Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19: Clinical Update

Elizabeth A. Talbot MD, Professor Dartmouth, Deputy State Epidemiologist, NH

GEISEL SCHOOL OF MEDICINE AT DARTMOUTH

What is driving the Pandemic?

EPIDEMIOLOGIC FEATURES

26 March 2020

Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Ho…

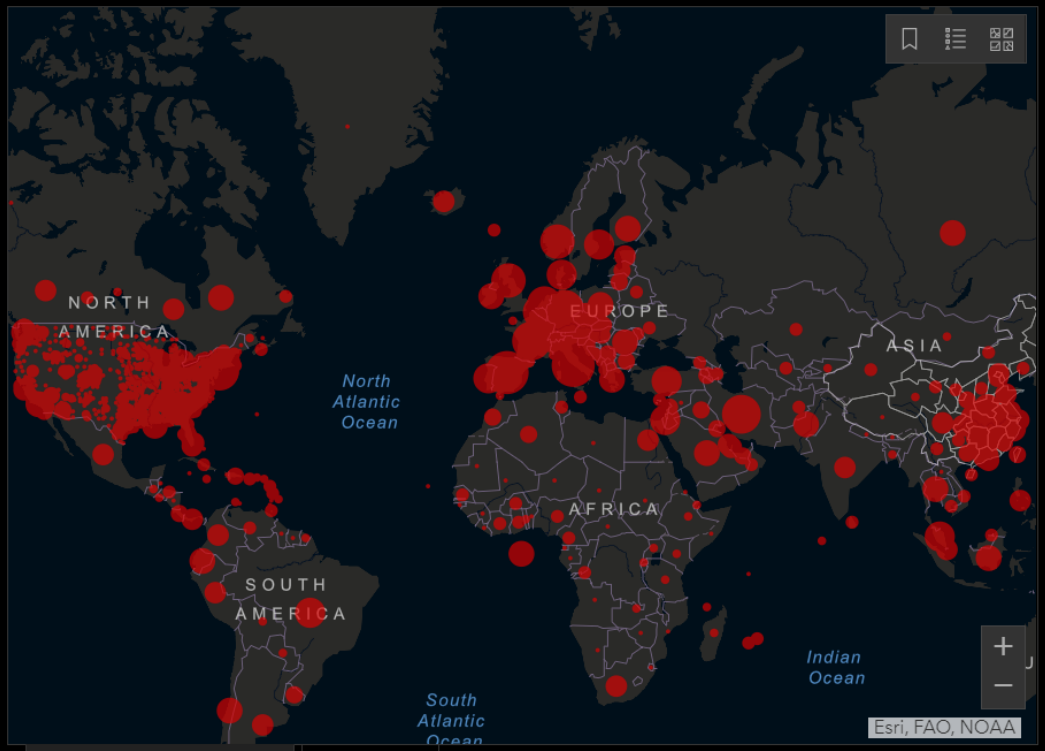
Total Confirmed
487,648

Confirmed Cases by Country/Region/Sovereignty

- 81,782 China
- 74,386 Italy
- 69,197 US
- 56,188 Spain
- 39,502 Germany
- 29,406 Iran
- 25,604 France
- 11,125 Switzerland
- 9,642 United Kingdom
- 9,241 Korea, South
- 6,440 Netherlands
- 6,235 Belgium

Admin1

Last Updated at (M/D/YYYY)
3/26/2020, 7:29:49 AM



Cumulative Confirmed Cases | Active Cases

175
countries/regions

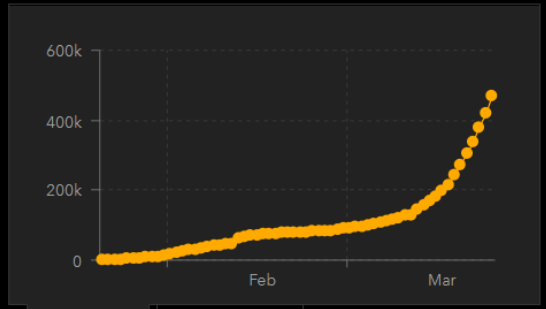
Lancet Inf Dis Article: Here. Mobile Version: Here. Visualization: JHU CSSE. Automation Support: Esri Living Atlas team and JHU APL. Contact US. FAQ.
Data sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports. Read more in this

Total Deaths
22,030

- 7,503 deaths Italy
- 4,089 deaths Spain
- 3,169 deaths **Hubei** China
- 2,234 deaths Iran
- 1,331 deaths France
- 465 deaths United Kingdom
- 356 deaths Netherlands

Total Recovered
117,749

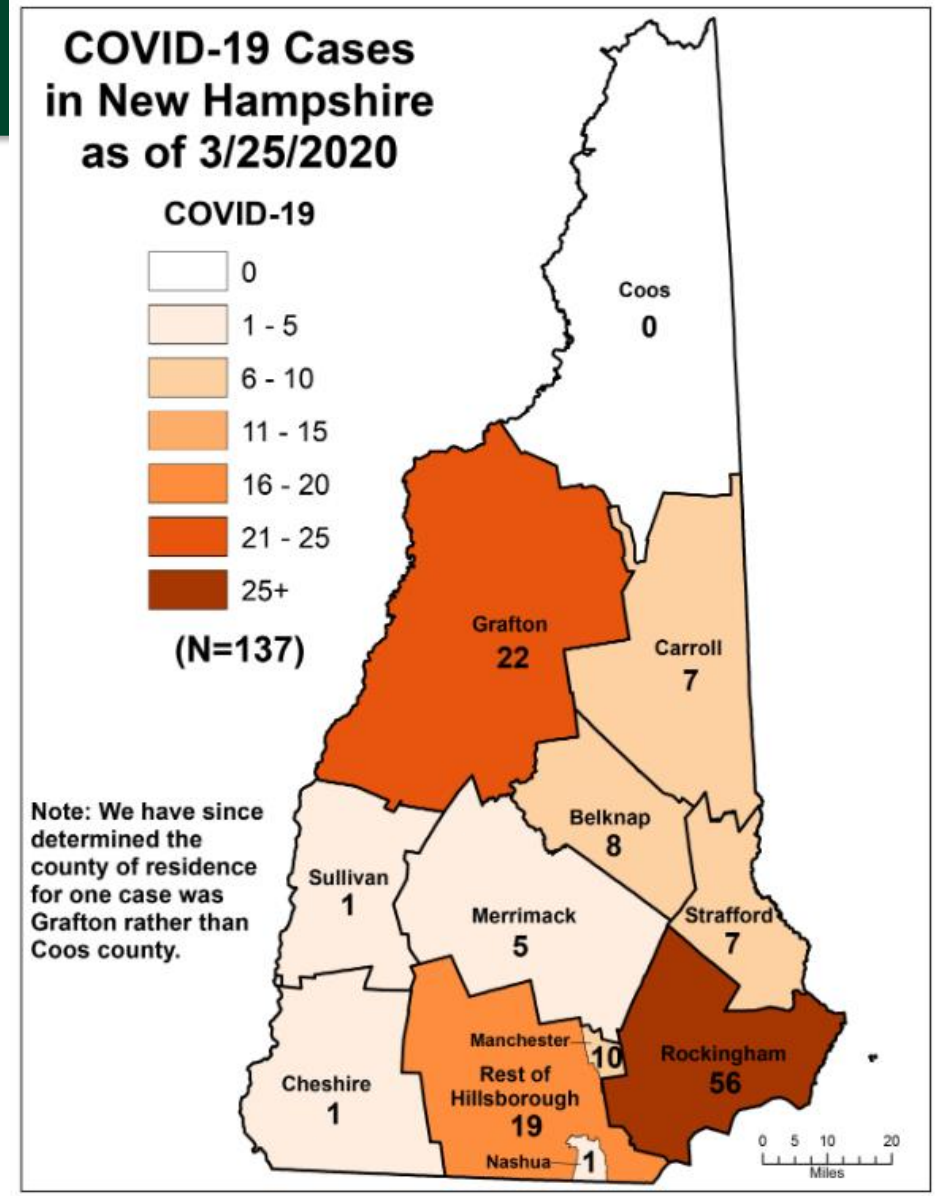
- 61,201 recovered **Hubei** China
- 10,457 recovered Iran
- 9,362 recovered Italy
- 7,015 recovered Spain
- 4,144 recovered Korea, South
- 3,900 recovered France
- 3,547 recovered Germany



Confirmed | Daily Increase

N.H. Cases

Confirmed Cases	137
Hospitalizations	19 (14%)
Deaths	1 (<1%)
Tests negative	3,001
Tests pending at PHL	712
Persons Monitored	650

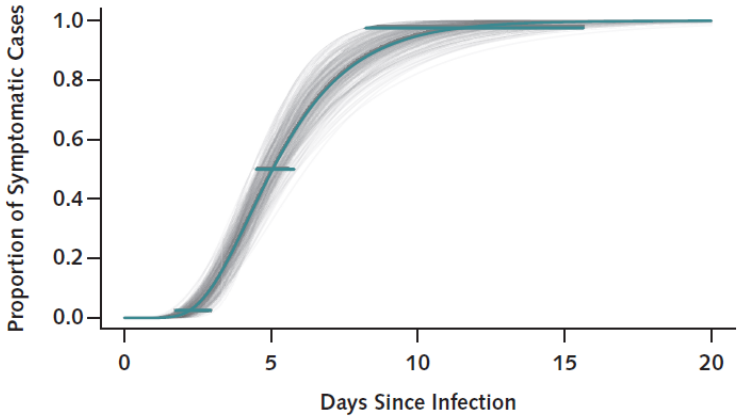


NH DHHS Website: https://www.dhhs.nh.gov/dphs/cdcs/2019-ncov.htm

Preliminary Epidemiologic Features

- Transmissibility: R_o 2-3
  - Superspreaders?
  - 15% secondary attack rate among household contacts
- Incubation period: 5-6d, range 0-14d
  - 97.5% present within 11.5d
- Serial interval: 4-4.6d

Figure 2. Cumulative distribution function of the COVID-19 incubation period estimate from the log-normal model.



The estimated median incubation period of COVID-19 was 5.1 days (CI, 4.5 to 5.8 days). We estimated that fewer than 2.5% of infected persons will display symptoms within 2.2 days (CI, 1.8 to 2.9 days) of exposure, whereas symptom onset will occur within 11.5 days (CI, 8.2 to 15.6 days) for 97.5% of infected persons. Horizontal bars represent the 95% CIs of the 2.5th, 50th, and 97.5th percentiles of the incubation period distribution. The estimate of the dispersion parameter is 1.52 (CI, 1.32 to 1.72). COVID-19 = coronavirus disease 2019.

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200219-sitrep-30-covid-19.pdf?sfvrsn=6e50645_6; Ilaria Dorigatti, Lucy Okell, Anne Cori et al for MRC Center for Global ID Analysis at Imperial College London; https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/; *Ann Intern Med.* doi:10.7326/M20-0504

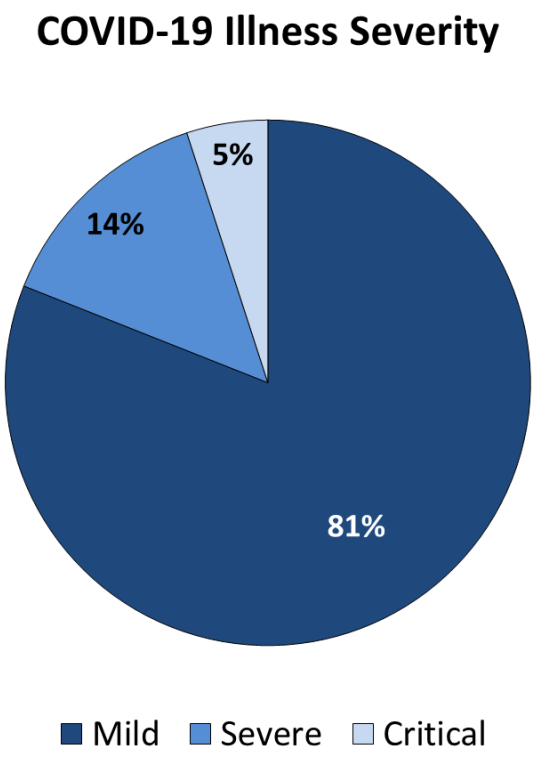
Presenting Features: 6 Chinese Cohorts

- Men predominate
- ~half had underlying diseases
  - Diabetes, hypertension, cardiovascular disease
- Common signs/symptoms: *gradual onset* of malaise, fatigue, fever, myalgia, then dry cough, SOB
  - Lymphopenia (63-83%), abnormal radiography
  - Less common: sputum production, HA, GI

Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020
Chen N, Zhou M, Dong X, et al. Epi and clinical characteristics of 99 cases . . . Lancet 2020
JAMA. doi:10.1001/jama.2020.1585; Published online February 7, 2020;
Guan W-j, Zheng-yi N, Hu Y, et al. Clin Chars of 2019 Novel Coronavirus infection in China.

Risk for Severity

- 44,672 confirmed cases in China
- Males 2.8% vs. females 1.7%
- Comorbidity:
  - CVD 10.5%
  - DM 7.3%
  - Chronic respiratory disease 6.3%
  - Hypertension 6%
  - Cancer 5.6%



https://emergency.cdc.gov/coca/calls/2020/callinfo_030520.asp
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

Disease Severity Talking Points

Case fatality rate 1.4%

- China 2.3% overall, 18% for Hubei
- Italy 8.3%

Infection fatality rate ~0.5-1%

For comparison

- 0.1% seasonal flu CFR
  - Annual U.S. impact 200,000 hospitalized, 35,000 die
- 2009 H1N1 pandemic CFR 0.4%
- SARS-CoV-1 and MERS CoV 10% and 35%, respectively

Case Fatality Rate by Location

China

Age	CFR%
Overall	1.8-3.4
0-19	0.2
20-29	0.2
30-39	0.2
40-49	0.4
50-59	1.3
60-69	3.6
70-79	8.0
≥80	14.8

S Korea (67)

Age	CFR%
<50	<0.01
50-60	0.12
60-69	1.42
70-79	4.74
≥80	8.3

Italy (2,900)

Age	CFR%
Overall	8.3
<30	0
30-39	0.3
40-49	0.5
50-59	1.1
60-69	3.9
70-79	13.4
80-89	20.6
≥90	23.1

U.S. (110)

Age	CFR%
Overall	1.8-3.4
0-19	0
20-44	0.1-0.2
45-54	0.5-0.8
55-64	1.4-2.6
65-74	2.7-4.9
75-84	4.3-10.5
≥85	10-4-27.3

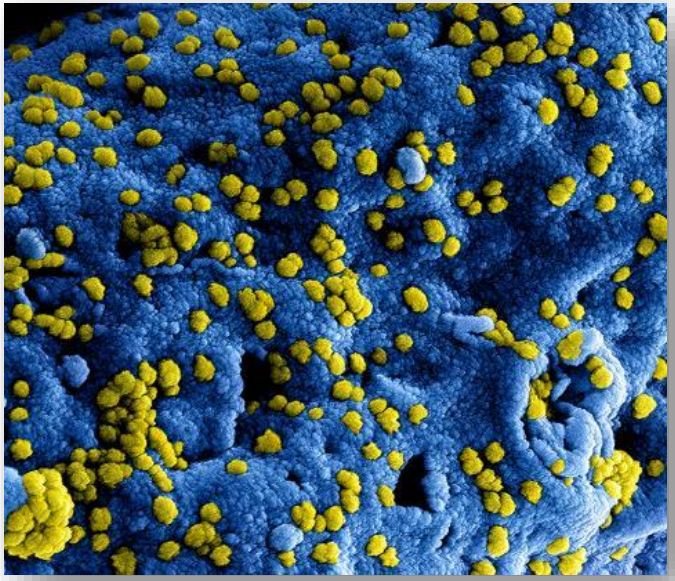
In U.S., cases have not completed their illness; 14.3-20.8% of aged 20-44y were hospitalized, with 2.0-4.2% requiring ICU admission

file:///C:/Users/Elizabeth.A.Talbot/Downloads/jama_livingston_2020_ig_200003.pdf
https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm#T1_down

See DHHS or CDC guidance

INFECTION CONTROL

Modes of Transmission

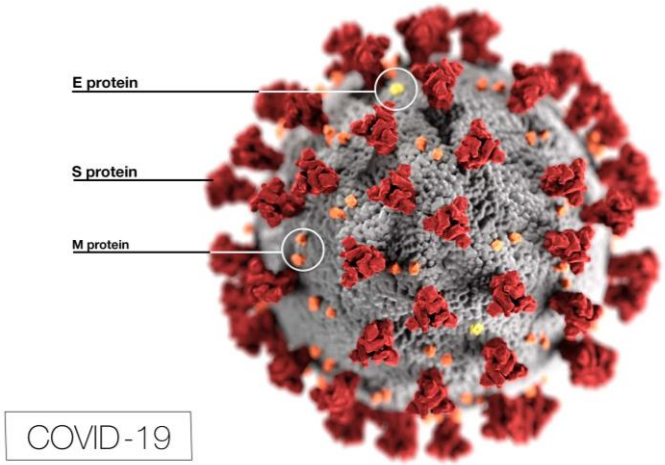


- No longer zoonotic
- Person-to-person
  - Droplet
  - Fomite
  - Nosocomial
  - No evidence of aerosol
    - Except during aerosol-generating procedures
  - Fecal?
  - Vertical?

Chan FJW, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating p2p transmission: a study of a family cluster. Lancet 2020; online Jan 24. Imai N, Cori, A, Dorigatti I, et al at WHO Collaborating Centre for Infectious Disease Modelling, MRC Centre for Global Infectious Disease Analysis, J-IDEA, Imperial College London, UK

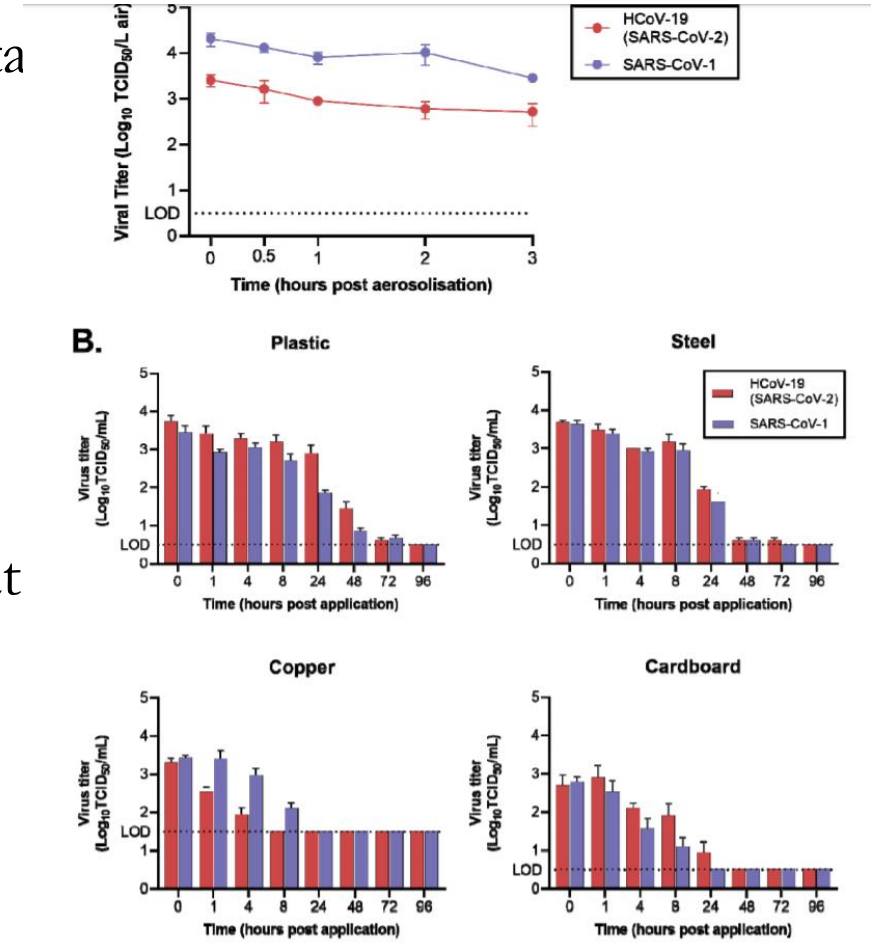
Asymptomatic Transmission

- Population rates of asymptomatic infection cannot be calculated until antibody-based serosurveys in large affected populations are performed
- WHO: contact tracing should identify persons within 2 days of case's symptom onset and quarantine
- CDC: extend contact investigations for high risk contacts 48 hours prior to onset
- "The driver of respiratory outbreaks is symptomatic people, not asymptomatic carriers," Dr. Fauci



SARS-CoV-2 Fomite Transmission

- Lab-generated viral viability data under controlled conditions
- Virus can remain viable and infectious
  - In aerosols for hours
  - On surfaces hours - days
- Fomite transmission plausible at high inoculum
- Similar to SARS-CoV-1
- Usual cleaning effective



Van Doremalen, et al. NEJM; March 17 2020

Infection Control Best Practices

- https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html
- Facemask, eye protection, gloves, gowns
- For aerosol-generating procedures* on patients with COVID-19 use fitted respirator masks (N95 respirators, FFP2, or equivalent), as opposed to surgical/medical masks, in addition to other PPE, in AIIR

*Aerosol-generating procedures in the ICU include: endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, physical proning of the patient, disconnecting the patient from the ventilator, non-invasive positive pressure ventilation, tracheostomy, and CPR.

Infection Control in the ICU

- For HCP providing usual care for non-ventilated COVID-19 patients, we suggest using surgical/medical masks, as opposed to respirator masks, in addition to other PPE*
- For HCP performing non-aerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19, we suggest using surgical/medical masks, as opposed to respirator masks, in addition to other PPE*
- Recommendations for intubation

*Weak Rec, Low Qual Evidence

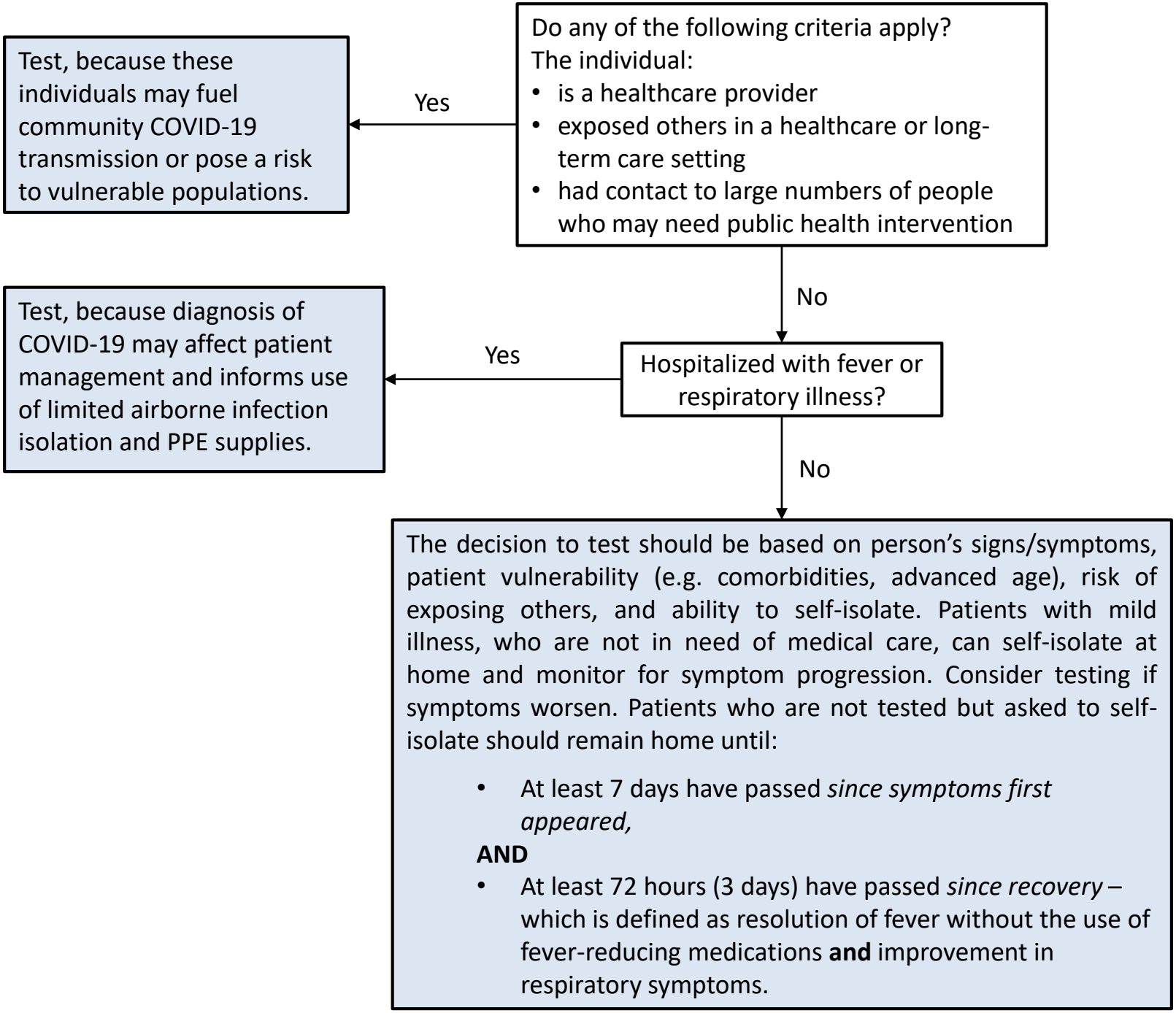
https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Improving, but still challenging

TESTING

Find Every Case: PCR-based Testing

- CDC real time RT-PCR
  - 2 March NH PHL
    - Other labs now
  - LOD: 10^0.5 copies/microliter (3160 copies per mL of transport media)
  - Analytic specificity high
- Other methods now
  - Cepheid Xpert
- Challenges in each step of the patient pathway


Do any of the following criteria apply?
The individual:
• is a healthcare provider
• exposed others in a healthcare or long-term care setting
• had contact to large numbers of people who may need public health intervention
Yes
Test, because these individuals may fuel community COVID-19 transmission or pose a risk to vulnerable populations.
No
Hospitalized with fever or respiratory illness?
Yes
Test, because diagnosis of COVID-19 may affect patient management and informs use of limited airborne infection isolation and PPE supplies.
No
The decision to test should be based on person's signs/symptoms, patient vulnerability (e.g. comorbidities, advanced age), risk of exposing others, and ability to self-isolate. Patients with mild illness, who are not in need of medical care, can self-isolate at home and monitor for symptom progression. Consider testing if symptoms worsen. Patients who are not tested but asked to self-isolate should remain home until:
• At least 7 days have passed *since symptoms first appeared,*
AND
• At least 72 hours (3 days) have passed *since recovery* – which is defined as resolution of fever without the use of fever-reducing medications **and** improvement in respiratory symptoms.

ICU Testing

- For intubated and mechanically ventilated adults with suspicion of COVID-19
- Obtain lower respiratory tract samples in preference to upper respiratory tract (NP or OP) samples*
  - Endotracheal aspirates preferred to bronchial wash or BAL samples*

*Weak Rec, Low Qual Evidence

https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Critical Care Guidelines

SUPPORTIVE TREATMENT

References for Clinical Management

- UpToDate
- CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
- Surviving Sepsis Campaign
  - https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US
- COVID-19 Treatment: A Review of Early and Emerging Options
  - Accepted Manuscript, Open Access

Erin K McCreary, PharmD, BCPS, BCIDP, Jason M Pogue, PharmD, BCPS, BCIDP, on behalf of the Society of Infectious Diseases Pharmacists, COVID-19 Treatment: A Review of Early and Emerging Options, *Open Forum Infectious Diseases*, , ofaa105, https://doi.org/10.1093/ofid/ofaa105

Nonspecific Treatments

- NSAIDS: insufficient evidence
  - Consider preferentially using acetaminophen
- ACE-2 recognized as co-receptor for viral entry. Hypothesis as to why hypertension such RF for severity
  - Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: insufficient evidence
    - Don't stop if already on; don't start if not already on
- HMG CoA reductase inhibitors: insufficient evidence
- Inhaled medications should be given by metered dose inhaler rather than nebulization
  - Not all patients require bronchodilators. Judicious use due to shortage.
- Inhaled corticosteroids: stop if able

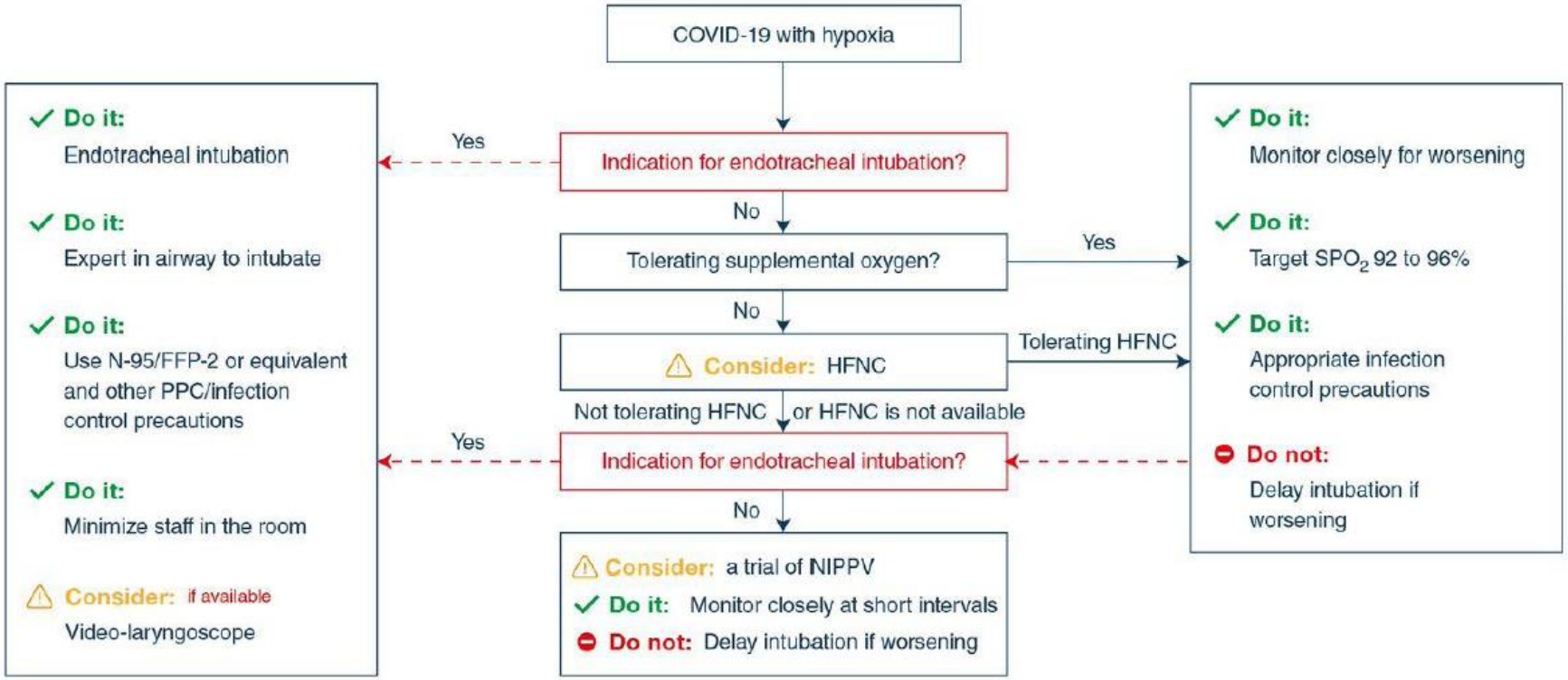
Systemic Steroids

- Routine use: AVOID
  - Consider if indicated for another reason
    - Refractory septic shock, transplant or underlying autoimmune disease
- For mechanically ventilated adults and respiratory failure
  - Without ARDS, suggest against routine use of systemic corticosteroids
  - With ARDS, suggest using systemic corticosteroids, over not using corticosteroids

https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Hemodynamic, Ventilatory Support

- Fluid therapy and vasoactive agents
  - Recommendations 8-22
- Ventilation
  - Recommendations 23-42



https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

COVID-19 with mild ARDS	COVID-19 with Mod to Severe ARDS	Rescue/Adjunctive therapy
✓ **Do:** Vt 4-8 ml/kg and P_{plat} < 30 cm H_2O	⚠ **CONSIDER:** Higher PEEP	? **Uncertain:** Antivirals, chloroquine, anti-IL6
✓ **Do:** Investigate for bacterial infection	⚠ **CONSIDER:** NMBA boluses to facilitate ventilation targets	⚠ **CONSIDER:** if proning, high P_{pll}, asynchrony NMBA infusion for 24 h
✓ **Do:** Target SPO2 92% - 96%	⚠ **CONSIDER:** if PEEP responsive Traditional Recruitment maneuvers	⚠ **CONSIDER:** Prone ventilation 12-16 h
⚠ **CONSIDER:** Conservative fluid strategy	⚠ **CONSIDER:** Prone ventilation 12-16 h	⚠ **CONSIDER:** STOP if no quick response A trial of inhaled Nitric Oxide
⚠ **CONSIDER:** Empiric antibiotics	⚠ **CONSIDER:** if proning, high P_{pll}, asynchrony NMBA infusion for 24 h	⚠ **CONSIDER:** follow local criteria for ECMO V-V ECMO or referral to ECMO center
? **Uncertain:** Systematic corticosteroids	⊖ **Don't do:** Staircase Recruitment maneuvers	
	⚠ **CONSIDER:** Short course of systemic corticosteroids	
	? **Uncertain:** Antivirals, chloroquine, anti-IL6	

https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Empiric Use of Antibiotics

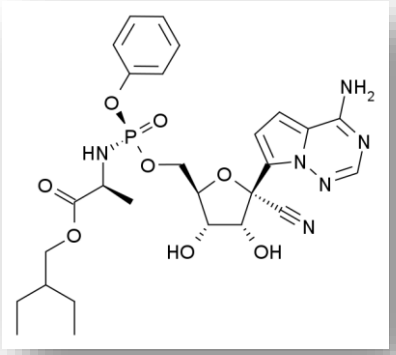
- For hospitalized patients, suggest starting empiric treatment for CAP: ceftriaxone+azithromycin (not doxy)
- In mechanically ventilated patients with COVID-19 and respiratory failure, suggest using empiric antimicrobials/antibacterial agents, over no antimicrobials
- If empiric antimicrobials, assess for de-escalation daily, and re-evaluate duration of therapy and spectrum of coverage based on microbiology results and patient's clinical status

https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Very Preliminary

SPECIFIC TREATMENT

Remdesivir



- 2014: IV nucleotide (adenosine) analog broad spectrum antiviral developed by Gilead, CDC, U.S. AMRIID
  - Blocks RNA polymerase
  - NIH dropped from Ebola trial
- China filed patent against Gilead Sciences' 2016 patent
- Compassionateaccess@gilead.com

E de Wit *et al.* Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *PNAS* DOI: 10.1073/pnas.1922083117.

Remdesivir Preliminary Data

- For MERS-CoV and SARS-CoV-1, in murine model, remdesivir improved lung function, reduced lung injury and viral loads
- For MERS-CoV in rhesus macaque model, remdesivir
  - Prophylaxis 24h *before* inoculation → lower viral load, prevented symptoms
  - Started 12h *after inoculation*, reduced viral load, decreased lung pathology, attenuated signs of infection
- For SARS-CoV-2
  - Remdesivir plus chloroquine effective *in vitro*
  - Clinical trials underway in US, Asian countries
    - 5- and 10-day courses active protocols
    - Preliminary results expected in April

Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222. doi:10.1038/s41467-019-13940-6

Chloroquine

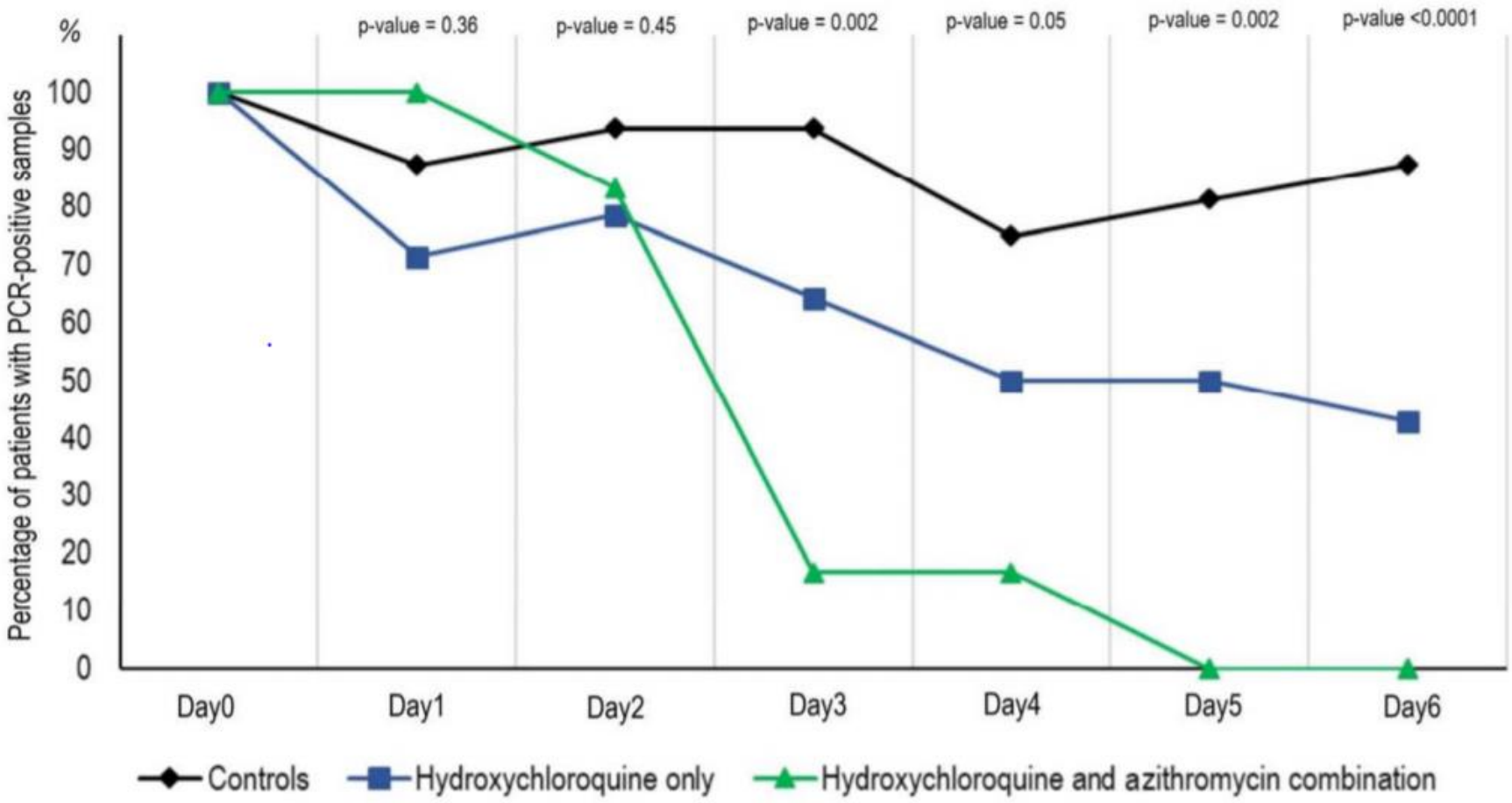
- Sulfate and phosphate salts of chloroquine and hydroxychloroquine
  - CDC reports hydroxychloroquine better than other forms
- Broad spectrum activity again RNA viruses recognized since 1960's
  - Increases pH of phagolysosome, which interrupts virus/cell fusion, and interferes with glycosylation of cellular receptors of SARS-CoV-2
    - In other antiviral attempts, *in vitro* to *in vivo* translation failed
      - Dengue and CHIK example, even with worse sequelae

Colson P, et al. IJAA 2020;55:105923. Touret F. Of chloroquine and COVID-19. Antiviral Research 2020;177:104762.

Hydroxychloroquine: 2 Trials

- In unpublished study of >100 patients in China, "it was superior to the control in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course"
- In preprint of study of 20 non-critical patients in France, treatment with hydroxychloroquine +/- azithromycin
  - 70% showed significant reduction of viral load at day 6
  - Shorter duration of carriage

Gao J, et al (2020) Breakthrough: Chloroquine phosphate . . .Biosci Trends; 4:72- 73; Colson P, et al. Chloroquine and hydroxychloroquine . . .*Intern J Antimic Agents* (2020), doi: https://doi.org/10.1016/j.ijantimicag.2020.105932



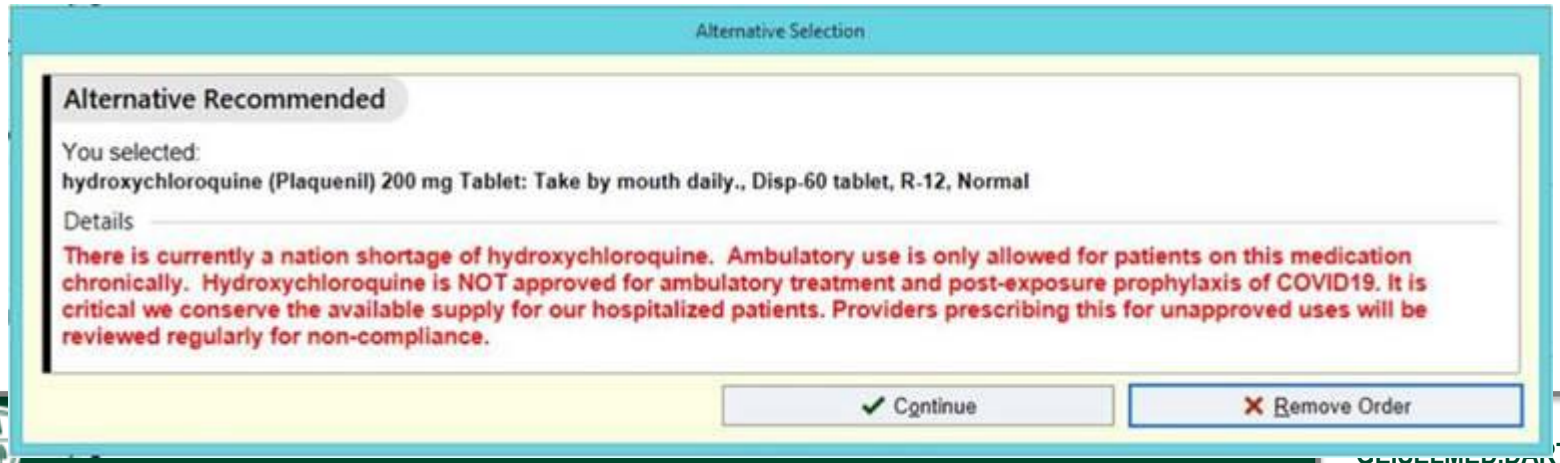
Colson P, et al. Chloroquine and hydroxychloroquine . . .*Intern J Antimic Agents* (2020), doi: https://doi.org/10.1016/j.ijantimicag.2020.105932

Using Hydroxychloroquine (Plaquenil)

- Dosing
  - Adult 400mg po bid for 1 day, then 200mg po BID for 4 days
  - Pediatric: 10 mg/kg (max of 600 mg/dose) PO BID x2 followed by 3 mg/kg PO TID (max of 200 mg/dose) for 5 days
- Can compound for pediatric use and for use in tube feeds
- Side effects
  - Common: diarrhea, nausea, QTc prolongation
  - Less common: retinopathy, SJS/TENS, pancytopenias, myopathies
- No dosage adjustment in renal impairment (use with caution)
- No dosage adjustment in hepatic dysfunction (use with caution)
- Contraindications: Porphyria (relative), G6PD deficiency
  - G6PD testing not necessary before use

Is Hydroxychloroquine Available?

- In outpatient settings, hydroxychloroquine is in short or restricted supply in the U.S.
- >100 million tablets available in manufacturer warehouses for hospital use
- Many settings restricting use to preserve for treatment



Systematic Review Lopinavir-Ritonivir

- SARS-CoV-1
  - 0/34 deaths in treated patients (some also received ribavirin), compared with 69/690 patients taking ribavirin
  - Retrospective matched cohort study of 1,052 patients: mortality 2.3% in 75 treated vs. 11% in 977 controls
  - Retrospective matched cohort study: less ARDS in treated group (2.4%) than historical controls (28.8%)
    - Decreased viral load, increased lymphocyte count
- MERS CoV retrospective study: PEP with LPV/r 40% decrease in risk of infection

Yao et al. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus. Submitted

Lopinavir-Ritonavir for SARS-CoV-2

- Trial of 18 patients underway in Singapore
  - Side effects common (GI, LFTs)
- Patient in Spain treated with LPV/r plus IFN-β, survived
- Randomized, controlled, open-label trial of hospitalized adults with confirmed SARS-CoV-2 infection: 100 and 99 received LPV/r and SOC
  - No difference in time to recovery, mortality, viral clearance
  - 13% had to discontinue due to side effects

Young et al., JAMA, 3/3/2020; Cao B, et al. Trial of L-R in adults . . .NEJM March 18 2020

Cytokine Storm Syndrome

- CSS: hyperinflammatory state characterized by fulminant multi-organ failure and elevation of cytokine levels
- In China cohorts, COVID-19 is associated with cytokine elevation profile similar to secondary hemophagocytic lymphohistiocytosis (HLH)
  - Can screen for secondary HLH using Hscore
- Intuitive to try immunosuppressive agents
  - Anti-IL6

Tocilizumab

- Humanized Ig blocks IL-6 receptor binding
- Approved for CSS and other IL-6 related inflammatory conditions
  - RA, juvenile idiopathic arthritis, CAR-T therapy
- May attenuate COVID-19 cytokine storm syndrome
- Limited supply

Putting It Together: UW Materials

UW Medicine

Evaluate for clinical trial eligibility
VTEU Remdesivir* (NCT04280705)

Not eligible

URTI/LRTI without O2 requirement

No risk factors
Symptomatic treatment

Risk factors[+]
Hydroxychloroquine

LRTI, with O2 requirement

First line: Hydroxychloroquine

Alternative: Lopinavir/ritonavir***

Management:
CXR, Chest CT as clinically indicated, not necessary for diagnosis or staging

LRTI, mechanical ventilation

Consider compassionate use remdesivir **

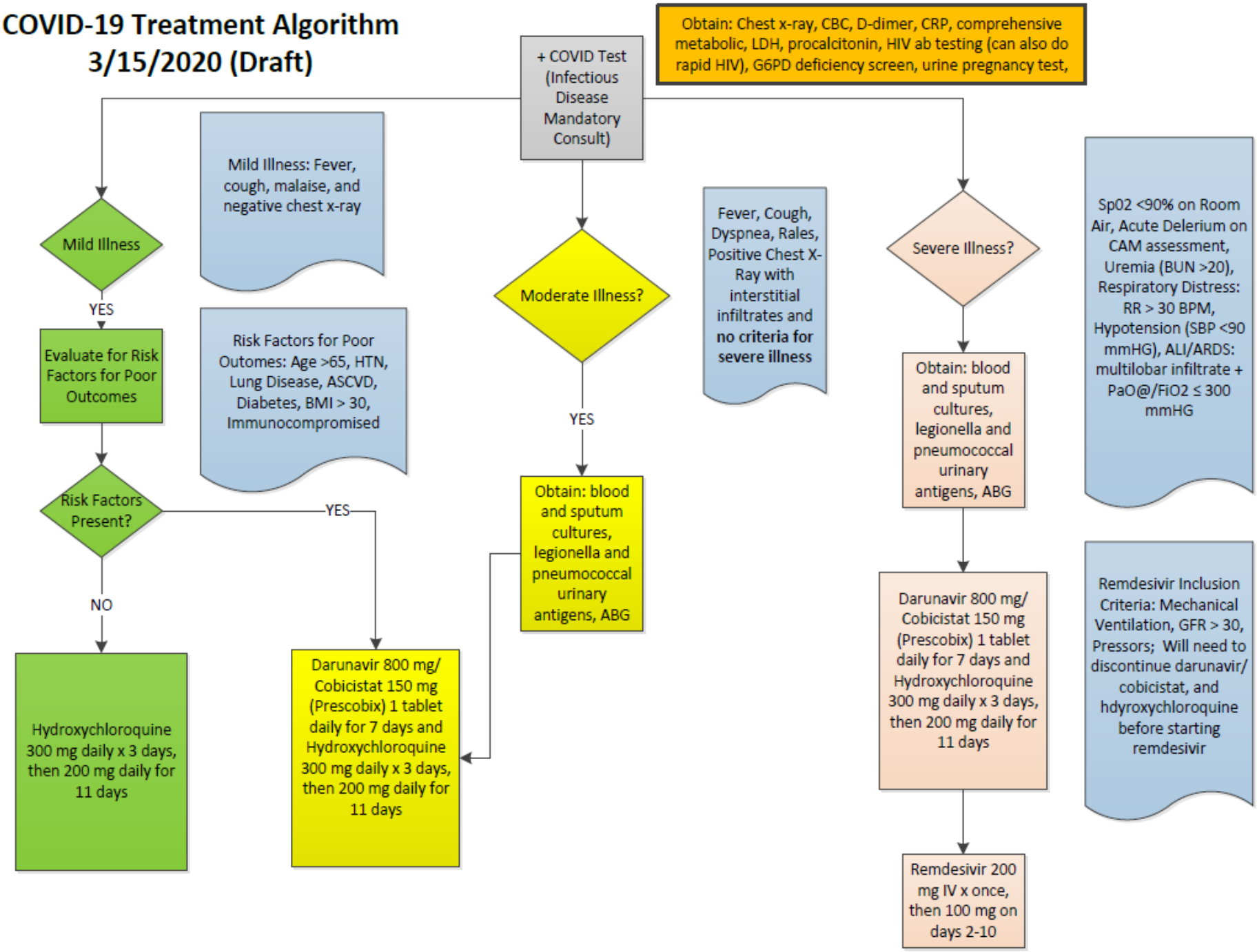
First Line: Hydroxychloroquine

Alternative: Lopinavir/ritonavir***

Management: Monitor for signs of cytokine release syndrome
Consider labs:
IL-6,Ferritin, Fibriongen
CRP,ESR,D-dimer

Consult with ID: Consider IL-6 blockade

COVID-19 Treatment Algorithm
3/15/2020 (Draft)



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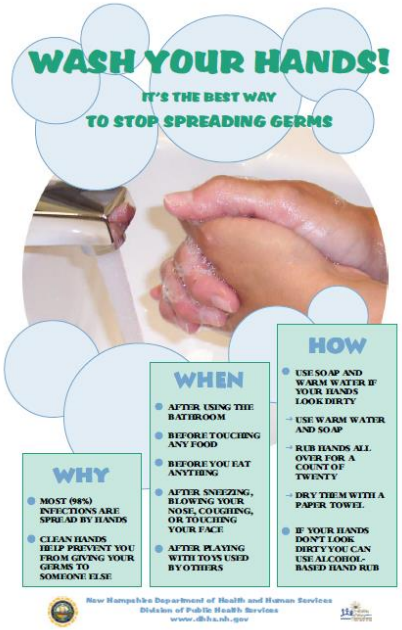
WASH YOUR HANDS!
IT'S THE BEST WAY
TO STOP SPREADING GERMS
WHEN
AFTER USING THE BATHROOM
BEFORE TOUCHING ANY FOOD
BEFORE YOU EAT ANYTHING
AFTER SNEEZING, BLOWING YOUR NOSE, COUGHING, OR TOUCHING YOUR FACE
AFTER PLAYING WITH TOYS USED BY OTHERS
HOW
USE SOAP AND WARM WATER IF YOUR HANDS LOOK DIRTY
USE WARM WATER AND SOAP
RUB HANDS ALL OVER FOR A COUNT OF TWENTY
DRY THEM WITH A PAPER TOWEL
IF YOUR HANDS DON'T LOOK DIRTY YOU CAN USE ALCOHOL-BASED HAND RUB
WHY
MOST (98%) INFECTIONS ARE SPREAD BY HANDS
CLEAN HANDS HELP PREVENT YOU FROM GIVING YOUR GERMS TO SOMEONE ELSE
New Hampshire Department of Health and Human Services
Division of Public Health Services
www.dhhs.nh.gov


STAY HEALTHY!
Follow these simple tips, every day
COVER your mouth when you cough or sneeze—use your sleeve
ONLY use your own glass and utensils—don't share
USE soap and warm water to wash hands often
GET plenty of sleep, exercise, and eat a healthy diet
HOME is where you belong when you're sick, not at work or school
New Hampshire Department of Health and Human Services
129 Pleasant St., Concord, NH 03301
www.dhhs.nh.gov


GERMS
are all around you.
Stay healthy.
Wash your hands.
www.cdc.gov/handwashing
CDC


DO YOUR PART
SLOW THE SPREAD OF GERMS
Stay home when you're sick
Cover your coughs and sneezes
Wash your hands often
CDC
For more information: www.cdc.gov/spi
1-800-CDC-INFO (232-4636) | www.cdc.gov/info