Covid-19

Kevin Shiley, MD
Catholic Health

TESTING

TREATMENT

5/4/2020

Erie County

Confirmed	Recovered	Deaths
3,710	479	268

New York

Confirmed	Recovered	Deaths
319K	-	19,415
+2,538		+226

United States

Confirmed	Recovered	Deaths
1.21M	160K	69,680
+21,278		+877

Worldwide

Confirmed	Recovered	Deaths
3.58M	1.17M	252K
+86,108		+976

Who Should be Tested?

CDC Guidance

PRIORITIES FOR COVID-19 TESTING

(Nucleic Acid or Antigen)

High Priority

- Hospitalized patients **with** symptoms
- Healthcare facility workers, workers in congregate living settings, and first responders **with** symptoms
- Residents in long-term care facilities or other congregate living settings, including prisons and shelters, **with** symptoms

Priority

- Persons **with** symptoms of potential COVID-19 infection, including: fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat.
- Persons **without** symptoms who are prioritized by health departments or clinicians, for any reason, including but not limited to: public health monitoring, sentinel surveillance, or screening of other asymptomatic individuals according to state and local plans.

Erie County DOH Guidance

GALE R. BURSTEIN, MD, MPH
COMMISSIONER OF HEALTH

May 5, 2020

Erie County Department of Health (ECDOH)/Erie County Public Health Lab (ECPHL)
Protocol for COVID-19 Diagnostic Testing

ECDOH is currently testing for the following persons:

- Any individual who has symptoms of COVID-19 (includes any of the following: fever of 100.4 degrees or higher, cough, shortness of breath, chills, repeated shaking with chills, muscle pain, headache, sore throat, diarrhea, new loss of taste or smell.)

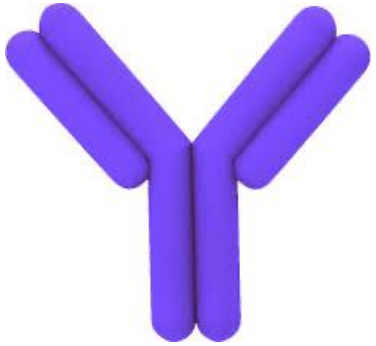
- Any individual who believes that they may have been exposed to COVID-19.

If you meet the above criteria, please call the ECDOH at 716-858-2929 to initiate the testing process.

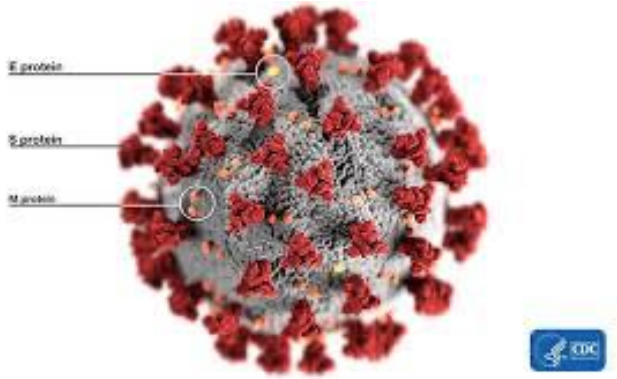
Which test?

Testing Options

Nucleic Acid Testing (PCR)

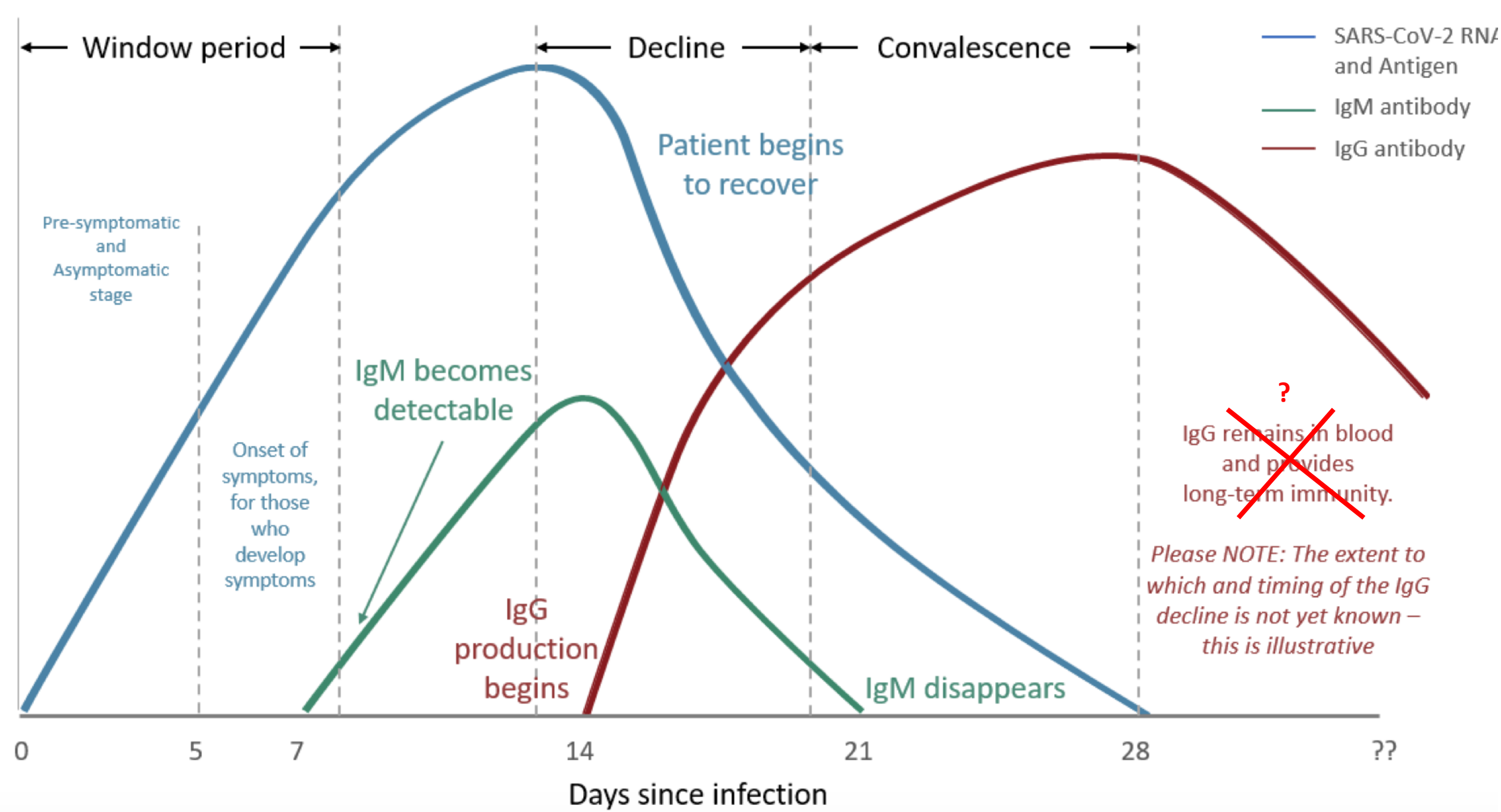


Antibody



Antigen

(in development)



*Disclaimer: This chart is for illustrative purposes only

Nucleic Acid Testing

- RT-PCR Detects viral RNA
- Cannot determine viable vs. non-viable viral material
- Debate regarding infectiousness of recovered individuals with positive PCR

NEJM

•**Non-Surgical Patients**

•Drive thru COVID testing is available every day, 7am-3pm, for patients seen by Catholic Medical Partners physicians.

Testing locations are:

- The Mercy Ambulatory Care Center (MACC) 3669 Southwestern Blvd., Orchard Park
- Kenmore Mercy Hospital 2950 Elmwood Avenue, Kenmore

• If a patient seen by a CMP provider is suspected of having COVID-19, the physician's office will obtain the patient's preferred testing site and complete an order for the test.

- **The physician's office will complete a** COVID-19 PCR Test Order **and fax it to the test site registration department who will then contact the patient to schedule them for a COVID-19 PCR test. Fax and telephone numbers for each testing location are included on the form.**
  - If COVID-19 is detected, the Lab will contact the physician's office with the results.
  - The physician's office will then be responsible for contacting the patient for further follow-up.

- **Pre-Surgical Patients:**

The physician's office will complete a COVID-19 PCR Test Order and fax it to the hospital schedulers, who will coordinate with Patient Access to schedule the patient for a COVID-19 PCR test.

○ If COVID-19 is detected, the Lab will contact the physician's office with the results.

○ The physician's office will then be responsible for contacting the patient to postpone the procedure until the patient is COVID-19 free.

Serological (Antibody) Testing SARS-CoV-2

- Serology may indicate active or past infection
- 70-100% people are seropositive by day 14 of infection in early studies
- IgG serology cannot differentiate recent vs old infection
- Presently, no data to support or refute lasting immunity to SARS-CoV-2
- Active viral shedding is possible after seroconversion (shedding common 2-4 weeks after initial PCR test)
- Cross reaction with other coronaviruses unclear; likely depends on assay
  - chemiluminescent microparticle immunoassay; low x-reactivity reported
- No test on market is actually FDA approved

Asymptomatic Covid-19

- Common in viral illnesses
    - Measles 8%
    - Norovirus 30%
    - Polio: 90-95%
- Asymptomatic and Pre-symptomatic Transmission
    - Difficult to determine if true asymptomatic vs. pre-symptomatic in current studies

Morbidity and Mortality Weekly Report

Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020

Wycliffe E. Wei, MPH[1,2]; Zongbin Li, MBBS[1]; Calvin J. Chiew, MPH[1]; Sarah E. Yong, MMed[1]; Matthias P. Toh, MMed[2,3]; Vernon J. Lee, PhD[1,3]

- Estimated 13% of transmission events in the outbreak were related to pre-symptomatic cases.
    - Most pre-symptomatic transmissions occurred with close prolonged contacts

Morb Mortal Wkly Rep 2020;69:312-313.
DOI: http://dx.doi.org/10.15585/mmwr.mm6911e2external icon

Rapid communication

Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020

Kenji Mizumoto[1,2,3], Katsushi Kagaya[2,4], Alexander Zarebski[5], Gerardo Chowell[3]

- 50% of infected individuals on Princess Diamond Cruise ship Asymptomatic before being disembarked

1.Eurosurveillance. Volume 25, Issue 10, 12/Mar/2020

ORIGINAL ARTICLE

Spread of SARS-CoV-2 in the Icelandic Population

Daniel F. Gudbjartsson, Ph.D., Agnar Helgason, Ph.D., Hakon Jonsson, Ph.D., Olafur T. Magnusson, Ph.D., Pall Melsted, Ph.D., Gudmundur L. Norddahl, Ph.D., Jona Saemundsdottir, B.Sc., Asgeir Sigurdsson, B.Sc., Patrick Sulem, M.D., Arna B. Agustsdottir, M.Sc., Berglind Eiriksdottir, Run Fridriksdottir, M.Sc., et al.

- 43% of positive screened Individuals reported no symptoms

- “In the population-screening group…none of the 848 children under the age of 10 years tested positive, as compared with 100 of 12,232 persons (0.8%; 95% CI, 0.7 to 1.0) 10 years of age or older."

NEJM April 14, 2020 DOI: 10.1056/NEJMoa2006100

RESEARCH ARTICLE

CORONAVIRUS

Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2)

Ruiyun Li[1]*, Sen Pei[2]*†, Bin Chen[3]*, Yimeng Song[4], Tao Zhang[5], Wan Yang[6], Jeffrey Shaman[2]†

- Asymptomatic transmission estimated to be about 50% less efficient than symptomatic transmission per encounter
- However, Asymptomatic cases estimated to contribute to up to 79% of all transmission events in Wuhan

Li et al., Science 368, 489–493 (2020) 1 May 2020

Serology and false positives

- Wadsworth (NYDOH) SARS-CoV-2 Antibody Testing 93-100% specificity

Erie County Week Ending	Total Ab tests	Positive Tests	% Results Test Positive	#Estimated False Positives tests (3% FP rate)	#Estimated False Positives tests (7% FP rate)
4/25/2020	1145	147	12.8%	34 (23% of all positive tests	80 (54% all positive tests)
5/2/2020	7078	532	7.5%	212 (39% of all positive tests)	495 (93% of all positive tests)

Serology and false positives

- Abbott SARS-CoV-2 IgG Testing 99.0-99.9% specificity (per Abbott)

Erie County Week Ending	Total Ab tests	Positive Tests	% Individuals Test Positive	#False Positives tests (0.5% FP rate)	# False Positives tests (1% FP rate)
4/25/2020	1145	147	12.8%	5 (3.8% of all positive tests	10 (7.6% of all positive tests
5/2/2020	7078	532	7.5%	35 (6.6% of all positive tests)	70 (13.2% of all positive tests)

Summary: Testing

- PCR Testing is required for diagnosis of acute infection
  - Drive trough testing available for CMP patients through Catholic Health
- Antibody Testing
  - Not for diagnosis of acute illness
  - Epidemiological relevance, role in individual care is uncertain
  - False Positive rate must be taken into consideration, especially in low disease prevalence settings

  Lasting immunity remains uncertain

Treatment

- Antivirals
- Immunomodulators
- Immunotherapy

FDA MedWatch Advisory 4/24/2020

"If a health care professional is considering use of hydroxychloroquine or chloroquine to treat or prevent COVID-19, FDA recommends checking www.clinicaltrials.gov for a suitable clinical trial and considering enrolling the patient. Consider using resources available to assess a patient's risk of QT prolongation and mortality."

Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2

Brandi N. Williamson[1], MPH; Friederike Feldmann[2], AS; Benjamin Schwarz[3], PhD; Kimberly Meade-White[1], MSc; Danielle P. Porter[5], PhD; Jonathan Schulz[1], BSc; Neeltje van Doremalen[1], PhD; Ian Leighton, BA[3]; Claude Kwe Yinda[1], PhD; Lizzette Pérez-Pérez[1], MSc; Atsushi Okumura[1], DVM; Jamie Lovaglio[2], DVM; Patrick W. Hanley[2], DVM; Greg Saturday[2], DVM; Catharine M. Bosio[3], PhD; Sarah Anzick[4], PhD; Kent Barbian[4], MSc; Tomas Cihlar[5], PhD; Craig Martens[4], PhD; Dana P. Scott[2], DVM; Vincent J. Munster[1], PhD; Emmie de Wit[1*], PhD

At necropsy on day 7 after inoculation, lung viral loads of remdesivir-treated animals were significantly lower and there was a clear reduction in damage to the lung tissue

No difference in upper airway viral loads but Fewer cases of overt pneumonia at day 7.

ORIGINAL ARTICLE

Compassionate Use of Remdesivir for Patients with Severe Covid-19

Jonathan Grein, M.D., Norio Ohmagari, M.D., Ph.D., Daniel Shin, M.D., George Diaz, M.D., Erika Asperges, M.D., Antonella Castagna, M.D., Torsten Feldt, M.D., Gary Green, M.D., Margaret L. Green, M.D., M.P.H., François-Xavier Lescure, M.D., Ph.D., Emanuele Nicastri, M.D., Rentaro Oda, M.D., et al.

- Uncontrolled, case series, 55 patients with follow-up data
- 36 patients (68%) had an improvement in oxygen-support
- 17 of 30 patients (57%) receiving mechanical ventilation who were extubated.
- 25 patients (47%) were discharged
- 7 patients (13%) died;
- mortality was 18% (6 of 34) among patients receiving invasive ventilation
- 5% (1 of 19) among those not receiving invasive ventilation.

NEJM April 10, 2020. DOI: 10.1056/NEJMoa2007

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 Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

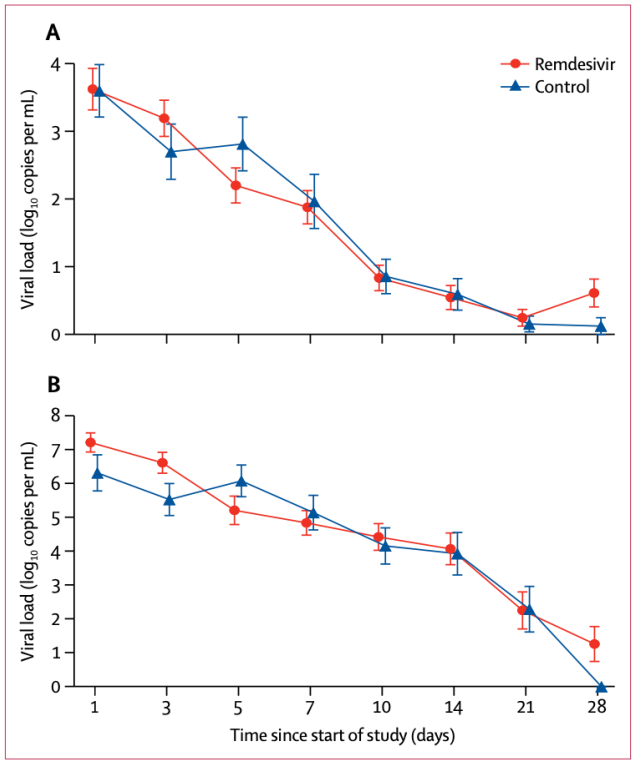
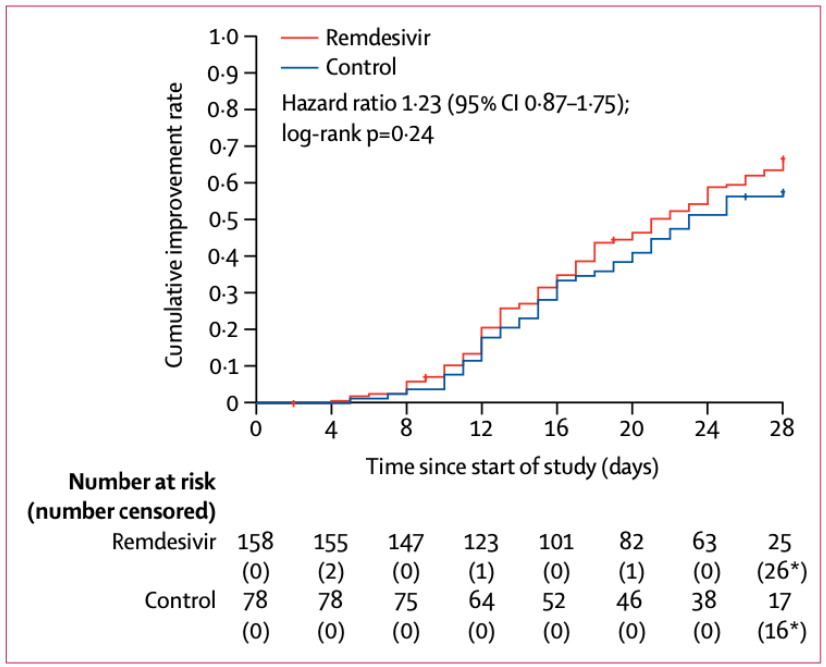


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual value; results of patients with viral-negative RNA are imputed with 0 log_{10} copies per mL.



Number at risk (number censored)								
Remdesivir	158	155	147	123	101	82	63	25
	(0)	(2)	(0)	(1)	(0)	(1)	(0)	(26*)
Control	78	78	75	64	52	46	38	17
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(16*)

Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.

April 29, 2020 https://doi.org/10.1016/S0140-6736(20)31022-9

NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19

April 29, 2020

"Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p<0.001$). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p=0.059$)."

NIH press release

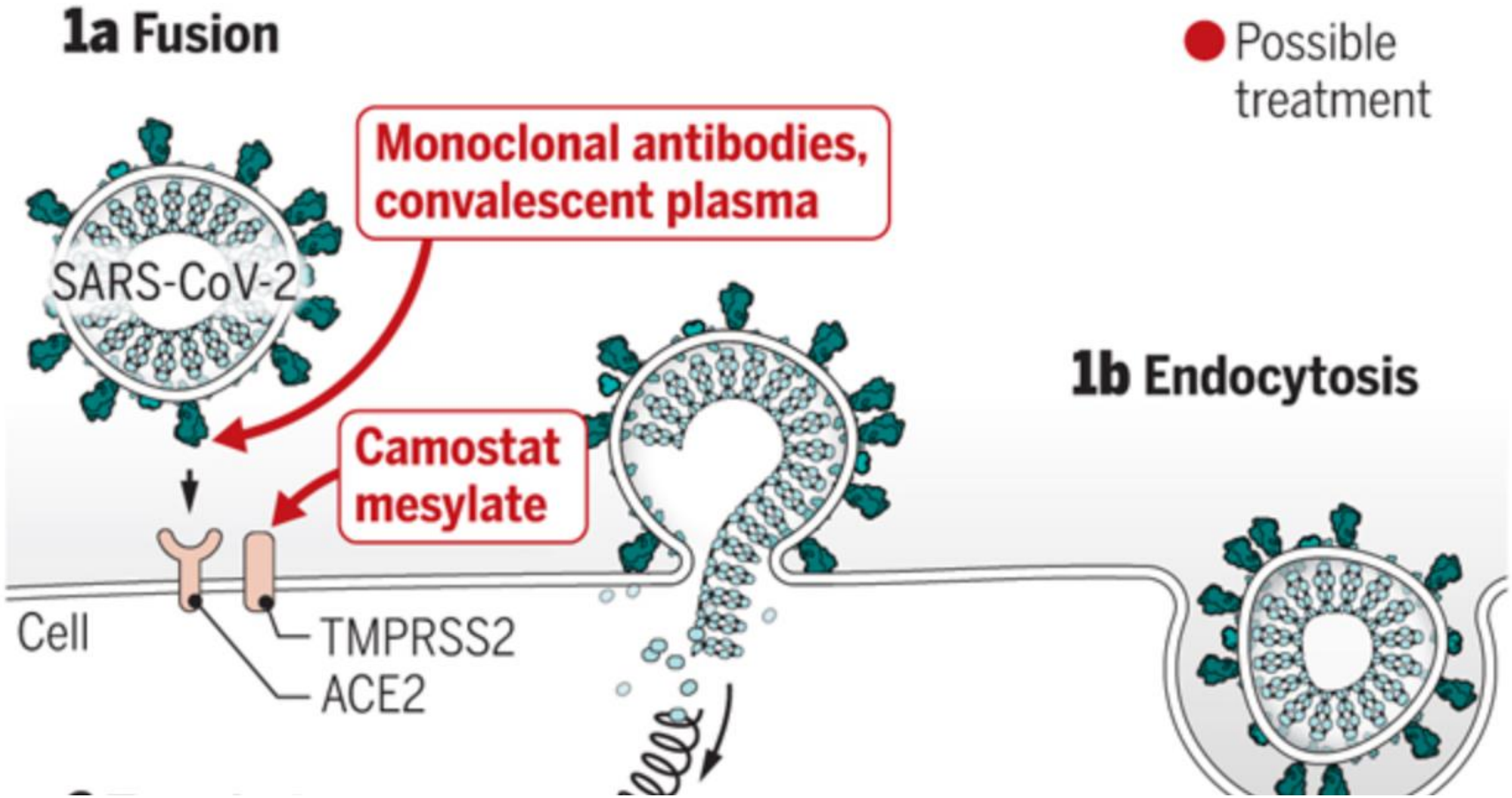
Antivirals: NIH Guidance

- **Hydroxychloroquine:** insufficient clinical data to recommend either for or against using **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19 **(AIII)**.
  - If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects, especially prolonged QTc interval **(AIII)**.
- **Remdesivir:** insufficient clinical data to recommend either for or against using the investigational antiviral drug **remdesivir** for the treatment of COVID-19 **(AIII)**.
  - Remdesivir as a treatment for COVID-19 is currently being investigated in clinical trials and is also available through expanded access and compassionate use mechanisms for certain patient populations.
- Except in the context of a clinical trial, the COVID-19 Treatment Guidelines Panel (the Panel)**recommends against** the use of the following drugs for the treatment of COVID-19:
  - The combination of **hydroxychloroquine plus azithromycin (AIII)** because of the potential for toxicities.
  - **Lopinavir/ritonavir (AI)** or other **HIV protease inhibitors (AIII)** because of unfavorable pharmacodynamics and negative clinical trial data.

FDA Statement on Remdesivir

- Distribution of the authorized remdesivir will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Gilead will supply remdesivir to authorized distributors[4], or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed;

- The remdesivir covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO2 ≤ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO);



Science 27 Mar 2020:

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

Kai Duan[a,b,1], Bende Liu[c,1], Cesheng Li[d,1], Huajun Zhang[e,1], Ting Yu[f,1], Jieming Qu[g,h,i,1], Min Zhou[g,h,i,1], Li Chen[j,1], Shengli Meng[b], Yong Hu[d], Cheng Peng[e], Mingchao Yuan[k], Jinyan Huang[l], Zejun Wang[b], Jianhong Yu[d], Xiaoxiao Gao[e], Dan Wang[k], Xiaoqi Yu[m], Li Li[b], Jiayou Zhang[b], Xiao Wu[d], Bei Li[e], Yanping Xu[g,h,i], Wei Chen[b], Yan Peng[d], Yeqin Hu[b], Lianzhen Lin[d], Xuefei Liu[g,h,i], Shihe Huang[b], Zhijun Zhou[d], Lianghao Zhang[b], Yue Wang[d], Zhi Zhang[b], Kun Deng[d], Zhiwu Xia[b], Qin Gong[d], Wei Zhang[d], Xiaobei Zheng[d], Ying Liu[d], Huichuan Yang[a], Dongbo Zhou[a], Ding Yu[a], Jifeng Hou[n], Zhengli Shi[e], Saijuan Chen[l], Zhu Chen[l,2], Xinxin Zhang[m,2], and Xiaoming Yang[a,b,2]

- Minimal effectiveness data for SARS-CoV-2
- Long history of CP use with other emerging infectious diseases
- Protective effect in primate model of SARS-CoV-2
- Unclear if benefit in patients with late disease
- Variability in antibody levels per donor

PNAS April 28, 2020 117 (17) 9490-949

Catholic Health Convalescent Plasma Program

- Hospitalized Patients with severe illness
- Partnered with Mayo Clinic Expanded Access Program (2100 Hospitals; >6000 treated to date)
- Convalescent Plasma Donors referred to RPCI for collection
  - Booked through May
  - Multiple treatments per donation
  - Able to bank frozen CP up to one year
- New York Blood Center and American Red Cross also provide plasma (non-referred)
- Work on program began March, 31.
- First patient treated April 16.
- If you are interested in signing up for the donor list, you can go to: https://forms.roswellpark.org/covid-plasma-donation

Effective treatment of severe COVID-19 patients with tocilizumab

Xiaoling Xu[a,1,2], Mingfeng Han[b,1], Tiantian Li[a], Wei Sun[b], Dongsheng Wang[a], Binqing Fu[c,d], Yonggang Zhou[c,d], Xiaohu Zheng[c,d], Yun Yang[e], Xiuyong Li[f], Xiaohua Zhang[b], Aijun Pan[e], and Haiming Wei[c,d,2]

[a]Respiratory and Critical Care Medicine, The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital), Hefei, Anhui 230000, People's Republic of China; [b]Respiratory and Critical Care Medicine, Anhui Fuyang Second People's Hospital, Fuyang, Anhui 230000, People's Republic of China; [c]Institute of Immunology and the Chinese Academy of Sciences (CAS) Key Laboratory of Innate Immunity and Chronic Disease, School of Life Science and Medical Center, University of Science and Technology of China, Hefei, Anhui 230000, People's Republic of China; [d]Hefei National Laboratory for Physical Sciences at Microscale, University of Science and Technology of China, Hefei, Anhui 230000, People's Republic of China; [e]Intensive Care Unit, The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital), Hefei, Anhui 230000, People's Republic of China; and [f]Hemodialysis Center, Anhui Fuyang Second People's Hospital, Fuyang, Anhui 236000, People's Republic of China

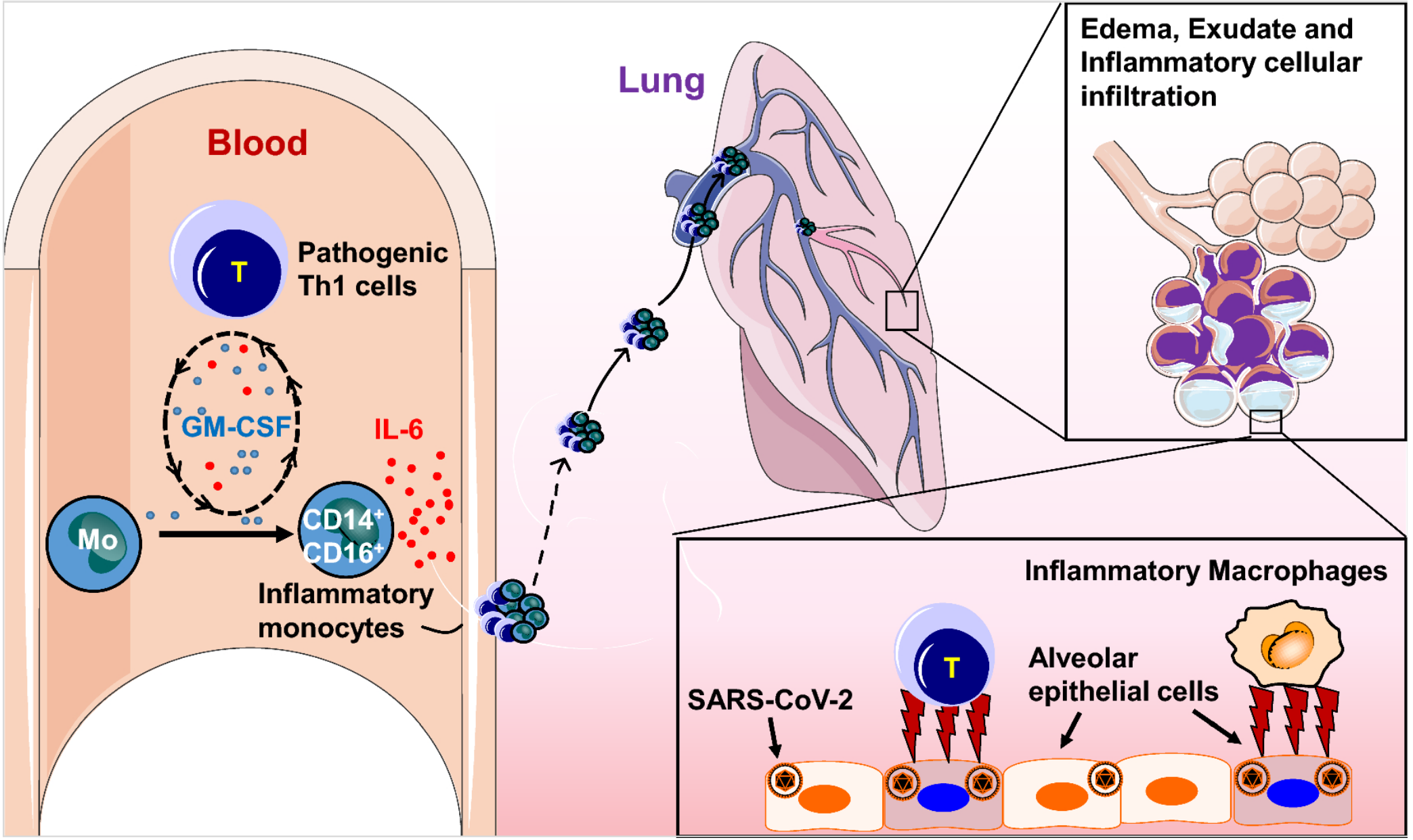
Edited by Zhu Chen, Shanghai Jiao Tong University, Shanghai, China, and approved April 14, 2020 (received for review March 25, 2020)

21 patients, uncontrolled, retrospective

***Actual* trials for various Il-6 Inhibitors are pending**

NIH Guidance Immuno-modulators

- There are insufficient clinical data to recommend either for or against the use of the following agents for the treatment of COVID-19 **(AIII)**:
  - **Interleukin-6 inhibitors** (e.g., sarilumab, siltuximab, tocilizumab)
  - **Interleukin-1 inhibitors** (e.g., anakinra)
- Except in the context of a clinical trial, the Panel **recommends against** the use of other immunomodulators, such as:
  - **Interferons (AIII)**, because of lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.
  - **Janus kinase inhibitors** (e.g., baricitinib, acalabrutinab) **(AIII),** because of their broad immunosuppressive effect.



Journal of Translational Medicine **volume 18**, Article number: 164 (2020)

NIH Guidance: Steroids and NSAIDS

Corticosteroids

- *For Critically Ill Patients with COVID-19:*
  - **recommends against** corticosteroids with COVID-19 *without* acute respiratory distress syndrome (ARDS)**(AIII)**.
  - For mechanically ventilated patients with ARDS, there is insufficient evidence to recommend for or against the use of systemic corticosteroids **(CI)**.
- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids **(BII)**.
- *Hospitalized, Non-Critically Ill Patients with COVID-19:*
  - **recommends against** corticosteroids for the treatment of COVID-19 in hospitalized patients

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

- Persons with COVID-19 who are taking NSAIDs for a co-morbid condition should continue therapy as previously directed by their physician **(AIII)**.
- Recommend no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 **(AIII).**

Bloomberg

Prognosis

Pfizer Starts U.S. Trials of Experimental Covid-19 Vaccine

By Cynthia Koons

May 5, 2020, 6:45 AM EDT *Updated on May 5, 2020, 9:41 AM EDT*

and at a variety of doses and schedules -- and will decide as the trials proceed which is the most effective. The aim is to have a shot ready for emergency use by the fall.

Phase 3 expansion is expected to involve 5000 volunteers; results from the earlier trials will be included in the efficacy follow-up. “The best-case scenario is that by the autumn of 2020, we have an efficacy result from phase 3 and the ability to manufacture large amounts of the vaccine, but these best-case timeframes are highly ambitious and subject to change”, Gilbert says. “Our ability to determine vaccine efficacy will be affected by the amount of virus transmission in the local population over the summer, and we are also beginning to think about initiating trials with partners in other countries to increase our ability to determine vaccine efficacy”, she says.

The Lancet, April 23, 2020: DOI: https://doi.org/10.1016/S0140-6736(20)30796-0

Summary: Treatments

Therapeutic Options Remain limited

- Convalescent plasma is most readily available option
  - Safe track record
  - Concentrated Immunoglobulin on horizon
- Remdesevir is most studied antiviral, remains difficult to obtain & evidence is still not complete
- Immune Modulation for Cytokine storm is commonly attempted
  - Anecdotal data driving use
  - Would not assume Laboratory end points (e.g. declining CRP) translate to clinical benefits
  - Increasing use of corticosteroids in some ARDS cases
  - Several Clinical Trials underway
- Managing hypercoaguable state (?) in severely ill patients