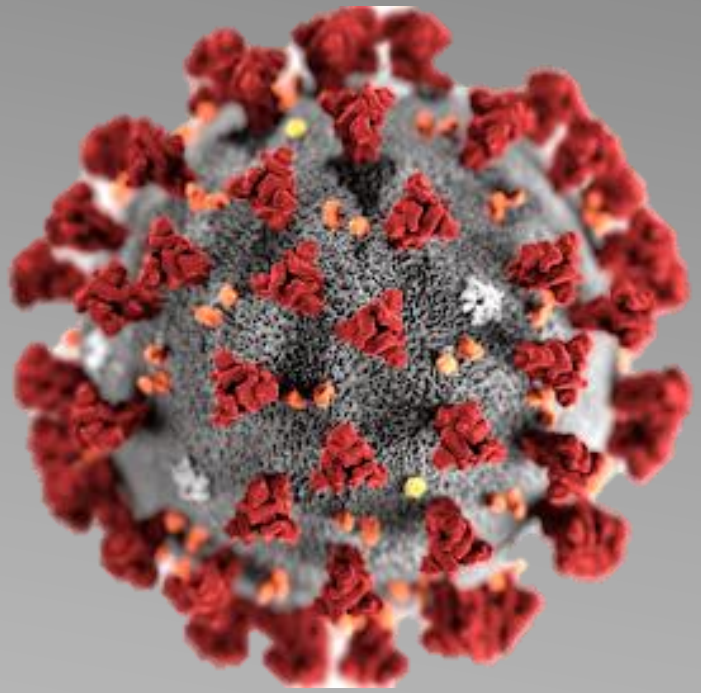
COVID-19:
Rethinking the Prescription

Amy L. Dzierba, PharmD, FCCM, FCCP, BCCCP
Clinical Pharmacist
Department of Pharmacy
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center
New York, New York



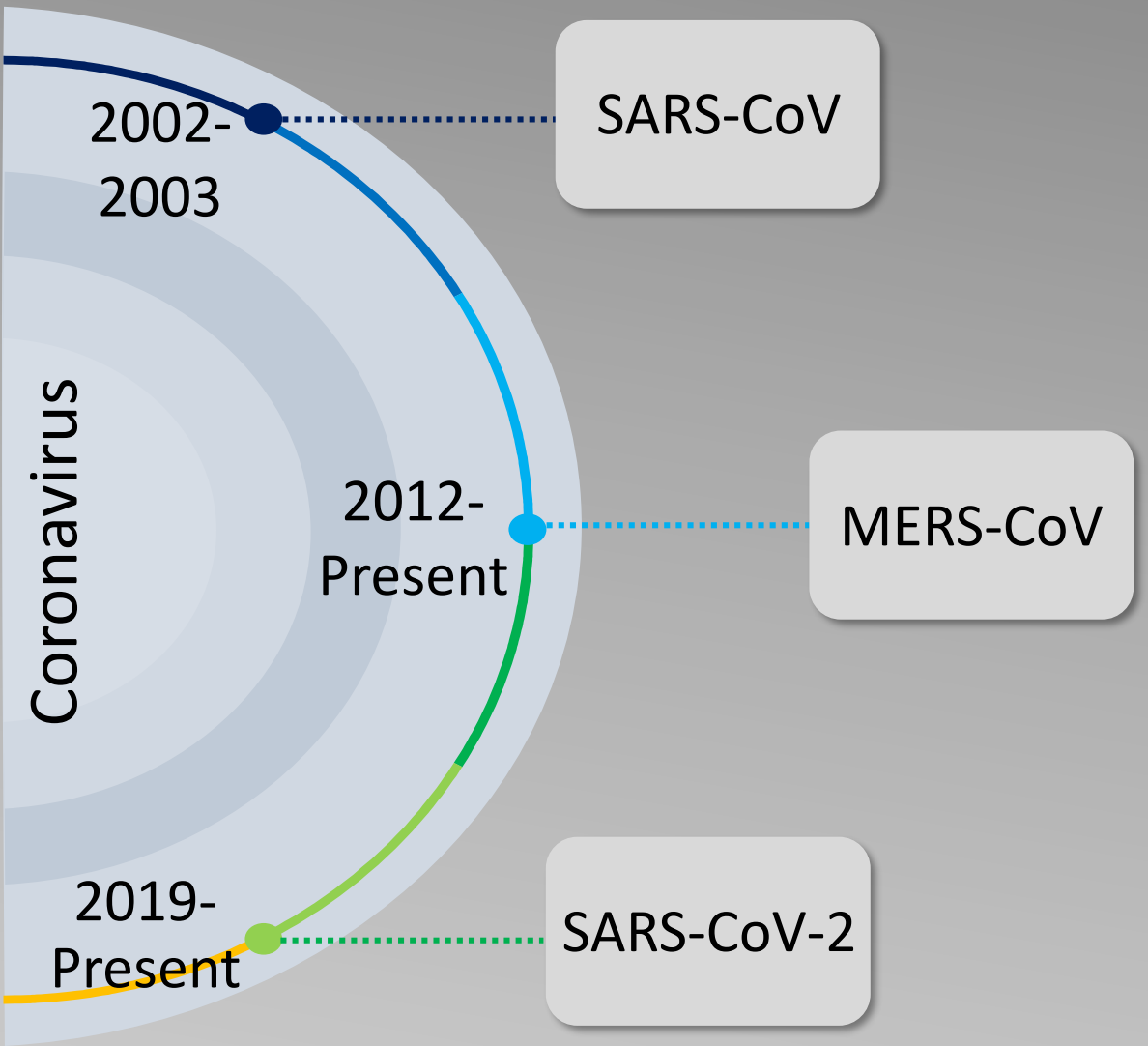
Disclosures

- Off-label drug use will be presented

Objectives

- Discuss epidemiologic trends and clinical characteristics of coronavirus disease 2019 (COVID-19)
- Summarize changes to operational and clinical hospital infrastructure during the coronavirus surge
- Describe strategies adopted during the pandemic to conserve supplies and optimize safety
- Assess recent pharmacologic challenges in the management of patients with COVID-19

Third Coronavirus in Two Decades

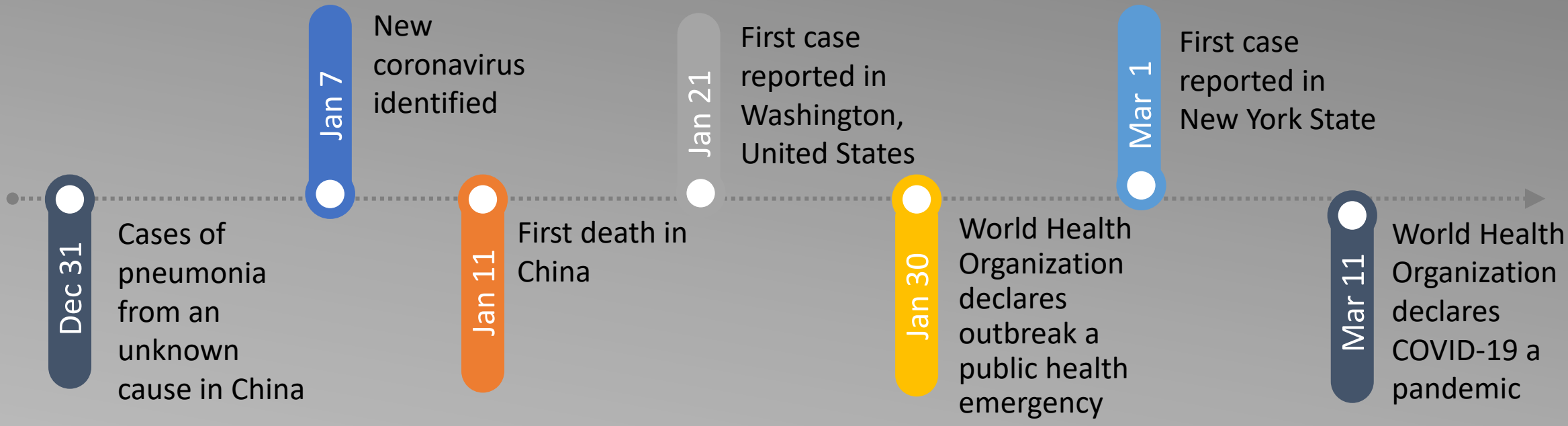


- Genomic similarity of SARS-CoV-2
  - 96% to bat coronavirus
  - 75-80% to SARS-CoV
  - 50% to MERS-CoV
- Entry receptor site
  - SARS-CoV and SARS-CoV-2: ACE2
  - MERS: DPP4

SARS-CoV=severe acute respiratory syndrome coronavirus; MERS-CoV=Middle East respiratory syndrome coronavirus; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; ACE2=angiotensin-converting enzyme 2; DPP4=dipeptidyl peptidase 4

Petrosillo N, et al. Clin Microbiol Infect. 2020 doi: 10.1016/j.cmi.2020.03.026.

Coronavirus Disease 2019 (COVID-19) Timeline

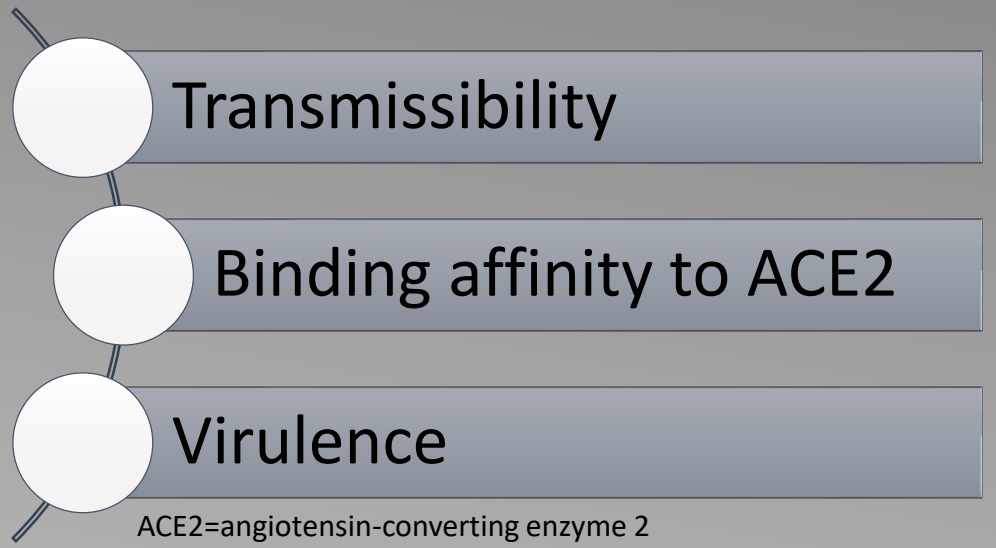


Wiersinga WJ, et al. JAMA. 2020 doi: 10.1001/jama.2020.12839.
https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19.

Why Did SARS-CoV-2 Propagate?

	COVID-19	SARS	MERS
Reproductive number (R_0)	2.5 (as high as 3.9)	2.4	<1

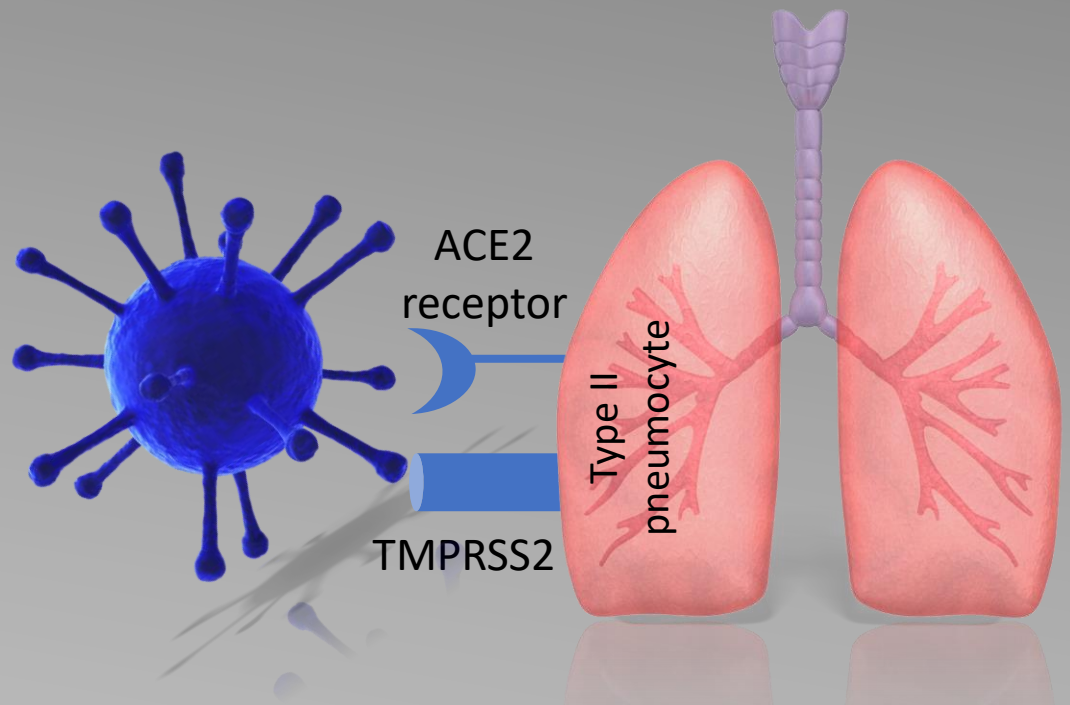
COVID-19=coronavirus disease 2019; SARS=severe acute respiratory syndrome; MERS=Middle East respiratory syndrome



ACE2=angiotensin-converting enzyme 2

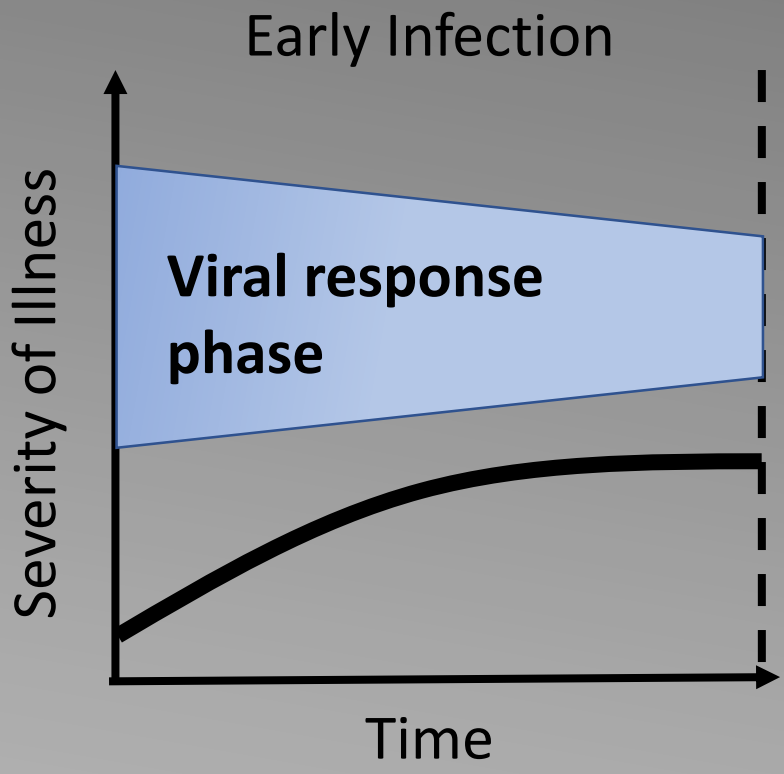
Peterson E, et al. Lancet. 2020 doi: 10.1016/S1473-3099(20)30484-9.
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_4.
https://www.who.int/csr/sars/en/WHOconsensus.pdf?ua=1. https://www.who.int/emergencies/mers-cov/mers-summary-2016.pdf?ua=1.

Stages of COVID-19



Day 1 — Day 5

Viral shedding



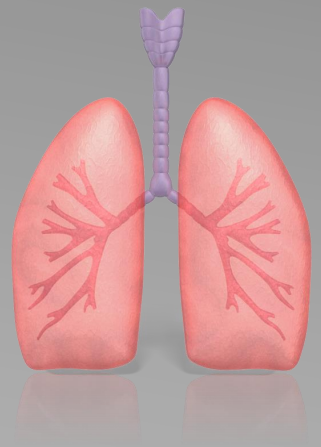
Fever, cough, myalgia

ACE2=angiotensin-converting enzyme 2;
TMPRSS2=transmembrane protease serine 2

Wiersinga WJ, et al. JAMA. 2020 doi: 10.1001/jama.2020.12839.
Siddiqi HK and Mehra MR. J Heart and Lung Transplant. 2020 doi: 10.1016/j.healun.2020.03.012.

Stages of COVID-19

Dysregulated Immune Response



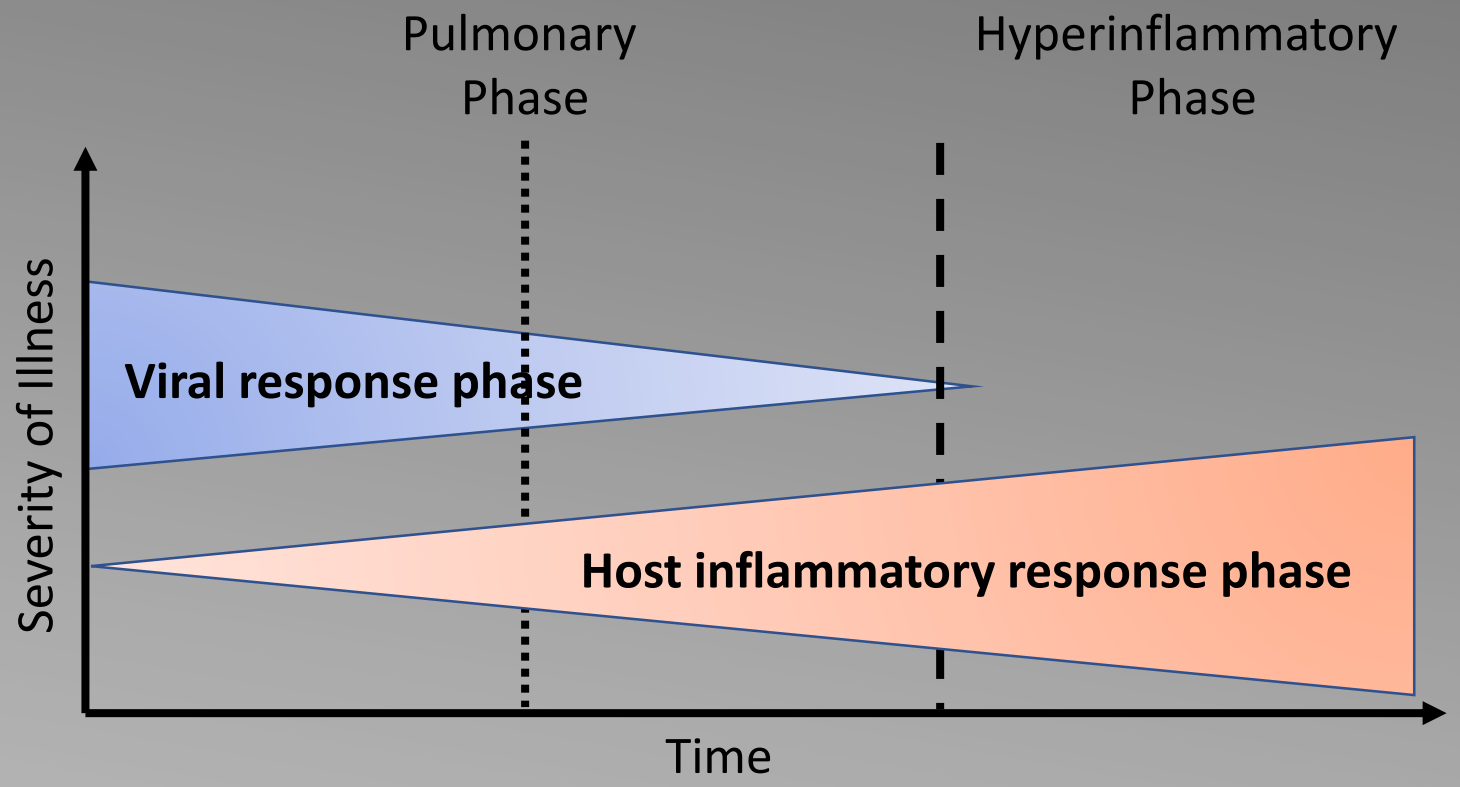
⇑ Interleukin-1
⇑ Interleukin-6
⇑ TNF-α

Inflammation

⇑ Thrombin production
⇓ Fibrinolysis

Thrombosis

Blood vessel



SOB=shortness of breath; ARDS=acute respiratory distress syndrome

Wiersinga WJ, et al. JAMA. 2020 doi: 10.1001/jama.2020.12839.
Siddiqi HK and Mehra MR. J Heart and Lung Transplant. 2020 doi: 10.1016/j.healun.2020.03.012.

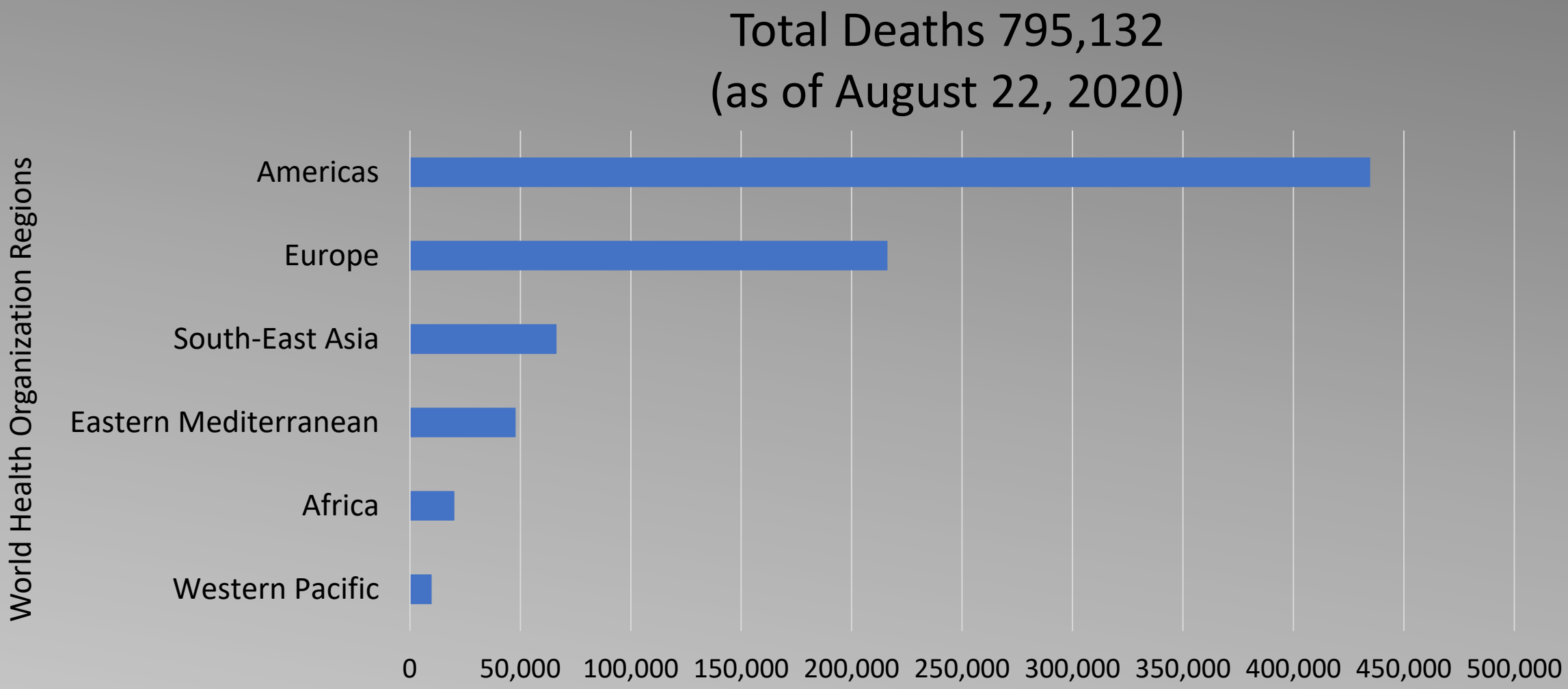
Clinical Complications in Hospitalized Patients

	COVID-19				SARS	MERS
	Wuhan, China[1]	NYC (NYPH)[2]	NYC (Northwell)[3]	NYC (NYU)[4]	Guangdong, China[5]	Jeddah, Saudi Arabia[5]
Intensive care unit admissions, %	5	24	14	27	23-34	53-89
Invasive mechanical ventilation, %	2.3	23	12	24	14-20	80
Acute kidney injury, %	0.5	34	22	-	7	41-50
Death, %	1.4	21	21	24^	4-16	30-40

NYC=New York City; NYPH=NewYork-Presbyterian Hospital; NYU=New York University Langone
^Death or hospice

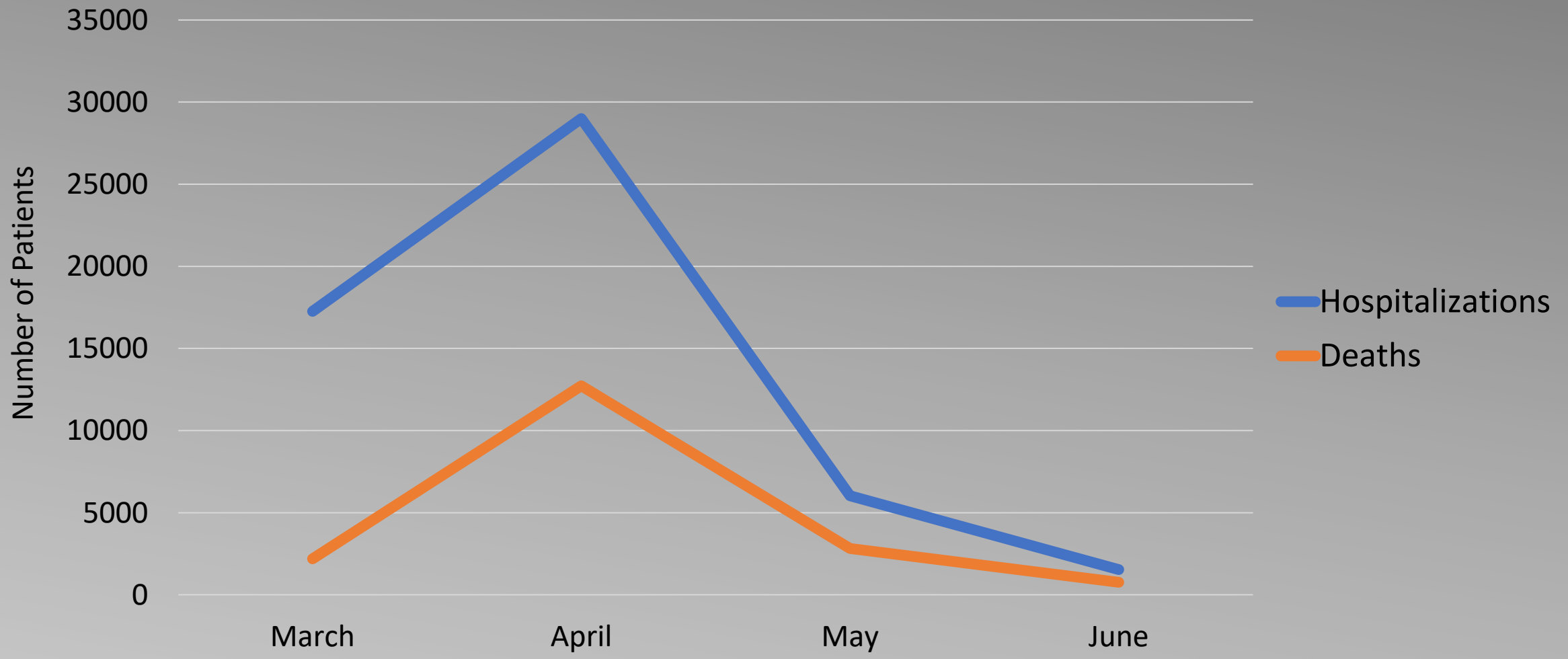
[1]Guan W, et al. N Engl J Med. 2020 doi: 10.1056/NEJMoa2002032.
[2]Argenziano MG, et al. BMJ. 2020 doi: 10.1136/bmj.m1996.
[3]Richardson S, et al. JAMA. 2020 doi: 10.1001/jama.2020.6775.
[4]Petrilli CM, et al. BMJ. 2020 doi: 10.1136/bmj.m1966.
[5]Petrosillo N, et al. Clin Microbiol Infect. 2020 doi: 10.1016/j.cmi.2020.03.026.

Worldwide COVID-19 Deaths



https://covid19.who.int.

New York City: Hospitalizations and Deaths

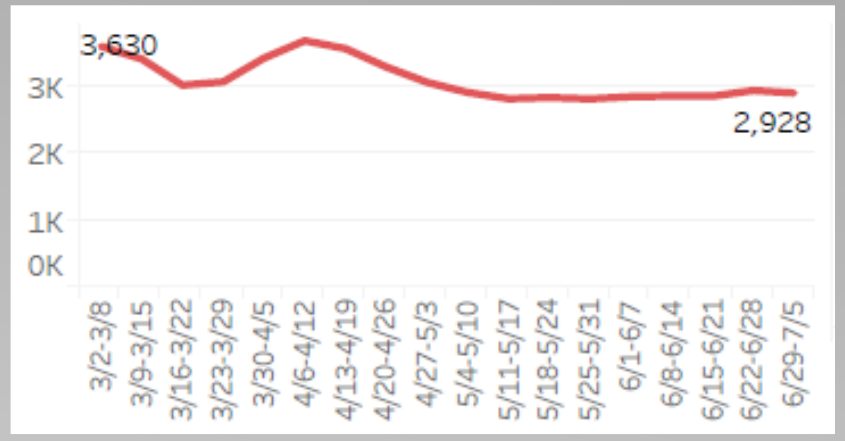


https://www1.nyc.gov/site/doh/covid/covid-19-data.page.

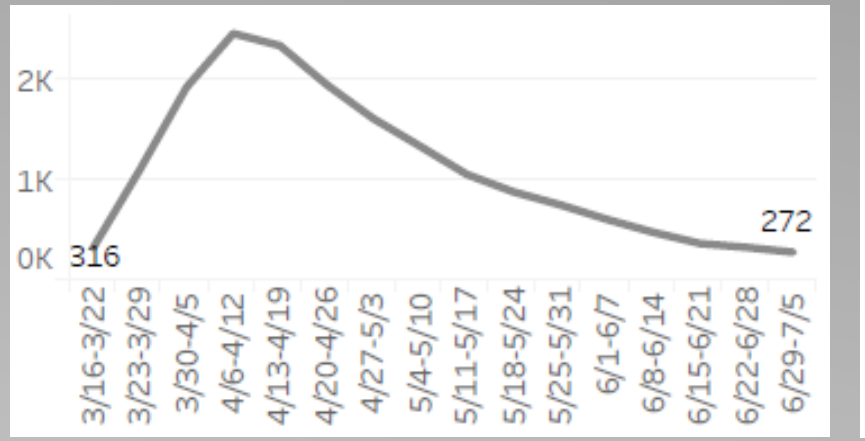
NewYork-Presbyterian: Building a COVID ~~Unit~~ ***Hospital Network***

- 9 hospitals
  - ~3,600 inpatient beds
  - ~378 intensive care unit (ICU) beds

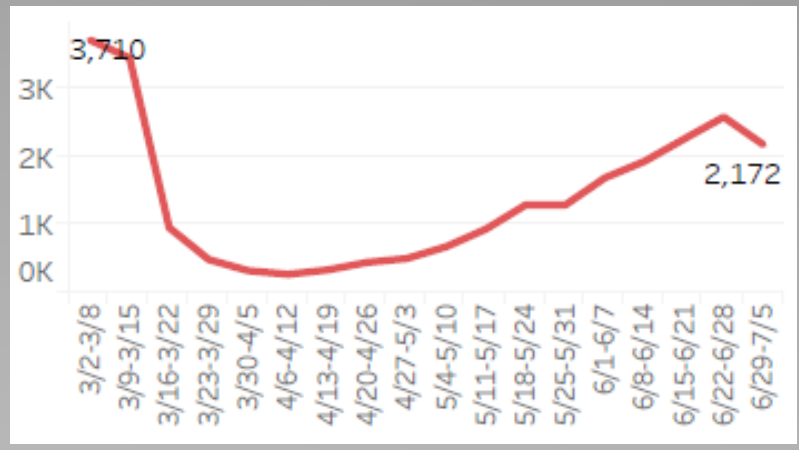
Inpatient Census



COVID-19 Inpatient Census

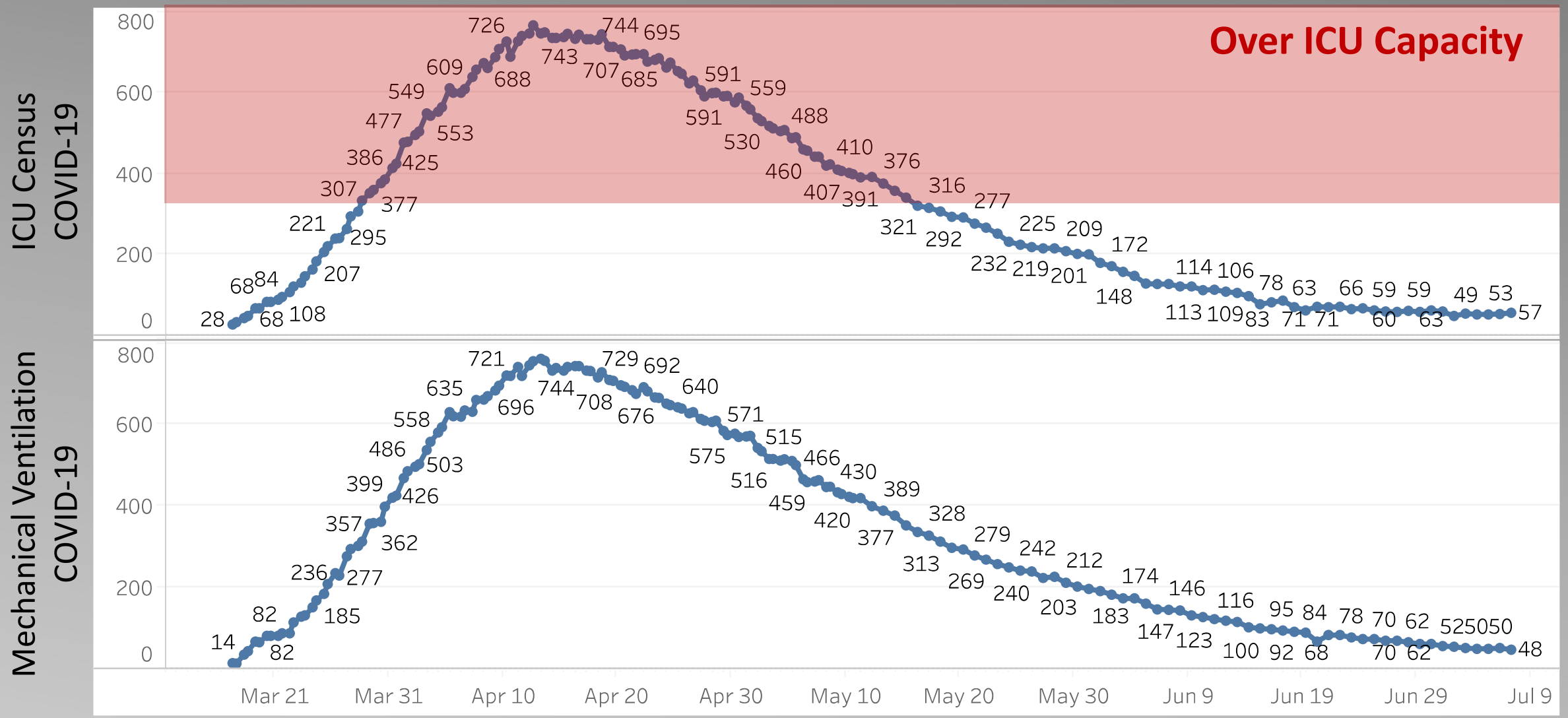


Surgeries



First SARS-CoV-2 case in New York State was identified on March 1

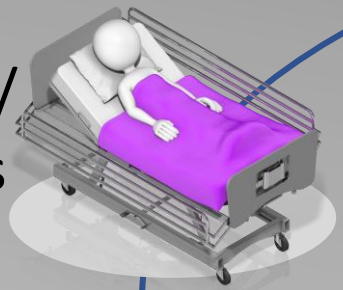
NewYork-Presbyterian: ICU Capacity



Resource Depletion

Life sustaining equipment

Medications



Hospital / ICU beds

Healthcare providers

Personal protective equipment (PPE)

Moving Beyond the Walls of Established ICUs

- Operating room
- Cardiac catheterization area
- Emergency room
- Stepdown units
- Field hospital
- Adjacent children's hospital

Columbia University Soccer Stadium

Photos: courtesy of Trisha Pedone, PharmD

Automatic Dispensing Cabinets

- Reconfigured for non-ICU areas servicing ICU patients
- Adjusted par levels to meet increased demand
- Purchased and distributed appropriately stocked machines
- Created virtual rapid sequence intubation kits throughout hospitals

Photo: courtesy of Trisha Pedone, PharmD

Managing Expanded ICU Capacity

Critical care
trained pharmacist

Critical care
trained pharmacist
AND
Non-critical care
trained pharmacist

Post-graduate year 2
critical care
pharmacy residents

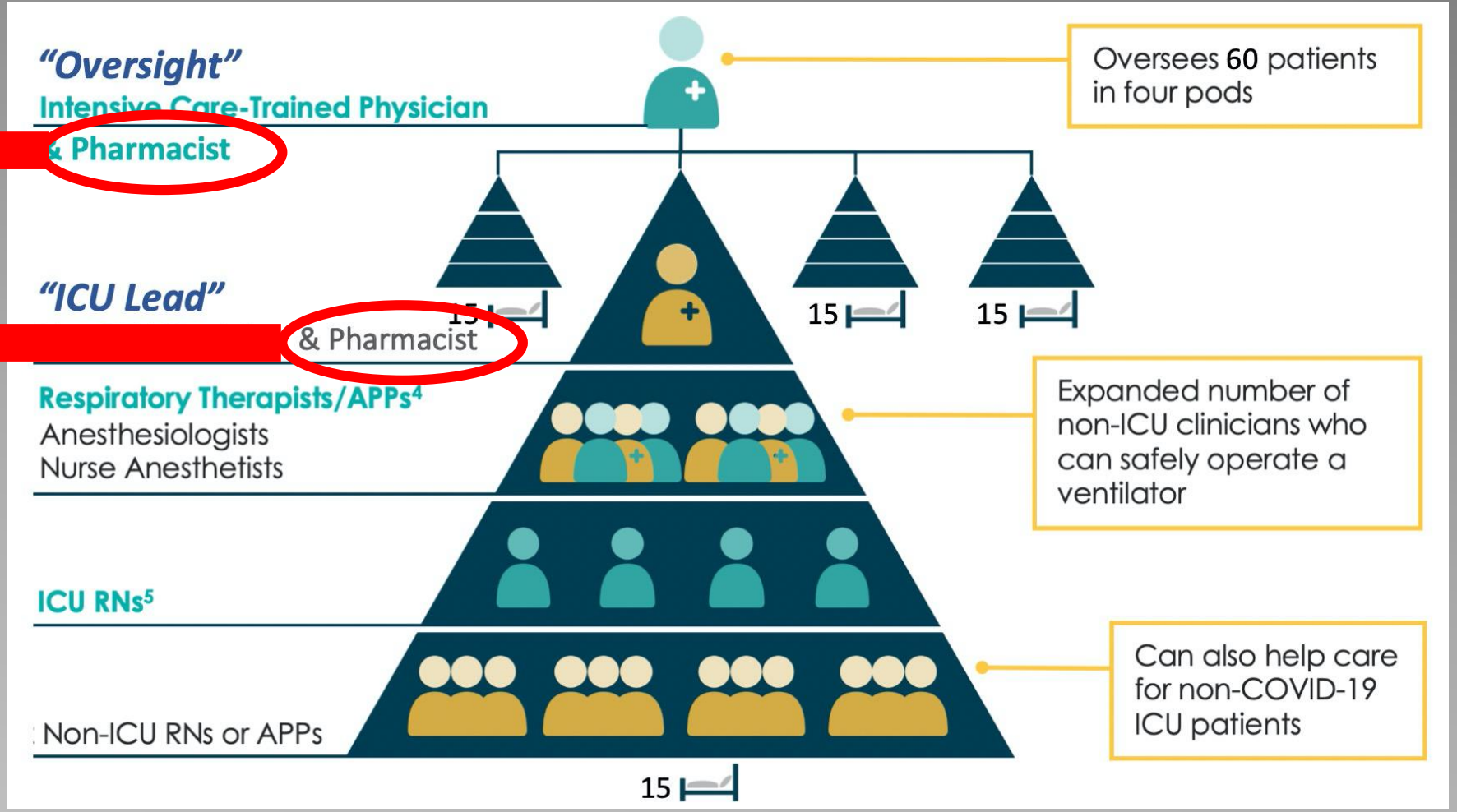


Diagram: courtesy of Jeremy Beitler, MD, MPH

Training of Non-Critical Care Trained Pharmacists

- Designed critical care lecture series / distributed critical care materials
  - Acute respiratory distress syndrome
  - Sedation and neuromuscular blocking agents
  - Components of FAST-HUG mnemonic
- Established twice weekly meetings to discuss clinical cases
- Created workflow document to highlight important clinical information

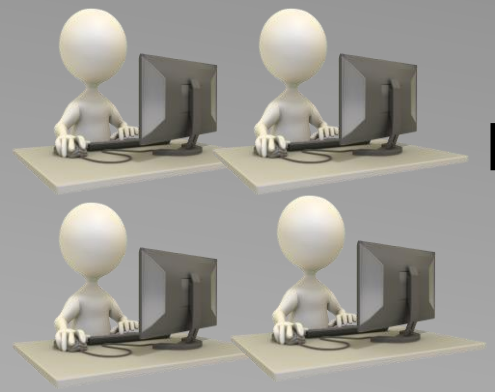
UNIT:		Date																														
					Mechanical Ventilation						Support								CV			Renal	DVT ppx / Therapeutic AC										
Bed	Name	Hx : Age, co-morbidies	ETT Date	ABG	Resp Rate	TV	FiO2	PEEP	P:F	Plateau Pressure	Paralyzed	iNO	Proned	ECMO	Sedation (meds/rate)	RASS Goal	COVID meds / Study enrollment	Micro / ABX	Pressors	EKG	ECHO	Cr / UOP CRRT/iHD i/o net	Regimen	aPTT	Anti-Xa	Plts	VAP ppx	Stress ulcer ppx	Other notable labs	Glucose / Regimen	Inflammatory Markers	Events/plan/overnight plan

FAST-HUG=feeding, analgesia, sedation, thromboembolic prophylaxis, head above bed, ulcer prophylaxis, glucose control

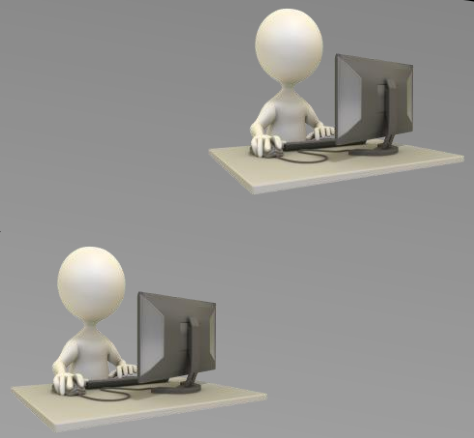
Vincent J. Crit Care Med. 2005 doi: 10.1097/01.ccm.0000165962.16682.46.

Workforce Alterations

Staff pharmacists



Remote verification



Clinical pharmacists

Team 1

Team 2

Onsite/virtual rounding

Team 1:
M/W/F (on-site)
Team 2:
Tu/Th (remote)

- ✓ Ensured social distancing
- ✓ Reduced travel / exposure risk
- ✓ Conserved PPE

Minimizing Exposure / PPE Conservation

- Relocated IV pumps to outside the patient room
- Shifted ventilator screens outside the patient room
- Bundled medication administration
- Created new guidelines for the management of hyperglycemia of critical illness

Photo: courtesy of Janine Solano, BSN, RN, CCRN

IV Pump Relocation

- Minimized number of times nurse entered the patient room
- Potentially reduced the time to change infusion rates and administer boluses or intermittent doses
- Challenges:
  - Required extension tubing
  - Increased drug waste
  - Delayed onset of action
  - Additive alarms
  - Posed a trip and infection hazard

Shah AG, et al. Crit Care Explor. 2020 doi: 10.1097/CCE.0000000000000168.
Photo: courtesy of Anjalina Samaroo, BSN, RN

Bundling Medications

- Scheduled enteral or other medications at the same time
  - Example: enoxaparin and pantoprazole daily at 9:00 a.m.
- Scheduled laboratory draws at the same time and minimized unnecessary laboratory tests
- Used medications with longer durations of action when available

BUNDDLE COVID-19:

- **B**uild a system
- On your **U**nit
- To keep **N**urses safe
- By **D**ecreasing **D**rug administration
- To **L**imit
- nurses **E**xposure
- To **COVID-19**

Mechanical Ventilators

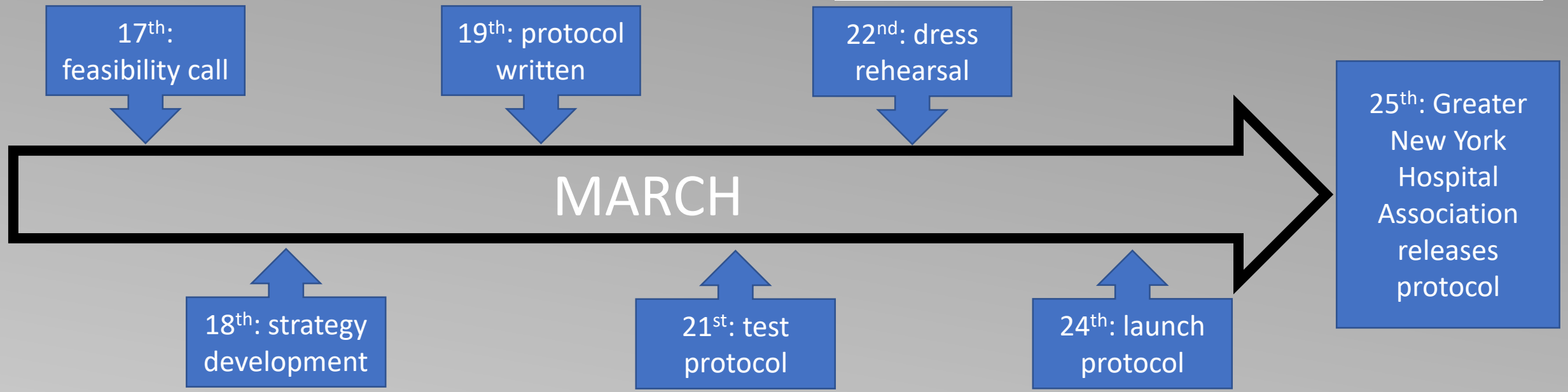
The New York Times

New York has only six days' worth of ventilators left.

The governor said that there were 2,200 ventilators in the state's stockpile and that about 350 new patients a day need them. At that pace, he said, "2,200 disappears very quickly."

'The Other Option Is Death': New York Starts Sharing of Ventilators

To keep coronavirus patients breathing, hospitals are pioneering a little-tested method.



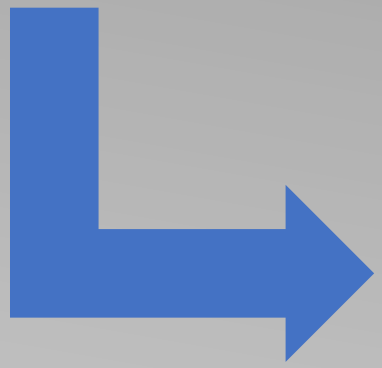
Ventilator Sharing: Duel-Patient Ventilation with a Single Mechanical Ventilator for use During Critical Ventilator Shortages

Jeremy R. Beitler, MD, MPH[1]
Richard Kallet, MSc, RRT[2]
Robert Kacmarek, PhD, RRT[3]
Richard Branson, MSc, RRT[4]
Daniel Brodie, MD[1]
Aaron M. Mittel, MD[5]
Murray Olson, RRT[6]
Laureen L. Hill, MD, MBA[6]
Dean Hess, PhD, RRT[3]
B. Taylor Thompson, MD[7]

Beitler JR, et al. Am J Respir Crit Care Med. doi: 10.1164/rccm.202005-1586LE.
https://www.gnyha.org/wp-content/uploads/2020/03/Ventilator-Sharing-Protocol-Dual-Patient-Ventilation-with-a-Single-Mechanical-Ventilator-for-Use-during-Critical-Ventilator-Shortages.pdf.
Photo: courtesy of Jeremy Beitler, MD, MPH

Dealing with Drug Shortages

- Management of inventory and procurement of drugs
- Used drug consumption calculators to anticipate needs
- Consolidated bulk ordering / centralized medications
- Executed drug conservation strategies (changed concentrations / product sizes and extended infusion times)
- Created guidelines on enteral opioid and sedative administration



Informatics

- Changed electronic medical record
  - Built new product concentrations / sizes (preferred defaulted)
  - Changed ordersets
  - Created alerts for restrictions / shortages

Keeping Up With COVID-19 Literature

https://www.sciencemag.org/news/2020/05/scientists-are-drowning-covid-19-papers-can-new-tools-keep-them-afloat
https://www.natureindex.com/news-blog/the-top-coronavirus-research-articles-by-metrics.

Hydroxychloroquine: What Were the Facts?

Study	Patients	Study Design	Primary Study Endpoint	Key Study Results
Gautret P, et al.[1]	36 hospitalized patients with confirmed COVID-19	Observational case series, prospective HCQ vs no HCQ	Virologic clearance at day 6	• 8/14 patients (57%) who received only HCQ and 6/6 patients (100%) who received HCQ+AZM had negative nasopharyngeal PCRs by day 6
Gautret P, et al.[2]	80 hospitalized patients with confirmed mild COVID-19	Observational case series, prospective HCQ vs HCQ+AZM vs standard care	Clinical outcome, length of stay	• 65 patients (81%) discharged to home or transferred to other units for continued treatment • 14 patients (17%) still hospitalized when the study results were published

AZM=azithromycin; HCQ=hydroxychloroquine; PCR=polymerase chain reaction

[1]Gautret P, et al. Int J Antimicrob Agents. 2020 doi: 10.1016/j.ijantimicag.2020.105949.
[2]Gautret P, et al. Travel Med Infect Dis. 2020 doi: 10.1016/j.tmaid.2020.101663.

Speed of Publications

Track Your Accepted Article

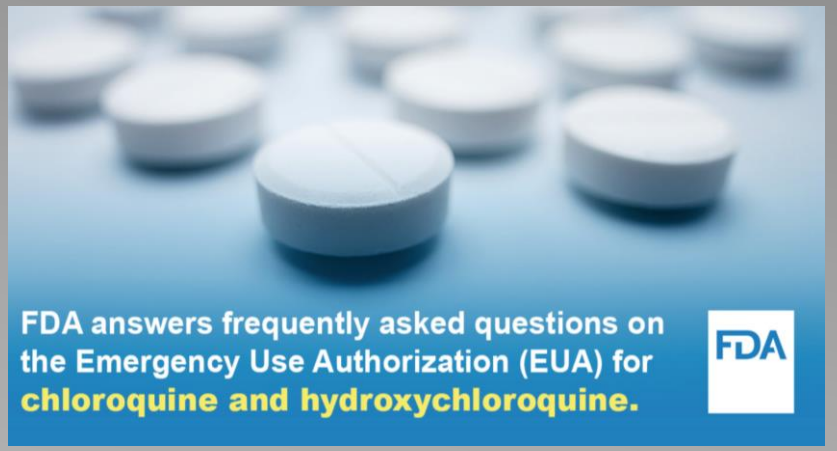
The easiest way to check the publication status of your accepted article

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

Article reference	ANTAGE_105949
Journal	International Journal of Antimicrobia
Corresponding author	Didier Raoult
First author	Philippe Gautret
Received at Editorial Office	16 Mar 2020
Article revised	17 Mar 2020
Article accepted for publication	17 Mar 2020
DOI	↗10.1016/j.ijantimicag.2020.105949

24 Hours!

11 Days After Publication



https://authors.elsevier.com/tracking/article/details.do?aid=105949&jid=ANTAGE&surname=Raoult.

Hydroxychloroquine Use at NYP/Columbia University Irving Medical Center

- First 1,000 patients with SARS-CoV-2 presenting to the emergency room between March 1st and April 5th

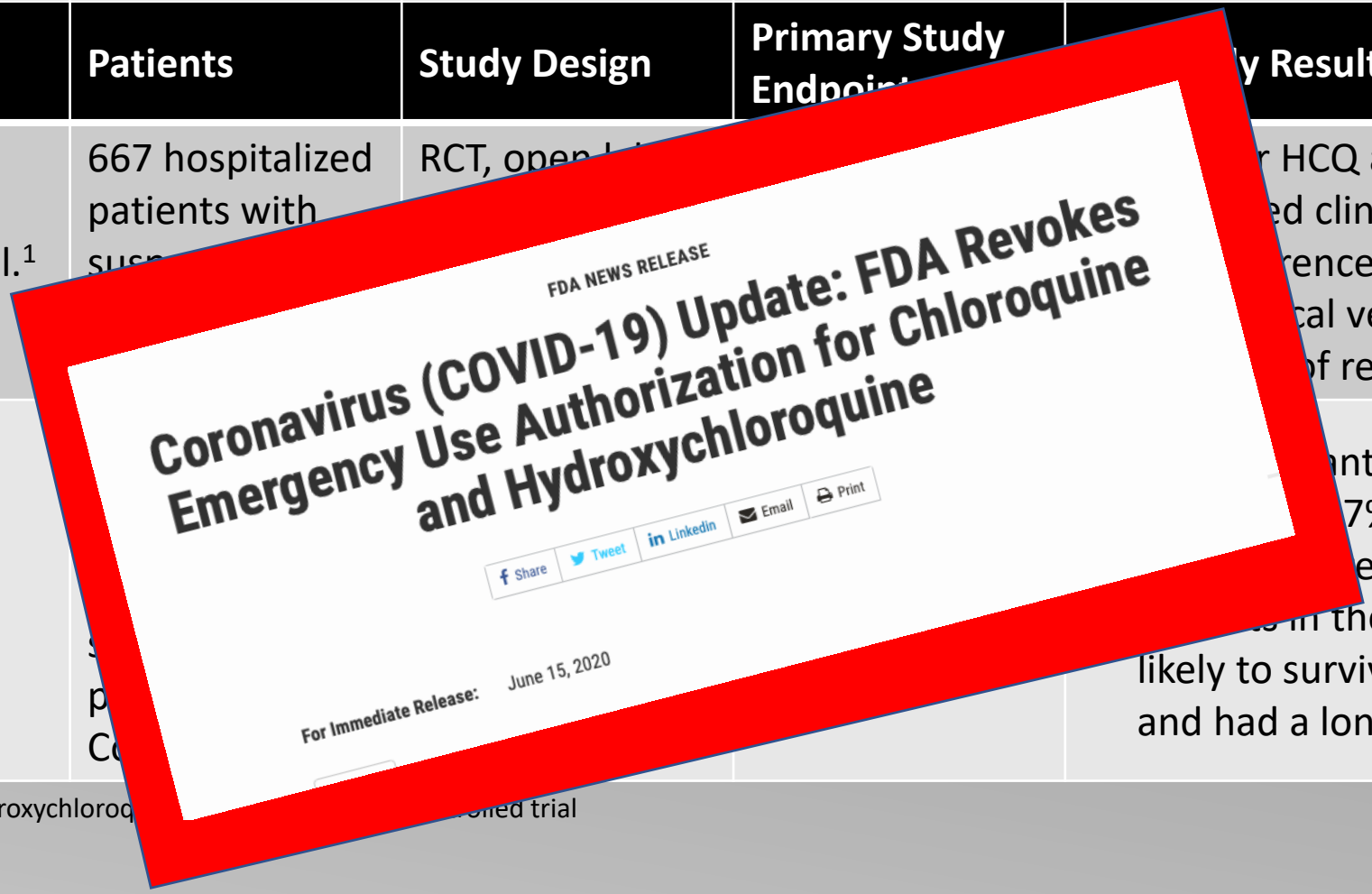
Characteristics, treatments, and complications	Highest level of care			Overall
	Emergency department (n=150)	In hospital (not intensive care units; n=614)	Intensive care units (n=236)	
Inpatient drug treatments				
Intravenous immunoglobulin	—	2; 0.3 (0.1 to 1.2)	5; 2.1 (0.9 to 4.9)	7/850; 0.8 (0.4 to 1.7)
Steroids	—	60; 9.8 (7.7 to 12.4)	118; 50 (43.7 to 56.3)	178/850; 20.9 (18.3 to 23.8)
Hydroxychloroquine	—	331; 53.9 (50.0 to 57.8)	212; 89.8 (85.3 to 93.1)	543/850; 63.9 (60.6 to 67.0)
Tocilizumab	—	13; 2.1 (1.2 to 3.6)	38; 16.1 (12 to 21.3)	51/850; 6 (4.6 to 7.8)
Remdesivir	—	7; 1.1 (0.6 to 2.3)	11; 4.7 (2.6 to 8.2)	18/850; 2.1 (1.3 to 3.3)
Lopinavir/ritonavir	—	1; 0.2 (0.0 to 0.9)	1; 0.4 (0.1 to 2.4)	2/850; 0.2 (0.1 to 0.9)
Any antibiotics	—	328; 53.4 (49.5 to 57.3)	224; 94.9 (91.3 to 97.1)	552/850; 64.9 (61.7 to 68.1)
Azithromycin	—	235; 38.3 (34.5 to 42.2)	170; 72 (66.0 to 77.4)	405/850; 47.6 (44.3 to 51.0)

Argenziano MG, et al. BMJ. 2020 doi: 10.1136/bmj.m1996.

Hydroxychloroquine: No More

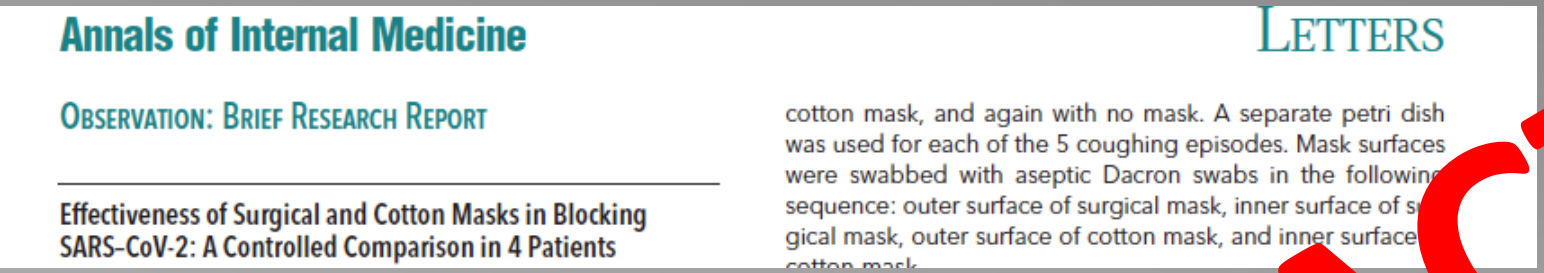
Study	Patients	Study Design	Primary Study Endpoi	y Results
Cavalcanti AB, et al.[1]	667 hospitalized patients with susp	RCT, open-l		r HCQ alone nor HCQ+AZM ed clinical outcomes at day 15 rences in progression to cal ventilation or being alive f respiratory support
Horby P, et al.[2] (RECOVERY)	p C			nt difference in 28-day 7% in the HCQ vs 25% in e), p=0.18 ts in the HCQ arm were less likely to survive the hospitalization and had a longer time to discharge

AZM=azithromycin; HCQ=hydroxychloroq olled trial



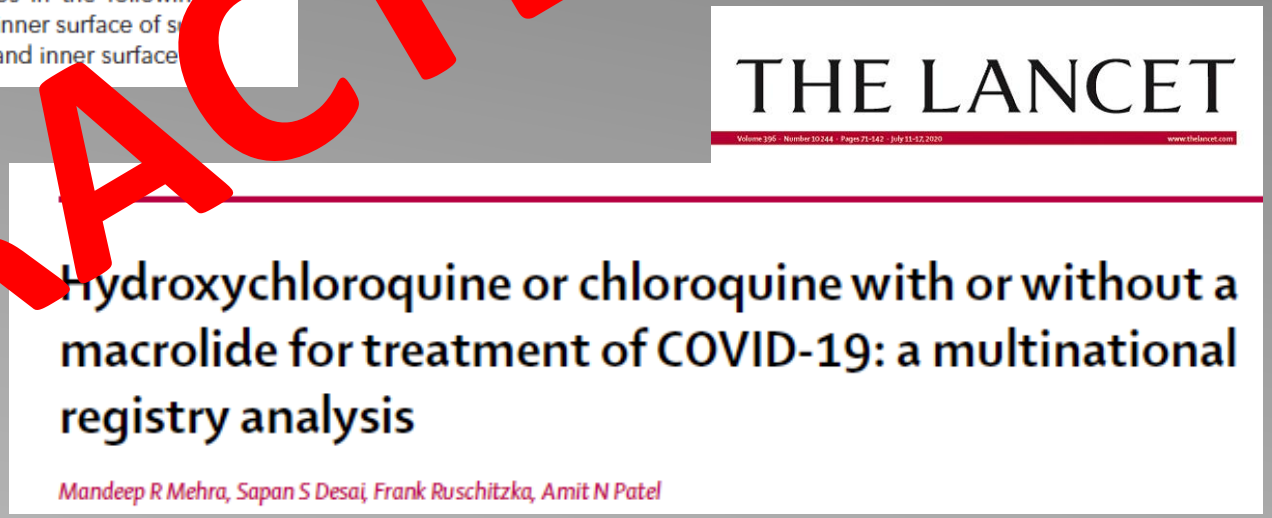
[1]Cavalcanti AB, et al. N Engl J Med. 2020 doi: 10.1056/NEJMoa2019014.
[2]Horby P, et al. BMJ. 2020 doi: https://doi.org/10.1101/2020.07.15.20151852.

Balance Between Speed and Accuracy



Published April 6, 2020 → Retracted June 2, 2020

Published May 1, 2020 → Retracted June 25, 2020

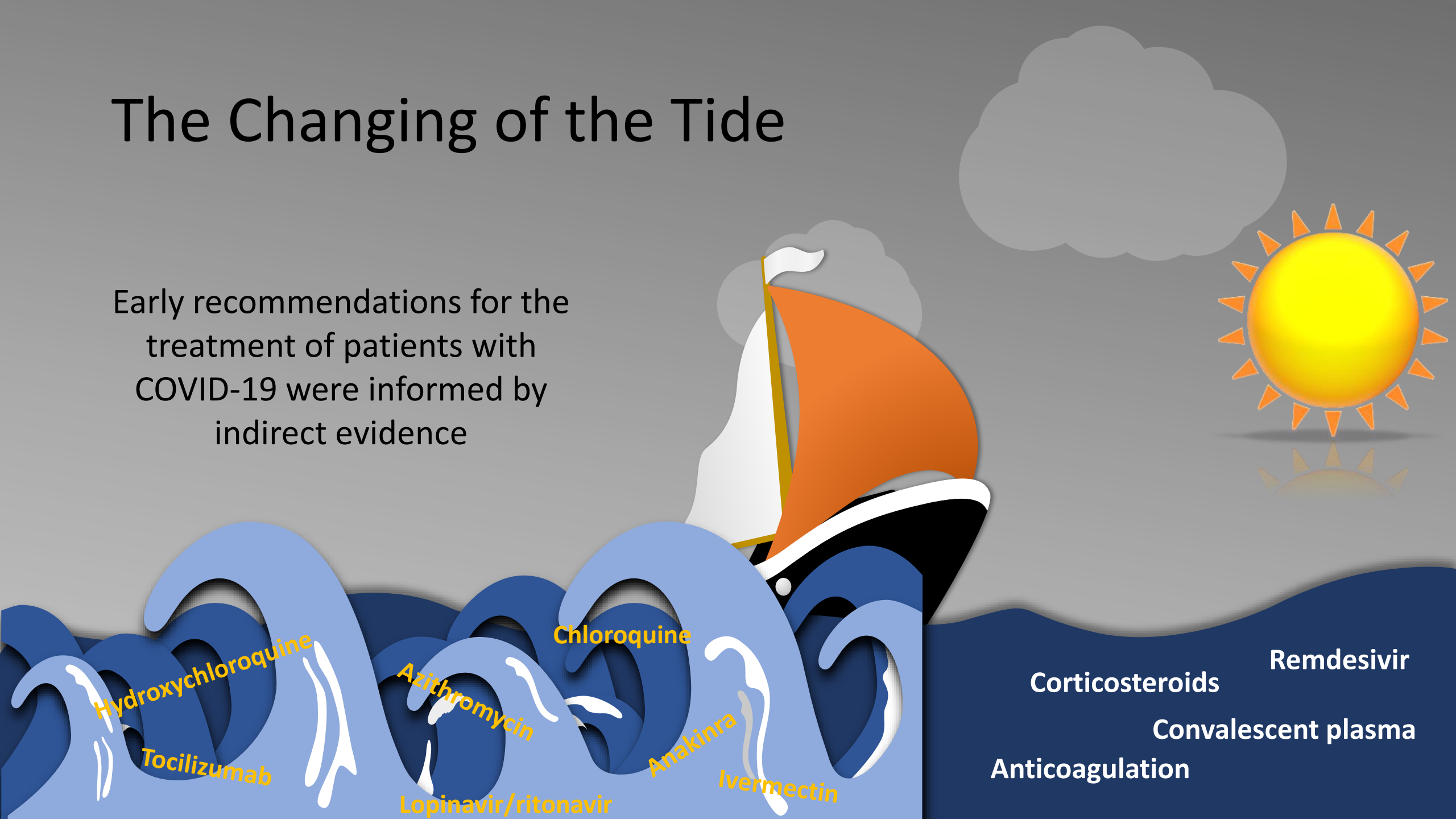


Published May 22, 2020 → Retracted June 25, 2020

RETRACTED

The Changing of the Tide

Early recommendations for the treatment of patients with COVID-19 were informed by indirect evidence



What We Know and What We Don’t Know

Polling Question:

In which group of hospitalized patients with COVID-19 do you recommend remdesivir?

A. All hospitalized patients with COVID-19
B. Only patients requiring supplemental oxygen (not on high-flow nasal cannula, noninvasive/invasive mechanical ventilation)
C. Only patients requiring invasive mechanical ventilation
D. I would not give remdesivir to any patient with COVID-19
E. Unsure / undecided

Adaptive COVID Treatment Trial (ACTT-1)

- 1063 hospitalized patients with COVID-19
- Randomized to remdesivir IV or placebo for 10 days (or until hospital discharge, whichever came first)

- Reduced time to recovery compared to placebo (11 days vs. 15 days, recovery rate ratio 1.32; 95% CI, 1.12-1.55; $P < 0.001$)
- Non-significant difference in survival by day 14 in the remdesivir arm compared to the placebo arm (7.1% vs. 11.9%; HR 0.70; 95% CI, 0.47-1.04)

Ordinal Scale at Enrollment	Results
5 - Supplemental oxygenation (n=421)	• Recovery rate ratio 1.47; 95% CI, 1.17-1.84 • Post-hoc analysis of deaths by day 14, HR for death 0.22; 95% CI 0.08-0.58

1	Not hospitalized, no limitations
2	Not hospitalized, with limitations
3	Hospitalized, no active medical problems
4	Hospitalized, not requiring oxygen
5	Hospitalized, requiring oxygen
6	Hospitalized, requiring high-flow oxygen or noninvasive mechanical ventilation
7	Hospitalized, requiring mechanical ventilation or extracorporeal membrane oxygenation
8	Death

Beigel JH, et al. N Engl J Med. 2020 doi: 10.1056/NEJMoa2007764.

SIMPLE-Severe

- Manufacturer-sponsored, multinational, randomized, open-label trial
- 397 hospitalized patients ≥ 12 years of age with COVID-19 assigned to receive intravenous remdesivir for either 5 days or 10 days
- Results
  - Two point improvement in clinical status: 65% of patients in the 5-day group and 54% of those in the 10-day group
  - Similar time to clinical improvement
  - Similar mortality

1	Death
2	Hospitalized, requiring invasive mechanical ventilation or ECMO
3	Hospitalized, requiring noninvasive ventilation or high-flow oxygen devices
4	Hospitalized, requiring low-flow supplemental oxygen
5	Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons
6	Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care specified in the protocol for remdesivir administration)
7	Not hospitalized

Goldman JD, et al. N Engl J Med. 2020 doi: 10.1056/NEJMoa2015301.

Remdesivir for Moderate Disease

- Manufacturer-sponsored, randomized, open-label trial
- 596 hospitalized patients with confirmed moderate COVID-19
- Randomized to remdesivir IV (5 or 10 days) or standard care
- Day 11: patients randomized to 5 days of remdesivir had a higher odds of a better clinical status than those receiving standard care (OR 1.65; 95% CI 1.09-2.48, p=0.02)

Uncertain clinical importance

1	Not hospitalized, no limitations
2	Not hospitalized, with limitations
3	Hospitalized, no active medical problems
4	Hospitalized, not requiring oxygen
5	Hospitalized, requiring oxygen
6	Hospitalized, requiring high-flow oxygen or noninvasive mechanical ventilation
7	Hospitalized, requiring mechanical ventilation or extracorporeal membrane oxygenation
8	Death

Remdesivir Use in COVID-19

Not currently FDA approved

Remdesivir allocation may be inadequate for number of patients

NIH COVID-19 Treatment Guidelines

July 24, 2020

- Mild or moderate COVID-19 → **<u>insufficient data</u>**
- Supplemental oxygen → **<u>recommend 5 days or until hospital discharge</u>**
- High-flow oxygen, noninvasive or mechanical ventilation, or ECMO → **<u>no recommendation</u>**

NIH=National Institutes of Health; ECMO=extracorporeal membrane oxygenation

https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/.

Polling Question:

In which group of hospitalized patients with COVID-19 do you recommend the use of corticosteroids?

- Receiving invasive mechanical ventilation only
- Receiving supplemental oxygen (invasive and non-invasive ventilation)
- On room air (no supplemental oxygen)
- All of the above
- Unsure/Undecided

Dexamethasone Use in COVID-19 (RECOVERY)

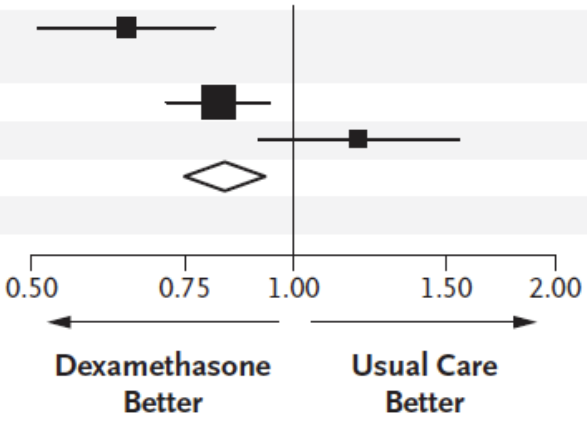
- 6,425 hospitalized patients with clinically suspected or confirmed SARS-CoV-2
- Randomized to dexamethasone 6 mg PO/IV daily up to 10 days vs usual care

Outcome	Dexamethasone (N = 2104)	Usual Care (N = 4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

Horby P, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2021436.

Dexamethasone Use in COVID-19 (RECOVERY)

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001
Chi-square trend across three categories: 11.5			



Patients requiring mechanical ventilation

Patients not requiring supplemental oxygen

Patients requiring supplemental oxygen (not invasive mechanical ventilation)

- Heterogenous group of patients requiring different levels of oxygen support

Horby P, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2021436.

Patients Requiring Oxygen Support (not mechanical ventilation)

32-year-old woman receiving 3 liters nasal cannula

65-year-old woman with diabetes mellitus receiving 5 liters nasal cannula

55-year-old obese man with diabetes receiving high flow nasal cannula at 40 liters/min on 100% FiO_2

FiO_2=fraction of inspired oxygen

Horby P, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2021436.

Corticosteroids in COVID-19

Trial	Patients	Study Design	Primary Study Endpoint	Key Study Results
Tomazini BM, et al.[1] (CoDEX)	299 adults with suspected or confirmed COVID-19 receiving MV with moderate to severe ARDS	RCT, open-label DEX 20 mg IV daily x5 days, followed by 10 mg IV daily x5 days vs standard care	Ventilator-free days (VFD) during the first 28-days	VFD: mean 6.6 in DEX group vs 4.0 in control group, p=0.04
Angus DC, et al.[2] (REMAP-CAP COVID-19)	384 adults with suspected or confirmed SARS-CoV-2 admitted to the ICU for respiratory or cardiovascular support	RCT, open-label HC 50 mg IV every 6h x7 days (fixed-dose) vs HC 100 mg IV every 6h while in shock up to 28 days (shock-dose) vs no HC	Respiratory and cardiovascular organ support-free days (OSD) up to 21 days	OSD: median (IQR) 0 (-1 to 15) for fixed-dose, 0 (-1 to 13) for shock-dose, and 0 (-1 to 11) days for no HC
Dequin P, et al.[3] CAPE COVID	149 adults with suspected or confirmed COVID-19 with acute respiratory failure	RCT, double-blind HC continuous infusion 200 mg daily x7 days, 100 mg x4 days, 50 mg daily x3 days vs placebo	Death or persistent dependency on MV or high-flow oxygen therapy	Treatment failure: 42.1% in HC group vs 50.7% in placebo group, p=0.29

ARDS=acute respiratory distress syndrome; DEX=dexamethasone; HC=hydrocortisone

[1]Tomazini BM, et al. JAMA. doi: 10.1001/jama.2020.17021.
[2]Angus DC, et al. JAMA. doi: 10.1001/jama.2020.17022.
[3]Dequin, P, et al. JAMA. doi: 10.1001/jama.2020.16761.

Corticosteroids: The Bottom Line

- Right Time
  - Balance between preventing collateral damage from immune response and interrupting the immune system
- Right Patient
  - 17% of RECOVERY patients were not deemed eligible
  - SARS-CoV-2 versus COVID-19
- Right Drug/Dose/Duration
  - Dexamethasone 6 mg PO/IV daily x10 days or clinical improvement used in RECOVERY
  - Meta-analysis: mortality 32.7% in patients randomized to corticosteroids and 41.4% in patients randomized to usual care or placebo (RR 0.66; 95%CI, 0.53-0.82)

Horby P, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2021436.
Sterne J, et al. JAMA. doi: 10.1001/jama.2020.17023.

Combination Therapy

- Remdesivir
- ✚
- Corticosteroids
- ✚
- Convalescent plasma
- ✚
- Others?

Case

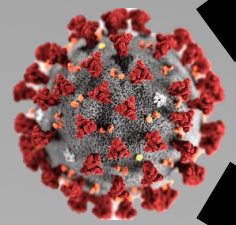
- A 62-year old man with a history of morbid obesity, diabetes, and hypertension presents to the emergency room with dyspnea over the last week.
- Vital signs
  - BP: 100/57 mmHg
  - HR: 120 beats/min
  - RR: 28 respirations/min
  - Oxygen sat: 93% on high flow nasal cannula at 60 liters/min on 100% FiO_2
- Pertinent laboratory data
  - WBC 4 x 10^3 cells/mm^3 (significant lymphopenia)
  - Platelets 200,000/mm^3
  - BUN 20 mg/dL
  - SCr 0.7 mg/dL
  - aPTT/PT WNL
  - Fibrinogen 800 mg/dL

What anticoagulation regimen would you give to this patient?

Polling Question:

- No anticoagulation is indicated
- Standard venous thromboembolism (VTE) prophylaxis dose
- Increased intensity VE prophylaxis
- Full anticoagulation
- Unsure / undecided

Coagulation Abnormalities in COVID-19



Proinflammatory Cytokines:

⇑ Interleukin-1
⇑ Interleukin-4
⇑ Interleukin-6
⇑ TNF-α

Inflammatory Markers:

⇑ C-reactive protein
⇑ Ferritin

Coagulopathy:

⇑ D-dimer
⇑ Fibrinogen
⇑ aPTT / PT
⇓ Platelets

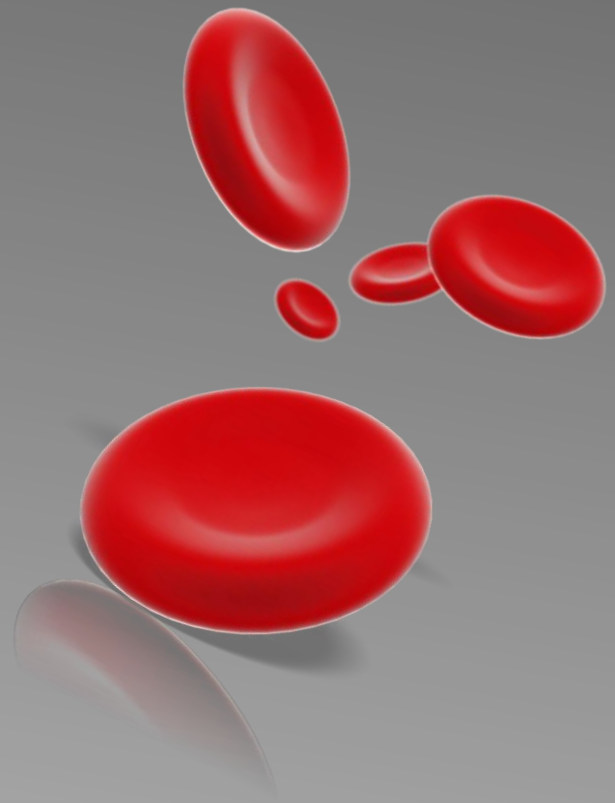
Thrombotic Events

COVID-19 infection infrequently
leads to bleeding
despite abnormal coagulation parameters

aPTT=activated partial thromboplastin time; PT=prothrombin time; TNF- α=tumor necrosis factor alpha

Chan N, et al. Lancet. 2020 doi: 10.1016/S0140-6736(20)30211-7.
Wang D, et al. JAMA. 2020 doi: 10.1001/jama.2020.1585.
Zhou F, et al. Lancet. 2020 doi: 10.1016/S0140-6736(20)30566-3.

Thrombosis in COVID-19



- Critically ill patients without COVID-19 (receiving standard dose VTE prophylaxis):
  - DVT: 5-8%[1-2]
  - PE: 1-2%[1]
- Critically ill patients with COVID-19:
  - Venous thromboembolism (VTE): 10-84%

[1]Cook D, et al. N Engl J Med. 2011 doi: 10.1056/NEJMoa1014475
[2]Zhang C, et al. Medicine. 2019 doi: 10.1097/MD.0000000000015833.

VTE Rates in Patients with COVID-19

Study	ICU Patients, n	Study Design	Pharmacologic VTE Prophylaxis	Thromboembolic (DVT/PE) Events, %
Cui S, et al. (China)[1]	81	Retrospective	None	25
Ren B, et al. (China)[2]	48	Prospective	Standard	85
Lodigiani C, et al. (Italy)[3]	61	Retrospective	Standard	27
Helms J, et al. (France)[4]	150	Prospective	70% standard; 30% therapeutic	2 DVT; 17 PE
Klok FA, et al. (The Netherlands)[5]	184	Retrospective	Mostly standard	27
Middeldorp S, et al. (The Netherlands)[6]	75	Retrospective	Mostly standard	47
Bilaloglu S, et al. (United States)[7]	829	Retrospective	Standard	9 DVT; 6 PE
Maatman TK, et al. (United States)[8]	109	Retrospective	Standard	28
Al-Samkari H, et al (United States)[9]	144	Retrospective	Mostly standard	8

VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism

[1]Cui S, et al. J Thromb Haemost. 2020 doi: 10.1111/jth.14830.
[2]Ren B, et al. Circulation. 2020 doi: 10.1161/CIRCULATIONAHA.120.047407.
[3]Lodigiani C, et al. Thromb Res. 2020 doi: 10.1016/j.thromres.2020.04.024.
[4]Helms J, et al. Intensive Care Med. 2020 doi: 10.1007/s00134-020-06062-x.
[5]Klok FA, et al. Thromb Res. 2020 doi: 10.1016/j.thromres.2020.04.013.
[6]Middeldorp S, et al. J Thromb Haemost. 2020 doi: 10.1111/jth.14888.
[7]Bilaloglu S, et al. JAMA. 2020 doi: 10.1001/jama.2020.13372.
[8]Maatman TK, et al. Crit Care Med. 2020 doi: 10.1097/CCM.0000000000004466.
[9]Al-Samkari H, et al. Blood. 2020 doi: 10.1182/blood.2020006520.

VTE Rates in Patients with COVID-19

- Multicenter, cohort study including 2,215 adults with COVID-19 admitted to an ICU at 65 hospitals across the US from March 4 to April 4, 2020

Treatment	Patients, No. (%)		
		Day 28	
	All patients (N = 2215)	Alive (n = 1431)	Died (n = 784)
Therapeutic anticoagulation[b]			
Any	920 (41.5)	570 (39.8)	350 (44.6)
Heparin drip	573 (25.9)	349 (24.4)	224 (28.6)
Enoxaparin	302 (13.6)	206 (14.4)	96 (12.2)
Bivalirudin	25 (1.1)	19 (1.3)	6 (0.8)
Argatroban	24 (1.1)	16 (1.1)	8 (1.0)

DVT = 6.3%

PE = 2.3%

VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism

Gupta S, et al. JAMA Intern Med. 2020 doi: 10.1001/jamainternmed.2020.3596.

Other Thrombosis in Patients with COVID-19

Study	ICU Patients, n	Pharmacologic VTE Prophylaxis	Other Thrombosis, %
Klok FA, et al. (The Netherlands)[1]	184	Mostly standard	1.6 ischemic stroke
Helms J, et al. (France)[2]	150	70% standard 30% therapeutic	97 CRRT circuit clot 1.3 ischemic stroke
Bilaloglu S, et al. (United States)[3]	829	Standard	3.7 ischemic stroke
Al-Samkari H, et al. (United States)[4]	144	Mostly standard	5.6 arterial

CRRT=continuous renal replacement therapy

[1]Klok FA, et al. Thromb Res. 2020 doi: 10.1016/j.thromres.2020.04.013.
[2]Helms J, et al. Intensive Care Med. 2020 doi: 10.1007/s00134-020-06062-x.
[3]Bilaloglu S, et al. JAMA. 2020 doi: 10.1001/jama.2020.13372.
[4]Al-Samkari H, et al. Blood. 2020 doi: 10.1182/blood.2020006520.

Guideline Recommendations for VTE Prophylaxis

	ISTH[1]	CHEST[2]	ASH[3]	NIH[4]
Recommended agent	LMWH or UFH	LMWH or UFH	LMWH or UFH	Per standard of care
Standard dose prophylaxis	Standard-dose anticoagulant	Standard dose anticoagulant	Standard dose anticoagulant	Standard dose anticoagulant
Intermediate dose prophylaxis	Consider in high risk patients	-	In the setting of a clinical trial	Insufficient data for or against outside a clinical trial
Therapeutic anticoagulation	Does not support	-	In the setting of a clinical trial unless other indication	
Recurrent clotting of devices or extracorporeal circuits	-	-	Reasonable to increase the intensity	Per standard of care

ISTH=International Society on Thrombosis and Haemostasis; ASH=American Society of Hematology; NIH=National Institutes of Health; LMWH=low molecular weight heparin; UFH=unfractionated heparin

[1]Spyropoulos AC, et al. J Thromb Haemost. 2020 doi: 10.1111/jth.14929.
[2]Moores, LK, et al. Chest. 2020 doi: 10.1016/j.chest.2020.05.559.
[3]https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation
[4]https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/antithrombotic-therapy/

VTE Prophylaxis in Patients with COVID-19

Standard prophylactic doses of LMWH or UFH
for all hospitalized patients
(adjust dose for renal function and/or obesity)

Therapeutic anticoagulation
for highly suspected or confirmed VTE
(consider with repeated circuit/device clotting)

Increased intensity prophylaxis or therapeutic anticoagulation
for elevated D-dimer (≥ 3.0 μg/mL) / ICU level of care

- D-dimer is a non-specific test
- Single-center experiences can be misleading
- Higher doses may not be more effective

Varying benefits and risks for increased intensity prophylaxis or therapeutic anticoagulation may exist with different stages of COVID-19

Summary

- COVID-19 has affected many people worldwide and put the NYC healthcare system on the brink of collapse
- Changes to operational and clinical infrastructure were critical to accommodate the surge of patients
- Strategies were quickly adopted to conserve supplies and optimize safety
- Staying abreast of published literature was vital to ensure nimble changes in practices

NYP: Spring 2020

Streets are empty. Stores are shuttered.

Subway is desolate. Broadway is dark.

Times Square, Manhattan
(Personal photo)

Times Square, Manhattan
(Personal photo)

Morn Those We Lost, Celebrate Those We Saved

John Modello, emergency medical technician in New York City

Dr. Lorna Breen, Director of Emergency Department in a New York City hospital

Dr. Tomoaki Kato, Surgical Director of Adult and Pediatric Liver and Intestinal Transplantation at NewYork-Presbyterian Hospital/Columbia University Irving Medical Center, leaving hospital after a 2 month hospitalization

https://nypost.com/2020/04/25/nyc-emt-commits-suicide-with-gun-belonging-to-his-dad.
https://www.nytimes.com/2020/04/27/nyregion/new-york-city-doctor-suicide-coronavirus.html.
https://healthmatters.nyp.org/dr-tomoaki-kato-i-survived-because-of-everybodys-hard-work/.

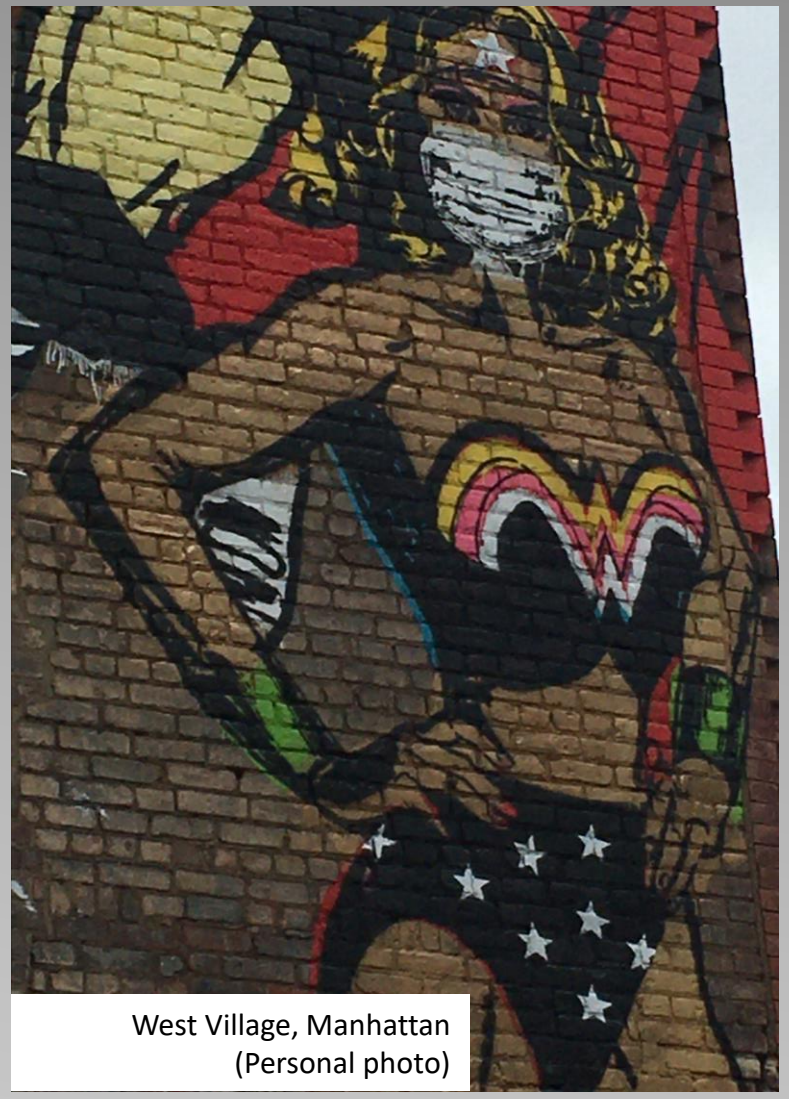
Will There Be a Second Wave?

Outside Jacobi Hospital, Bronx (Image: NY Post)

Outside Bellevue Hospital, Manhattan (Image: NY Post)

https://nypost.com/2020/03/28/nurses-protest-coronavirus-mask-and-glove-shortage-in-the-bronx/.
https://nypost.com/2020/03/24/makeshift-morgue-for-coronavirus-victims-set-up-outside-nyc-hospital/.

To All Frontline Workers: Thank You



West Village, Manhattan
(Personal photo)

NYPH, Manhattan
(Personal photo)