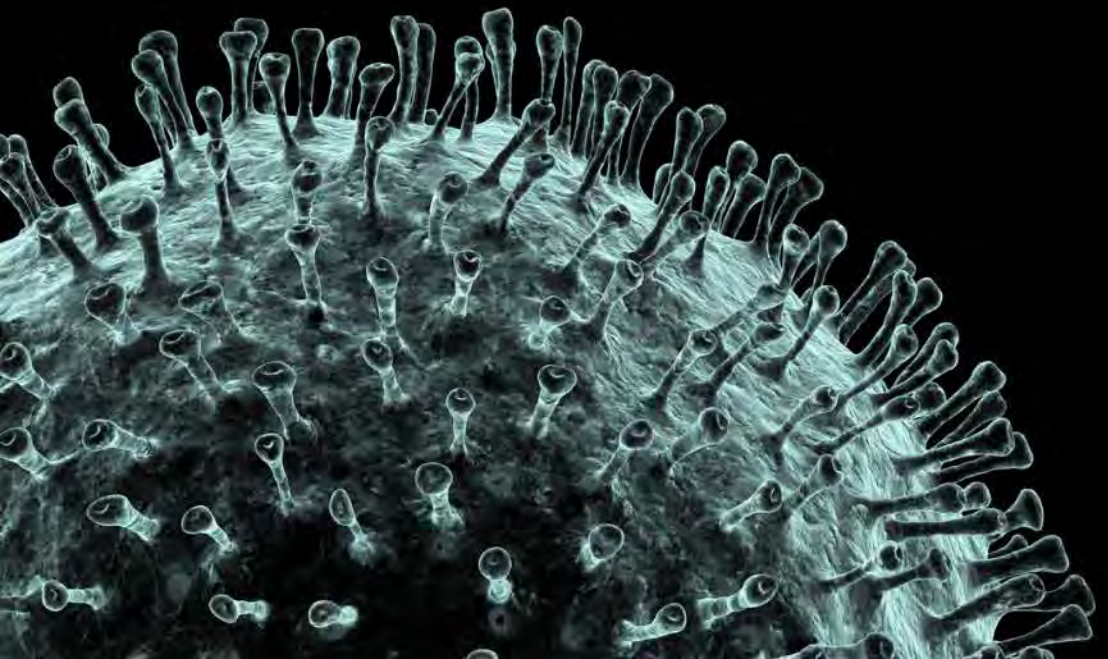
COVID-19 Conversations

Rajesh Gandhi

Professor of Medicine, Harvard Medical School
Director of HIV Clinical Services and Education,
Massachusetts General Hospital



COVID19Conversations.org
#COVID19Conversations

APHA
AMERICAN PUBLIC HEALTH ASSOCIATION
For science. For action. For health.

50 years
NATIONAL ACADEMY of MEDICINE

Multidimensional Challenge of Treating COVID-19

Rajesh T. Gandhi, MD

Massachusetts General Hospital

Professor of Medicine, Harvard Medical School

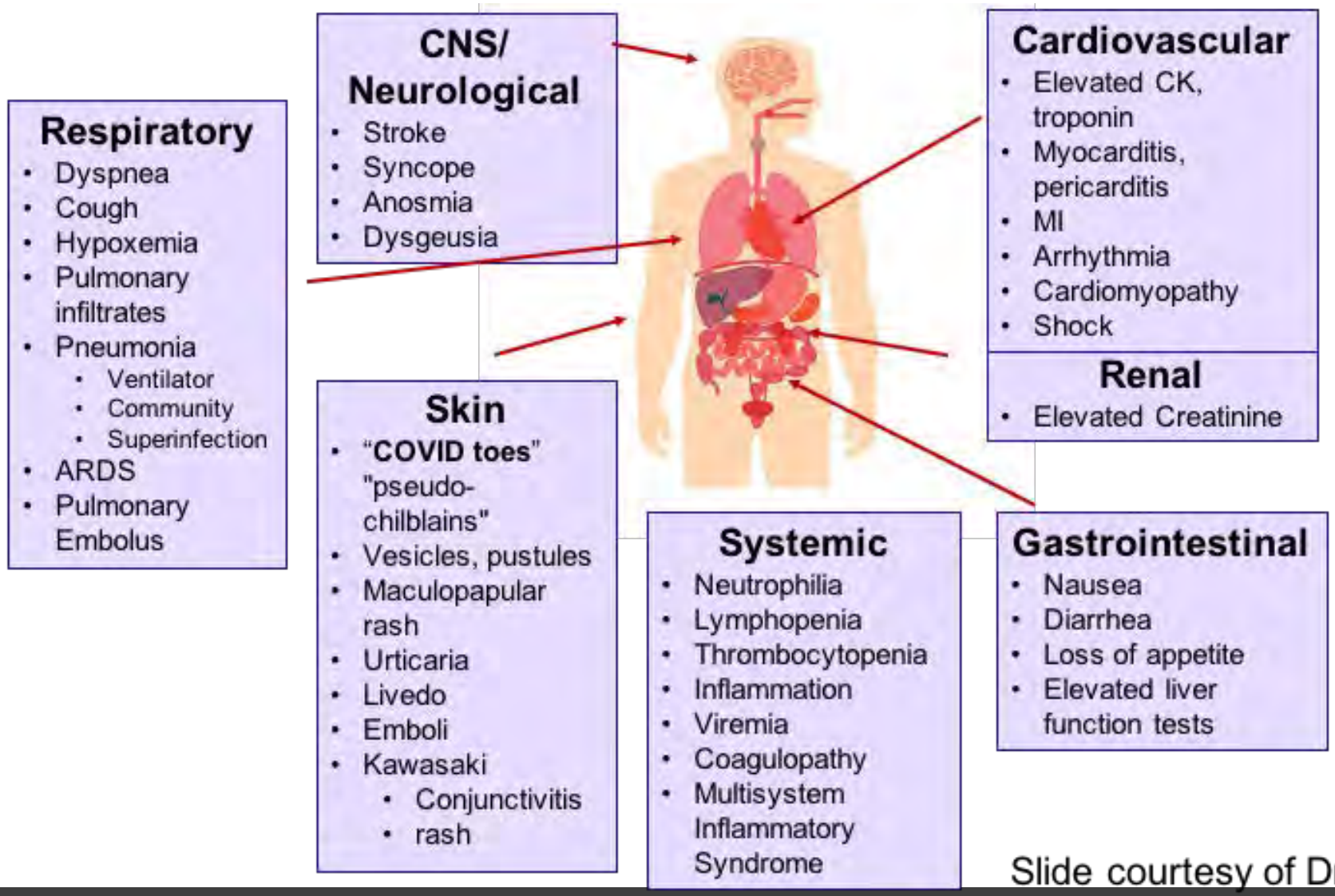
Acknowledgments: Arthur Kim, Mark Siedner, Eric Meyerowitz, Boris Juelg, Rochelle Walensky, Elizabeth Hohmann, Alice Pau, Trip Gulick, Adarsh Bhimraj, Mass CPR, Delaney Taylor, Malini Gandhi, Carlos del Rio

Disclosure: Dr Gandhi has served on scientific advisory board for Merck & Co, Inc. (Updated 6/1/20)

Multidimensional Challenge of Treating COVID-19

Host	• Adults • Children • Risk factors for severe disease
Stage and Severity	• Early vs. late infection • Mild, moderate, severe, critical disease
Intervention	• Antivirals • Immunomodulators • Combination therapy • Rx complications: anticoagulation, ventilation

Host: Clinical Presentation of SARS-CoV-2 Infection in Adults



Slide courtesy of Dr. Jay Fishman

Host: Risk Factors for Severe COVID-19 in Adults

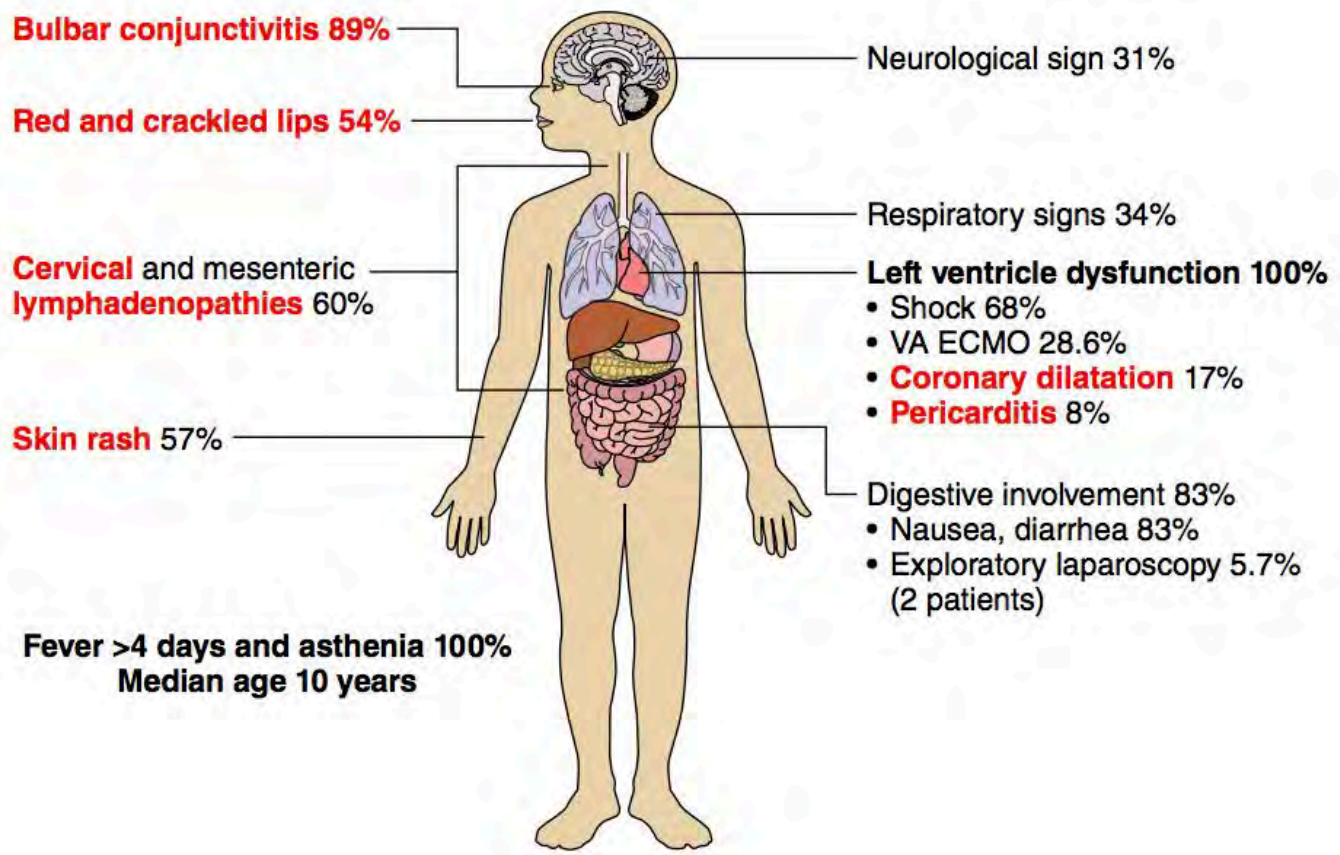
Table 1. Established and Potential Risk Factors for Severe Covid-19.*
Older age (e.g., >65 years)
Chronic lung disease
Cardiovascular disease
Diabetes mellitus
Obesity
Immunocompromise†
End-stage renal disease
Liver disease

- Immunosuppression, including advanced HIV (CD4 cell count <200), is risk factor for complications of other respiratory viruses. Not known if people with HIV are at increased risk for severe COVID-19.
- Disproportionate burden of COVID-19 among racial and ethnic minorities, Native Americans

Gandhi RT, Lynch JB, del Rio C, NEJM 2020

Host: Multisystem Inflammatory Syndrome in Children

- Acute vasculitis with some similarities to Kawasaki disease
- Fever, rash, conjunctivitis, abdominal pain, shock and cardiac dysfunction
- Children may have had recent SARS CoV-2 infection – MIS-C may represent a post-infectious hyper-inflammatory syndrome



Belhadjer Circulation 2020 https://doi.org/10.1161/CIRCULATIONAHA.120.048360;
Jones Hospital Peds 2020 https://doi.org/10.1542/hpeds.2020-0123
Verdoni Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31103-X

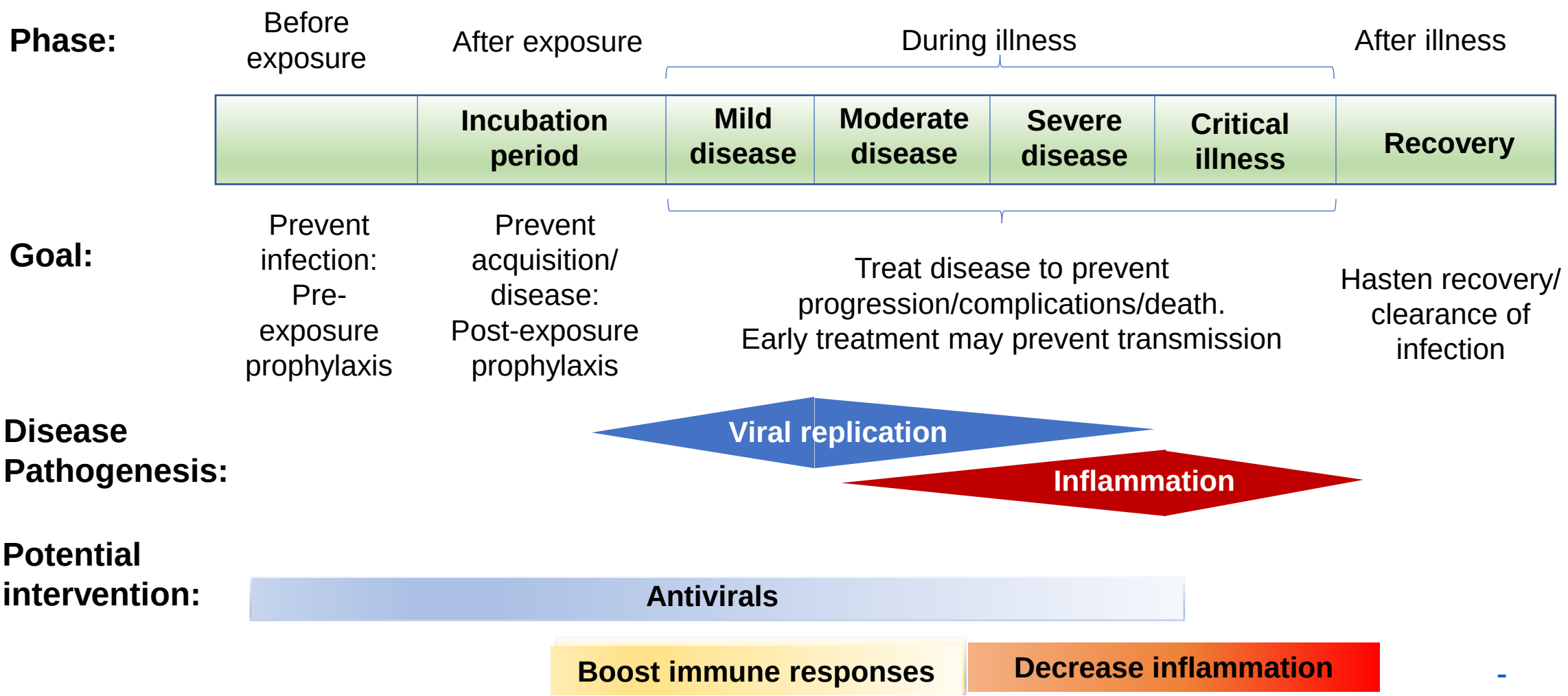
COVID-19 Spectrum

	Stage	Characteristics
	Asymptomatic/ presymptomatic infection	▪ Positive test for SARS-CoV-2 but no symptoms
~80%	Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, taste/smell disturbance) but no shortness of breath or abnormal imaging
~80%	Moderate illness	▪ SpO_2 ≥94% & lower respiratory disease (clinical or imaging findings)
~15%	Severe illness	▪ SpO_2 < 94%, PaO_2/FiO_2 < 300, respiratory rate >30/min, or lung infiltrates > 50%
~5%	Critical illness	▪ Respiratory failure, shock, and/or multiorgan dysfunction

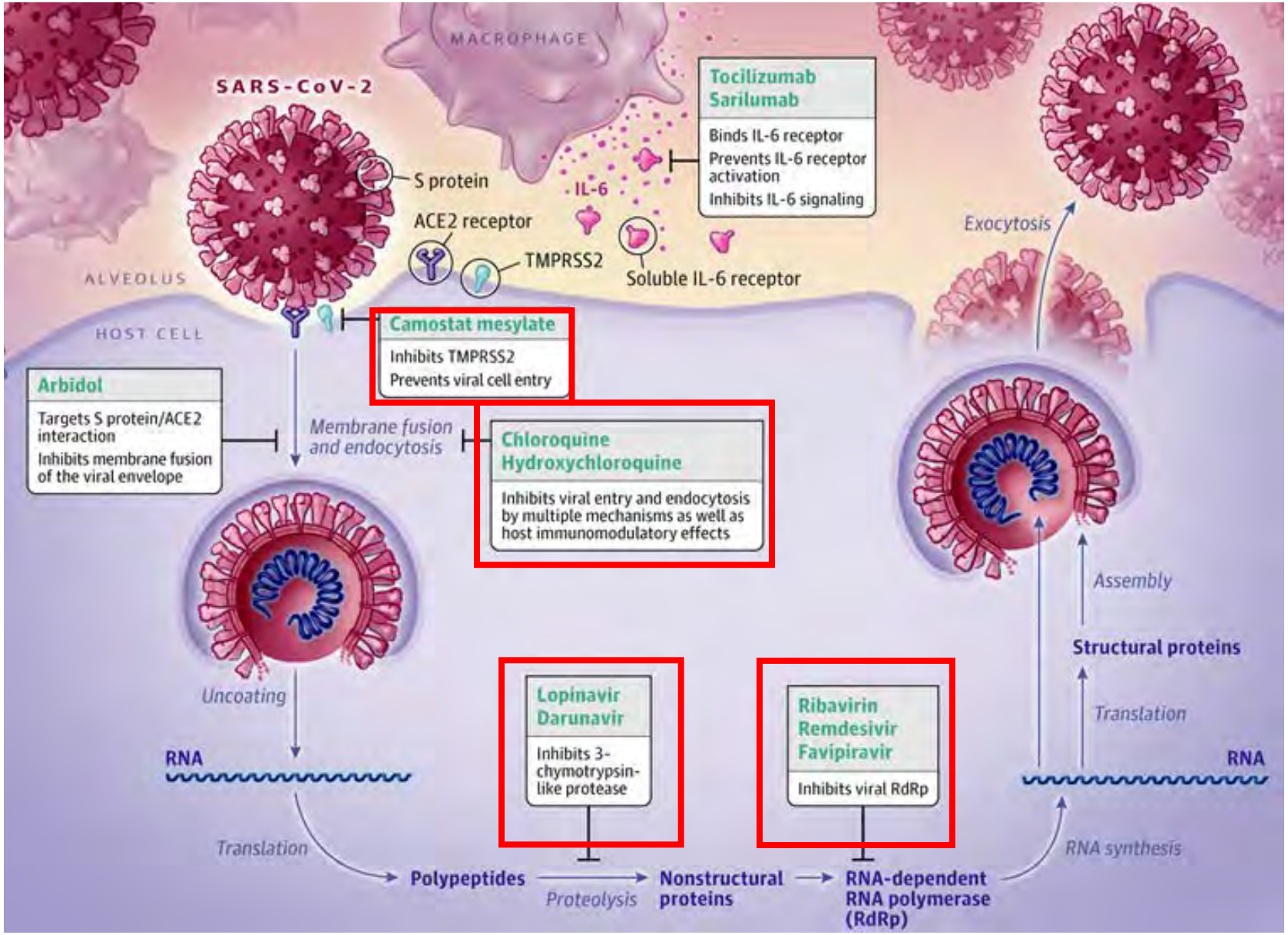
Wu Z et al, JAMA 2020

NIH COVID-19 Treatment Guidelines. Last updated June 11, 2020. www.covid19treatmentguidelines.nih.gov.

Goals of Treatment Across the COVID-19 Spectrum



Adapted from slide by Dr. Arthur Kim, MGH



Antiviral targets

- Viral entry: ACE2 and TMPRSS2: camostat
- Membrane fusion and endocytosis: hydroxychloroquine (HCQ)
- Viral protease: lopinavir/ritonavir
- RNA-dependent RNA polymerase: remdesivir, favipiravir

Sanders et al JAMA 2020

Case of HCQ: From single arm studies and observational cohorts …

International Journal of Antimicrobial Agents
Available online 20 March 2020, 105949
In Press, Journal Pre-proof

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret [a, b, $], Jean-Christophe Lagier [a, c, $], Philippe Parola [a, b], Van Thuan Hoang [a, b, d], Line Meddeb [a], Morgane Mailhe [a], Barbara Doudier [a], Johan Courjon [e, f, g], Valérie Giordanengo [h], Vera Esteves Vieira [a], Hervé Tissot Dupont [a, c], Stéphane Honoré [i, j], Philippe Colson [a, c], Eric Chabrière [a, c], Bernard La Scola [a, c], Jean-Marc Rolain [a, c], Philippe Brouqui [a, c], Didier Raoult [a, c]

the bmj | BMJ 2020;369:m1844 | doi: 10.1136/bmj.m1844

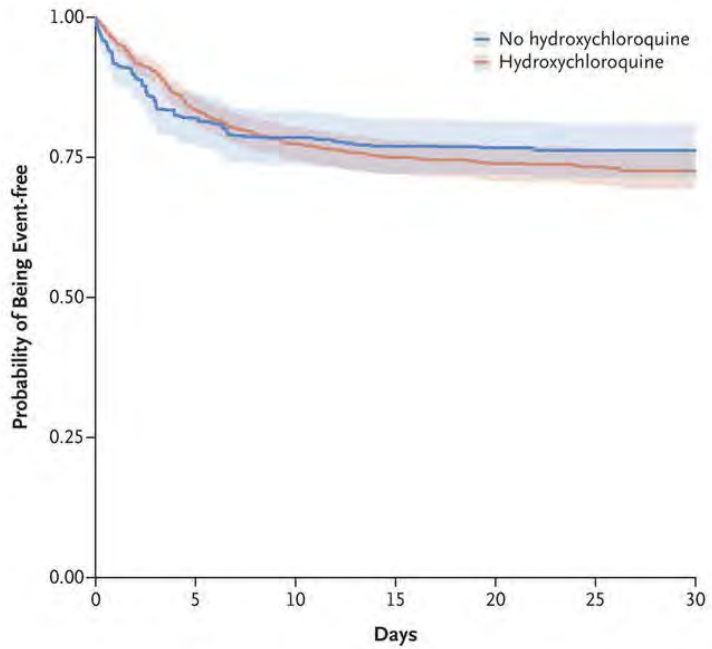
Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data

Matthieu Mahévas,[1] Viet-Thi Tran,[2] Mathilde Roumier,[3] Amélie Chabrol,[4] Romain Paule,[3] Constance Guillaud,[1] Elena Fois,[1] Raphael Lepeule,[5] Tali-Anne Szwebel,[6] François-Xavier Lescure,[7] Frédéric Schlemmer,[8] Marie Matignon,[9] Mehdi Khellaf,[1] Etienne Crickx,[1] Benjamin Terrier,[6] Caroline Morbieu,[6] Paul Legendre,[6] Julien Dang,[2] Yoland Schoindre,[3] Jean-Michel Pawlotsky,[10] Marc Michel,[1] Elodie Perrodeau,[2] Nicolas Carlier,[11] Nicolas Roche,[11] Victoire de Lastours,[12] Clément Ourghanlian,[13] Solen Kerneis,[14] Philippe Ménager,[15] Luc Mouthon,[6] Etienne Audureau,[16] Philippe Ravaud,[2] Bertrand Godeau,[1] Sébastien Gallien,[17] Nathalie Costedoat-Chalumeau[2,6]

ORIGINAL ARTICLE

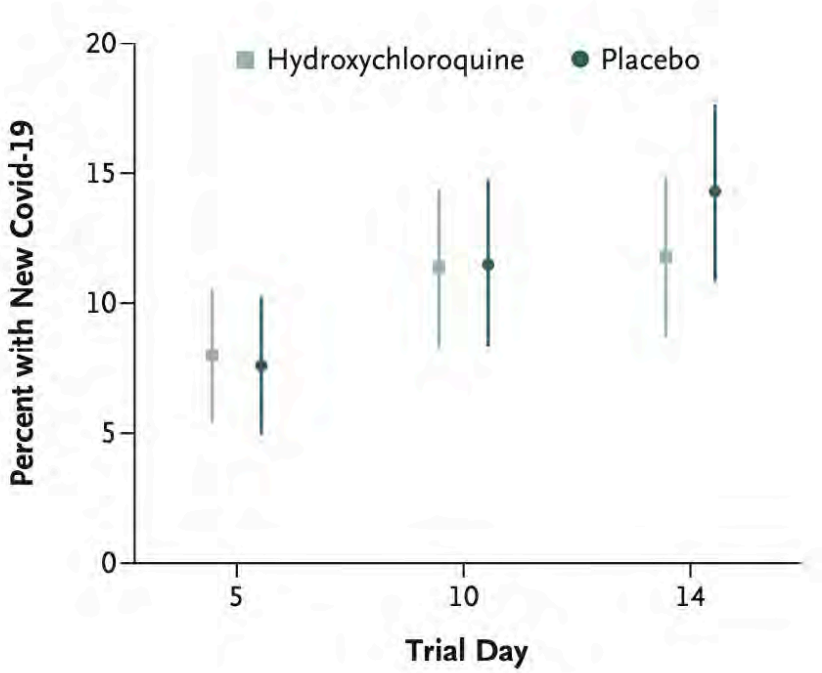
Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.



HCQ: To randomized controlled trials…

Post-exposure prophylaxis



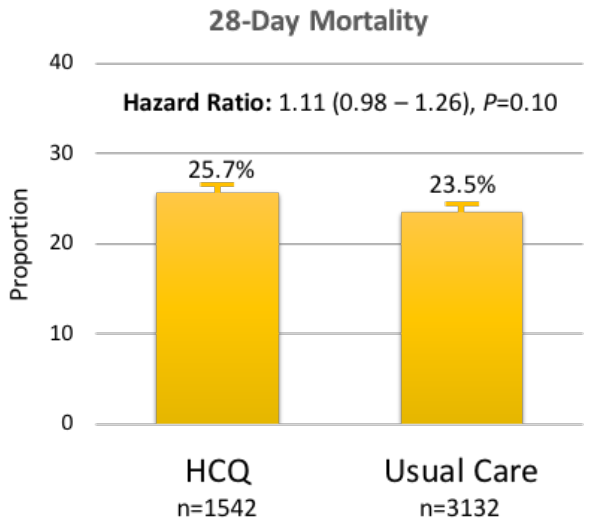
Limitations: most participants enrolled 3-4 days after exposure; only 2-3% had confirmed dx

Hospitalized patients

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020

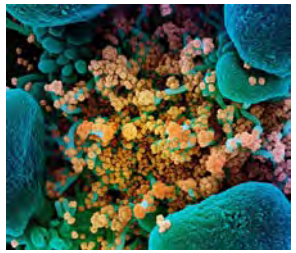
No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19



Media Advisory Saturday, June 20, 2020

NIH halts clinical trial of hydroxychloroquine

Study shows treatment does no harm, but provides no benefit



Boulware et al, NEJM 2020

The Case of Remdesivir (RDV)

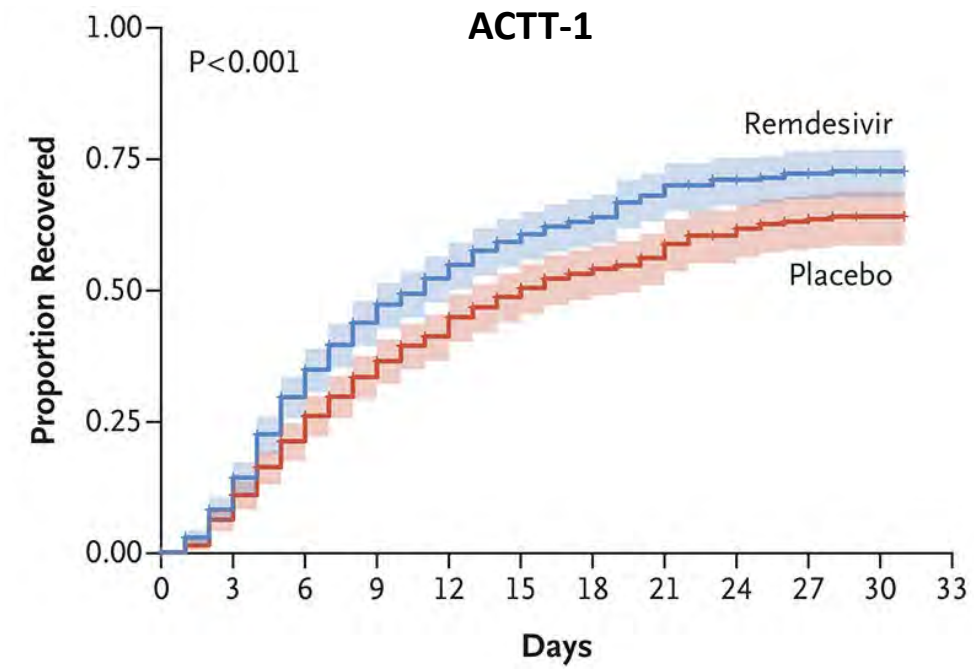
- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- Macaques: reduced SARS CoV-2 levels in lung (not upper respiratory tract), ameliorated disease
- Preliminary analysis of randomized ACTT-1: recovery more rapid with RDV than placebo (11 vs 15 d)
  - Mortality at 14 days: 7.1% RDV, 11.9% placebo (hazard ratio 0.7, 95% CI, 0.47 to 1.04).
  - Benefit of RDV clearest in those on oxygen supplementation but not yet intubated
- SIMPLE trial: in people with severe COVID-19 but not yet intubated, 5 days of RDV as good as 10 days

nature
https://doi.org/10.1038/s41586-020-2423-5
Accelerated Article Preview

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

Received: 23 April 2020
Accepted: 2 June 2020
Accelerated Article Preview Published online 9 June 2020

Brandi N. Williamson, Friederike Feldmann, Benjamin Schwarz, Kimberly Meade-White, Danielle P. Porter, Jonathan Schulz, Neeltje van Doremalen, Ian Leighton, Claude Kwe Yinda, Lizzette Pérez-Pérez, Atsushi Okumura, Jamie Lovaglio, Patrick W. Hanley, Greg Saturday, Catharine M. Bosio, Sarah Anzick, Kent Barbian, Tomas Cihlar, Craig Martens, Dana P. Scott, Vincent J. Munster & Emmie de Wit

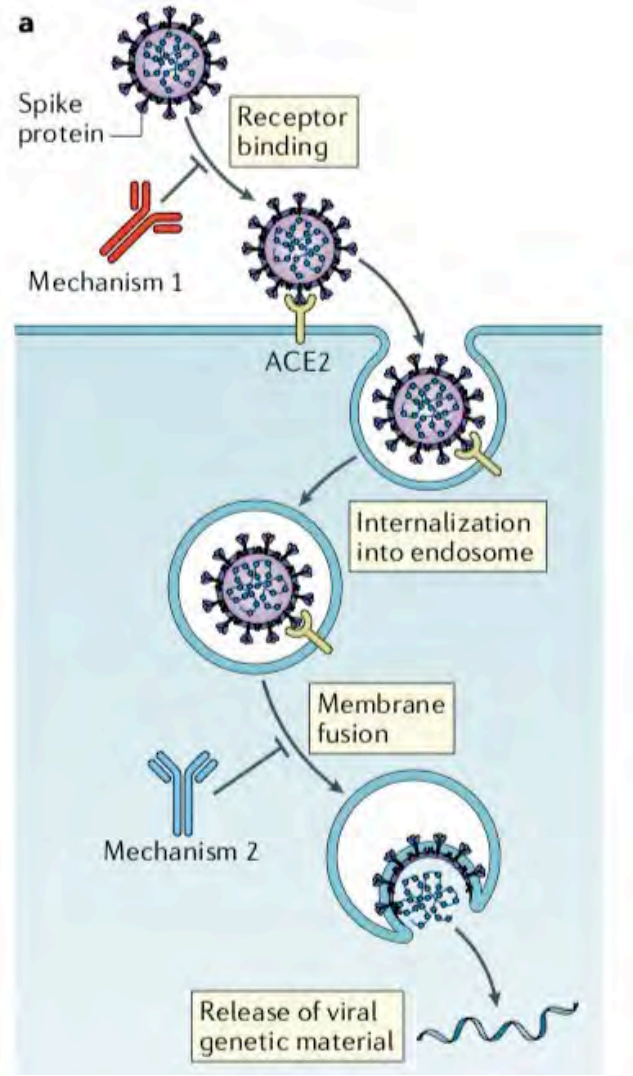


Williamson BN et al, Nature, 2020; Beigel JH et al, NEJM 2020; Goldman JD et al, NEJM 2020

Boost immune responses

Passive Antibody Therapy

- Passive transfer of neutralizing Ab: eg convalescent plasma (CP), monoclonal antibodies (mAb)
- CP used to treat other viral infections, eg Argentine hemorrhagic fever
- Case series of CP in people with COVID-19 showed radiographic improvement, reduction of viral shedding
- Open label randomized trial suggested benefit of CP in severe COVID-19 (treatment given late in disease course)
- Risks: transfusion reactions (rare), antibody dependent enhancement (theoretic)
- Ongoing prophylactic and therapeutic trials of CP, mAb



Abraham J, Nature Reviews Immunology, 2020; Shen et al, JAMA 2020; Li JAMA 2020

Decrease inflammation

Steroids: Case of Dexamethasone

RECOVERY
Randomised Evaluation of COVID-19 Therapy
Open label, 175 NHS Hospitals in the UK

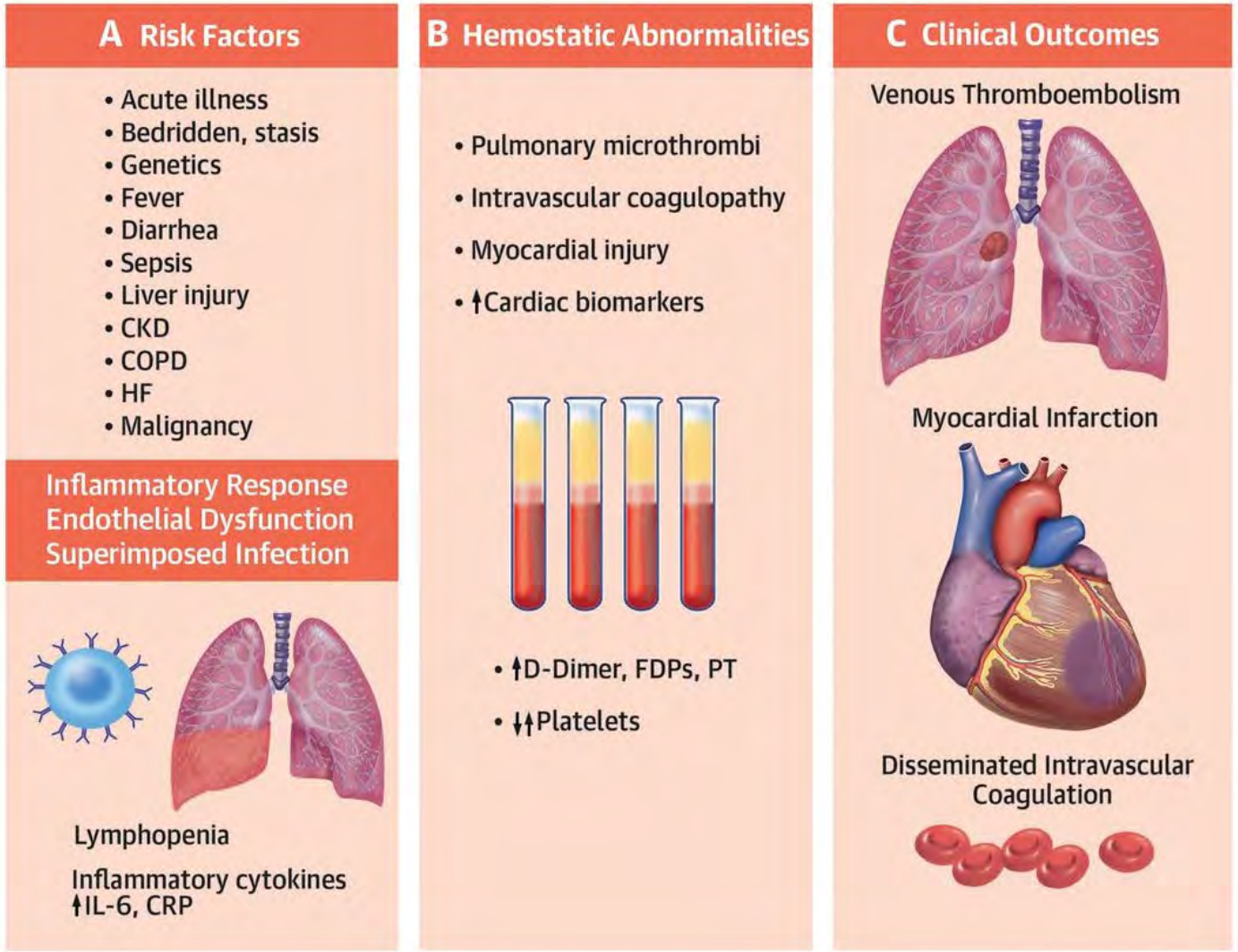
- Controversy regarding use of steroids in viral pneumonia, acute respiratory distress syndrome
- Given hyperinflammatory state in COVID-19, steroids evaluated as potential intervention
- Open label, randomized trial among hospitalized patients in the UK: 2104 received dex, 4321 usual care

	Dex	Usual Care	RR mortality
No oxygen required	85/501 (17%)	137/1034 (13%)	**1.22** (0.86 – 1.75)
Oxygen only	275/1279 (21.5%)	650/2604 (25%)	**0.8** (0.67 – 0.96)
Ventilation/ECMO	94/324 (29%)	278/683 (40.7%)	**0.65** (0.45 – 0.88)
All participants	454/2104 (21.6%)	1065/4321 (24.6%)	**0.83** (0.74-0.92) **p=0.0007**

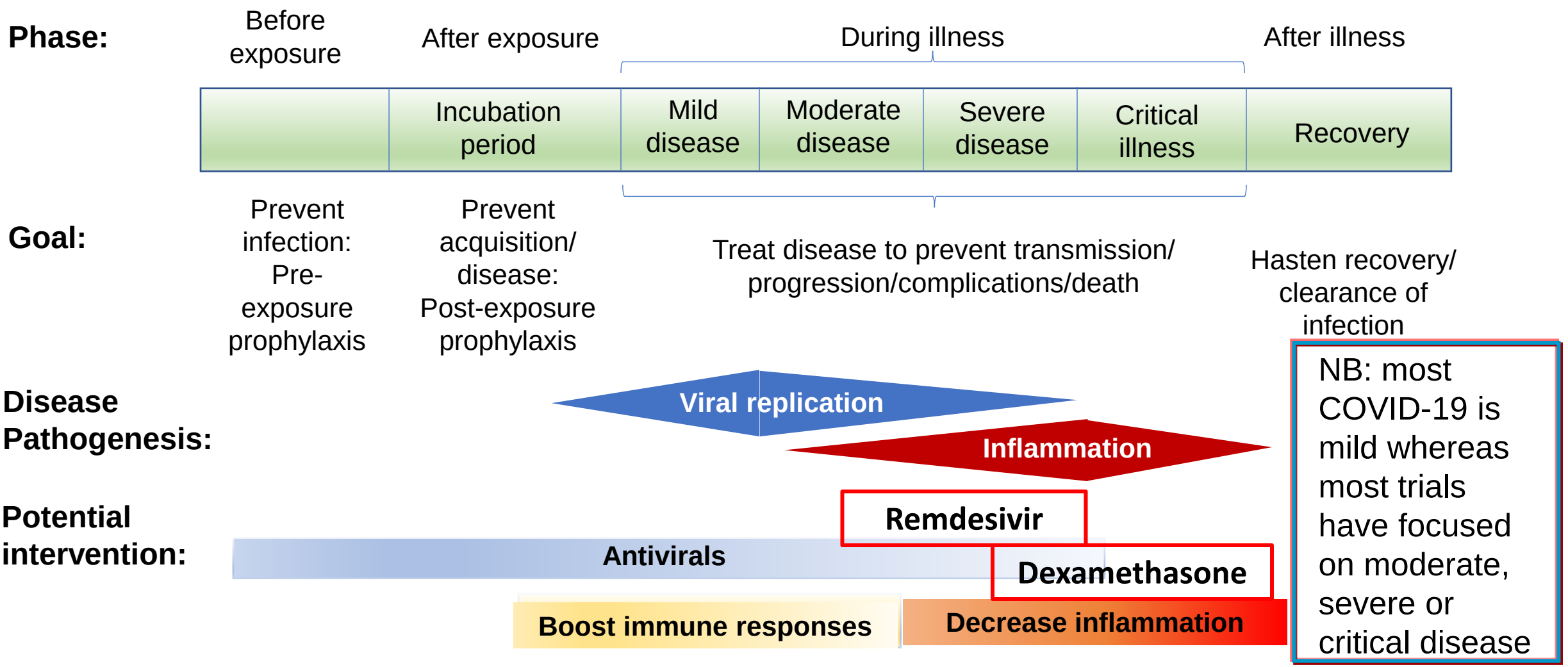
Conclusion: Dexamethasone associated with decreased mortality among those on supplemental oxygen or on mechanical ventilation/ECMO. No benefit in those not requiring oxygen.

Treating Complications: Role of Anticoagulation

- Infection with SARS-CoV-2 associated with an inflammatory and pro-thrombotic state
- Thromboembolic disease reported in people with COVID-19, particularly in those with critical illness
- Hospitalized patients should receive venous thromboembolism prophylaxis
- Ongoing and upcoming trials of anticoagulation in COVID-19

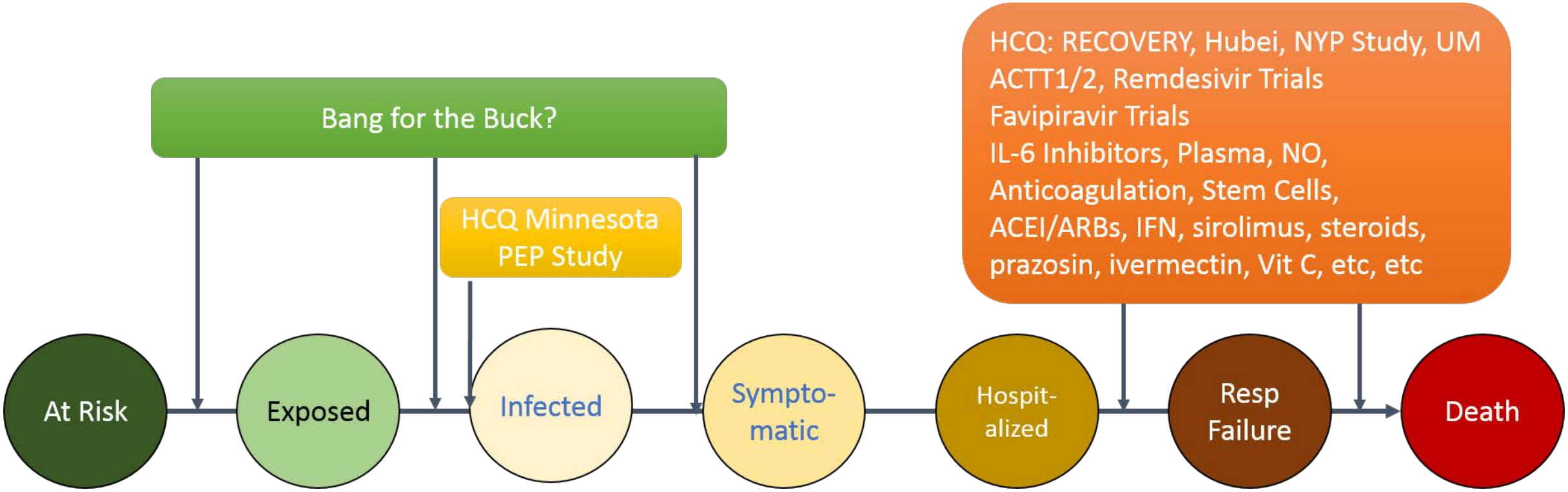


Goals of Treatment Across the COVID-19 Infection Spectrum



Adapted from slide by Dr. Arthur Kim, MGH

Treatment Across the COVID-19 Infection Spectrum



Slide from Dr. Mark Siedner, MGH

Final Thoughts

- COVID-19 treatment requires multidimensional approach, with an understanding of the host, the stage/severity of disease, and intervention
- Depending on host, stage and severity of disease, optimal intervention may differ: antiviral therapy, immunomodulator, combinations (antiviral + immunomodulator)

- **Lessons from HIV**
  - Pressure to deploy interventions must be tempered by importance of finding out if a treatment works: our guide must be the science
  - Iterative process, building on advances until tipping point is achieved
  - Critical to address disparities & inequities revealed by these “twin” pandemics


The Journal of Infectious Diseases

PERSPECTIVE

IDSA Infectious Diseases Society of America hivma hiv medicine association

Desperate Times Call for Temperate Measures: Practicing Infectious Diseases During a Novel Pandemic

Mark J. Siedner,[1,2] Rajesh T. Gandhi,[1] and Arthur Y. Kim[1]

[1]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA, and [2]Africa Health Research Institute, KwaZulu-Natal, South Africa