in sensitivity by assay type
- Lower sensitivity than PCR
- High specificity

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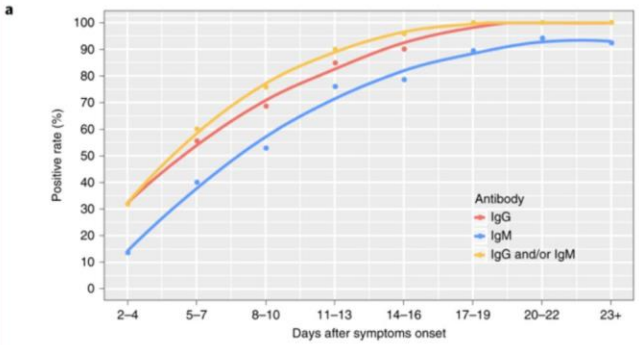
SARS-CoV-2 Antibody

Long QX et al, Nature Medicine 2020;26:1200–4

- Most patients have detectable antibody by day 21 of symptom onset
- Unclear role in initial diagnosis

Fig. 1: Antibody responses against SARS-CoV-2.



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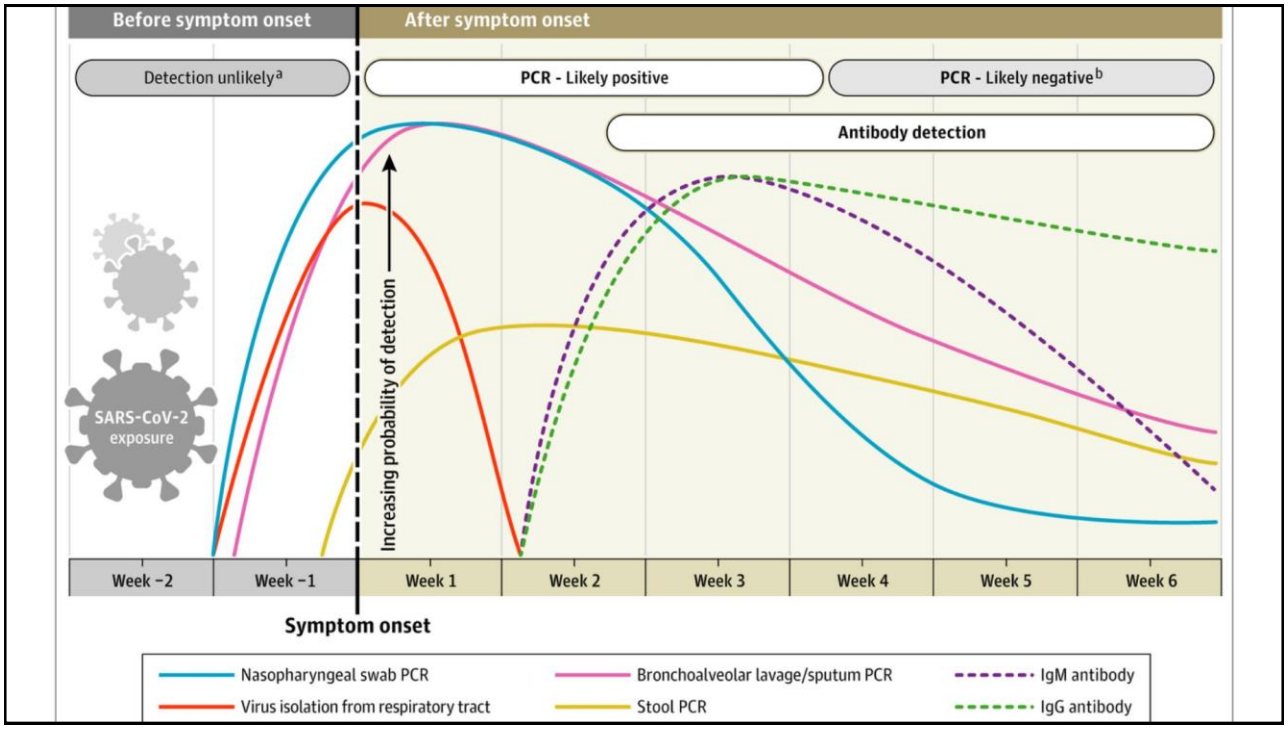

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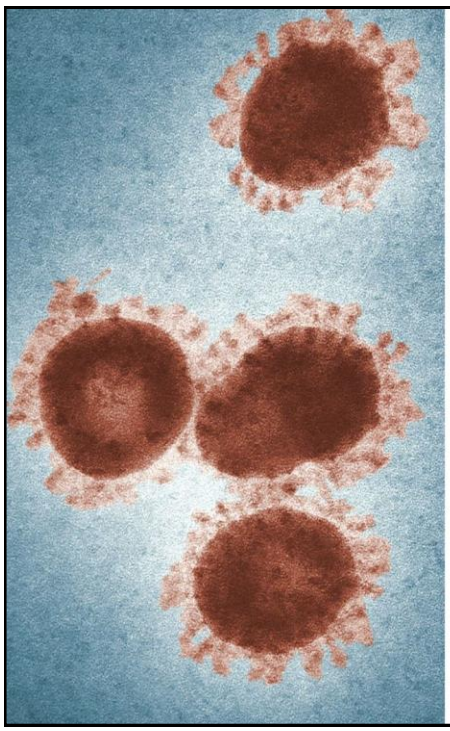

Take home points

Presentation

- **Very low threshold to test**
  variable presentations
- **ARDS delayed presentation**
  10-14 days from symptom onset
- **Normal CXR does not rule out Covid-19**
  CT scan is more sensitive, but unclear role in diagnosis
- **Bacterial vs. viral pneumonia**
  Imaging is not helpful

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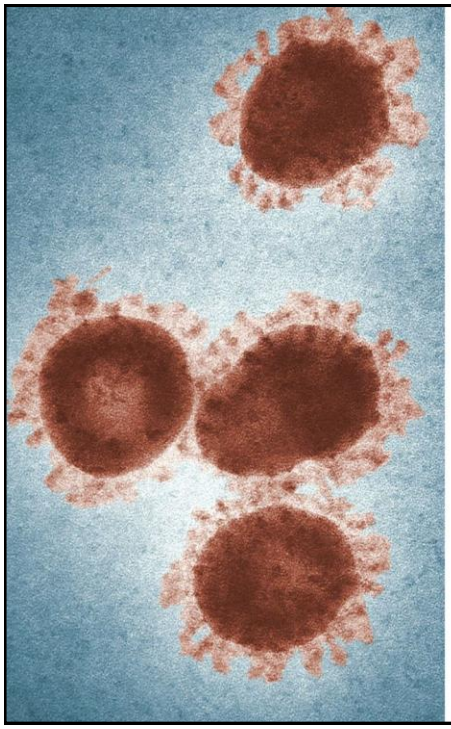

Take home points

Diagnosis

- **PCR-based assays - standard for diagnosis**
- **Sensitivity is variable, false positives possible**
  retest patients with high index of suspicion
- **Antigen assays are less sensitive than PCR**
- **SARS-CoV-2 Antibodies**
  unclear role in diagnosis

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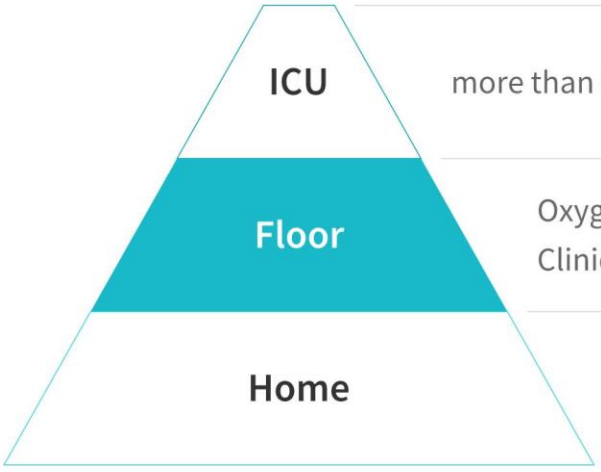
Triage

May be influenced by institutional policies and available resources



more than 6 to 10L oxygen requirement

Oxygen requirement up to 6L
Clinical concern/judgment

No Oxygen requirement
Clear CXR, normal labs

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COVID-19 hospitalized adult: Pharmaceutical management

Maria (Gaby) Frank, MD, FACP, SFHM

Medical Director, Biocontainment Unit

Hospitalist and Associate Director DOM

Denver Health Hospital Authority

Associate Professor of Medicine

University of Colorado, School of Medicine

❖**No Financial COI**

❖**ACTT Site PI**

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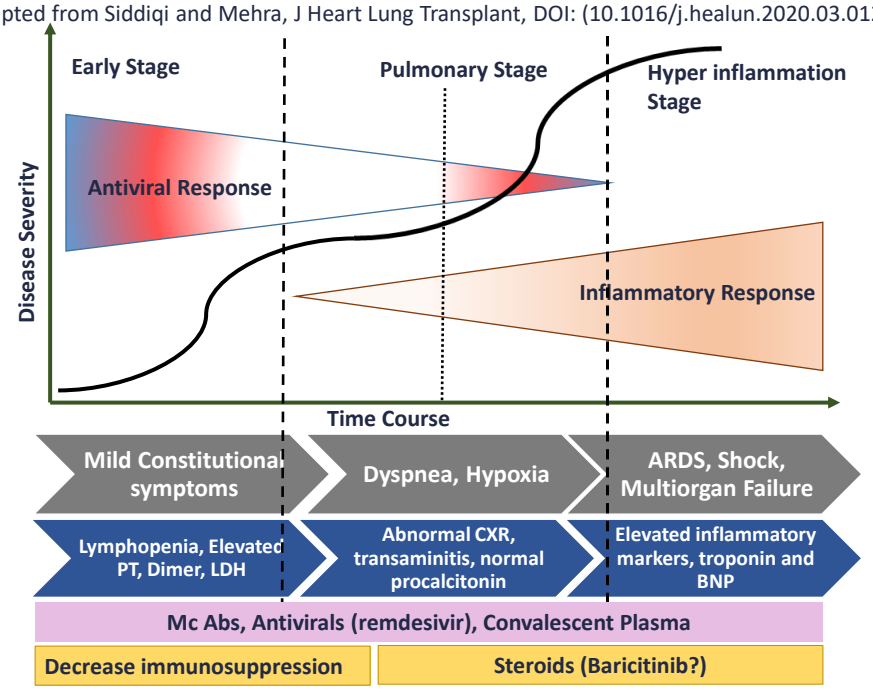
Adapted from Siddiqi and Mehra, J Heart Lung Transplant, DOI: (10.1016/j.healun.2020.03.012



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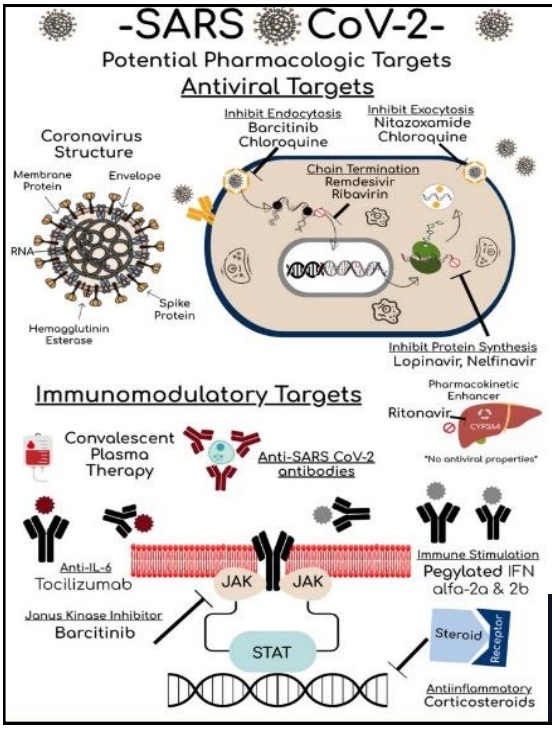

Therapeutic Agents

- Antivirals
- Blood products
  - **Convalescent Plasma**
  - MSC
  - IVIG
- Immuno-modulators
  - **Dexamethasone**
  - IL-1 inhibitors
  - IL-6 Inhibitors(IL-6 mcAb, IL-6 R mcAb)
  - Kinase inhibitors(BTK, **JAK**)
  - INF alfa and beta
- Associated therapies
  - Antithrombotics
  - Vitamin C
  - Vitamin D

Pharmacotherapy 2020;40(5):416–437) doi: 10.1002/phar.2398

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Hydroxychloroquine/ chloroquine:

- **Mechanism of Action (both):** Increase endosomal pH , inhibiting the fusion of to cell membrane. Chloroquine also inhibits glycosylation of ACE-2 Receptor, inhibiting binding of virus to cell membrane (postulated)
- Beyond the in-vitro effect, **in vivo effect has not been demonstrated,** (with or without azythromycin).
- **NO Benefit. +++ Adverse Events**
- **Adverse effects**:
  - Prolonged QTc, torsades des pointes, ventricular arrhythmias
  - hypoglycemia, rash, nausea
  - Retinopathy
  - Could interfere with the antiviral effect of RDV

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*Safe during pregnancy and breastfeeding

Lopinavir/ Ritonavir

- Inhibition of 3CL-pro in vitro. Low sensitivity index , requiring high doses to achieve effect in vivo for SARS-CoV-2
- Darunavir/ cobicistat also inhibit PL-pro
- **Adverse Effects**:
  - Nausea, vomiting, diarrhea
  - QTc prolongation
  - Hepatotoxicity
- **Usual doses don't reach the serum concentration needed to inhibit SARS-CoV-2 replication**

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April 10th , 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

ABSTRACT

May 22nd , 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

April 29th , 2020

Articles

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Gou, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang

Summary

The NEW ENGLAND JOURNAL of MEDICINE

May 27th, 2020

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D., Ronald G. Nahass, M.D., Yao-Shen Chen, M.D., Devi SenGupta, M.D., Robert H. Hyland, D.Phil., Anu O. Osinusi, M.D., Huyen Cao, M.D., Christiana Blair, M.S., Xuelian Wei, Ph.D., Anuj Gaggar, M.D., Ph.D., Diana M. Brainard, M.D., William J. Towner, M.D., Jose Muñoz, M.D., Kathleen M. Mullane, D.O., Pharm.D., Francisco M. Marty, M.D., Karen T. Tashima, M.D., George Diaz, M.D., and Aruna Subramanian, M.D., for the GS-US-540-5773 Investigators*

Research

August 21st , 2020

JAMA | Original Investigation

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19

A Randomized Clinical Trial

Christoph D. Spinner, MD; Robert L. Gottlieb, MD, PhD; Gerard J. Criner, MD; José Ramón Arribas López, MD; Anna Maria Cattelan, MD; Alex Soriano Viladomiu, MD; Onyema Ogbuagu, MD; Prashant Malhotra, MD; Kathleen M. Mullane, DO; Antonella Castagna, MD; Louis Yi Ann Chai, MD; Meta Roestenberg, MD; Owen Tak Yin Tsang, MD; Enos Bernasconi, MD; Paul Le Turnier, MD; Shan-Chwen Chang, MD; Devi SenGupta, MD; Robert H. Hyland, DPhil; Anu O. Osinusi, MD; Huyen Cao, MD; Christiana Blair, MS; Hongyuan Wang, PhD; Anuj Gaggar, MD, PhD; Diana M. Brainard, MD; Mark J. McPhail, MD; Sanjay Bhagani, MD; Mi Young Ahn, MD; Arun J. Sanyal, MD; Gregory Huhn, MD; Francisco M. Marty, MD; for the GS-US-540-5774 Investigators

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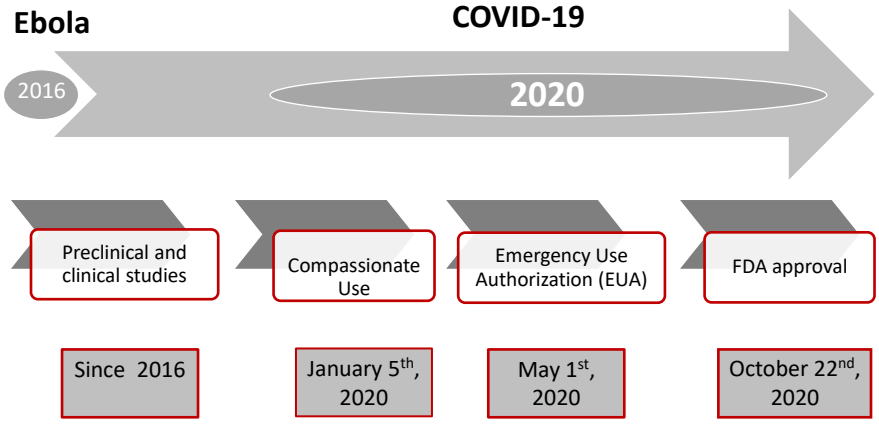
GS- 5734 >> Remdesivir >> Veklury



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Remdesivir

- **Loading dose:** 200 mg IV qd
- **Maintenance dose**: 100 mg IV qd x 5-10 days
- **Adverse effects**:
  - Headache
  - Constipation
  - Nausea and vomiting
  - Anorexia
  - Reversible changes in hepatic enzymes and coagulation
  - Local reactions

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

ABSTRACT

Multi-centric, randomized, open-label study of hospitalized patients for COVID-19. Sponsored by National Health Service (UK).

Decreased mortality in patients with O2 requirement.

Preliminary analysis of 6.425 patients: 2.104 Dexa/ 4.321 SOC. **28 day- Mortality: 22.9% (dexa), 25.7% (SOC) p<0,001. Patients on mechanical ventilation: 29.3% (dexa), 41.4% (SOC)**

O2 requirement (not ventilated): 23.3% (dexa), 26.2% (SOC)

Not on O2: 17% (dexa), 14% (SOC)

Lower risk of progression to MV in the dexamethasone group.

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1. **Dexamethasone (6 mg)**
2. Prednisone (40 mg)
3. Methylprednisolone (32 mg)
4. Hydrocortisone (160 mg)

Corticosteroids (Dexamethasone)

- **Recommended for:**
  - Hospitalized patients in mechanical ventilation (AI)
  - Hospitalized patients not on mechanical ventilation but with O2 requirement (BI)
- **Do not use in patients without O2 requirement (AI)**
- **Dose**: 6 mg/ d x 10 days
- **Adverse Effects**:
  - Hyperglycemia
  - Secondary Infections
  - Avascular necrosis
  - Neurologic events

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

Michael J. Joyner[1*], Stephen A. Klassen[1], Jonathon W. Senefeld[1], Patrick W. Johnson[1], Rickey E. Carter[2], Chad C. Wiggins[1], Shmuel Shoham[3], Brenda J. Grossman[4], Jeffrey P. Henderson[5,6], James M. Musser[7,8,9], Eric Salazar[7,9], William R. Hartman[10], Nicole M Bouvier[11,12], Sean T. H. Liu[11,12], Liise-anne Pirofski[13], Sarah E. Baker[1], Noud van Helmond[14], R. Scott Wright[15,16], DeLisa Fairweather[17], Katelyn A. Bruno[17], Nigel S. Paneth[18,19], and Arturo Casadevall[20]

Abstract

To determine the effect of COVID-19 convalescent plasma on mortality, we aggregated patient outcome data from randomized clinical trials, matched control, and case-series studies. Fixed effects analyses demontrated that hospitalized COVID-19 patients transfused with convalescent plasma exhibited a ~57% reduction in mortality rate (13%) compared to matched-patients receiving standard treatments (25%, OR: 0.43, $P < 0.001$). These data provide evidence favouring the efficacy of human convalescent plasma as a therapeutic agent in hospitalized COVID-19 patients.

Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

Michael J. Joyner[1*], M.D., Jonathon W. Senefeld[1], Ph.D., Stephen A. Klassen[1], Ph.D., John R. Mills[2], Ph.D., Patrick W. Johnson[3], Elitza S. Theel[2], Ph.D., Chad C. Wiggins[1], Ph.D., Katelyn A. Bruno[4], Ph.D., Allan M. Klompas[1], M.B., B.Ch., B.A.O., Elizabeth R. Lesser[3], Katie L. Kunze[3], Ph.D., Matthew A. Sexton[1], M.D., Juan C. Diaz Soto[1], M.D., Sarah E. Baker[1], Ph.D., John R.A. Shepherd[1], M.D., Noud van Helmond[5], M.D., Nigel S. Paneth[7,8#], M.D., M.P.H., Ph.D., DeLisa Fairweather[4#], Ph.D., R. Scott Wright[9,10#], M.D., Rickey E. Carter[3#], Ph.D., Arturo Casadevall[11#], M.D., Ph.D., *the US EAP COVID-19 Plasma Consortium,*

Results: The 35,322 transfused patients had heterogeneous demographic and clinical characteristics. This cohort included a high proportion of critically-ill patients, with 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation at the time of plasma transfusion. The seven-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients transfused within 3 days of COVID-19 diagnosis but 11.9% [11.4%-12.2%] in patients transfused 4 or more days after diagnosis ($p<0.001$). Similar findings were observed in 30-day mortality (21.6% vs. 26.7%, $p<0.0001$). Importantly, a gradient of

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Convalescent Plasma

- **Approved by FDA on August 23rd for Emergency Use Authorization** based by reported results by the Mayo Clinic's Expanded Access Program (EAP)
- **NIH changed treatment guidelines on September 1st highlighting**:
  - Insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19
- **Dose**: 1 unit (200 ml). May repeat
- **Adverse Effects**: Low Incidence
  - Transfusional Reactions (<1%)
  - Thromboembolic or thrombotic events (<1%)
  - Cardiac events (3%)

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FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19

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For Immediate Release: November 09, 2020

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Bamlanivimab is authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms (about 88 pounds), and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes those who are 65 years of age or older, or who have certain chronic medical conditions.

While the safety and effectiveness of this investigational therapy continues to be evaluated, bamlanivimab was shown in clinical trials to reduce COVID-19-related hospitalization or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo.

Bamlanivimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. A benefit of bamlanivimab treatment has not been shown in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Banlanivimab

- 12+
- 40 Kg +
- Mild-mod
- Risk for progressing
- Outpatient
- Not on O2

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NIH Guidelines: Updated November 3rd, 2020

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS (*Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.*)
Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] *or* **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] *or* **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** *or* **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[e] If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See Corticosteroids for more information.
[f] The combination of dexamethasone and remdesivir has not been studied in clinical trials; see text for the rationale for using this combination.

Key: ECMO = extracorporeal membrane oxygenation; IV = intravenously; PO = orally

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Antivirals

Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: November 3, 2020

Summary Recommendations

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.** For more information on these antiviral agents, see Table 2.

Remdesivir

- See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone.

Chloroquine or Hydroxychloroquine With or Without Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without azithromycin for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** using **lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial.

Ivermectin

- The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

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Blood-Derived Products

Blood-Derived Products Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
  - **COVID-19 convalescent plasma**
  - **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
- The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
  - **Mesenchymal stem cells (AII)**
  - **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII).** This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

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Immuno-modulators

Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: November 3, 2020

Summary Recommendations
Dexamethasone and Other Corticosteroids • The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of dexamethasone (or other corticosteroids) with or without remdesivir can be found in the Therapeutic Management of Patients with COVID-19.
Other Immunomodulators There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • Interleukin (IL)-1 inhibitors (e.g., **anakinra**). • **Interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • Anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab**, **tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) **(BI)**. • **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**. • Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and Janus kinase inhibitors (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

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Conclusion: Remdesivir

- Many trials, some controversial. **NIH recommends using on all hospitalized patients with moderate or severe COVID-19 for a total of 5 days.** ECMO and ventilated patients excluded from recommendation. **FDA approved for all hospitalized COVID patients**
- Decreased time to recovery by 50%
- Trend to lower mortality
- Efficacy in extremes of clinical stages still unknown

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Conclusion: Steroids

- Decreased mortality in patients with severe COVID-19 (on O2)
- Recommended for hospitalized patients on mechanical ventilation (AI)
- Recommended for hospitalized patients requiring O2, not ventilated (BI)
- Don't use in patients not requiring O2 (AI)
- Dexamethasone 6 mg/ d x 10 d
- More randomized, and D-B trials are needed. Follow up final results RECOVERY trial.

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Conclusion: Convalescent Plasma

- Current evidence (no randomized, controlled prospective studies) suggest efficacy when used early in the disease (53% decrease in mortality)
- Low incidence of adverse events
- Approved by FDA for EUA on August 23rd, 2020
- NIH doesn't recommend for standard treatment of COVId-19 patients (further research needed)

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Associated Therapies

- **VTE Prophylaxis, Hospitalized patients**: Follow institutional guidelines
- **VTE prophylaxis at discharge**: not recommended unless:
  - Modified IMPROVE-VTE score >/= 4
  - Modified IMPROVE- VTE score >/= 2 and D-dimer>2 ULN
  - Age>75
  - Age >60 y D-Dimer >/= 2 ULN
  - Age between 40-60 , D-Dimer >/- 2 ULN y prior VTE or cancer

Rivaroxaban or Betrixaban

- **Anticoagulation**: similar to non-COVID-19 patients
- **Vitamin C**: insufficient information (variable results in ARDS)
- **Vitamin D**: postulated effect, ongoing trials
- **Zinc:** recommendation against its use.
- **Associated Therapies**
  - ACEi/ARBs: as prescribed
  - Steroids: don't use in patients not requiring O2
  - NSAIDs: similar to non-COVID-19
  - Statins: as prescribed

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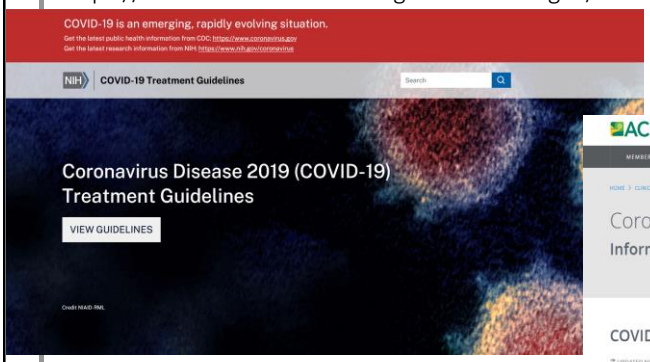
https://www.covid19treatmentguidelines.nih.gov/



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https://www.nejm.org/coronavirus

https://jamanetwork.com/collections/46099/coronavirus-covid19

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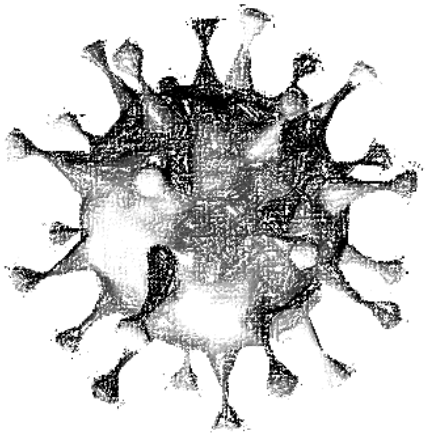
THANK YOU

Maria.Frank@dhha.org



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Typical clinical course

- **Worsening of respiratory status typically occurs between days 7-10**
  - **Suggests to me that severe disease is probably not directly virally mediated**

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Actual Case

38 year old active male with BMI of 46 and no other significant PMHx. Admitted initially on 2L on day 7 of symptoms.

- **On HD #1, increased O2 to 3-4L. Considered for discharge given relatively low O2 needs.**
- **Some hesitation about DC given increased O2 needs over first 24h.**
- **Additionally had high ferritin (~900)/CRP values (200) at admission.**
- **Over next 48h, persistent hypoxemia requiring 50L HHF at 100% FiO2.**
- **Still hospitalized on 50L at 70% FiO2 ten days later.**

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Risk factors for decompensation

- **Demographics and PMHx**
  - **Male**
  - **Obese (BMI 30+; definitely if BMI 40+)**
  - **Uncontrolled diabetes/HTN usually with proteinuria**
- **Exam**
  - **Tachypnea**
- **Lab values: Very high initial CRP/ferritin (women usually have lower values)**
  - **CRP > 150**
  - **Ferritin ~ 1000 mg/dL**
- **Radiographic findings**
  - **Extent of opacities on initial CXR**

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Ongoing Monitoring

- **Clinical monitoring**
  - Respiratory status (RR, O2 requirements, desaturations and recovery time)
  - Volume status (often difficult 2/2 habitus in these patients)

- **Lab monitoring**
  - **CRP** (trend usually follows disease course)
  - **Ferritin** (less useful for daily trending, tends to lag; useful later in course)
  - Hepatic panel (for Remdesivir treatment monitoring)
  - Basic metabolic panel and CBC
  - POC glucose (co-morbidities of diabetes/obesity + dexamethasone)
  - *pro-BNP* (can help with high BMI patients to suggest/monitor prn diuresis)

Ongoing Monitoring

Radiographic monitoring

- CXR
  - Repeat for acute increase in O2
  - Nearly always shows just worsening of initial infiltrates
- CT PE
  - If clinical concern at admission or markedly elevated D-dimer
  - Clinical worsening after initial improvement without CXR progression
  - Plateau in O2 needs at high level after 5-7 days

Cardiac monitoring

- TTE +/- bubble study

Typical clinical course of hypoxemia

Day 7-10 **Day 14-17** **Day 17+**

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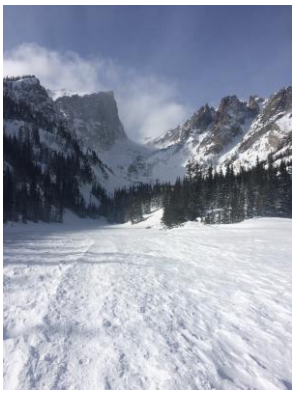
Clinical course after intubation



Intubation and mechanical ventilation
Typically ARDSnet protocol, high PEEP pathway
Paralysis and lots of sedation often needed for oxygenation
Frequently prone patients while on the vent
Very slow wean and duration of mechanical ventilation is long with lots of complications
-VAP/CAUTI
-Critical illness polyneuropathy
-Prolonged delirium
-Decubitus wounds/tongue swelling/facial wounds

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What to do if worsening

Repeat CXR, low threshold for CT PE. Consider trial of diuresis if can tolerate HD.

- Upgrade patient to heated high flow oxygen early, if available (NRB OK)
- Have patient lie prone
- Some patients have a particular position in which they can maintain better sats—have them get in it and stay in it as much as possible!
  - Surprisingly similar to fetal decelerations in pregnancy
  - Trial/Error may be required to determine optimal position to maintain sats
  - Best position doesn't always correlate with radiographic findings
- With HHF and positioning, can avoid intubation in many patients
- MV often prolonged and a/w severe delirium, polyneuropathy, 2ary infections

Etiologies to consider if non-improvement

- Pulmonary embolism
  - CT PE (D-dimer usually low yield as almost always abnormally elevated)
- CHF/arrhythmia
  - EKG with Trop/pro-BNP (assumes you have prior data points)
  - TTE
- Secondary infections
  - Repeat cultures/chest imaging
  - Sputum culture
- Thyrotoxicosis: check TFTs
- Organizing pneumonia
  - CT chest and pulmonary consult

Considerations of discharge

Need to be through the "Keyhole of truth" (day 7-10) if patient has risk factors for acute and severe decompensation. Caution against discharge if:

- **BMI > 40, male**
- **Markedly elevated CRP/ferritin that have not improved significantly from prior**
- **Severe lung involvement on CXR**
- **Non-resolved tachypnea**
- **Increasing O2 needs (even if low)**

Signs of DC appropriateness

- ***Passed through the "Keyhole of truth" (days 7-10) if high risk of progression***
- No oxygen requirement great, but
- OK for DC if stable oxygen requirements for 24-48h
  - High, stable needs not a contraindication (3-4L at rest, up to 6L with exertion)
- Afebrile 24-48h
- Eating/ambulating
- Exertional O2 challenge prior to discharge important
  - If marked desats occur with exertion, exertion requires prolonged recovery, or tachypnea/coughing fit develops-->not ready for DC

*We have gotten more "aggressive" about DC with supplemental oxygen since April

Logistics of discharge

- Arrange for home O2
- Transporation (AMR if no friends/family/self)
- Written instructions on self-isolation procedure
- If family/friends
  - Patient gets surgical mask
  - Advise family to use mask
  - Patient in back passenger seat
  - Drive with windows DOWN
- Ideally have mechanism in place to check in with patients by phone after discharge
- Pulse oximeter as discharge and teaching on use/interpretation is helpful
- "Activated" respite for homeless patients (single room), supported by community

Questions?

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Evaluation

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