PROGRAM
CTS MARCH 2022 CONFERENCE

Thursday, March 10, 2022

7:00 pm – 8:30 pm
Meet & Greet Reception With Hors d'oeuvres and Mini-Presentation

Friday, March 11, 2022

FROM THE INTENSIVE CARE UNIT TO HOME AGAIN: LESSONS LEARNED FROM THE COVID-19 PANDEMIC

7:00 am – 8:00 am
Registration & Breakfast

8:00 am – 8:15 am
Welcome and Pre-Test
Kristina Kudelko, MD and Gaurav Singh, MD, MPH

8:15 am – 9:05 am
Update on Evidence-Based Therapies for COVID-19
Ryan Maves, MD
Keynote Speaker

9:05 am – 9:50 am
Unconventional and Advanced Modes of Ventilation and Proning
Krystal Craddock, MSRC, RRT, RRT-ACCS, RRT-NPS, AE-C, CCM and Justin Phillips, RCP, RRT-ACCS

9:50 am – 10:35 am
ECMO as Bridge to Recovery for Severe COVID-19
Oren Friedman, MD

10:35 am – 10:50 am
Break

10:50 am – 11:35 am
Lung Transplantation for Severe COVID-19
Nick Kolaitis, MD and Leslie Seijo, MD

11:35 am – 12:20 pm
Long COVID Pulmonary Management: Establishing Post-COVID-19 Models of Care
Lekshmi Santhosh, MD, MA

12:20 pm – 1:20 pm
Lunch

1:20 pm – 2:20 pm
Hands-On Session: ICU Ventilators, Oxygen Delivery Devices, Manual and Self-Proning
Krystal Craddock, MSRC, RRT, RRT-ACCS, RRT-NPS, AE-C, CCM; Justin Phillips, RCP, RRT-ACCS; Daniel Stemen, MSRS, RCP, RRT-ACCS, ECMOS; Brian Smith, MSRC, RRT; and Emma Blackmon, PhD, RN, CCRN

ADVANCES IN LUNG CANCER DIAGNOSTIC AND THERAPEUTIC STRATEGIES

2:20 pm – 3:05 pm
Advances in Diagnosis and Staging
Harmeet Bedi, MD

3:05 pm – 3:50 pm
Molecular Testing and Targeted Therapies
Millie Das, MD

3:50 pm – 4:05pm
Break

4:05 pm – 4:50 pm
Palliation Therapies (Stents, Laser Therapy, Indwelling Pleural Catheters)
George Chaux, MD

4:50 pm – 5:00 pm
Post-Test and Adjourn
Kristina Kudelko, MD and Gaurav Singh, MD, MPH

5:30 pm – 7:30 pm
Trainee Poster Session (NON-CME)

CALIFORNIA THORACIC SOCIETY

ANNUAL EDUCATIONAL CONFERENCE

Friday, March 11, 2022

FROM THE INTENSIVE CARE UNIT TO HOME AGAIN: LESSONS LEARNED FROM THE COVID-19 PANDEMIC; ADVANCES IN LUNG CANCER DIAGNOSTIC AND THERAPEUTIC STRATEGIES

REGISTRATION & BREAKFAST

7:00 a.m. – 8:00 a.m.

WELCOME AND PRE-TEST

8:00 a.m. – 8:15 a.m.

KRISTINA KUDELKO, MD
STANFORD UNIVERSITY

Dr. Kristina Kudelko is a Clinical Associate Professor in the Division of Pulmonary, Allergy, and Critical Care Medicine at Stanford University. Dr. Kudelko sub-specializes in pulmonary hypertension in which she completed an advanced fellowship in 2009. She is highly invested in teaching, mentorship, and wellness. She is the Program Director for the eBay fellowship in pulmonary vascular disease at Stanford and the Director of Education and Steering Committee member of the Vera Moulton Wall Center for Pulmonary Vascular Disease.

GAURAV SINGH, MD, MPH
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Dr. Gaurav Singh received his medical degree from UCSF and completed a Masters of Public Health at UC Berkeley. Currently, he is a Staff Physician at the VA Palo Alto Health Care System in the Section of Pulmonary, Critical Care, and Sleep Medicine. He is also an Affiliated Clinical Assistant Professor at Stanford University, where he completed training in Internal Medicine, followed by Pulmonary and Critical Care fellowship as well as Sleep Medicine fellowship. Dr. Singh has been involved with CTS since 2018 and has been a speaker for the Northern California Annual Conferences in 2019 and 2020. He served on the planning committee for the cancelled CTS Northern California Annual Conference in 2021. He is Conference Co-Chair for the 2022 CTS Annual Educational Conference.

Update on Evidence-Based Therapies for COVID-19

8:15 a.m. – 9:50 a.m.

RYAN MAVES, MD, FCCM, FCCP, FIDSA
WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE
KEYNOTE SPEAKER

Dr. Ryan Maves is a Professor of Medicine and Anesthesiology at the Wake Forest School of Medicine in Winston-Salem, North Carolina, where he serves as medical director of transplant infectious diseases and as a faculty intensivist at Wake Forest Baptist Medical Center. A graduate of the University of Washington School of Medicine, he completed his internal medicine residency and fellowships in infectious diseases and critical care medicine at the Naval Medical Center in San Diego, California. Following fellowship, he served at the Naval Medical Research Unit No. 6 in Lima, Peru, leading studies in antimicrobial drug resistance and vaccine development. He returned to NMCSD in 2010, serving as ID division head. In 2012, Dr. Maves deployed to the NATO Role 3 Multinational Medical Unit at Kandahar Airfield, Afghanistan, as Director of Medical Services. After returning from deployment, he later served as vice chair of medicine and ID fellowship program director. He was the DoD coordinating principal investigator (PI) for the NIAID-sponsored Adaptive Covid-19 Treatment Trial (ACTT) and the San Diego site PI for the AstraZeneca/Oxford phase 3 ChAdOx1 SARS-CoV-2 vaccine trial. He retired from the United States Navy with the rank of Captain in 2021 after 22 years of active-duty service and joined the faculty at Wake Forest.

Dr. Maves is board-certified in internal medicine, infectious diseases, and critical care medicine. He is the vice chair of the Fundamental Disaster Management committee in the Society of Critical Care Medicine and is the chair of the American College of Chest Physician's Covid-19 Task Force and the Disaster Response and Global Health Section. He lives in Winston-Salem with his wife, Robin, and their three children. His research currently focuses on the epidemiology and treatment of severe viral diseases, including SARS-CoV-2, as well as disaster responses to public health emergencies.

COVID-19:
Clinical trials and management update

Ryan C. Maves, MD, FCCM, FCCP, FIDSA
Professor of Medicine and Anesthesiology
Sections on Infectious Diseases and Critical Care Medicine
Wake Forest School of Medicine
Winston-Salem, North Carolina, USA

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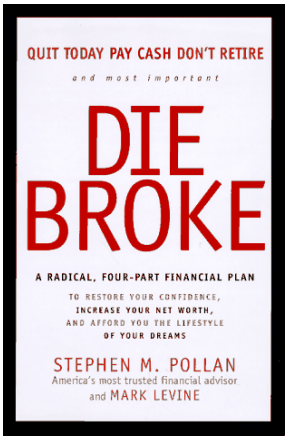
Disclaimers

- Research support to my institutions:
  - **AstraZeneca**, AiCuris, **Sound Pharmaceuticals**, ReViral.
- Advisory panel memberships:
  - Trauma Insights, **EMD Serono**
- Travel support:
  - American College of Chest Physicians, Society of Critical Care Medicine
- Off-label medication uses may be discussed.



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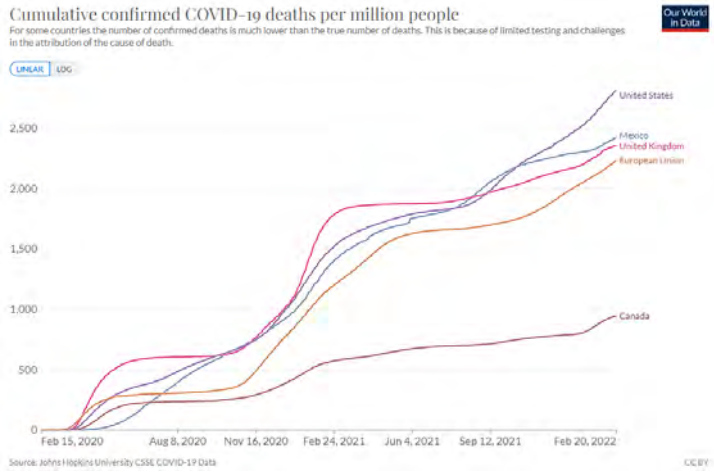
COVID-19



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Competing schools of thought in critical care

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Competing schools of thought in critical care

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https://www.history.com/news/1918-pandemic-public-health-campaigns

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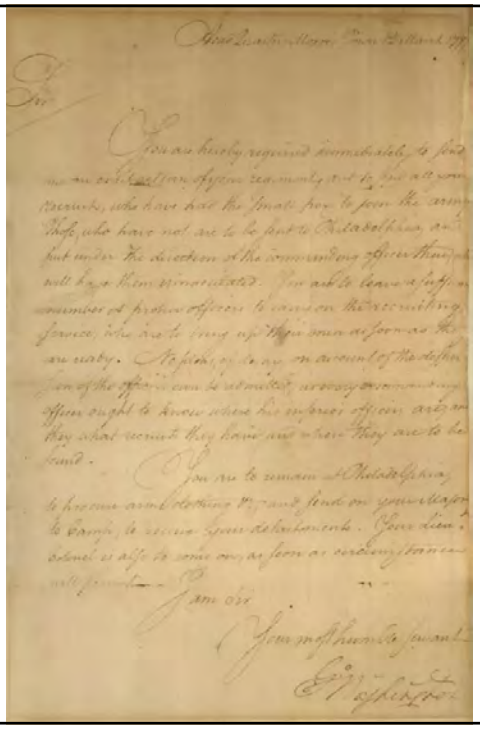

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Objectives

- Focus on therapy for active infection:
  - Inpatient and outpatient
  - Antivirals, immunomodulators, antithrombotics
- Will not touch on:
  - Vaccine efficacy
  - Prophylaxis (e.g., tixagevimab/cilgavimab)
  - Non-pharmacologic interventions

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Clinical Infectious Diseases

BRIEF REPORT

Clinical Outcomes of Coronavirus Disease 2019 With Evidence-based Supportive Care

Derek T. Larson,[1] John H. Sherner,[2] Kia M. Gallagher,[3] Cynthia L. Judy,[4] Madison B. Paul,[5] Alexandra M. Mahoney,[5] and Peter J. Weina[1]

[1]Division of Infectious Disease, Fort Belvoir Community Hospital, Fort Belvoir, Virginia, USA, [2]Department of Pulmonary and Critical Care Medicine, Fort Belvoir Community Hospital, Fort Belvoir, Virginia, USA, [3]Department of Internal Medicine, Fort Belvoir Community Hospital, Fort Belvoir, Virginia, USA, [4]Public Health, Fort Belvoir Community Hospital, Fort Belvoir, Virginia, USA, and [5]Department of Family Medicine, Fort Belvoir Community Hospital, Fort Belvoir, Virginia, USA

Calls for adherence to evidence-based medicine have emerged during the initial wave of the COVID-19 pandemic but reports of outcomes are lacking. This retrospective study of an institutional cohort including 135 patients with confirmed COVID-19 demonstrates positive outcomes when organizational standards of care consist of evidence-based supportive therapies.

Keywords. COVID-19 outcomes; supportive care; evidence-based medicine.

DOI: 10.1093/cid/ciaa678

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COVID-19 Clinical Trials

As of 11:38 AM Pacific Time on 07 March 2022:

- **3,212 interventional trials** for COVID-19 that are active, recruiting or completed on clinicaltrials.gov
  - 954 in the United States
  - 950 in Europe and the UK
  - 325 in South and Central America
  - 278 in China
  - 276 in the Middle East
  - 203 in Africa
  - 175 in Canada
  - 143 in India
  - 127 in Mexico
  - Plus Southeast Asia, Australia, Japan…

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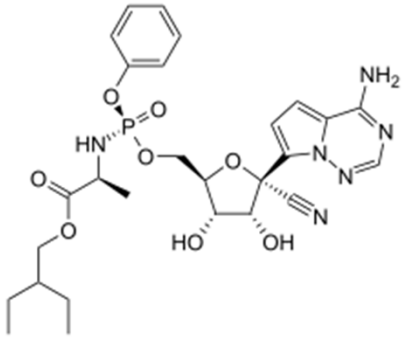
Remdesivir

- Viral RNA polymerase inhibitor
- Previously available through expanded access protocols, emergency use authorization, and RCTs.
- Gilead submitted NDA to FDA for approval on 10 August 2020 ("Veklury"), now FDA-approved.



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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

- First RCT of remdesivir vs placebo, conducted in Wuhan, China
- 237 patients, 2:1 allocation, 10 days of remdesivir IV
- Median age 64-66 years, more men in placebo group (65% vs 56%).
- Concomitant use of antiretrovirals, interferons, corticosteroids permitted.
- 11/158 (7%) of drug patients on MV vs 10/78 (13%) of placebo patients.
- Trial stopped early due to end of outbreak in Wuhan
  - Reduction in statistical power (80% -> 58% ability to detect a HR of 1.4 for clinical improvement).

https://doi.org/10.1016/S0140-6736(20)31022-9

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	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (−8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	−3·6% (−16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (−8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (−4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (−8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (−5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	−4·0 (−14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	−12·0 (−41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	−2·5 (−11·0 to 3·0)

https://doi.org/10.1016/S0140-6736(20)31022-9

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Adaptive COVID-19 Treatment Trial (ACTT)

- Sponsored by NIAID
- **1063 patients, randomized to remdesivir vs placebo**
- 68 centers (US, Denmark, Germany, Greece, Japan, Republic of Korea, Mexico, Singapore, Spain, UK).
- Primary outcome: time to clinical improvement
  - Hospitalized but not requiring supplemental O2 or needing medical care
  - Not hospitalized but w/ limitations in activities and/or on O2
  - Not hospitalized, no limitations
- Completed initial enrollment at midnight, 20 April 2020.

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Remdesivir for the Treatment of Covid-19 — Final Report

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

- Decreased **time to recovery** (15 to 10 days) with remdesivir.
- **Benefit greatest in those requiring supplemental O2** but not on HFNC/NIV/MV/ECMO.
- Mortality reduction not statistically significant (hazard ratio for death, 0.73; 95% CI: 0.52 to 1.03) but benefit again most marked in those only on supplemental O2.

DOI: 10.1056/NEJMoa2007764
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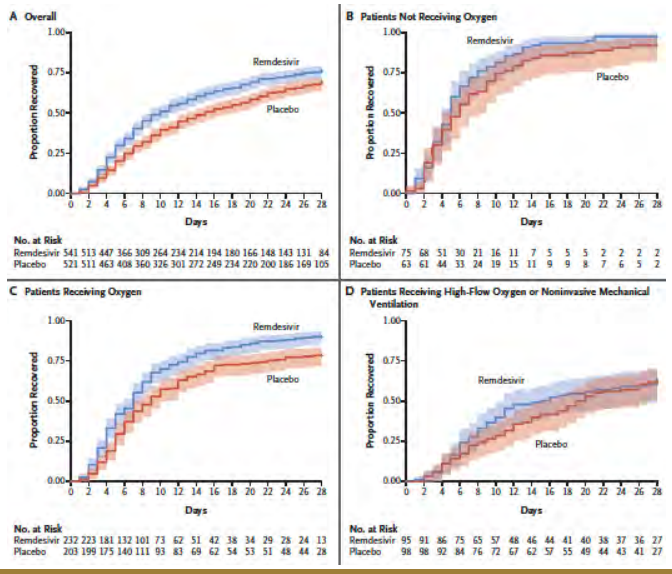

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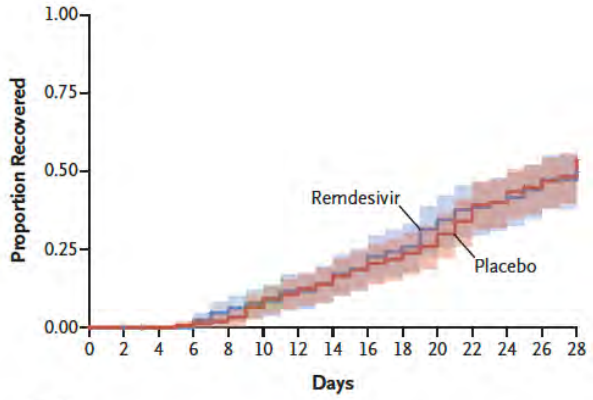
E Patients Receiving Mechanical Ventilation or ECMO



No. at Risk

Remdesivir	131	131	129	129	122	118	113	110	103	96	87	79	76	69	42
Placebo	154	153	152	151	149	142	136	130	121	116	110	98	89	79	48

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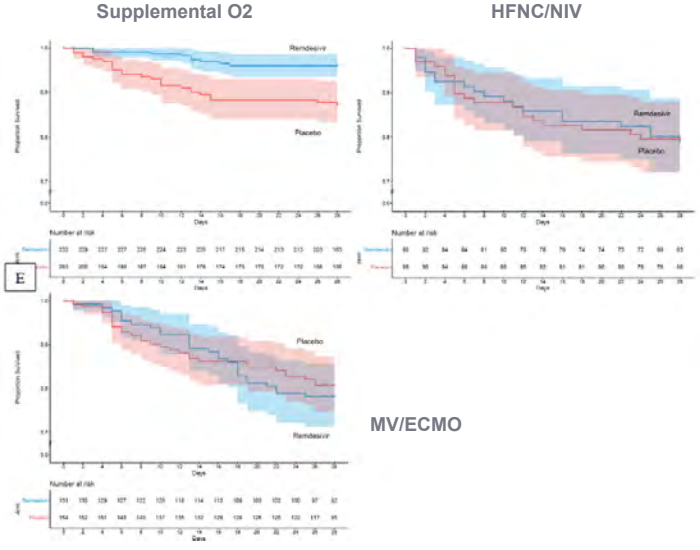

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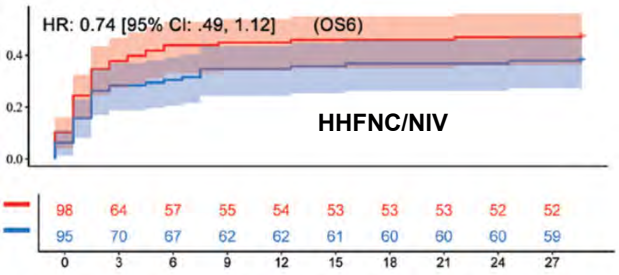

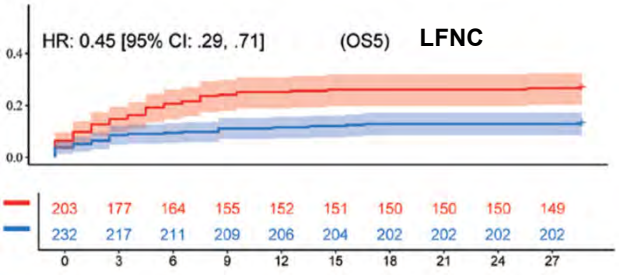

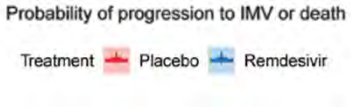

HR for progression to IMV/death with RDV vs placebo – **0.45**

- note: low use of dexamethasone in this trial (predates RECOVERY)

Paules CI, Gallagher SK, Rapaka RR, et al. Remdesivir for the prevention of invasive mechanical ventilation or death in COVID-19 - A post-hoc analysis of the Adaptive COVID-19 Treatment Trial-1 Cohort. *Clin Infect Dis*. 2021;ciab695. doi:10.1093/cid/ciab695

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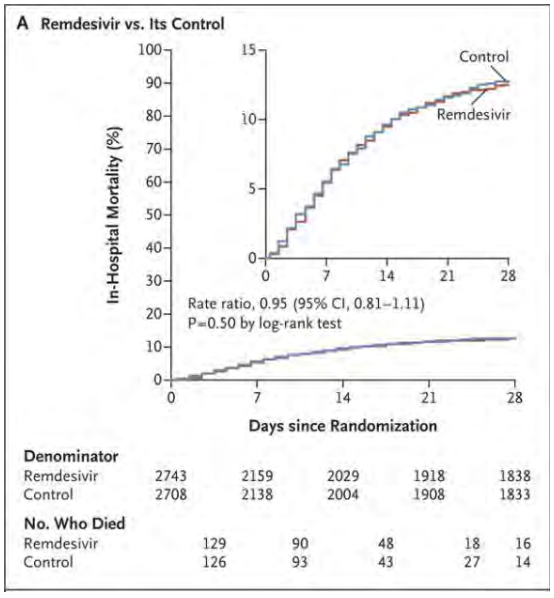
Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

- WHO-sponsored adaptive trial:
  - 405 hospitals, 30 countries, 11,266 adults.
  - 2750 allocated remdesivir, 954 hydroxychloroquine, 1411 LPV/r, 651 IFN+LPV/r, 1412 IFN, and 4088 SOC only.
- Kaplan-Meier 28-day mortality was 12%
  - 39% if already ventilated at randomization, 10% otherwise.

WHO Solidarity Trial Consortium. N Engl J Med 2020. DOI: 10.1056/NEJMoa2023184



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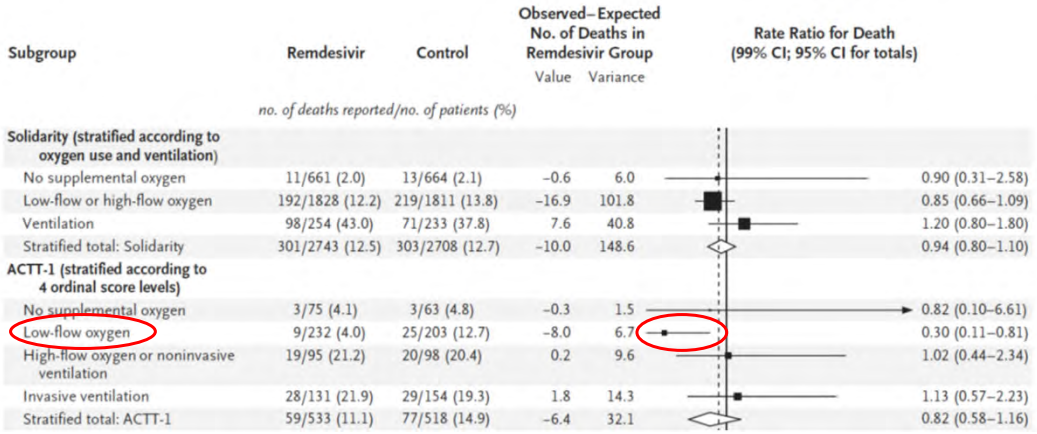

Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group (Value)	(Variance)	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)

WHO Solidarity Trial Consortium. N Engl J Med 2020. DOI: 10.1056/NEJMoa2023184

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Limitations of SOLIDARITY

- No placebo
- No double-blinding
- Limited data monitoring
- No diagnostic confirmation of infection
- No timing of symptoms duration before treatment initiation
- Unknown baseline physiological severity
- Unknown supportive care provided
- Unknown health care capacity status of enrolling sites

Slide courtesy of Dr. Neera Ahuja (Stanford), Dr. Andre Kalil (UNMC), and Dr. David Lye (Singapore).

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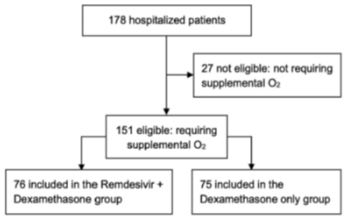
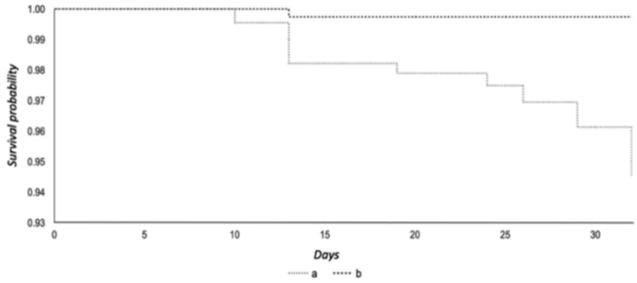


- Quasi-experimental study, two sequential cohorts.
- Adults, hospitalized, supplemental O2, not on IMV.
- Lower mortality in combination therapy arm.
  - **1.3% vs 16% (p=0.005) mortality**
  - Worse baseline P/F in combination therapy arm (231 vs 242)
  - Weakness – before/after design, non-concurrent control groups.



Marrone A, Nevola R, Sellitto A, et al. Remdesivir plus dexamethasone versus dexamethasone alone for the treatment of COVID-19 patients requiring supplemental O2 therapy: a prospective controlled non-randomized study. *Clin Infect Dis*. 2022;ciac014. doi:10.1093/cid/ciac014

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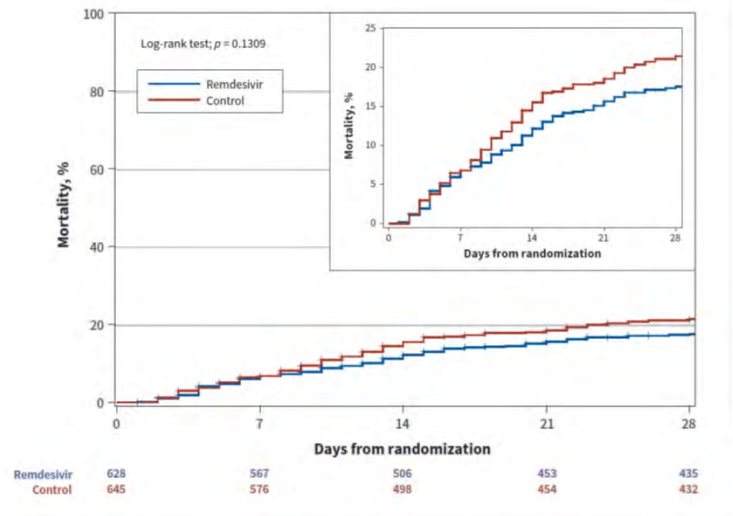

- **Canadian Treatments for COVID-19 (CATCO)** trial: open-label RCT, dex vs RDV/dex
- Similar in setting to ACTT-1, similar in design to Solidarity
- 40% female, median age 65 yrs.
- 21% in ICU at randomization
- **8.0% progression to IMV with RDV, vs 15.0% in controls** (RR 0.53, 95%CI 0.38-0.75)
- Non-significant decrease in mortality with RDV but very close in low-flow O2 group.

CMAJ 2022.doi: 10.1503/cmaj.211698; early-released January 19, 2022

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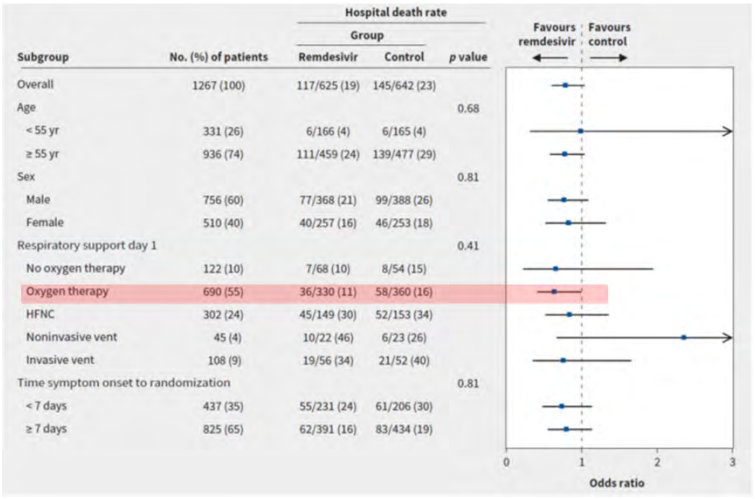

Subgroup	No. (%) of patients	Hospital death rate: Group: Remdesivir	Control	p value
Overall	1267 (100)	117/625 (19)	145/642 (23)	
Age				0.68
< 55 yr	331 (26)	6/166 (4)	6/165 (4)	
≥ 55 yr	936 (74)	111/459 (24)	139/477 (29)	
Sex				0.81
Male	756 (60)	77/368 (21)	99/388 (26)	
Female	510 (40)	40/257 (16)	46/253 (18)	
Respiratory support day 1				0.41
No oxygen therapy	122 (10)	7/68 (10)	8/54 (15)	
Oxygen therapy	690 (55)	36/330 (11)	58/360 (16)	
HFNC	302 (24)	45/149 (30)	52/153 (34)	
Noninvasive vent	45 (4)	10/22 (46)	6/23 (26)	
Invasive vent	108 (9)	19/56 (34)	21/52 (40)	
Time symptom onset to randomization				0.81
< 7 days	437 (35)	55/231 (24)	61/206 (30)	
≥ 7 days	825 (65)	62/391 (16)	83/434 (19)	

- **Canadian Treatments for COVID-19 (CATCO)** trial: open-label RCT, dex vs RDV/dex
- Similar in setting to ACTT-1, similar in design to Solidarity
- 40% female, median age 65 yrs.
- 21% in ICU at randomization
- **8.0% progression to IMV with RDV, vs 15.0% in controls** (RR 0.53, 95%CI 0.38-0.75)
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CMAJ 2022.doi: 10.1503/cmaj.211698; early-released January 19, 2022

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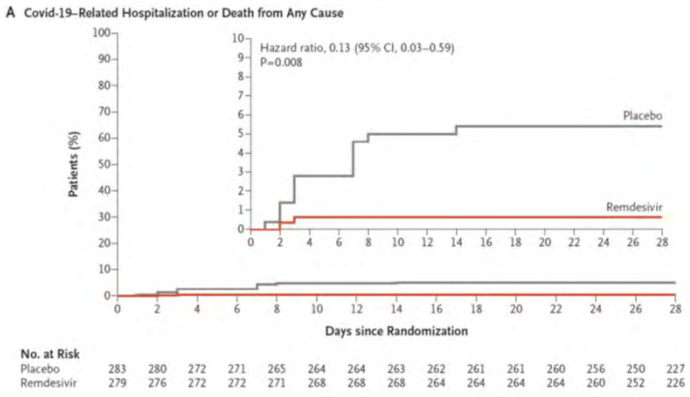
Outpatient remdesivir



- **PINETREE trial**
  - Double-blind RCT of high-risk outpatients with COVID-19
  - 3 days of IV RDV
  - Median 50 years, 47.9% women, 41.8% Hispanic/Latinx.
  - **87% reduction in hospitalization** (0.7% vs 5.3%; no deaths by day 28).

Gottlieb RL et al. NEJM 2021, DOI: 10.1056/NEJMoa2116846

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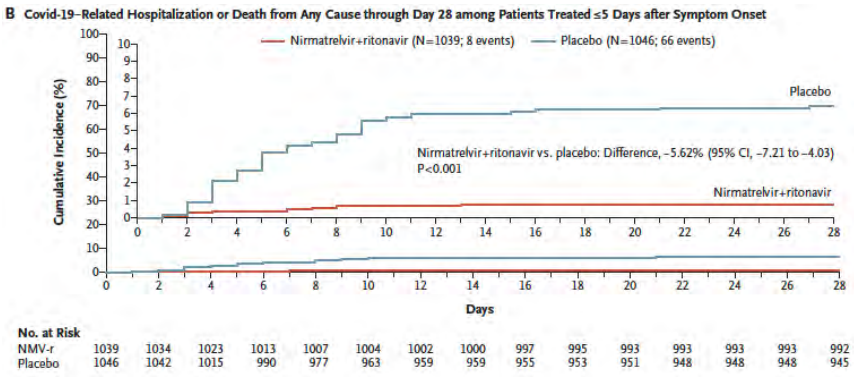
Remdesivir – a proposed summary

- Effective in early COVID-19:
  - **Admitted with hypoxemia** but before requiring NIV/HHFNC/IMV
  - **High-risk outpatients**
- Reduces risk of progression to IMV
- Potential mortality benefit
- Personal argument: response is based on **physiology**, not time
- Not a panacea: likely limited benefit in resource-limited settings

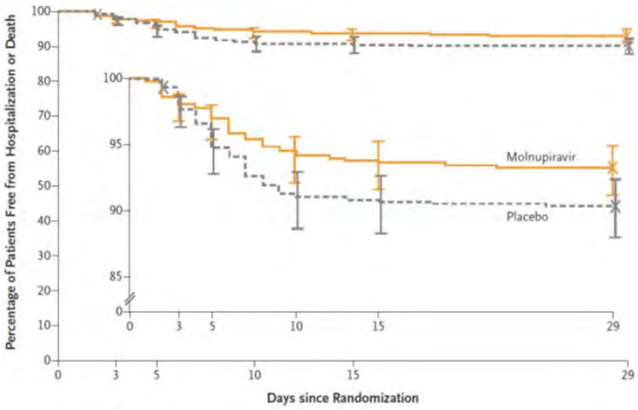
Nirmatrelvir-ritonavir (Paxlovid)



- Oral protease inhibitor, boosted with ritonavir.
- 89% relative reduction in hospitalization or death (absolute reduction, 6.32%).
- Many drug interactions: CNIs, statins

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19 [published online ahead of print, 2022 Feb 16]. *N Engl J Med*. 2022;10.1056/NEJMoa2118542.

Molnupiravir



Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med*. 2022;386(6):509-520. doi:10.1056/NEJMoa2116044

- Small molecule viral RNA polymerase inhibitor
- 1,433 patient RCT
  - Unvaccinated
  - 51% female
  - Median 43 years
  - 99.4% with risk factor for severe COVID-19 (BMI >30 in 73.7%)
- ITT: 89% reduction in mortality, **31% reduction in hospitalization**
- Teratogenicity concerns

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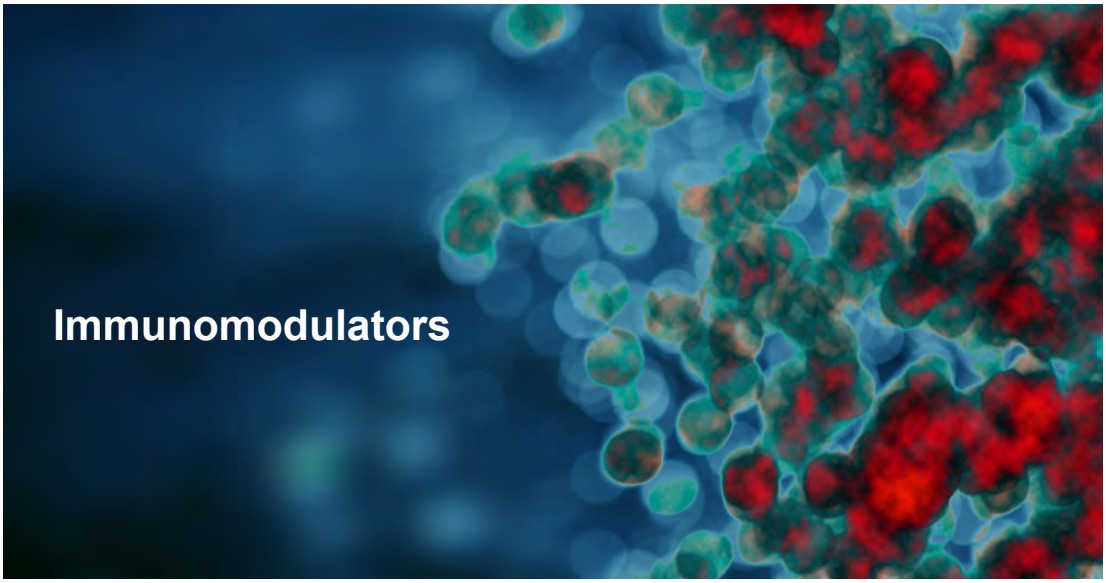

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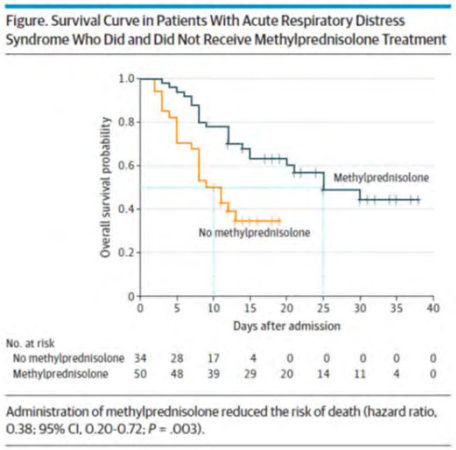
Glucocorticoids

- Recommended for vasopressor-resistant shock
- Not previously recommended for viral pneumonias, but cautiously advised by SSC and supported by some early Chinese data (**Wu C et al, *JAMA Intern Med* 2020**, 84 patients with ARDS)



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RECOVERY
Randomised Evaluation of COVID-19 Therapy

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

- Open-label, multi-arm RCT in the UK.
- Clinically-suspected or proven SARS-CoV-2 infection
- Conducted 176 UK hospitals between March and June 2020
- Dexamethasone 6 mg IV/PO/NG daily x 10 days vs SOC
- Primary outcome: 28-day mortality

- 6,418 patients, 1:2 allocation (dex vs SOC).
- 8% of SOC group received dexamethasone as well.
- Very little remdesivir used in this trial (5 patients total).
- Very high baseline mortality (**26.2%** in SOC patients **not** receiving mechanical ventilation).

DOI: 10.1056/NEJMoa2021436

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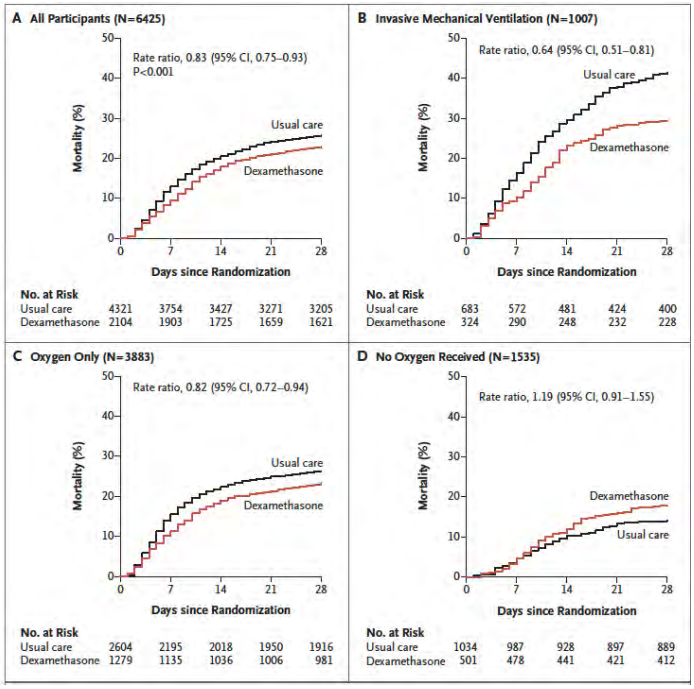

DOI: 10.1056/NEJMoa2021436

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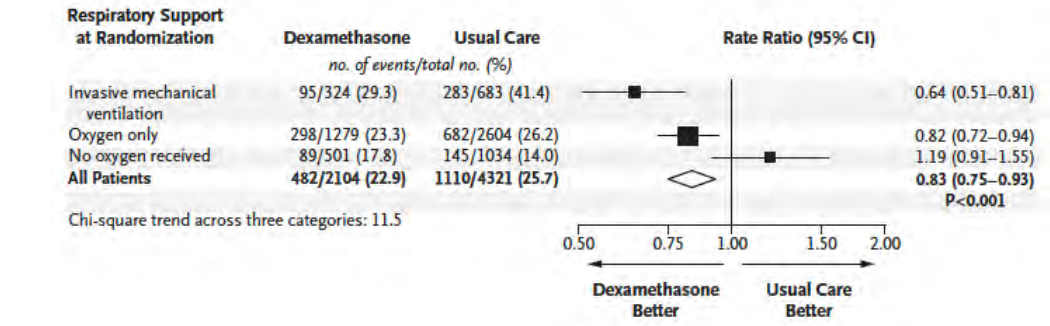

DOI: 10.1056/NEJMoa2021436

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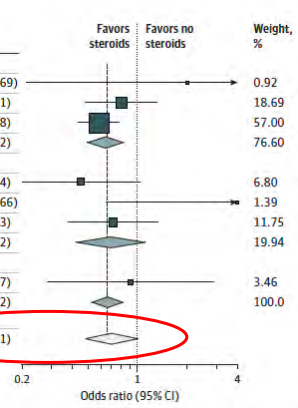
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



JAMA. doi:10.1001/jama.2020.17023
Published online September 2, 2020

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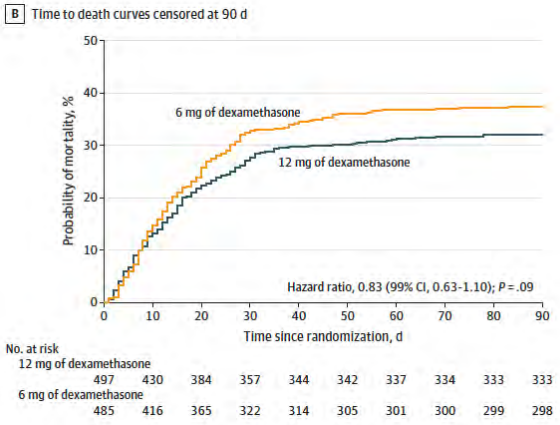
COVID-STEROID 2 Trial



- International RCT of **6 mg vs 12 mg** of dexamethasone for severe/critical COVID-19.
- 1000 adults, hospitalized, requiring at least 10 L/m supplemental O2.
  - 80% in ICU, 20% on IMV at enrollment
  - 62% on RDV
  - 12% on IL-6 or JAK antagonists
- **Non-significant reduction in 90-day mortality** with higher-dose dexamethasone (32.0% vs 37.7%, p=0.09)
- Planned Bayesian re-analysis (Granholm A et al, ICM 2022; 28:45-55) estimates a 95.7% probability of benefit at 90 days.

Munch MW, Myatra SN, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA*. 2021;326(18):1807-1817. doi:10.1001/jama.2021.18295

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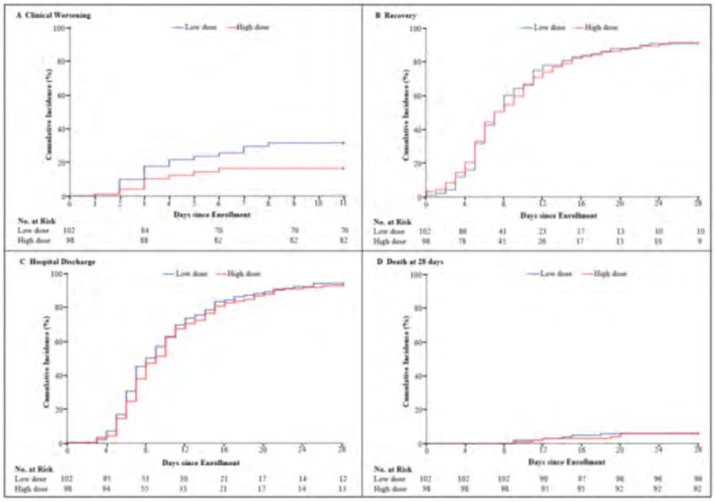

- Open-label RCT in Spain:
  - 200 adult patients hospitalized with COVID-19 on supplemental O_2 but requiring ≤50% FiO_2.
  - Dexamethasone 6 mg daily vs 20 mg daily x 5 days, then 10 mg daily x 5 days (similar to DEXA-ARDS)
  - Decreased rate of clinical worsening (16.4% vs 31.4%) with high-dose but no change in time to recovery or 28-day mortality.

Taboada M, Rodríguez N, Varela PM, *et al*. Effect of high *versus* low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 Pneumonia: an open-label, randomised clinical trial. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.02518-2021).

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Baricitinib

- Janus kinase inhibitor
- Compared with placebo (plus RDV) in ACTT-2 – small benefit seen in time to recovery, most marked in HHFNC/NIV.
- Comparable to dexamethasone in ACTT-4 but no real advantage seen
- Possible alternative to dexamethasone but lacking combination data until recently.

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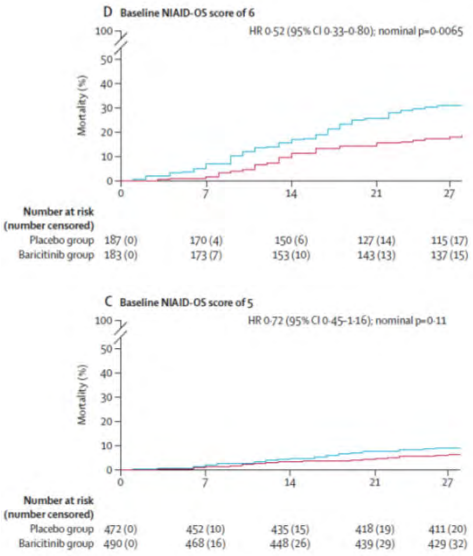

COV-BARRIER

- Industry-sponsored double-blind RCT of baricitinib + SOC vs SOC
- 1525 adult patients (101 centers, Asia, Europe, North America, South America)
  - supplemental O2, HHFNC, NIV (no IMV at baseline)
- 91.3% received dexamethasone, 18.9% RDV
- **38.2% reduction** in all-cause mortality with baricitinib vs SOC (NNT=20) -> most marked in patients on NIV/HHFNC at enrollment
- No increase in VTE

Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418. doi:10.1016/S2213-2600(21)00331-3

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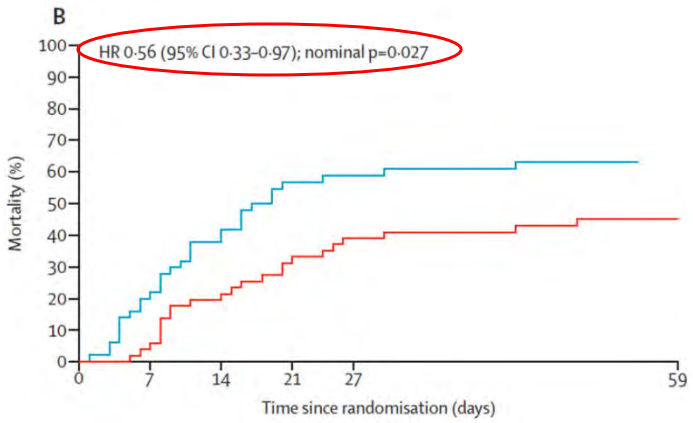

Exploratory RCT of bari+SOC in IMV/ECMO

- Same basic design as COV-BARRIER
- 101 patients randomized
- 17% absolute mortality reduction, 44% relative reduction
- Preliminary but…?

Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med*. 2022;S2213-2600(22)00006-6. doi:10.1016/S2213-2600(22)00006-6

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IL-6 antagonists

- IL-6 antagonists: **Tociluzimab** and **sarilumab**
- HLH- or CRS-like syndrome with elevated IL-6, ferritin levels identified in subset of critically-ill COVID-19 patients.
  - Widely used early in pandemic based on HLH/CRS experience and anecdotal reports of benefit.
- Two manufacturer-sponsored phase 3 RCTs (Roche, Regeneron) of both agents terminated due to lack of benefit in critically-ill patients.

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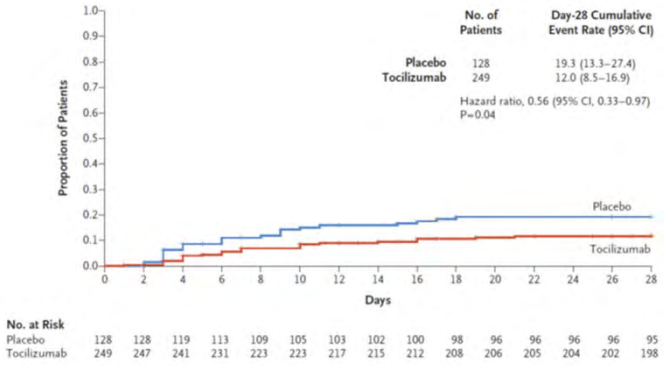
Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

- EMPACTA trial
- Multinational RCT of 389 hospitalized patients (2:1 allocation).
- Composite endpoint:
  - 28-day mortality
  - Progression to mechanical ventilation
- Improvement in composite endpoint (12.0% vs 19.3%) in treatment arm but **no improvement in 28-day mortality** (10.4% vs 8.6%).



N Engl J Med 2021;384:20-30.
DOI: 10.1056/NEJMoa2030340

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Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

- Open-label RCT in Brazil.
- Composite endpoint:
  - 15-day mortality
  - Progression to mechanical ventilation
- Terminated early due to increased mortality in treatment arm.

Outcomes	Tocilizumab group (n=65)	Control group (n=64)
Primary endpoint		
Receiving mechanical ventilation or died at day 15*	18 (28)	13 (20)
Clinical status (7 level ordinal scale) at day 15:		
1: Not admitted to hospital, no limitation on activities	32 (49)	26 (41)
2: Not admitted to hospital, limitation on activities	3 (5)	5 (8)
3: Admitted to hospital, not receiving supplemental oxygen	6 (9)	6 (9)
4. Admitted to hospital, receiving supplemental oxygen	6 (9)	10 (16)
5. Admitted to hospital, receiving non-invasive ventilation or high flow oxygen through nasal cannula	0 (0)	4 (6)
6: Admitted to hospital, receiving mechanical ventilation	7 (11)	11 (17)
7: Death	11 (17)	2 (3)
Secondary endpoints		
Mortality up to 28 days	14 (21)	6 (9)
In-hospital mortality	14 (21)	6 (9)

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thebmj | BMJ 2021;372:n84 | doi: 10.1136/bmj.n84

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Kate Beaton, http://www.harkavagrant.com

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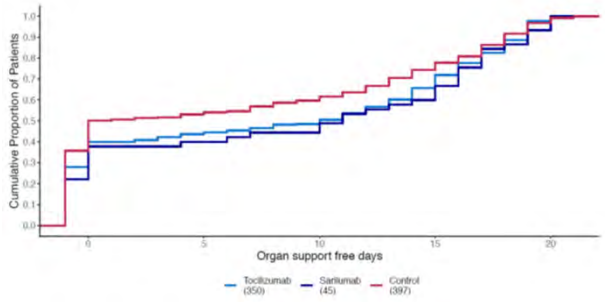
Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report

The REMAP-CAP Investigators

- Immune modulation arm of a large, adaptive open-label RCT.
- 895 patients with critical illness due to Covid-19, randomized to IL-6 inhibitor (mostly tociluzimab) vs placebo.
- Organ support-free days up to day 21 (more is better).



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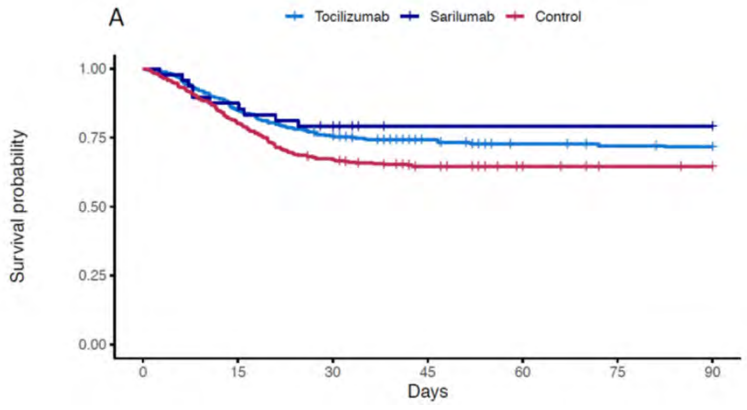
Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report

- No major change in days free of organ support BUT **decrease in mortality**
  - **28.0%** (98/350) for tocilizumab
  - **35.8%** (142/397) for control



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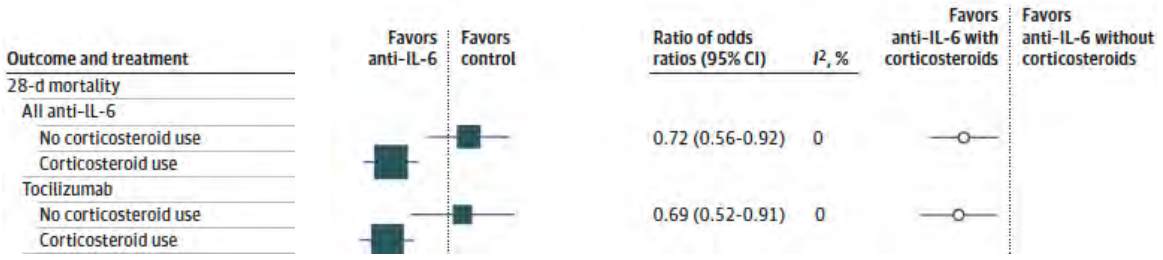

WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA*. 2021;326(6):499-518. doi:10.1001/jama.2021.11330

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Sotrovimab

Table 2. Efficacy Outcomes through Day 29 (Intention-to-Treat Population).*

Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†
Alive and not hospitalized — no. (%)	284 (98)	270 (92)

Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934

- Monoclonal antibody
- Derived from patient who recovered from original recipe SARS!
- Active against Omicron
- **85% reduction in risk of hospitalization (p=0.002).**

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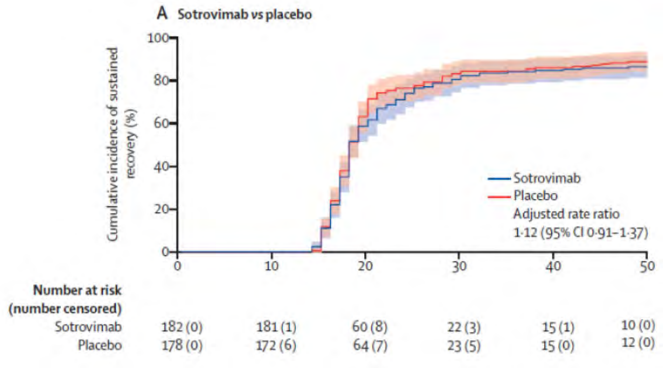
Sotrovimab



- Monoclonal antibody
- Derived from patient who recovered from original recipe SARS!
- **Ineffective in hospitalized patients (ACTIV-3/TICO trials)**

Self WH et al, Lancet Infect Dis 2021
https://doi.org/10.1016/S1473-3099(21)00751-9

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Immunomodulators – a proposed summary

- Dexamethasone 6 mg daily is the cornerstone of care for severe COVID-19.
- In patients who are decompensating (i.e., progressing to NIV/HHFNC/IMV):
  - Add baricitinib 4 mg PO daily **OR**
  - Add tocilizumab **OR**
  - Increase dexamethasone to 12 mg daily
- Sotrovimab is an excellent outpatient therapy (for now) but not useful in inpatients at current doses.

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Immunomodulators – a proposed summary

- Bariticinib
  - Contraindications: ALC <200, ANC <500, CrCl <30, active or recent VTE
  - Advantages: 14 days of baricitinib is ½ the cost of one dose of toci.
- Tocilizumab
  - Contraindications: active secondary infection
  - Advantages: more robust data in intubated patients
- Dexamethasone 12+ mg
  - Contraindications: none that I can think of.
  - Advantages: less compelling data but certainly safe and inexpensive

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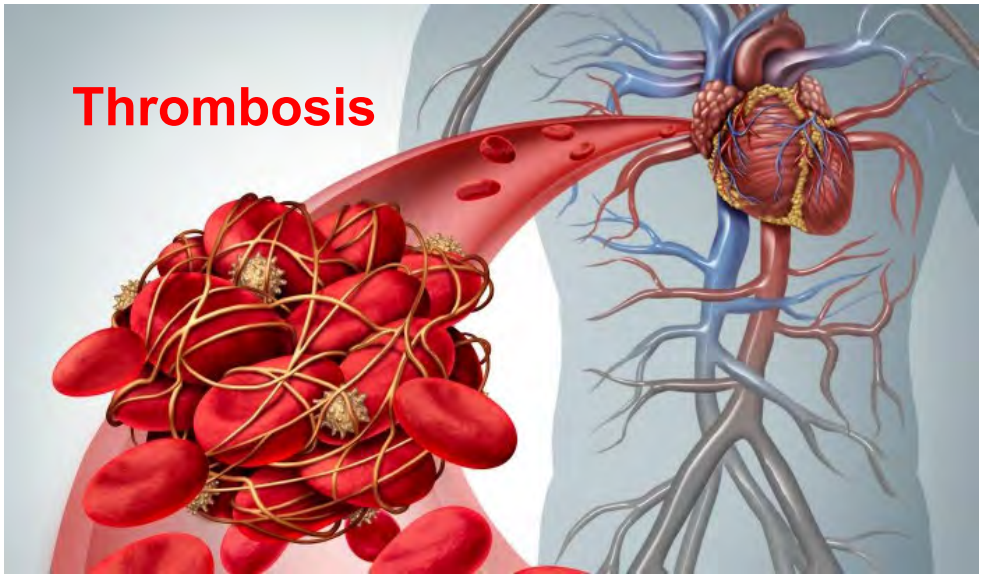

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COVID-19, thrombosis, and VTE

- Increased risk of VTE, PE, cardiovascular events well-documented early in pandemic.
- Highly variable strategies for anticoagulation:
  - Standard VTE prophylaxis (e.g., enoxaparin 40 mg SC daily)
  - "Enhanced" prophylaxis (e.g., enoxaparin 0.5 mg/kg SC bid)
  - Full anticoagulation empirically for all hypoxemic or intubated patients.
- **Retrospective series with highly variable results.**

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COVID-19, thrombosis, and VTE

- **17.0% pooled incidence for VTE**
  - 12.1% DVT, 7.1% PE
  - Higher with screening (33.1% vs 9.8% by clinical diagnosis)
  - Higher in the ICU (27.9% vs 7.1% in the ward)
  - Higher in prospective studies (25.5% vs 12.4% in retrospective studies)

Jiménez D, García-Sanchez A, Rali P, et al. *Chest* 2021;159(3):1182-1196

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Anticoagulation

Outcome	Therapeutic-Dose Anticoagulation (N=536)	Usual-Care Thromboprophylaxis (N=567)
	median no. (IQR)	
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)
	no. of patients/total no. (%)	
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)
Death in hospital	199/534 (37.3)	200/564 (35.5)
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)
Death in hospital	199/534 (37.3)	200/564 (35.5)
Major bleeding§	20/529 (3.8)	13/562 (2.3)

REMAP-CAP, ACTIV-4a, ATTACC (NEJM 2021)

- Platform trials looking at anticoagulation strategies for hospitalized patients with COVID-19.

ICU patients –
No benefit to empiric **full** anticoagulation

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Anticoagulation

Outcome	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis
	no. of patients/total no. (%)	
Survival until hospital discharge	1085/1171 (92.7)	962/1048 (91.8)
Survival without organ support at 28 days‖	932/1175 (79.3)	789/1046 (75.4)
Progression to intubation or death**	129/1181 (10.9)	127/1050 (12.1)
Major thrombotic event or death	94/1180 (8.0)	104/1046 (9.9)
Major thrombotic event	13/1180 (1.1)	22/1046 (2.1)
Death in hospital	86/1180 (7.3)	86/1046 (8.2)
Major bleeding	22/1180 (1.9)	9/1047 (0.9)

REMAP-CAP, ACTIV-4a, ATTACC (NEJM 2021)

- Platform trials looking at anticoagulation strategies for hospitalized patients with COVID-19.

Non-ICU patients-
High NNT but significant reduction in need for organ support and death with empiric full anticoagulation

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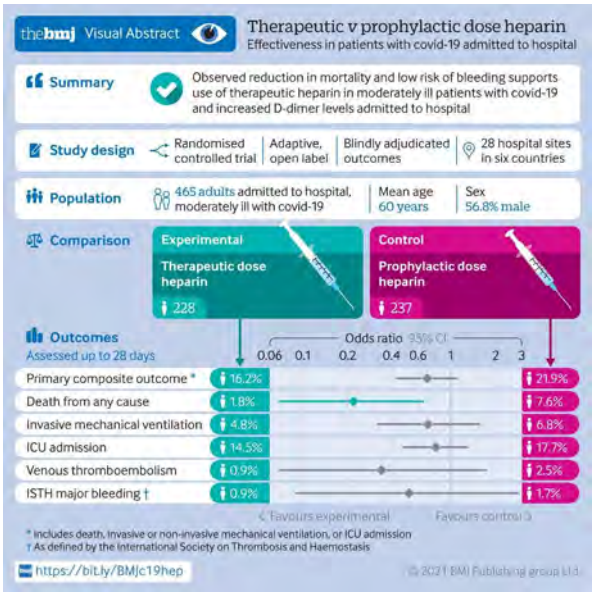

- **RAPID trial**
  - 28 hospitals in Brazil, Canada, Ireland, Saudi Arabia, UAE, USA
  - 465 adults admitted to wards with COVID-19
  - Randomized to therapeutic vs prophylactic heparin/LMWH
  - Improvement in all major endpoints with therapeutic heparin/LMWH.
    - **Mortality: 1.8% vs 7.6% - only significant endpoint**
    - IMV 4.8% vs 6.8%
    - VTE 0.9% vs 2.5%
    - Bleeding 0.9% vs 1.7% (nonsignificant but weird)

Sholzberg M, Tang G H, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. *BMJ* 2021; 375 :n2400
doi:10.1136/bmj.n2400

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Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Primary efficacy outcome				
VTE, ATE, or death	37/129 (28.7)	52/124 (41.9)	0.68 (0.49-0.96)	.03
Non-ICU stratum	14/84 (16.7)	31/86 (36.1)	0.46 (0.27-0.81)	.004
ICU stratum	23/45 (51.1)	21/38 (55.3)	0.92 (0.62-1.39)	.71
VTE + ATE	14/129 (10.9)	36/124 (29.0)	0.37 (0.21-0.66)	<.001
Death	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	.28

- **HEP-COVID trial**
  - 12 hospitals in USA
  - 253 adults admitted to hospital with COVID-19
  - Randomized to therapeutic vs prophylactic heparin/LMWH
  - Improvement in all major endpoints with therapeutic heparin/LMWH in ward patients.
    - **Mortality: 19.4%% vs 25.0% -**
    - VTE+ATE 10.9% vs 29.0%
    - Benefit not seen in ICU patients

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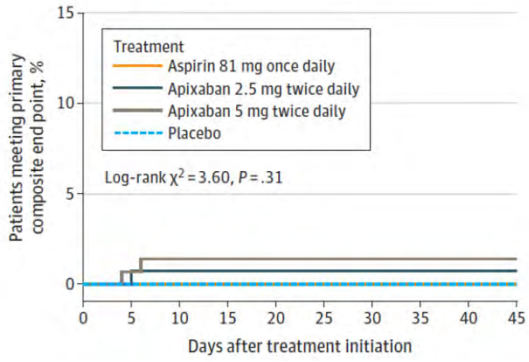
A Cumulative incidence of adjudicated primary end point



ACTIV-4B

- RCT of antithrombotic/antiplatelet therapy in symptomatic outpatients
- Target enrollment: 7000
- Stopped at 657 due to futility
- 80% White, 38% Latino ethnicity, 60% female, median 54 yrs
- 35% HTN, 28% DM, 20% smokers
- No difference between individual or composite endpoints:

Cardiopulmonary hospitalizations
Deep vein thrombosis or pulmonary embolism
Myocardial infarction, stroke or other arterial embolism
Death

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Updated CHEST VTE Guidelines

Recommendation 1: In acutely ill hospitalized patients with COVID-19 who have low risk of bleeding, with consideration for the remarks below, we suggest therapeutic dose heparin (UFH or LMWH) over current standard dose anticoagulant thromboprophylaxis (conditional recommendation, ungraded consensus-based statement).

Recommendation 3: In critically ill patients with COVID-19, we suggest current standard dose anticoagulant thromboprophylaxis (with UFH or LMWH) over therapeutic dose anticoagulation (conditional recommendation, ungraded consensus-based statement).

Moores LK, Tritschler T, Brosnahan S, et al. Thromboprophylaxis in Patients with COVID-19. A Brief Update to the CHEST Guideline and Expert Panel Report [published online ahead of print, 2022 Feb 12]. *Chest*. 2022;S0012-3692(22)00250-1. doi:10.1016/j.chest.2022.02.006

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But what about…?

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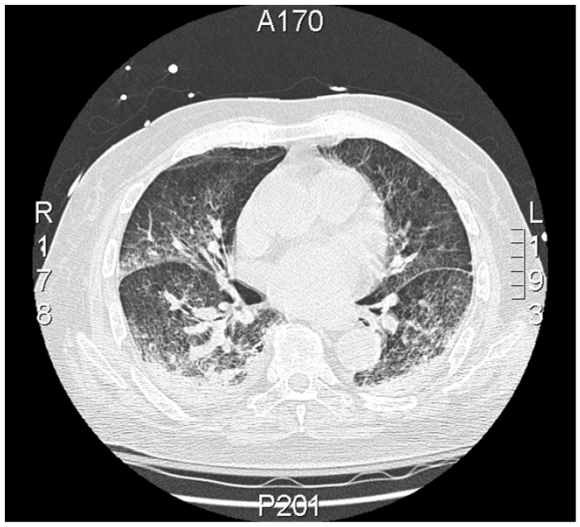

86 y/o man presenting to ED for evaluation of progressive weakness and cough.

Recently hospitalized for evaluation of chest pain – nonexertional, pleuritic, cardiac evaluation negative.

Family reports decline in functional status over week prior to admission, accompanied by scant hemoptysis, chills, and arthralgias.

Not vaccinated against SARS-CoV-2.

10 LPM by NRB, progressive hypoxemia and delirium, intubated, admitted to MICU.

Sputum obtained for analysis.

Ivermectin initiated.

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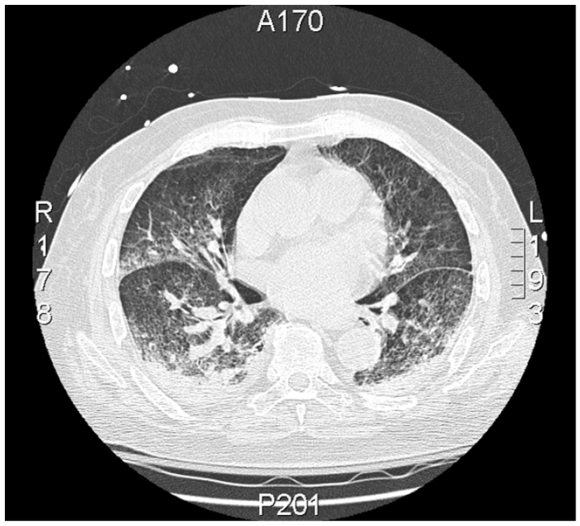

86 y/o man presenting to ED for evaluation of progressive weakness and cough.

Recently hospitalized for evaluation of chest pain – nonexertional, pleuritic, cardiac evaluation negative.

Family reports decline in functional status over week prior to admission, accompanied by scant hemoptysis, chills, and arthralgias.

Not vaccinated against SARS-CoV-2 because it was 2005

10 LPM by NRB, progressive hypoxemia and delirium, intubated, admitted to MICU.

Sputum obtained for analysis.

Ivermectin initiated because he had disseminated strongyloidiasis

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JAMA Internal Medicine | Original Investigation

Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities
The I-TECH Randomized Clinical Trial

Steven Chee Loon Lim, MRCP; Chee Peng Hor, MSc; Kim Heng Tay, MRCP; Anilawati Mat Jelani, MMed; Wen Hao Tan, MMed; Hong Bee Ker, MRCP; Ting Soo Chow, MRCP; Masliza Zaid, MMed; Wee Kooi Cheah, MRCP; Han Hua Lim, MRCP; Khairil Erwan Khalid, MRCP; Joo Thye Cheng, MRCP; Hazfadzila Mohd Unit, MRCP; Noralfazita An, MMed; Azraai Bahari Nasruddin, MRCP; Lee Lee Low, MRCP; Song Weng Ryan Khoo, MRCP; Jia Hui Loh, MRCP; Nor Zaila Zaidan, MMed; Suhaila Ab Wahab, MMed; Li Herng Song, MD; Hui Moon Koh, MClinPharm; Teck Long King, BPharm; Nai Ming Lai, MRCPCH; Suresh Kumar Chidambaram, MRCP; Kalaiarasu M. Peariasamy, MSc; for the I-TECH Study Group

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of high-risk patients with mild to moderate COVID-19, ivermectin treatment during early illness did not prevent progression to severe disease. The study findings do not support the use of ivermectin for patients with COVID-19.

JAMA | Original Investigation

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19
A Randomized Clinical Trial

Eduardo López-Medina, MD, MSc; Pío López, MD; Isabel C. Hurtado, MD; Diana M Dávalos, MD, MPH, DrPH; Oscar Ramírez, MD, MPhil; Ernesto Martínez, MD; Jesus A. Díazgranados, MD; José M. Oñate, MD; Hector Chavarriaga, MD, MS; Sócrates Herrera, MD; Beatriz Parra, PhD; Gerardo Libreros, PhD; Roberto Jaramillo, MD; Ana C. Avendaño, MD; Dilian F. Toro, MD; Miyerlandi Torres, DrPH; Maria C. Lesmes, MD; Carlos A. Rios, MD; Isabella Caicedo, MD

CONCLUSION AND RELEVANCE Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.

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A possible path forwards

- **Outpatients without hypoxemia:**
  - Supportive care only for low-risk patients
  - Preferred options for high-risk: sotrovimab versus Paxlovid
  - Second line options for high risk: outpatient RDV versus molnupiravir

- **Patients with hypoxemia on low-flow supplemental O2**
  - **Therapeutic-dose** LMWH or UFH
  - Remdesivir x 5 days (or until discharge)
  - Dexamethasone 6 mg daily x 10 days (or until discharge)

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A possible path forwards

- **Patients requiring HHFNC/NIV**
  - Prophylactic-dose LMWH or UFH
  - Dexamethasone 6 mg daily **plus:**
    1. Baricitinib
    2. Tocilizumab
    3. High-dose dex
  - +/- Remdesivir for 5-10 days

- **Patients requiring IMV/ECMO**
  - Prophylactic-dose LMWH or UFH
  - Dexamethasone 6 mg daily **plus:**
    1. Tocilizumab
    2. Baricitinib
    3. High-dose dex
  - Maybe remdesivir if significantly immunocompromised

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Thank you again for the opportunity to speak to you all today.

Stay safe.

rmaves@wakehealth.edu

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Unconventional and Advanced Modes of Ventilation and Proning

9:05 a.m. – 9:50 a.m.

KRYSTAL CRADDOCK
MSRC, RRT, RRT-ACCS, RRT-NPS, AE-C, CCM
UC DAVIS

Krystal Craddock has been a licensed RT since 2007. She received her graduate degree in Respiratory Care in 2020 from Boise State University. Currently Krystal works as the Clinical Operations Manager and COPD Case Management Coordinator at UC Davis Health. She also is adjunct faculty for San Mateo Community College District instructing in the Bachelors of Respiratory Care Program. She also serves as the CTS Liaison for the California Society for Respiratory Care.

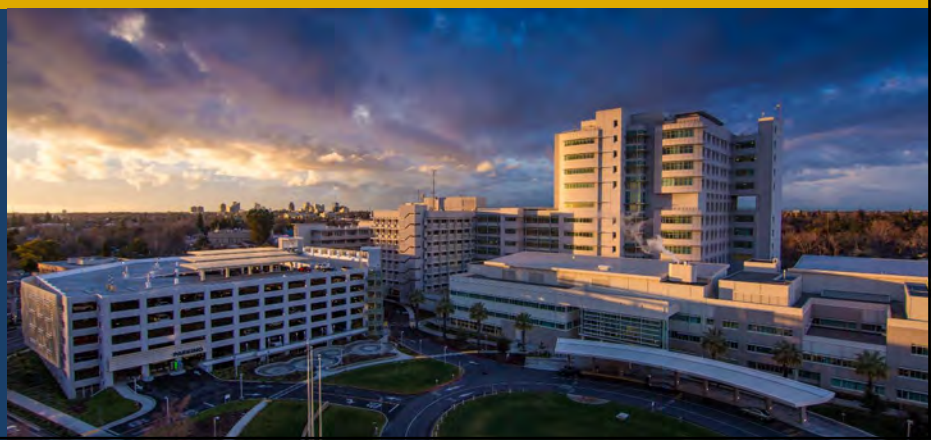
JUSTIN PHILLIPS, RCP, RRT-ACCS
UC SAN FRANCISCO – ZUCKERBURG

Justin Phillips is a Adult Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as a bedside therapist and educator. Justin is a lecturer for the Critical Care Residency Program at ZSFG and has spoken nationally at a number of respiratory and critical care conferences. Additionally, he is Adjunct Faculty for the Respiratory Care Program at Ohlone College for Health Sciences and Technology. Justin's clinical interests include enhancing mechanical ventilation delivery through innovation and strategic ventilator practices.

Newer Tools to Measure Pulmonary Mechanics and Use of Prone Positioning

Krystal Craddock, MSc, RRT, RRT-NPS, RRT-ACCS, AE-C, CCM

Clinical Operations Manager, Respiratory Care



1

No perceived COI

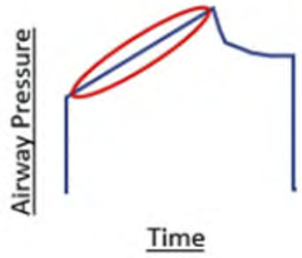
2

$$V_t = V_i \times e^{-t/T}$$

$$\Delta P = E_{RS} \times V_T = V_T / C_{STAT} = P_{PLAT} - PEEP_{TOT}$$

$$R_I = (PIP - P_{plat}) / \dot{V}_I$$

$C_{rs} = \Delta V/\Delta P$ =VT/Plateau Pressure (Pplat) – PEEP.



$$P_{AW(t)} = P_0 + E(V)_{(t)} + R\left(\dot{V}\right)_{(t)}$$

$$R_E = (P_{plat} - PEEP) / \dot{V}_{EXH}$$

$$1/C_{rs} = 1/C_{lung} + 1/C_{chest\ wall}$$

3

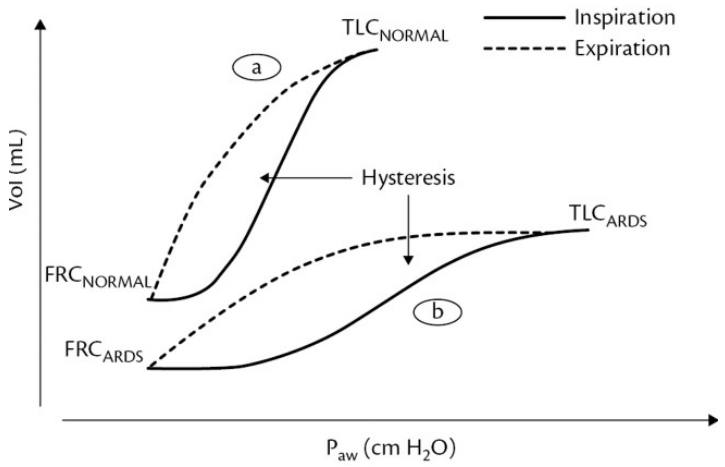
Advanced Respiratory Mechanics – Why?

- The understanding of a patient's pulmonary mechanics is a necessary piece of the assessment of a patient on mechanical ventilation.
  - Provide effective gas exchange
  - Maintain alveolar recruitment
  - Reduce VILI
  - Ensure hemodynamic stability
- Advanced Respiratory Mechanics
  - PV Tool
  - Esophageal Manometry
  - Electronic Impedance Tomography (EIT)

4

PV Loops and ARDS

The inflation and deflation limbs of the PV loop will demonstrate a change in slope, meaning respiratory compliance varies at different levels of pressure.



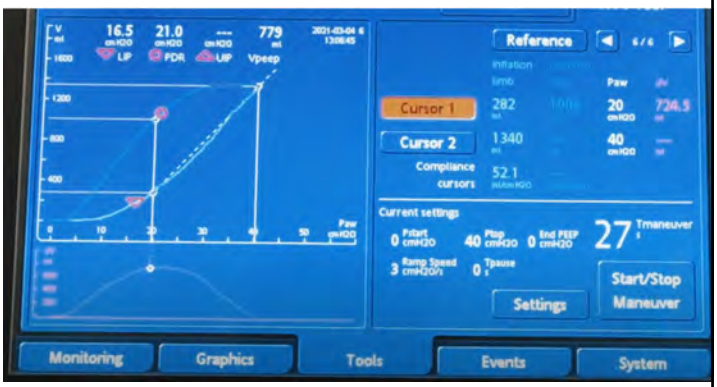
Gattinoni et al. (2006)

Pressure-volume curve (P/V) and its hysteresis. (a) P/V curve from a normal patient. (b) P/V curve from a patient with ARDS. (In: Cordioli, R and Brochard, L, Respiratory system compliance and resistance in the critically ill, Oxford Textbook of Critical Care, ISBN: 9780198855439.)

5

Protective Ventilation (P/V) Tool

- Quasi-statice P-V loop can assess the potential for recruitment and predict whether a recruitment maneuver can be effective.
  - The lower inflection point of the inflation pressure/volume curve
  - The linear compliance of the inflation pressure/volume curve
  - The hysteresis



Gertler (2021)

6

Esophageal Manometry

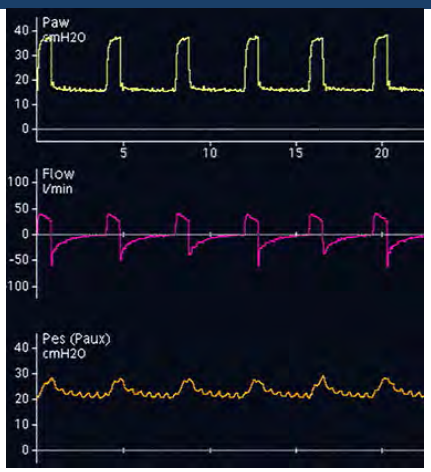
- PEEP must be individually determined for each patient.
  - Basic PEEP trial methods involve monitoring compliance, PIP, and P_{plat}
- Transpulmonary pressure (P_{TP}) is the difference between the pressure inside the alveoli and the pressure surround the lung.
  - $P_{TP} = P_{alv} - P_{pl}$
- Pleural pressure is estimated by measuring the pressure in the lower third of the esophagus using an esophageal balloon catheter
  - Elevated in ARDS, obesity, increased intraabdominal pressure
- The use of P_{TP} supports titration of pressures based on actual pressure.
  - To allow optimal recruitment, PEEP could be increased until P_{TP} becomes positive and end-expiration.

Piraino et al. (2011)
Yoshida et al. (2018)

7

Esophageal Manometry

- $P_{TP} = P_{alv} - P_{pl}$
- Esophageal pressure can be used as an estimate of mean pleural pressure.
- Technical aspects of this measurement are important
  - Characteristics of the manometer
  - Placement position
  - Balloon inflating volume
  - Data interpretation



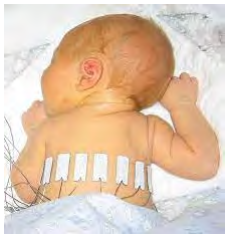
Hamilton Medical (2018). Retrieved from https://www.hamilton-medical.com/en_US/News/Newsletter-articles/Article~2018-10-19~Bedside-Tip%3A-How-to-measure-esophageal-pressure-correctly~5189d03b-e7b4-4eed-966e-2fae8f42a13a~.html

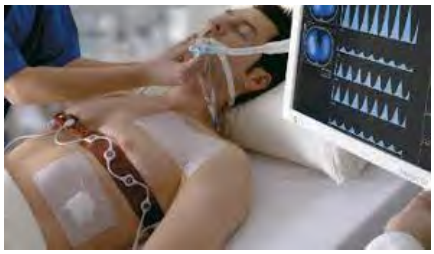
Gertler (2021)
Yoshida et al. (2018)

8

Electrical Impedance Tomography (EIT)

- Breath-by-breath dynamic imaging of regional ventilation distribution through measuring impedance changes across lung regions.
- Can detect changes in lung impedance associated with recruitment maneuvers and incremental or decremental PEEP trials.
  - Non-invasive and radiation-free imaging
  - 16 to 32 leads
- In patients with ARDS, EIT-guided PEEP titration has been associated with improved oxygenation, compliance, driving pressure, and weaning success rates.





Zhao et al. (2019)
Sella et al. (2021)

Zhao et al. 2019

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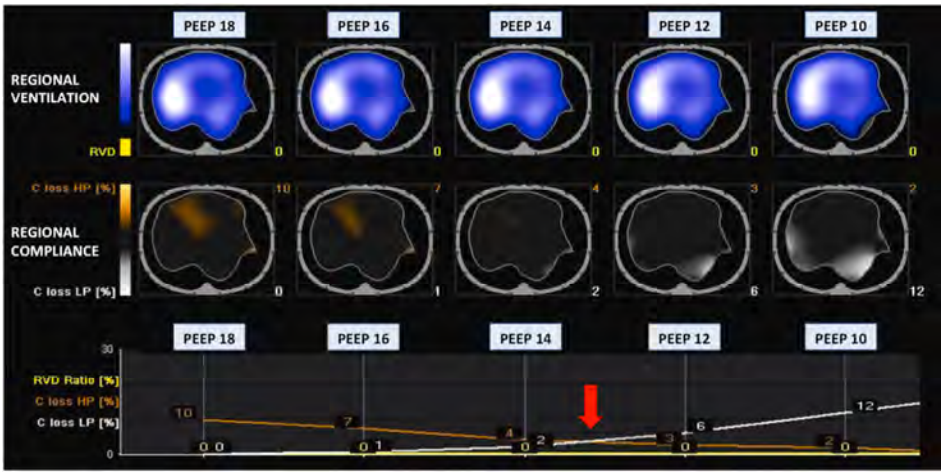
EIT



Sella et al. (2021). Retrieved from: https://www.resmedjournal.com/article/S0954-6111(21)00261-4/fulltext

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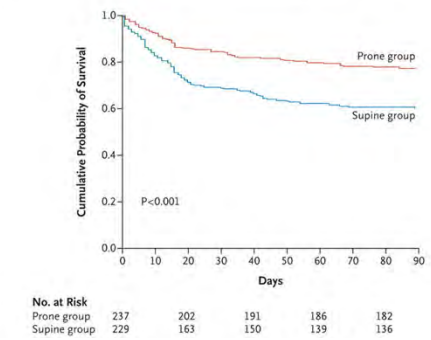
Prone Positioning

11

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 6, 2013 VOL. 368 NO. 23

Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaele Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group*



Cochrane Library

Cochrane Database of Systematic Reviews

Prone position for acute respiratory failure in adults (Review)

Bloomfield R, Noble DW, Sudlow A

12

Prone Positioning

- Awake prone positioning appears to be a safe and tolerable intervention for non-intubated patients with hypoxemic respiratory failure attributable to ARDS or COVID-19.
- Prone positioning in non-intubated, spontaneously breathing patients' effectiveness in improving oxygenation and reducing intubation rate and mortality, and its tolerability, timing, and optimal duration are unclear.
- Potential benefits include improved oxygenation and mortality rate, but no significant effects on incidence of intubation or critical care admission were found in one systematic review.
- Future research with well-designed trials are needed to explore the subject more rigorously and to confirm clinical effectiveness.

Fazzini et al. 2022

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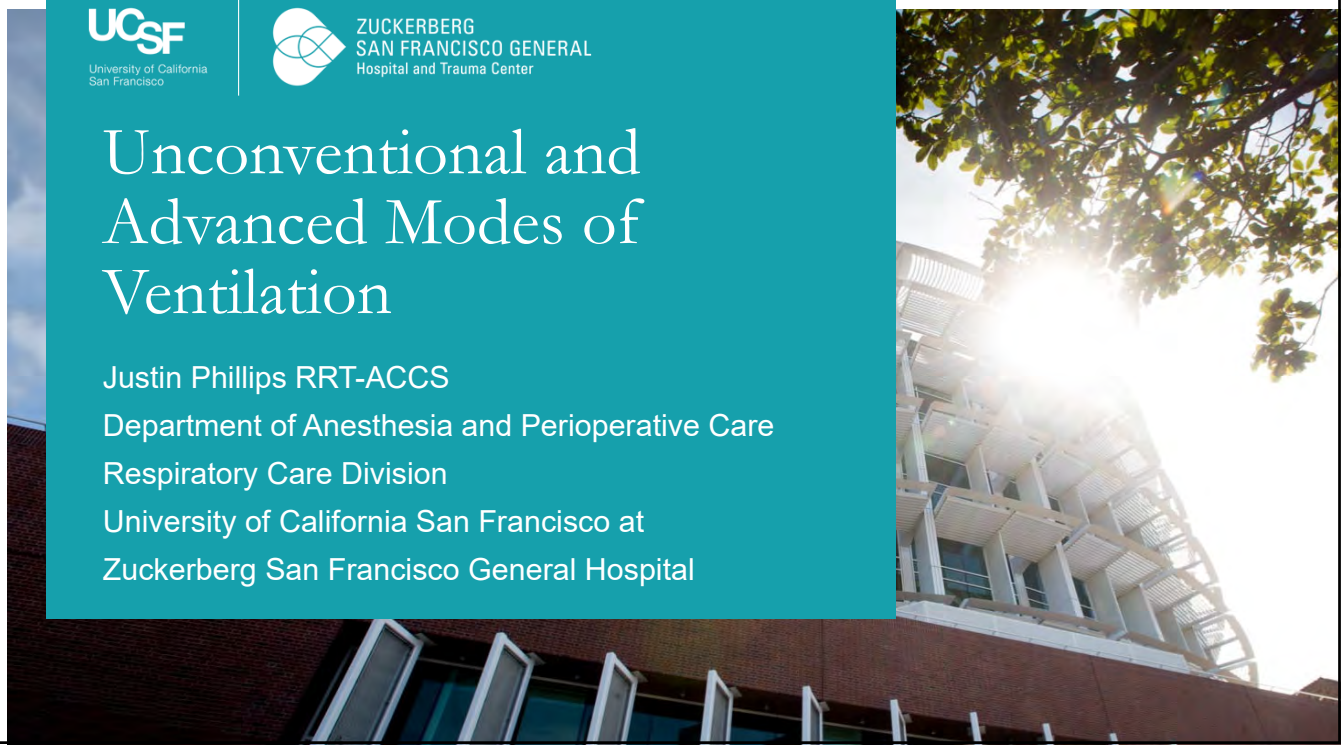

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Disclosures

- Content and Financial Disclosure: I have received honoraria for lectures and content creation for ContinuED online continuing education.
- This lecture does focus on modes of mechanical ventilation that may be exclusively featured on specific ventilators or from a specific manufacturer, none of whom I have financial relationships with.

UCSF

2

UCSF

Basic Principles

3

Goals of Mechanical Ventilation

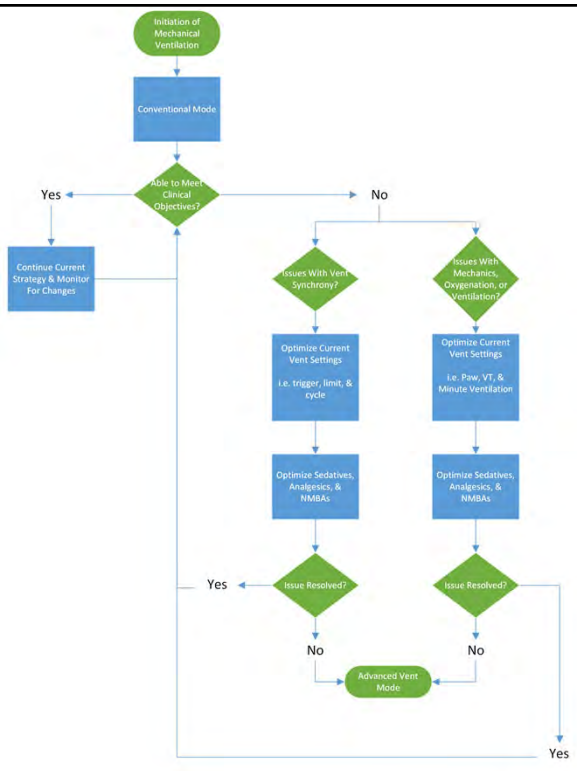
- Guarantee of the adequacy of gas exchange (oxygenation, ventilation/acid-base balance)
  - Minute Ventilation (VT x RR)
  - PEEP (preserve or re-establish FRC which is the “alveolar volume” and therefore primary determinant of arterial oxygenation)
  - FiO2
- Fully or partially support the power of breathing
  - Power of Breathing: Work/min = Work/L x V_E (L/min)
  - Determinants: Raw and C_{RS} and V_E demand

4

Why Differentiate From the "Standard"

- New shiny toy
- New approach to clinical goals
- Better optimization of mechanical support
- Rescue

5



6

Common Alternatives

Caveats to implementation

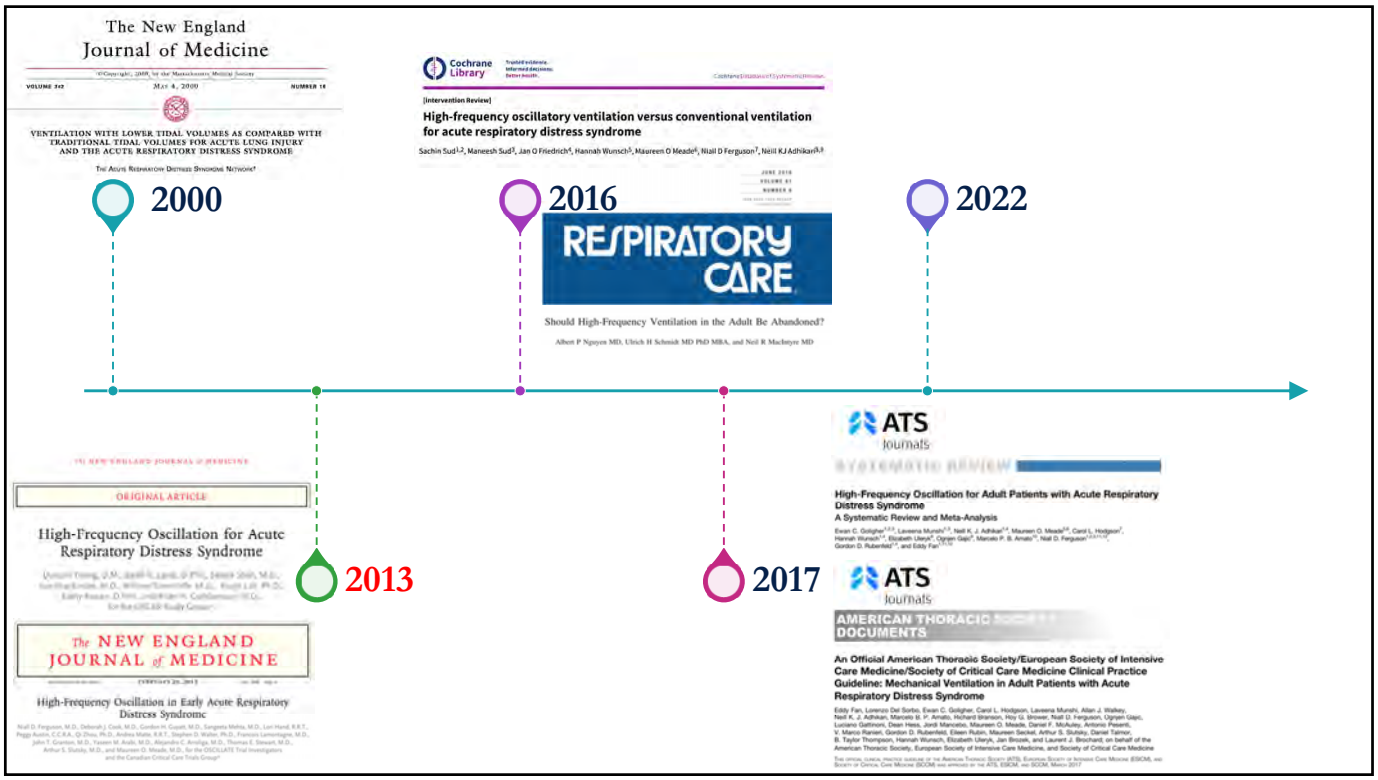
- Outcome data
- Standardization
- Clinician familiarity
- Operational limitations

7

Common Alternatives

- Non-Conventional
  - HFOV
  - HFPV
  - HFJV
- Advanced Modes
  - PAV
  - NAVA
  - APRV
  - ASV, Automode, SmartCare, etc.

8



9

High Frequency _____ Ventilation

HFPV
VDR-4 Percussionaire

HFOV
3100B Vyaire

10

High Frequency Percussive Ventilation

Volumetric Diffusive Respirator (VDR-4)

- High-frequency flow (flow regulated), pressure-limited, time-cycled, low-frequency VT (similar to VT in CMV)
- Low-frequency VT & High-frequency VT not measured
- Larger ETT diameters, changes in i:e, or reduced HF rate can increase HF VT
  - VT likely to exponentially decrease with increases to frequency

11

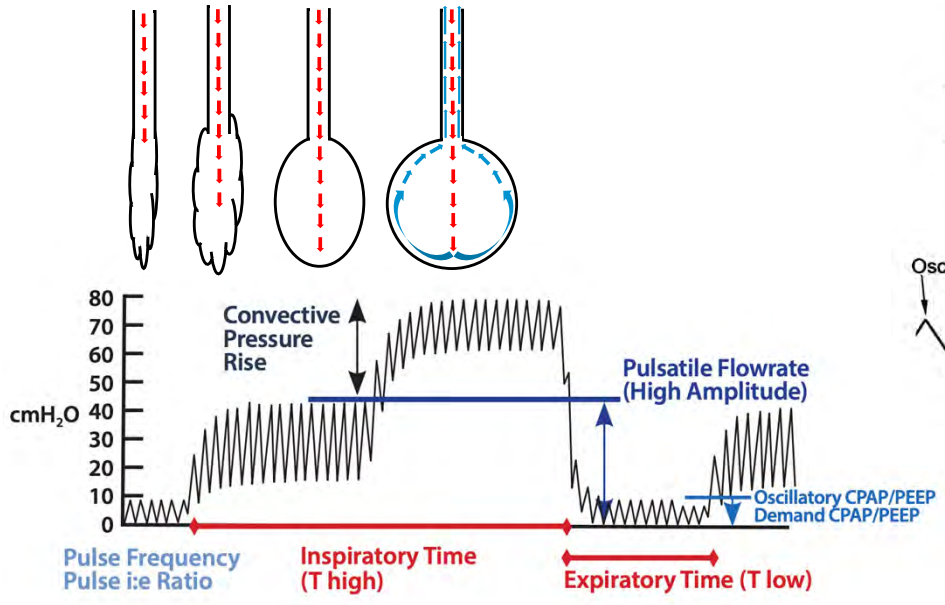
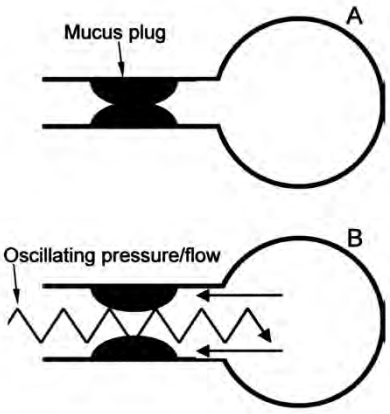


Image Courtesy of Percussionaire



Chatburn RL. High-frequency assisted airway clearance. Respir Care. 2007 Sep;52(9):1224-35; discussion 1235-7. PMID: 17716388.

12

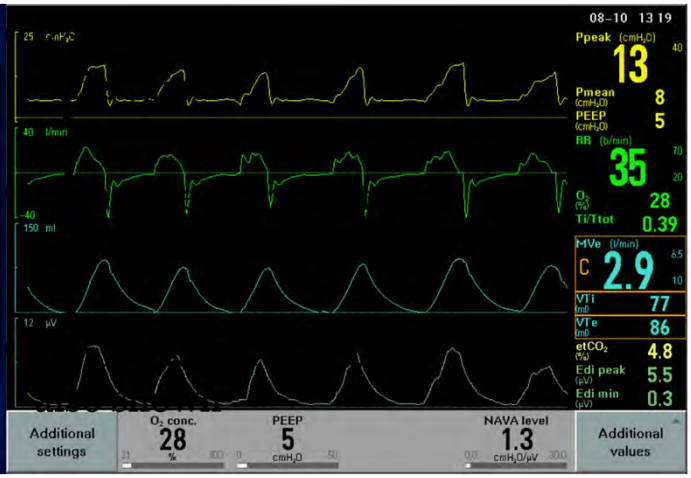
13

Proportional Modes

PAV and NAVA

- Ventilator asynchrony is common and can require frequent interventions by the clinician
- Respond to changes in ventilatory demand
- Balance of unloading WOB and relinquishing control of ventilation to the patient
- Limited outcome data but in theory, if the patient is appropriate for PSV then proportional modes may be a reasonable alternative

14



Proportional Assist Ventilation (PAV)

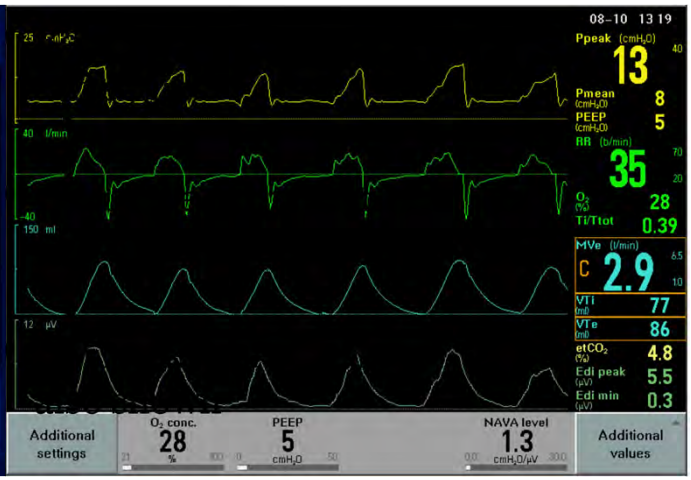
$P_{total} = P_{mus} + P_{vent}$ = (VT x Elastance) + (Flow x Raw)

Estimated R + E to calculate P_{total}

Neurally Adjusted Ventilatory Assist (NAVA)

P_{peak} = NAVA level x (Edi peak – Edi min) + PEEP

15



Proportional Assist Ventilation (PAV)

Percentage of total WOB

i.e. 70/30 = 70% of P_{total} by vent

Neurally Adjusted Ventilatory Assist (NAVA)

Swap equation of motion for electrical activity (diaphragm, cm H_2O/millivolt)

Increased vent response

Trigger = Edi

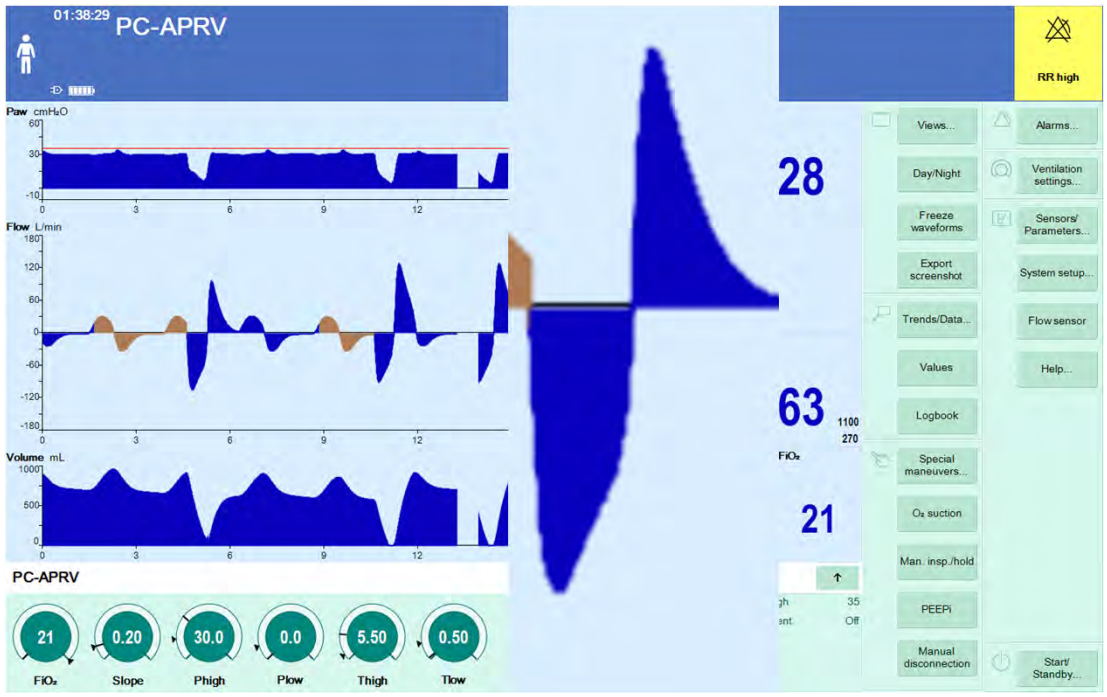
16

Airway Pressure Release Ventilation

APRV

- Inverse Ratio, Pressure Controlled, Intermittent Mandatory Ventilation **WITH** Unrestricted Spontaneous Breathing
- Open Lung Ventilation
- Often regarded as rescue therapy for life-threatening hypoxia in ARDS
- Attractive alternative to conventional or “traditional” modes of ventilation due
  - Preservation of spontaneous breathing
  - Reduction of sedatives, analgesics, and NMBAs
  - Hemodynamically advantageous

17



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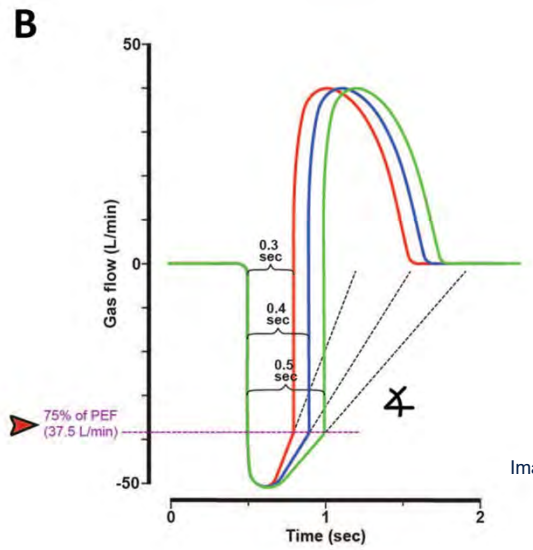
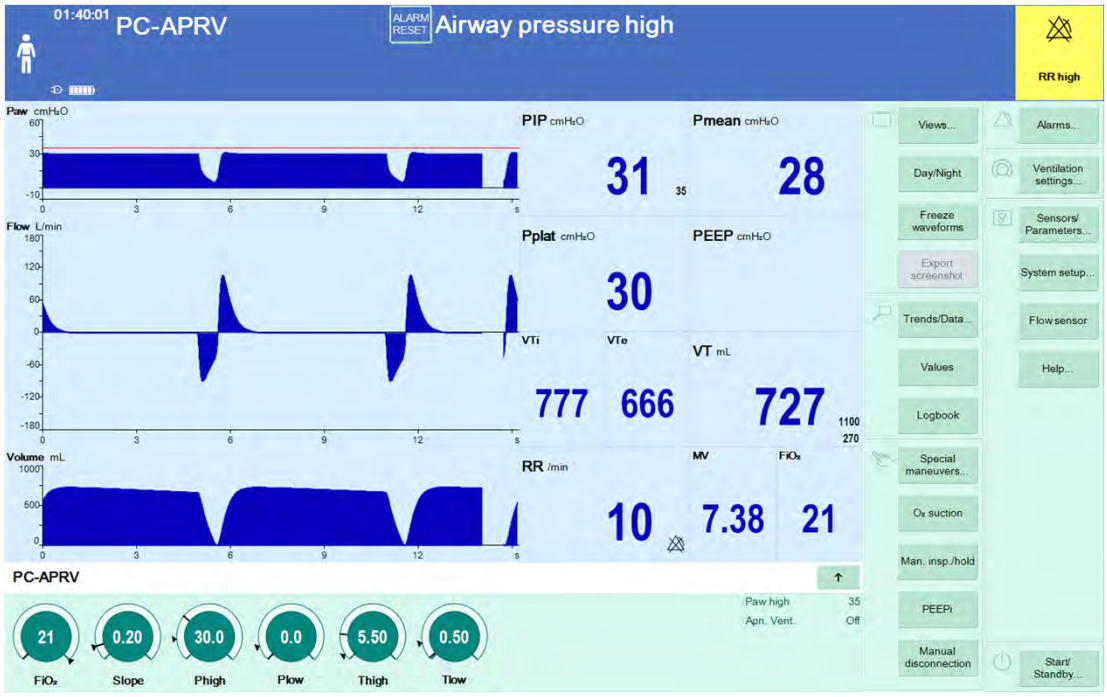


Image courtesy of APRV-TCAV Network

STEP 1: 37.5 L/MIN PEAK EXPIRATORY FLOW x 0.75 = 28.1 L/MIN TERMINAL FLOW

STEP 2: Set T_{LOW} at the point of which terminal flow equals 28.1 L/MIN

19



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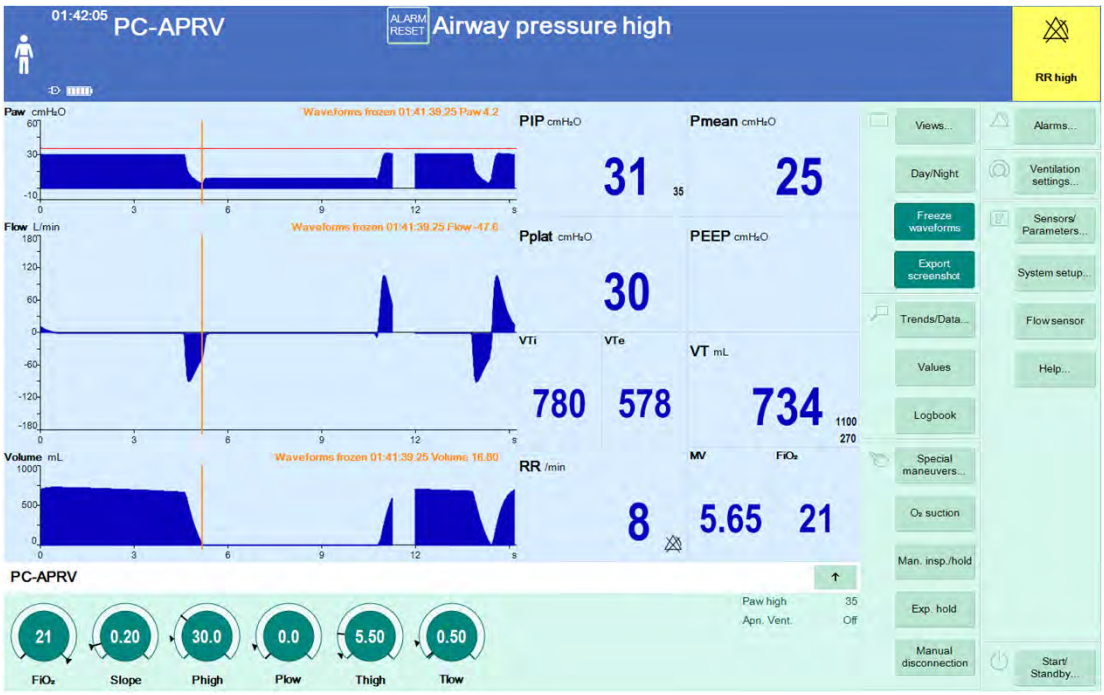
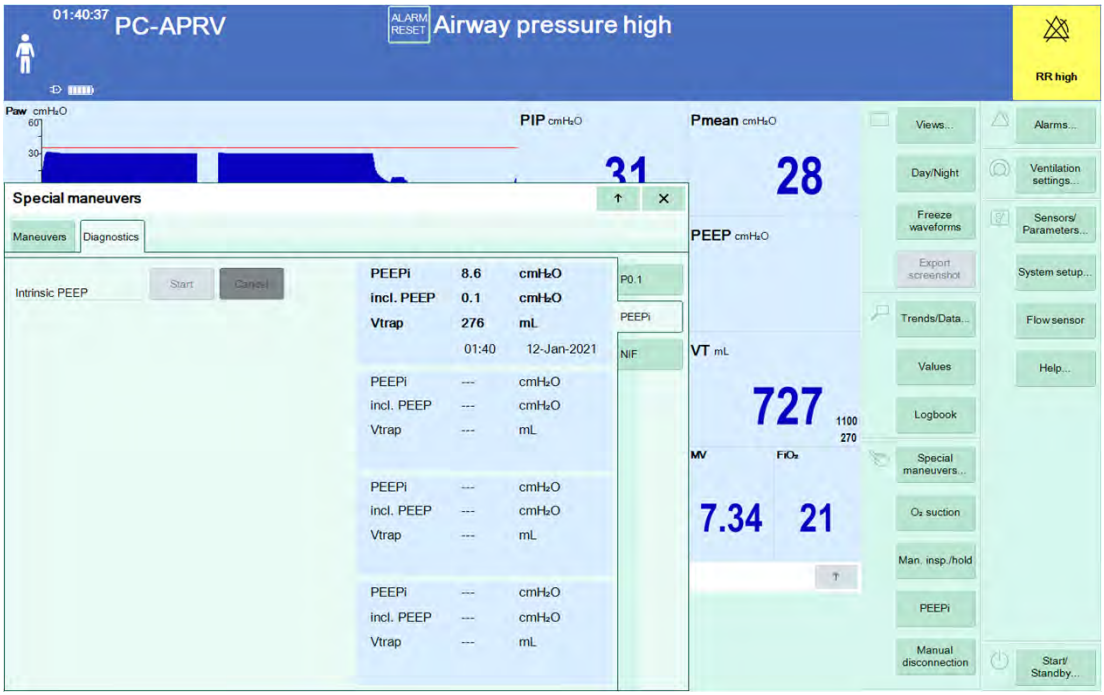


21 Unconventional and Advanced Modes of Ventilation

UCSF

21

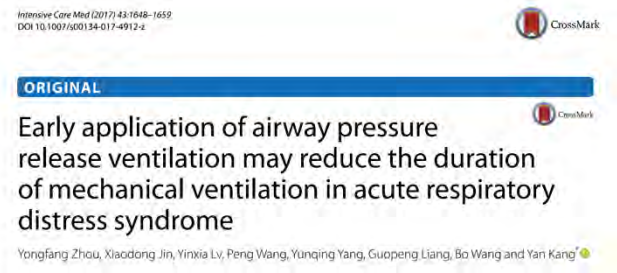


22 Unconventional and Advanced Modes of Ventilation

UCSF

22

UCSF



Intensive Care Med (2017) 43:1648–1659
DOI 10.1007/s00134-017-4912-z

ORIGINAL

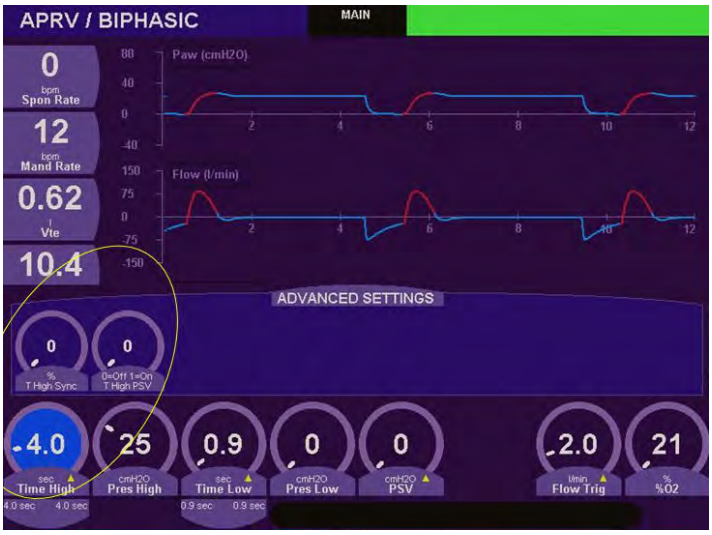
Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome

Yongfang Zhou, Xiaodong Jin, Yinxia Lv, Peng Wang, Yunqing Yang, Guopeng Liang, Bo Wang and Yan Kang*

- Perhaps the best evidence on use of APRV on patients with ARDS
- 138 patients with a diagnosis of ARDS
- Randomized patients within 48 hours to:
  - Conventional low tidal volume (LTV) ventilation with a low PEEP strategy
  - APRV with a clearly defined implementation protocol.
- Ventilator free days (median APRV = 2 days vs LTV = 19)

Considerations

- Manufacturers implement different iterations of APRV
- Your mileage may vary across various platforms and software
- Lack of a standardized approach to setting optimization
  - Although clinical guides are available


APRV / BIPHASIC
MAIN
Paw (cmH2O)
Flow (l/min)
0
Spon Rate
12
Mand Rate
0.62
Vte
10.4
ADVANCED SETTINGS
-4.0
Time High
25
Pres High
0.9
Time Low
0
Pres Low
0
PSV
-2.0
Flow Trig
21
%O2


Mode
Bi-Vent
Admit patient
Nebulizer
Status
24
42
40
7.8
Set Ventilation Mode
Bi-Vent
RR 14 b/min
I:E 13.7:1
Basic
Insp. times
Trigger
Supported breath
P high 30
T high 4.1
Trigg. Pressure 0
PS above P high 0
PEEP 5
T PEEP 0.3
Insp. cycle off 30
PS above PEEP 0
O2 conc. 100
T insp. rise 0.00

25


54
216
11
1:3.1
2.9
5.1
2.81
216
Setup
Setup Vent
Enter predicted body weight
50 kg (110lb)
— OR —
gender and height
Vent
Apnea
Alarms
More Settings
Ventilation Type Invasive NIV
Mode A/C SIMV SPONT BiLevel
Mandatory Type PC
Spontaneous Type PS TC
Trigger Type P-Trig V-Trig
10 18 0.74 0 2.0 100 100
50 3.0
25
Previous Setup
Close
Adult
BiLevel PC PS
50 kg
10 18 0.74 0 2.0 100
50 3.0
25
08:59:27pm

26

ACC Acute and Critical Care

Acute and Critical Care 2021 May 36(2):143-150
https://doi.org/10.4266/acc.2021.00017

pISSN 2586-6052 | eISSN 2586-6060

Airway pressure release ventilation in mechanically ventilated patients with COVID-19: a multicenter observational study

John S. Zorbas[1], Kwok M. Ho[2,3,4], Edward Litton[3,5], Bradley Wibrow[1,3], Edward Fysh[6], Matthew H. Anstey[1,3]

- "Patients who received APRV had a lower probability of survival than did those on other forms of ventilation"
- Fewer vent-free survival days with APRV vs non-APRV
- "...we urge caution with the use of APRV in COVID-19"

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Utilization of Airway Pressure Release Ventilation as a Rescue Strategy in COVID-19 Patients: A Retrospective Analysis

Journal of Intensive Care Medicine
2021, Vol. 36(10) 1194-1200
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DOI: 10.1177/0885066621030899
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SAGE

Omar Mahmoud, MD[1], Deep Patadia, MD, MPH[2], and James Salonia, MD[2]

Table 3. Study Outcomes.

	Before APRV	During APRV	P value
PaO_2/FIO_2 ratio	103 (75-154.23)	131.75 (94.15-221)	0.0001
FiO_2 (%)	100 (75-100)	80 (60-100)	0.0034
pH	7.265 (7.16-7.39)	7.31 (7.25-7.38)	0.0736
PaO_2 (mm Hg)	80 (65-103)	91.5 (76-135.5)	0.0072
$PaCO_2$ (mm Hg)	54 (42-73)	45.8 (41-56.75)	0.0051
TV (mL)	421.93 ± 89.56	525.78 (188.68)	<0.0001
TV/PBW (mL/Kg)	6.58 (5.69-7.86)	7.86 (7.06-9.85)	<0.0001
Minute ventilation (L/min)	12.39 ± 2.99	10.87 ± 3.11	0.0005
Ventilatory ratio	2.85 (2.07-3.85)	2.24 (1.72-2.72)	0.0054
Dynamic compliance (mL/cm H_2O)	21.07 (13.33-25.42)	19.25 (14.14-24.65)	0.3324

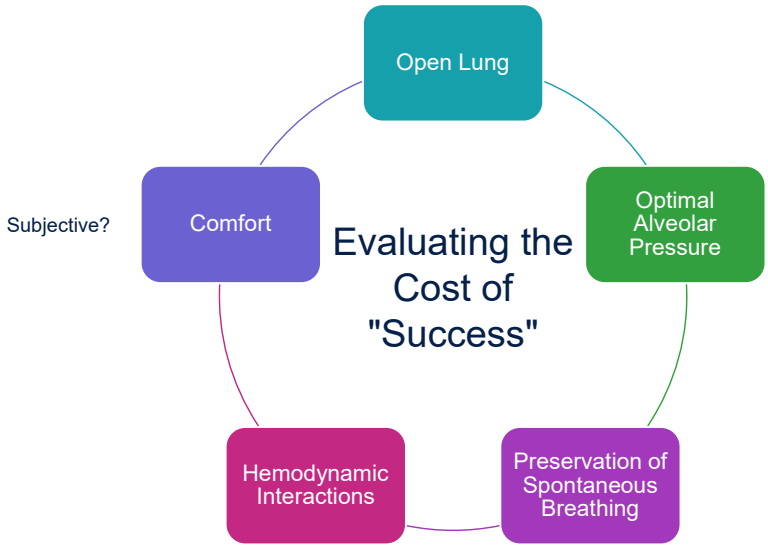
- Retrospective (01/20 - 06/30) analysis of multiple hospitals across the Mount Sinai Health System
- P/F <200 (PEEP 5 + FIO2 >/= 0.70)
- Positive impact on oxygenation & ventilation
- Positive impact on Vd/Vt, regional V/Q matching, and alveolar ventilation
- Presumed non-standardized application on APRV

28

Does improvements in gas exchange define success?

29

LPV is predicated on maintaining OLV



Subjective?

Changing mechanics can be harder to identify and be problematic

Situational, impact on respiratory muscle perfusion over vital organs prompts conversation of full vs partial support

30

University of California
San Francisco

Justin.Phillips@ucsf.edu

@JustinScott_RRT

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ECMO as Bridge to Recovery for Severe COVID-19

9:50 a.m. – 10:35 a.m.

OREN A. FRIEDMAN, MD
CEDARS-SINAI MEDICAL CENTER

Dr. Oren Friedman is the Associate Medical Director, Cardiac Surgery Intensive Care Unit, Heart Institute at the Cedars-Sinai Medical Center, Los Angeles, California. He is a clinical pulmonary and critical care physician with an interest in resuscitation, airway management, cardiac arrest, and pulmonary embolism. In addition, he has spent significant time in his career devoted to education. He has experience in creating and directing simulation courses, directing critical care ultrasound courses, creating written and interactive curricula, giving many lectures including at national forums, and more recently have chaired the education committee for the national PERT consortium, and created and directed an educational podcast focused on pulmonary embolism. He has been involved in scholarship centered on pulmonary embolism and cardiac arrest resuscitation including several chapters review articles and have been sub investigator on several pulmonary embolism research projects.

VV ECMO for the COVID patient

Overview of V-V
General Management of the V-V patient
V-V ECMO for COVID ARDS
1st v 2nd wave
Controversies in COVID ECMO

Oren Friedman Pulmonary and Critical Care
Cedars-Sinai

1

Disclosures

Bristol-Myers Squibb/Pfizer – speakers bureau

Inari Medical – consultation

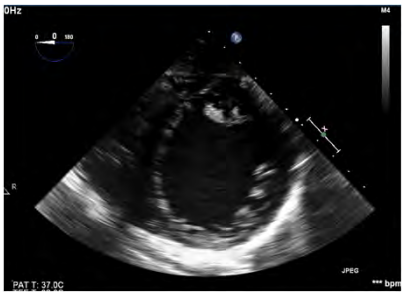
The above disclosures are not relevant to this lecture

2

V-A ECMO "Veno-arterial"

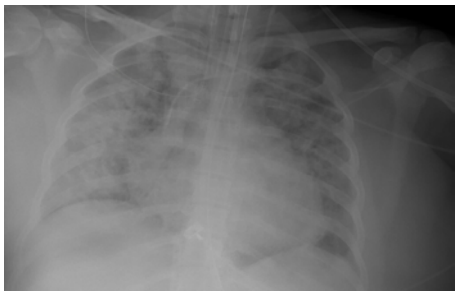
- Venous access + Arterial return
- Provides: complete cardiopulmonary support

Treats: Cardiogenic Shock and bridges to device/transplant/recovery



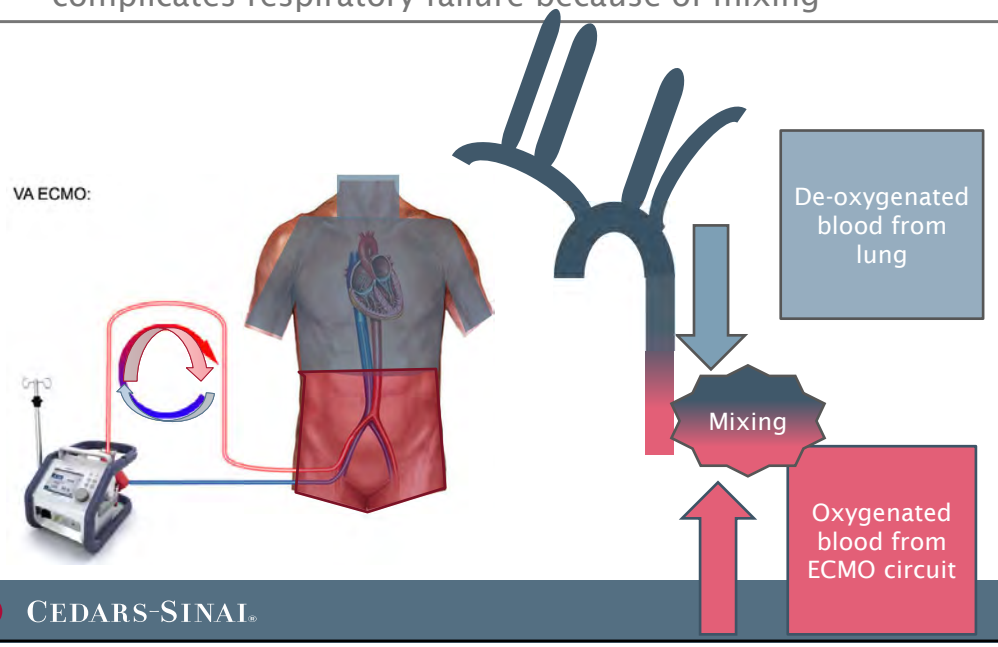
V-V ECMO "Veno-Venous"

- Venous access + venous return
- Provides: Oxygenation and Ventilation but no hemodynamic support
- Treats : ARDS



3

V-A ECMO can cause differential hypoxemia and complicates respiratory failure because of mixing



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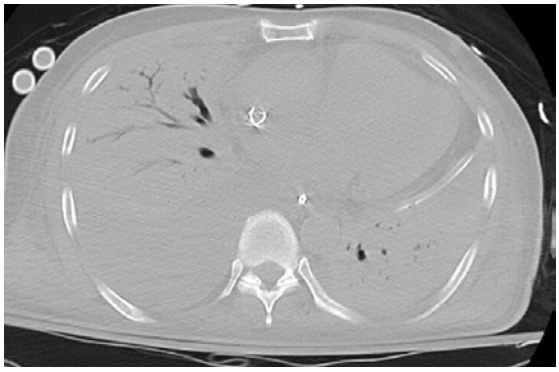
4

VV ECMO has two broad applications

I can't live without it



It will theoretically provide me with a better way to get the job done

- Ultra lung protective ventilation
- Reduce Fio2 and O2-trauma
- Reduce the hemodynamic burden of mechanical ventilation
- Provide an alternative way to support through the crisis
  - Wake the patient
  - exercise the patient
  - extubate the patient

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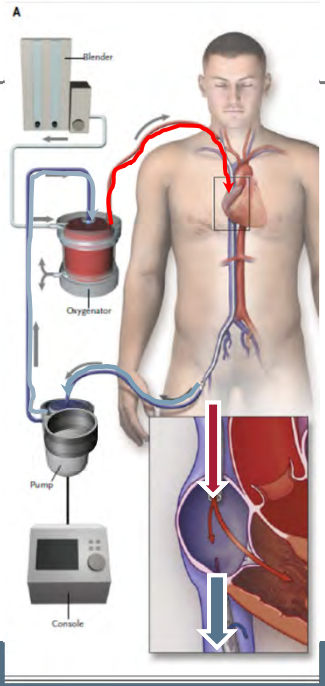

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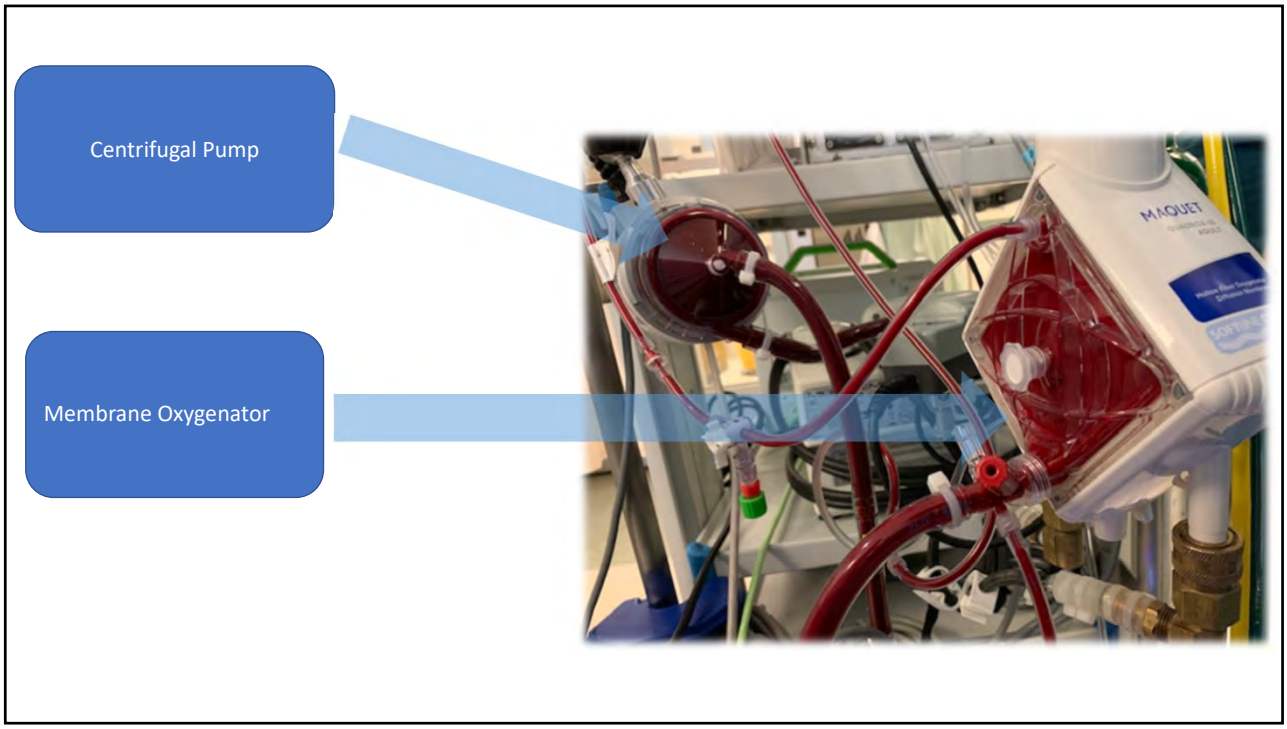

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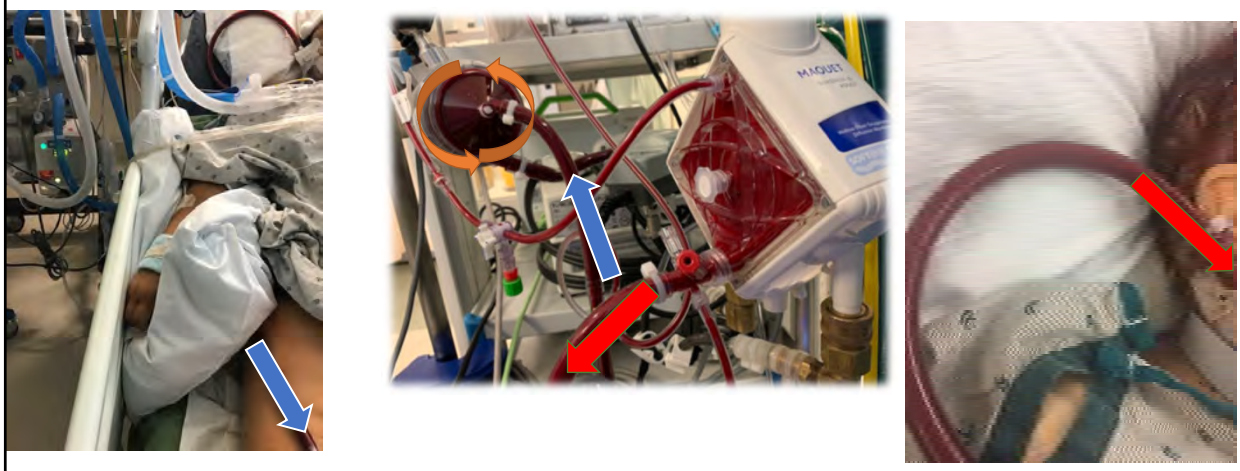
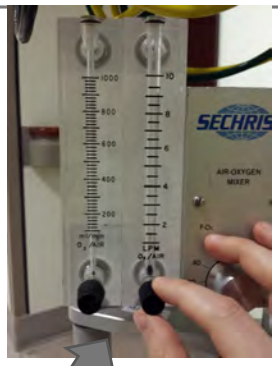


8

The VV ECMO circuit behaves like an artificial lung before the patient's blood enters their defective lung



Sweep
~
Ventilation

Flow + Blender
~
Oxygenation

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9

ECMO FLOW

Oxygenation

Big catheters in good position

Adequate Volume

Low intra-abd/intrathoracic pressure

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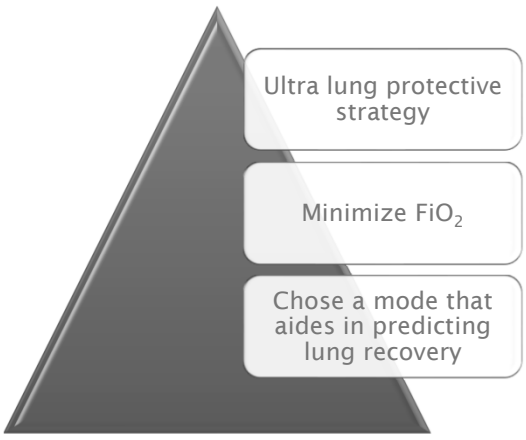
Hypoxemia on VV

- Maximize flow
- Maximize capture of cardiac output

11

Set your mechanical ventilator during ECMO to be protective and predictive



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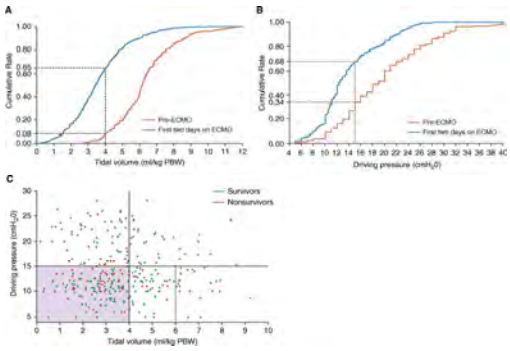
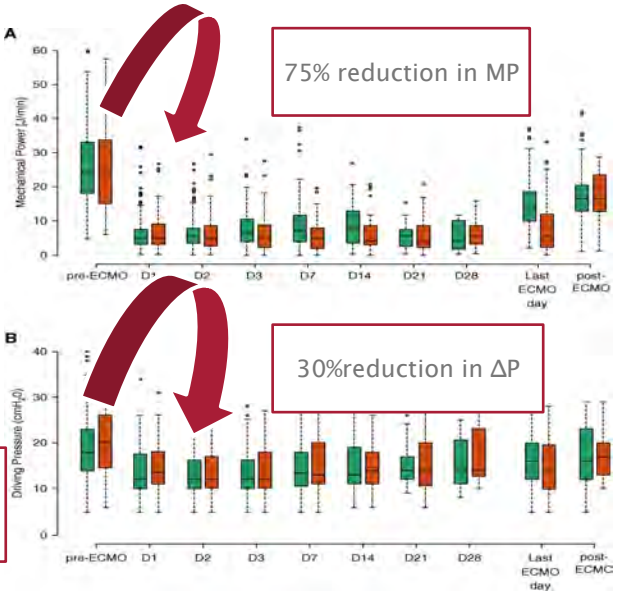
American Journal of Respiratory and Critical Care Medicine

Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. An International Multicenter Prospective Cohort





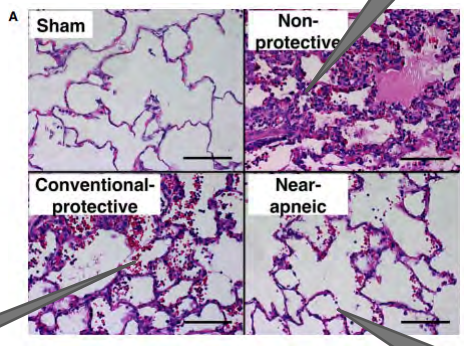
Initiation of ECMO associated with a drop in TV, RR, and driving pressure

13

Near-Apneic Ventilation Decreases Lung Injury and Fibroproliferation in an Acute Respiratory Distress Syndrome Model with Extracorporeal Membrane Oxygenation

Joaquin Araos[1], Leyla Alegria[1], Patricio Garcia[2], Pablo Cruces[3,4], Dagoberto Soto[1], Benjamín Erranz[5], Macarena Amthauer[1], Tatiana Salomon[6], Tania Medina[7], Felipe Rodriguez[1], Pedro Ayala[8], Gisella R. Borzone[8], Manuel Meneses[9], Felipe Damiani[1,10], Jaime Retamal[1,3], Rodrigo Cornejo[3,11], Guillermo Bugedo[1,3], and Alejandro Bruhn[1,3]

10 cc /kg
PEEP 5



6 cc/kg
PEEP 10

PEEP 10 PS 10

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Suggested Mechanical Ventilator settings the "10 10 10 rule"

- Mode:
  - Use Pressure control ventilation: rationale=as the patient improves and compliance improves their tidal volumes will return to normal
- Settings
  - RR 10 Driving pressure 10 PEEP 10
  - Wean FIO_2 as low as possible (goal down to 30%)

Try to address oxygenation and ventilation problems through the ECMO circuit and not the vent.

Hit hard then pull away fast

Acute phase

- First week…
- The lung is hot and angry
- Sedate +/- paralysis
- Ultra lung protective ventilation
- Positive fluid balance may be necessary to maintain flow
- *Rest the lung and take over*

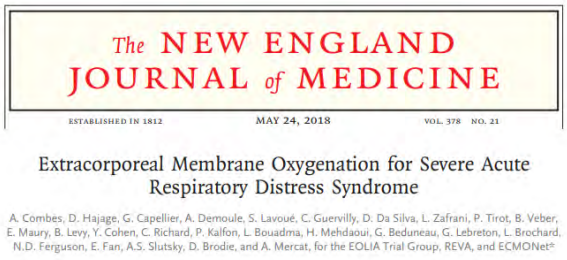
"Rest is Best"

Recovery Phase

- Week ~ 2 and on
- The lung is recovering
- Wake the patient
- Mobilize the patient
- Liberalize tidal volumes
- Make the patient negative
- *Use and test the lung*

"Use it or lose it "

Who should go on?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 24, 2018 VOL. 378 NO. 21

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

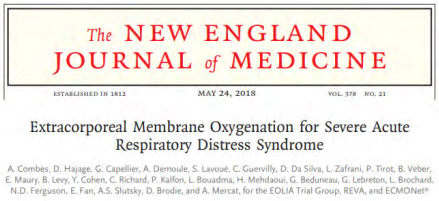
A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*

EOLIA criteria

- ARDS
- Vent <7days
- PF<50 for 3 hours
- PF<80 for 6 hours
- OR pH ≤7.25/≥60 for >6 hr
- with RR 35 Plateau <32 FiO_2 ≥0.8 TV 6 cc/kg/PWB and PEEP≥ 10

17

17



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- Underpowered
- 28% crossover
- Study terminated early

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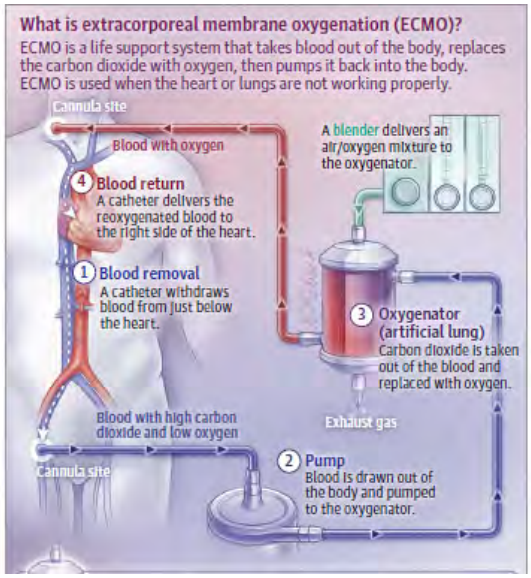
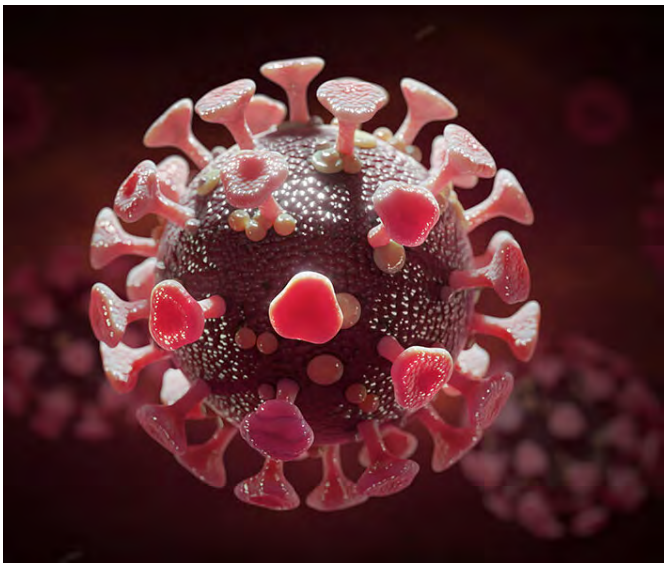
So, what about using ECMO for COVID?





19

Early ECMO data from Feb/Mar 2020 was dismal

Table 1
Comparison of studies that reported Extra Corporeal Membrane Oxygenation (ECMO) as a rescue therapy for patients with acute respiratory distress ...ie (ARDS) due to COVID-19.

	Huang C et al.[3]	Nanshan Chen et al.[4]	Wang D et al.[5]	Yang X et al.[6]	Guan WJ et al.[7]	...ou F et al.[8]
Study type	Cross-sectional	Retrospective, observational	Case series	Retrospective, observational	Cross-sectional	...trospective, cohort study
n	41	99	138	710	1099	191
ICU admission, proportion,% (95% CI)	31.7 (18.08–48.08)	17.17 (10.33–26.06)	26.08 (18.98–34.24)	7.32 (5.51–9.49)	5.0 (3.79–6.46)	26,17 (20.09–33.01)
ARDS, proportion,% (95% CI)	29.26 (16.13–45.53)	17.17 (10.33–26.06)	19.56 (13.3–27.17)	4.93 (3.45–6.78)	3.36 (2.38–4.6)	30.89 (24.1–37.96)
Risk of death during ECMO support, relative risk (95% CI)	Data were unavailable to calculate	0.46 (0.09–2.39)	Data were unavailable to calculate)	0.89 (0.61–1.29)	2.88 (1.65–5.01)	0.96 (0.66–1.41)
Overall mortality rate, proportion,% (95% CI)	14.63 (5.56–29.17)	11.11 (5.67–19.01)	4.34(1.61–9.22)	4.50 (3.10–6.30)	1.36 (0.76–2.24)	28,27 (22.0–35.22)

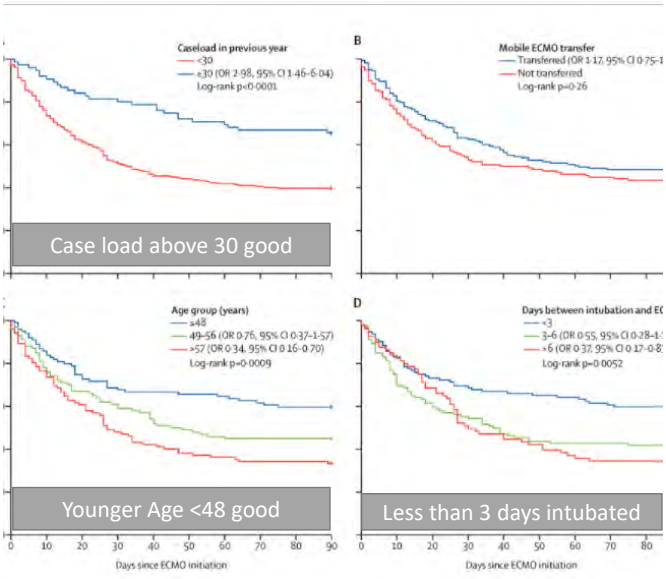
Average mortality of 82% and as high as 96%!

From S.A Namendys Silver Heart and Lung July 2020

20

Paris Experience March ->June 2020

- 302 patients 17 ICUs – central site –
- 6 mobile ECMO teams
- March ->June 2020



Lebreton ECMO network organisation in Greater Paris Lancet 2021

21

Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study

*Guillaume Lebreton, Matthieu Schmidt, Maharajah Ponnaiah, Thierry Folliguet, Marylou Para, Julien Guihaire, Emmanuel Lansac, Édouard Sage, Bernard Cholley, Bruno Mégarbane, Pierrick Cronier, Jonathan Zarka, Daniel Da Silva, Sebastien Besset, Tristan Morichau-Beauchant, Igor Lacombat, Nicolas Mongardon, Christian Richard, Jacques Duranteau, Charles Cerf, Gabriel Saiydoun, Romain Sonneville, Jean-Daniel Chiche, Patrick Nataf, Dan Longrois, Alain Combes, Pascal Leprince, and the Paris ECMO-COVID-19 investigators**

Criteria to go on:
PF<80 for for 6
PF <50 for 3
Age <70
No serious comorbidities

Median age 52
Pre ECMO 94% proned, median PF 61, most paralyzed >50% on iNO

BAD:
43% Major bleeding 27 ICH
43% RRT
18% PE

Results:
Median duration 14 (8-26)
46% alive after 90 days after ECMO

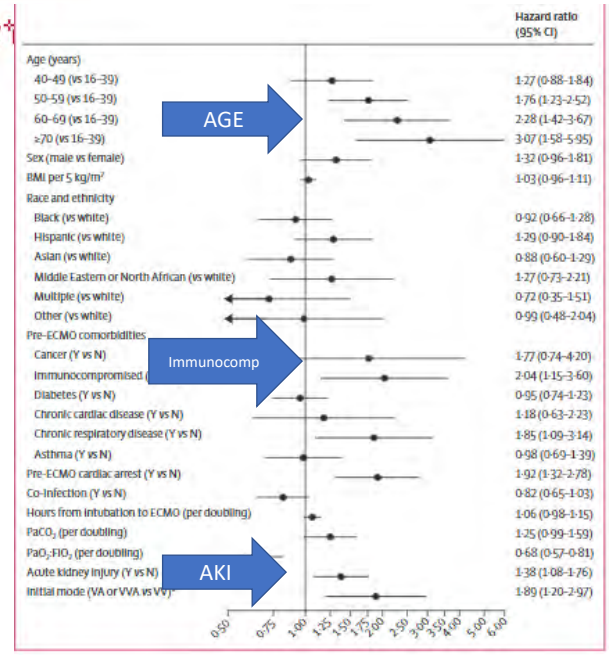
Better to be younger than 48
No renal failure to start

22

Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry

Ryan P Barbaro*, Graeme MacLaren*, Philip S Boonstra, Theodore J Iwashyna, Arthur S Slutsky, Eddy Fan, Robert H Bartlett, Joseph E Tonna, Robert Hyslop, Jeffrey J Fanning, Peter T Rycus, Steve J Hyer, Marc M Anders, Cara L Agerstrand, Katarzyna Hryniewicz, Rodrigo Diaz, Roberto Lorusso†, Alain Combes†, Daniel Brodie†, for the Extracorporeal Life Support Organization‡

- Lancet October 2020 1k patients estimated mortality 90d 37.4%
- Age and underlying health conditions more important than severity of ARDS at initiation



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ELSO registry results were encouraging

COVID ELSO registry up to Oct 2020

90-day mortality 37%

EOLIA trial

60-day mortality 35%

24

August 11, 2020

Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure

Asif K. Mustafa, MD, PhD[1,2]; Phillip J. Alexander, MD[1,2]; Devang J. Joshi, MD[1,2]; et al

Author Affiliations | Article Information

JAMA Surg. 2020;155(10):990-992. doi:10.1001/jamasurg.2020.3950

The Rush experience

- ECMO Criteria:
  - Age<70
  - PF<50 more than 3 hours
  - PF<80 more than 6 hours
  - pH <7.25, PCO>60 more than 6 hours
- Despite max vent settings=
  - FIO2 at least 80% PEEP at least 10 TV 6cc/kg/PBM with Plat<32
- Average data:$FIO_2$100 PEEP 17 ph7.24 PF 69 paralyzed proned pressors

25

August 11, 2020

Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure

Asif K. Mustafa, MD, PhD[1,2]; Phillip J. Alexander, MD[1,2]; Devang J. Joshi, MD[1,2]; et al

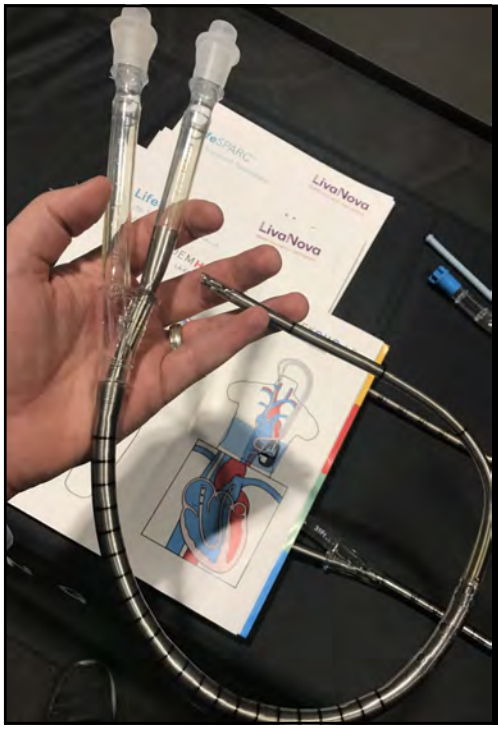
Author Affiliations | Article Information

JAMA Surg. 2020;155(10):990-992. doi:10.1001/jamasurg.2020.3950

140 patients 17% mortality, 82.5% alive at home!

- **Features:**
- Pro-Tek Duo® Cannula Awakening
- Extubation
- Early mobilization
- Majority used direct thrombin inhibitor

26



Pro Tek Duo® has some advantages (used @Rush)

- Access in neck
- Improved mobility
- RV support

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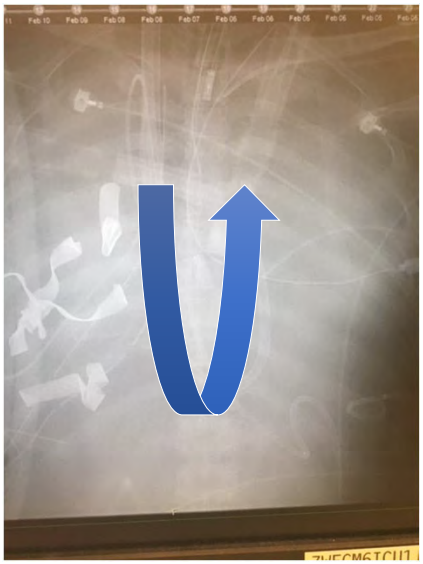
Tandem ProTek Duo® with RIJ cannulation



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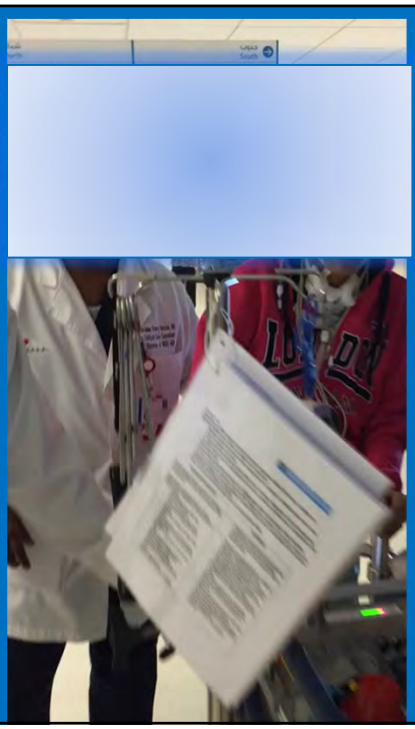
Fem-Fem can be ambulated as well



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What about *longer* term survival

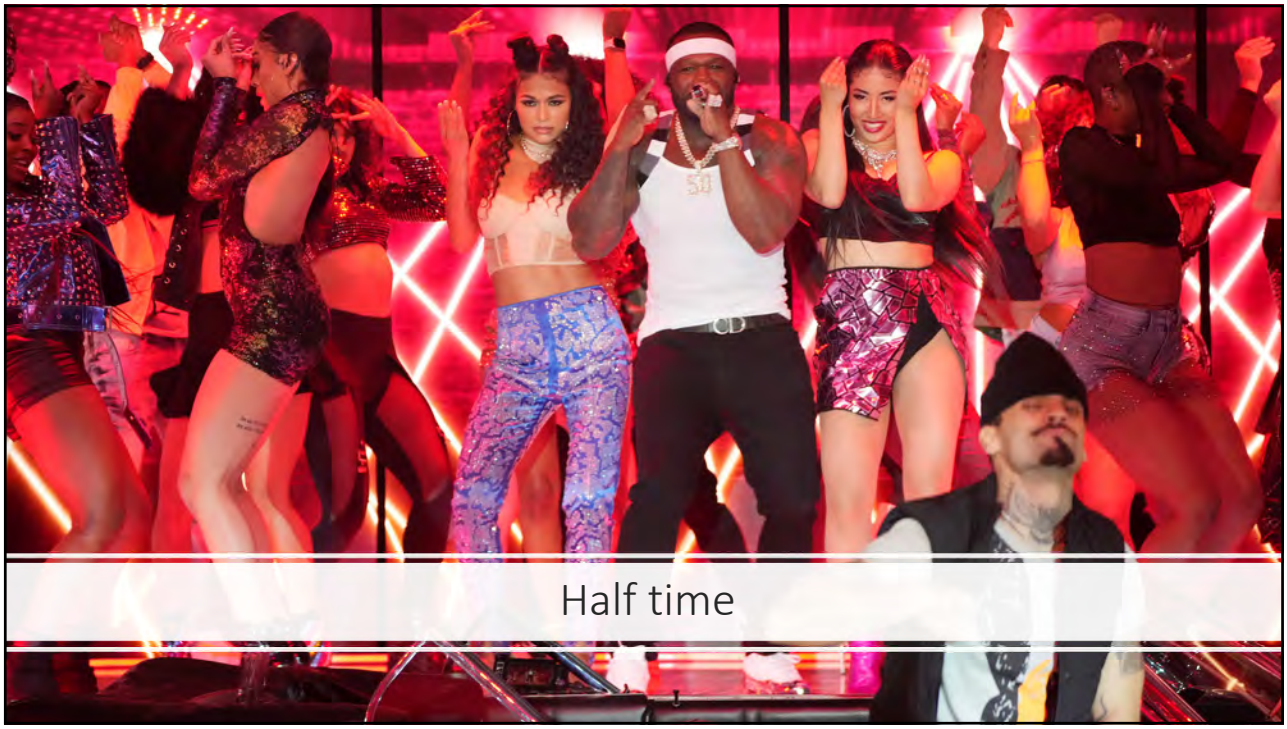
Journal of Cardiothoracic and Vascular Anesthesia

Original Article

Six-Month Survival After Extracorporeal Membrane Oxygenation for Severe COVID-19

Start March/April 2020
132 patients average age 51
47.7% died on ECMO and 52% died during hospitalization
6 month all cause mortality was 53%

30



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Then the “second wave” hit…

CEDARS-SINAI

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Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry

Ryan P Barbaro*, Graeme MacLaren*, Philip S Boonstra, Alain Combes, Cara Agerstrand, Gail Annich, Rodrigo Diaz, Eddy Fan, Katarzyna Hryniewicz, Roberto Lorusso, Matthew L Paden, Christine M Stead, Justyna Swol, Theodore J Iwashyna†, Arthur S Slutsky†, Daniel Brodie†, for the Extracorporeal Life Support Organization

≤ May 2020
90d
mortality
37%

> May 2020
90d
mortality
51%

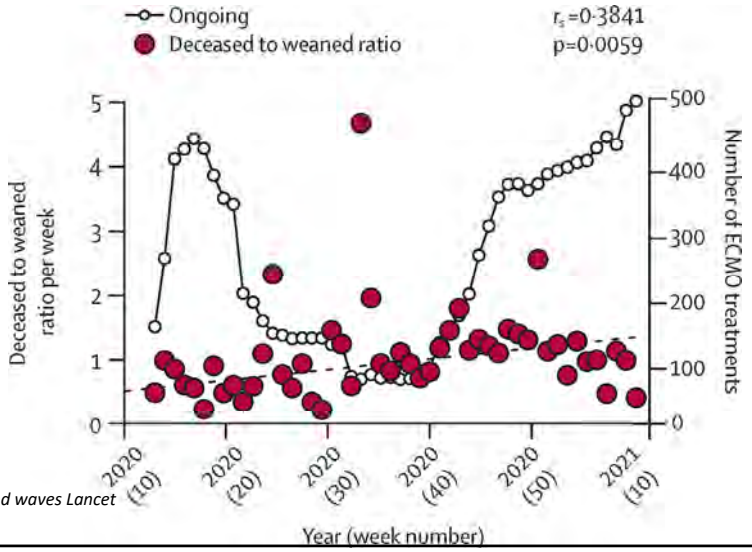
Mortality
↑15%
length of run
↑ by 6 days

33

Flip in the deceased to wean ratio from wave 1 to wave 2

First wave
Wean 58%
Survival 53%

Second wave
Wean 47%
Survival 44%



Broman ECMO for COVID19 during first and second waves Lancet Aug 2021

34

Why was the second wave worse?

Increased mortality in patients with COVID-19 receiving extracorporeal respiratory support during the second wave of the pandemic

Jordi Riera[1,2,3*], Roberto Roncon-Albuquerque Jr[4], María Paz Fuset[5], Sara Alcántara[6], Pablo Blanco-Schweizer[7] and on behalf of ECMOVIBER Study Group

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- 319 ECMO for ARDS
- First wave prior to June 2020 n151 40% mortality
- Second wave n168 60% mortality
- Second wave: older, more comorbidities, longer time between admission to ICU, more steroids, more VAPs

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Before and After

Pre pandemic V-V 40% mortality avg 12 day run

COVID-19 mortality 50% median time 20 days

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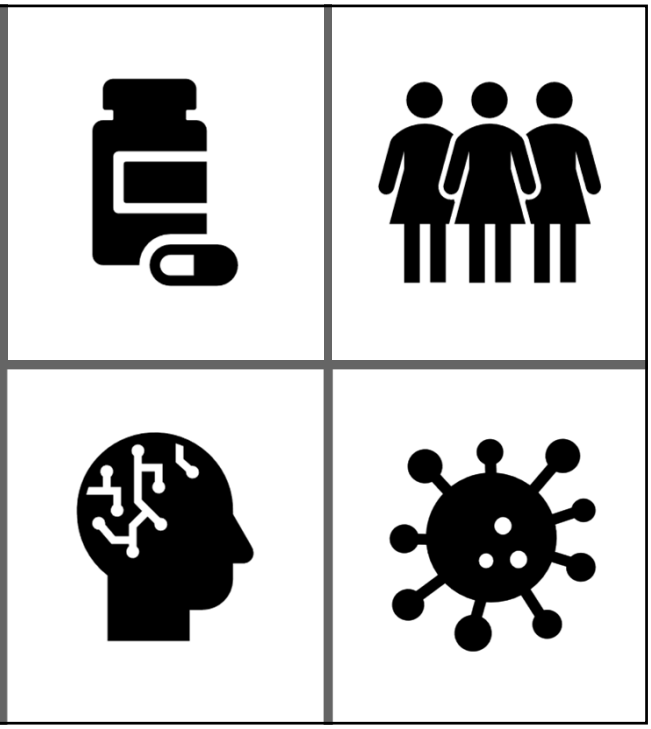
What has changed?

- Different variants Δ
- Change in therapeutics
- Change in patient population affected
- Change in attitudes RE ECMO
- Liberalize criteria/tighten criteria



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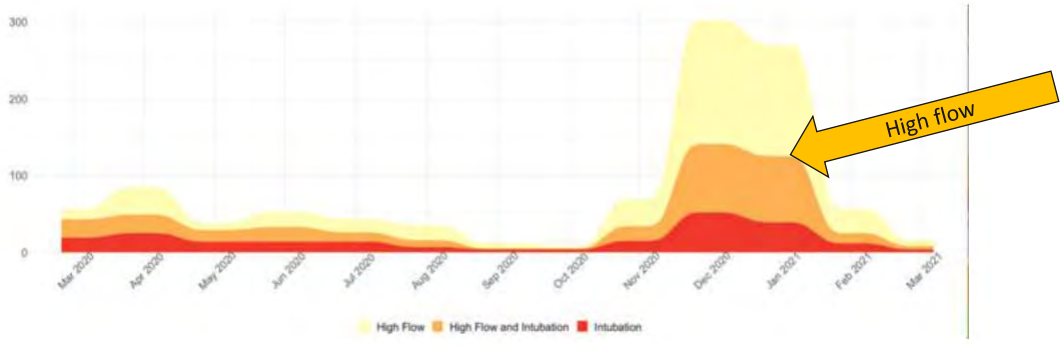
Our "Second Wave" was characterized by an increase in HFNC and longer pre intubation HFNC use

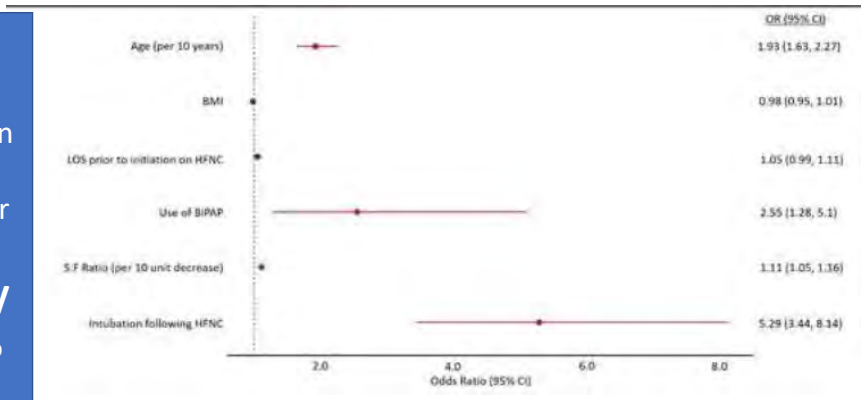


Unpublished Data from Cedars on 1K patients

38

Patients who received HFNC followed by intubation did worse than intubation up front

Hospital mortality:
HFNC without intubation 27.2%
Intubation without prior HFNC 40%
HFNC followed by intubation 53.9%



Submitted unpublished data from Cedars

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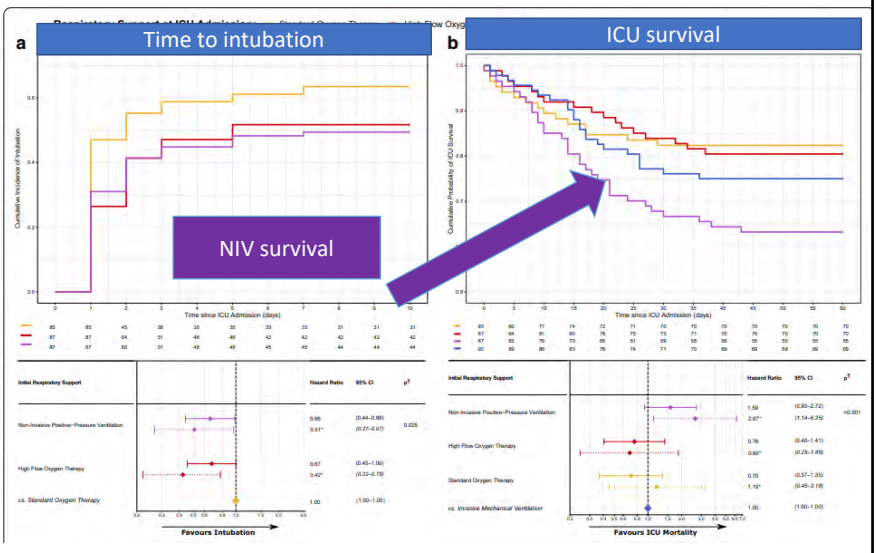
Critical Care

RESEARCH Open Access

Implications of early respiratory support strategies on disease progression in critical COVID-19: a matched subanalysis of the prospective RISC-19-ICU cohort

351 pts
prospective registry
Standard oxygen(SOT)
HFNC
NIV
Early IMV
NIV associated with higher ICU mortality

Self induced lung injury may be the cause of worse outcome in the NIV group



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Controversies in COVID ECMO

CEDARS-SINAI

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Is COVID ECMO different than non-COVID ECMO?

- More CNS hemorrhage
- More clot
- More pump changes.
- Longer Runs
- Worse survival

- But…. complications may normalize for length of run

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COMPLICATIONS			COMPLICATIONS PER 1k HOURS		
	COVID	Non COVID		COVID	Non COVID
CNS hemorrhage	6%	2.8%		0.14	0.14
Oxygenator Failure	8%	3.3%		0.2	0.2
Pump Failure				0.02	0.03
Circuit Change	15%	5.7%		0.37	0.37
Circuit Clot	5%	2.9%		0.11	0.186

Data adopted from Barbaro Lancet 2020

43

How long do you go?

Short answer: no one knows

Long answer: young/single organ failure –keep going

Successful native lung recovery reported after 28 days of support[1], no signal for decreased recovery up to 40 days[2]

1. Dreier ECMO in COVID-19 Prolonged therapy needed? Perfusion 2021
2. Barabaro ECMO support in COVID-19 Lancet 2020

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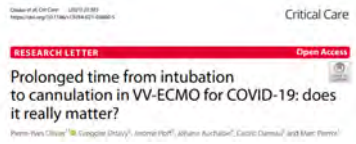
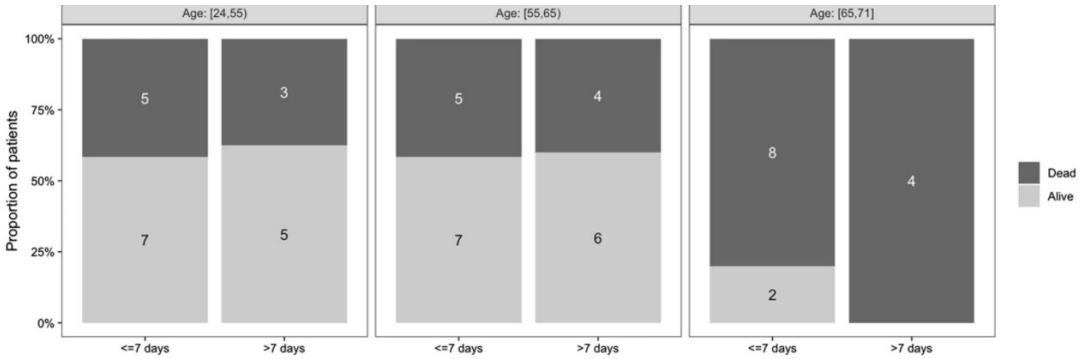
Should V-V be restricted to <7days of mechanical ventilation ?


Critical Care

RESEARCH LETTER Open Access

Prolonged time from intubation to cannulation in VV-ECMO for COVID-19: does it really matter?



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Should Anticoagulation for COVID ECMO be enhanced?

- NON COVID
  - AC is complicated
  - Bleeding and clotting abound
  - Discordance between anti-XA, PTT, ACT
  - Loss of vMF monomers
  - Platelet dysfunction
- COVID
  - May be prothrombotic state
  - Heparin resistance: increased in COVID – pro-inflammatory molecules and antithrombin resistance
  - No evidence that targets need to be adjusted

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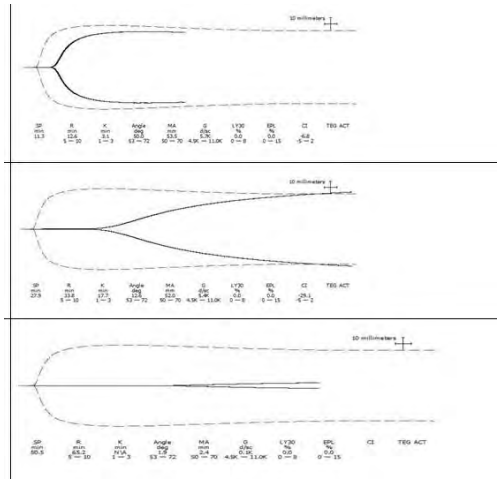
A tale of 3 TEGs on ECMO



ACT	• 125 • Therapeutic effect
ACT	• 169 • Slightly supratherapeutic
ACT	• 164 • Severely supratherapeutic

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VV ECMO for COVID = works

- VV ECMO for COVID First wave 60% survival, second wave 50/50
- Runs are longer
- Management is similar
- Patient selection is similar (perhaps loosen time from intubation ->cannulation)
- A strategy of awakening, extubation, ambulation may be best

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BREAK
EXHIBIT HALL OPEN

10:35 a.m. – 10:50 a.m.

Lung Transplantation for Severe COVID-19

10:50 a.m. – 11:35 a.m.

NICK KOLAITIS, MD
UC SAN FRANCISCO

Dr. Nicholas Andreas Kolaitis is an Assistant Professor of Medicine at the University of California, San Francisco, with a focus on lung transplantation and pulmonary hypertension. He is the director of bronchoscopy for the Division of Pulmonary, Critical Care, Allergy and Sleep Medicine. Dr. Kolaitis' research focuses on ways to improve quality of life for patients with advanced lung disease. Dr. Kolaitis is the Chair of the CTS Career Development Committee, and one of the CTS representatives to the American Thoracic Society Council of Chapter Representatives.

LESLIE SEIJO, MD
UC SAN FRANCISCO

Dr. Leslie Seijo is an Advanced Lung Disease and Lung Transplant Fellow at UCSF. Before moving to the Bay Area, Dr. Seijo completed her Internal Medicine residency at Icahn School of Medicine at Mount Sinai Beth Israel, where she was also Chief Resident. Dr. Seijo is interested in health disparities research, using implementation science methods to address gaps in care for vulnerable patients with end-stage lung disease and lung transplant.

1

Disclosures

Kolaitis

- Consulting: Acceleron, Janssen, United Therapeutics
- Advisory Board: Janssen, United Therapeutics, Bayer

Seijo

- None

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2

Questions for Audience

https://pollev.com/lung

Or Text “lung” to 22333

Enter Username
i.e., @LungTxptMD or @lsejoMD

Click refresh with each question

https://pollev.com/lung UCSF

3

Goals for today

- Case presentations
- Brief overview of lung transplantation
- First transplants for COVID-19
- Current state of lung transplantation for COVID-19
- How the COVID-19 vaccine impacts transplant
- UCSF Experience

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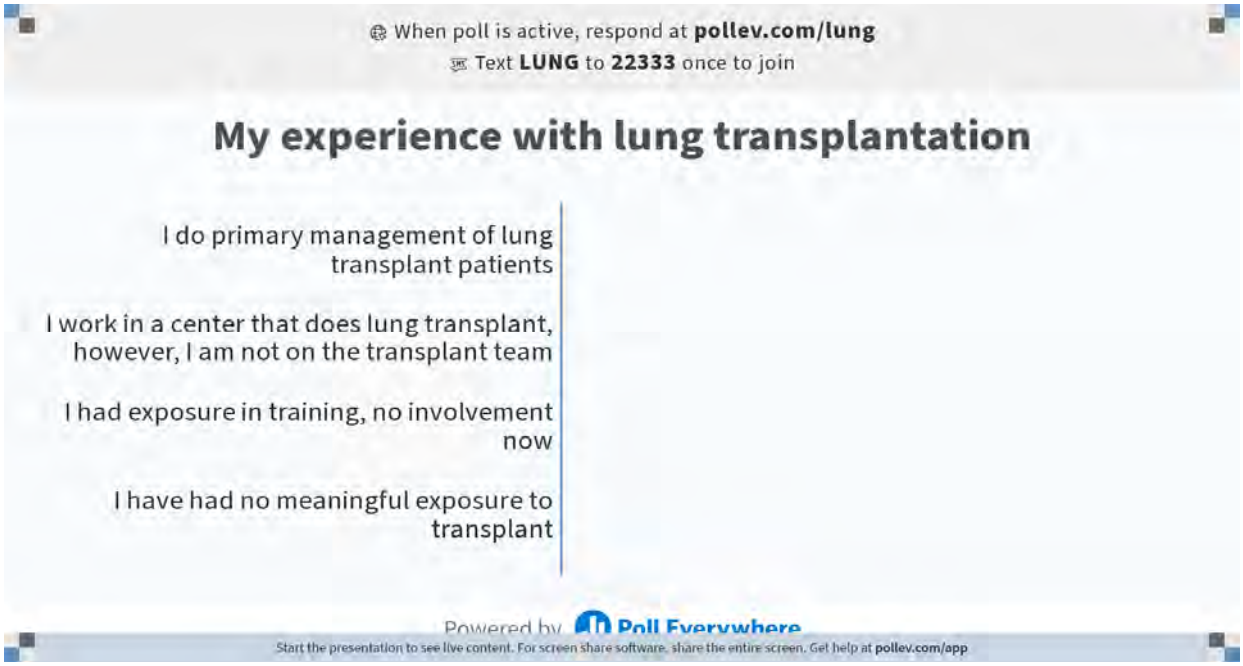
4



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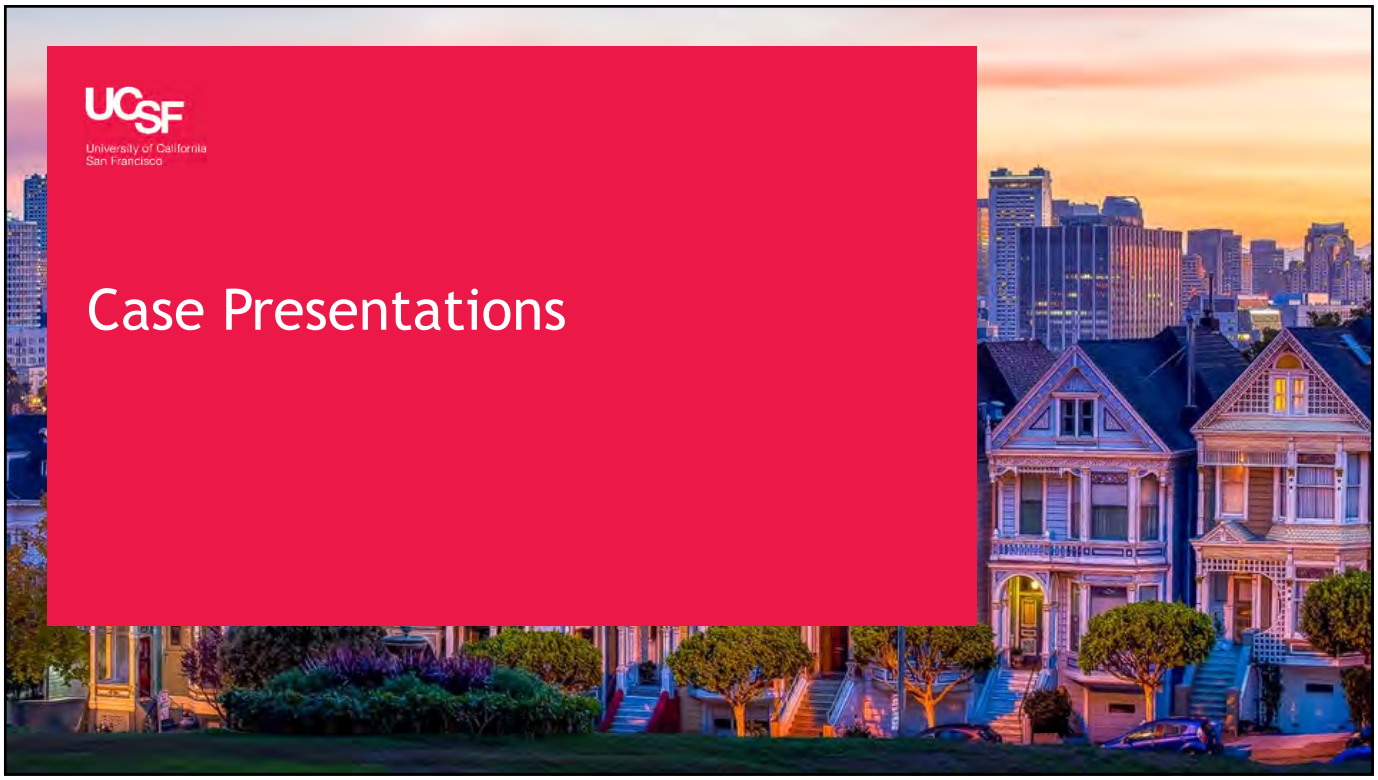

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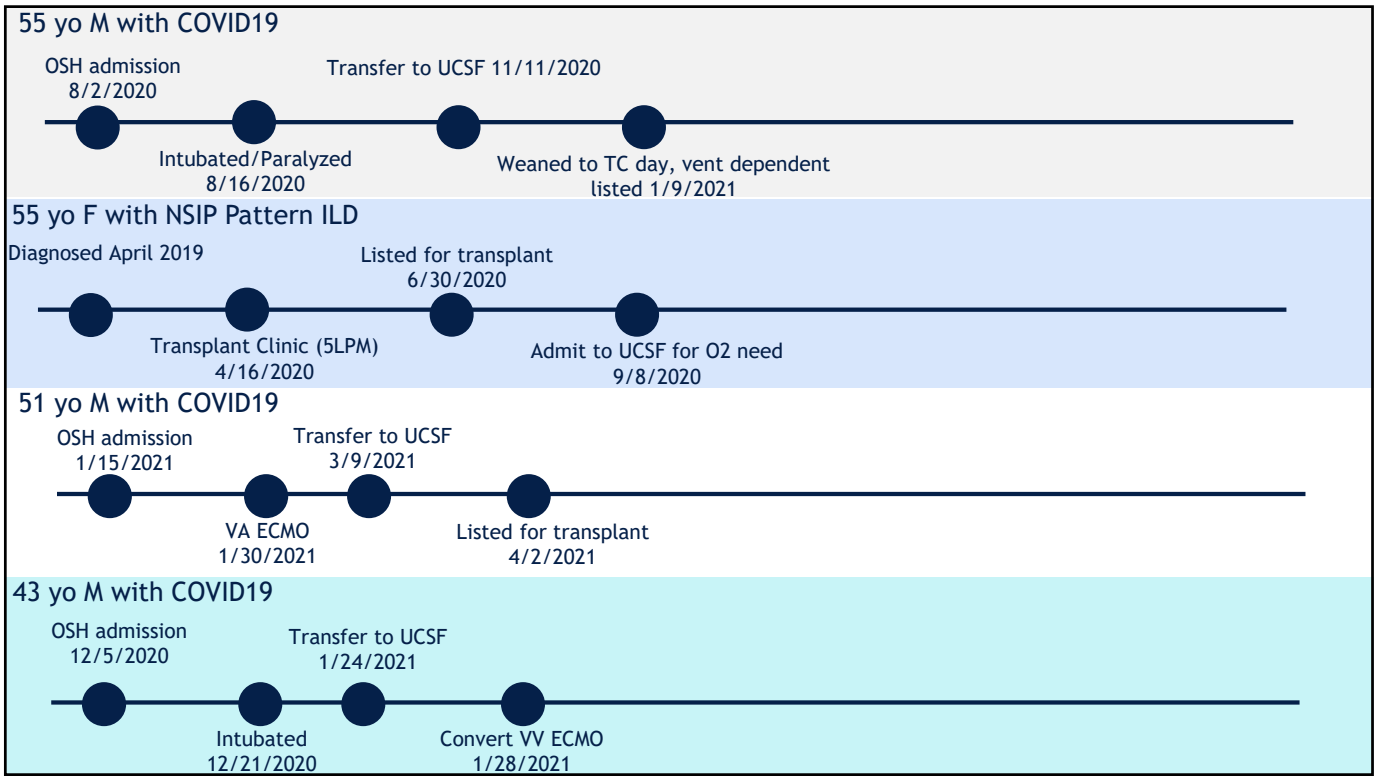
55 yo M with COVID19
OSH admission
8/2/2020
Intubated/Paralyzed
8/16/2020
Transfer to UCSF 11/11/2020
Weaned to TC day, vent dependent
listed 1/9/2021
55 yo F with NSIP Pattern ILD
Diagnosed April 2019
Transplant Clinic (5LPM)
4/16/2020
Listed for transplant
6/30/2020
Admit to UCSF for O2 need
9/8/2020
51 yo M with COVID19
OSH admission
1/15/2021
VA ECMO
1/30/2021
Transfer to UCSF
3/9/2021
Listed for transplant
4/2/2021
43 yo M with COVID19
OSH admission
12/5/2020
Intubated
12/21/2020
Transfer to UCSF
1/24/2021
Convert VV ECMO
1/28/2021

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University of California
San Francisco
Brief overview of lung transplantation

8

Two primary aims of lung transplantation

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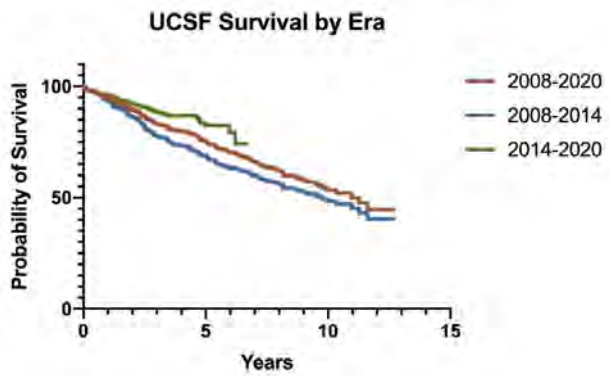
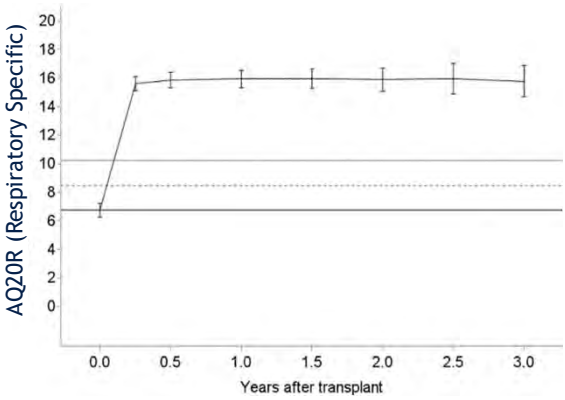
9

Two primary aims of lung transplantation





Internal UCSF Data
Singer Am J Transplant 2017

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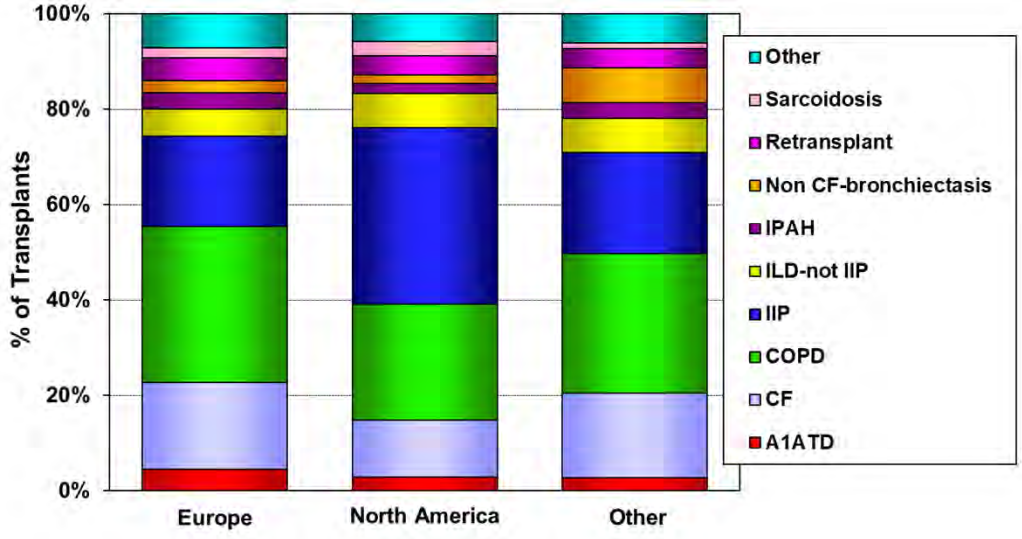
Indications for lung transplantation



ISHLT Registry 2019

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11

Ideal Scenario

- Patient with chronic disease has ability to comprehend need for transplant over a long period of time
- Able to understand risks and benefits of transplant
- Patients come to terms with potential loss of life and can have that as a basis to stand tall when faced with challenges of transplant
- Ideally patients walk into the transplant
- Disease for which transplant is being performed is irreversible

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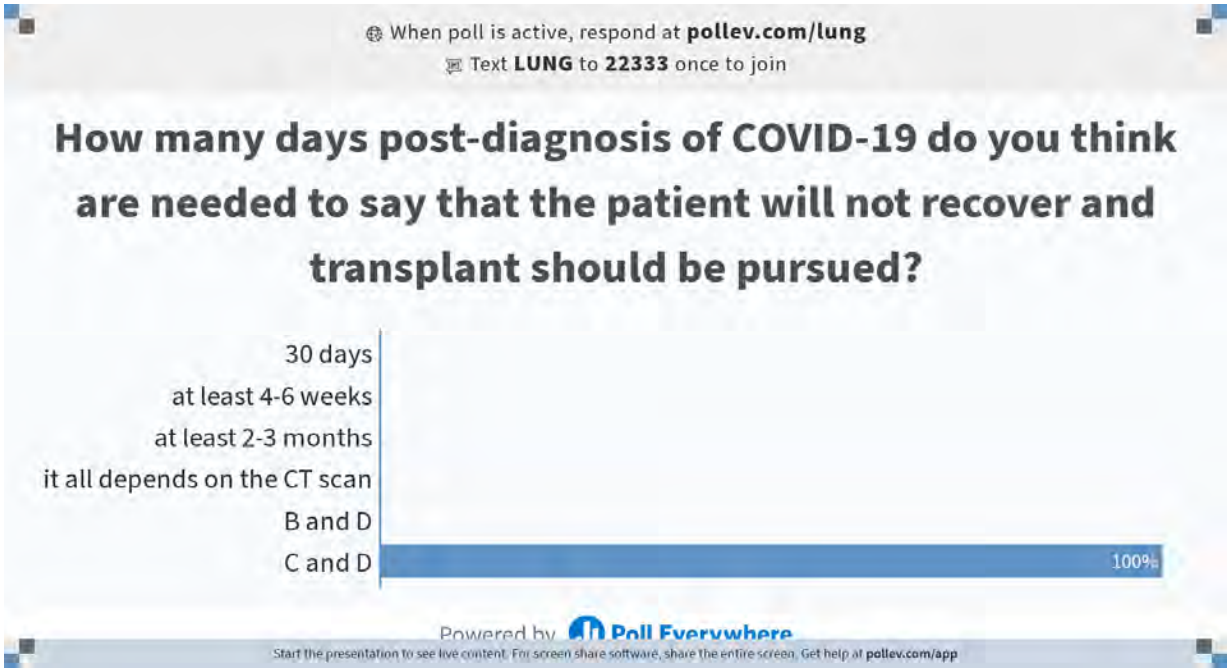

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Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation

Lorriana E. Leard, MD,[a] Are M. Holm, MD, PhD,[b] Maryam Valapour, MD, MPP,[c]
Allan R. Glanville, MBBS, MD,[d] Sandeep Attawar, MBBS, MS, MCh,[e]
Meghan Aversa, MD,[f] Silvia V. Campos, MD,[g] Lillian M. Christon, PhD,[h]
Marcelo Cypel, MD, MSc,[f] Göran Dellgren, MD, PhD,[i]
Matthew G. Hartwig, MD, MHS,[j] Siddhartha G. Kapnadak, MD,[k]
Nicholas A. Kolaitis, MD, MAS,[a] Robert M. Kotloff, MD,[l]
Caroline M. Patterson, MD,[m] Oksana A. Shlobin, MD,[n]
Patrick J. Smith, PhD, MPH,[j] Amparo Solé, MD, PhD,[o]
Melinda Solomon, MD, MSc,[p] David Weill, MD,[q]
Marlies S. Wijsenbeek, MD, PhD,[r] Brigitte W.M. Willemse, MD, PhD,[s]
Selim M. Arcasoy, MD, MPH,[t] and Kathleen J. Ramos, MD, MSc[k]

Leard LE J Heart Lung Transplant 2021

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"Since lung transplant is a lifesaving procedure, the principle of utility requires that survival be maximized when choosing transplant candidates…Candidates should be carefully selected, as an unsuccessful lung transplant affects not only the individual who was transplanted, but also a potential alternative recipient who did not have the opportunity to be transplanted due to the prevailing organ shortage."

Leard LE J Heart Lung Transplant 2021

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"Case reports describing bilateral lung transplant for COVID-19 associated ARDS have started to emerge since January 2020. Experts in the field recommend waiting at least 4-6 weeks after the onset of respiratory failure due to COVID-19 prior to considering lung transplant. While it seems likely that these cases should be evaluated like other patients with post-viral ARDS, it is too early to make conclusive recommendations at this time."

Acute Respiratory Distress Syndrome (ARDS)	
2021 Consensus Statement	Consensus N (%)
Timing of Listing and Referral Persistent requirement for mechanical ventilatory support and /or ECLS without expectation of clinical recovery and with evidence of irreversible lung destruction.	24 (100%)

Leard LE J Heart Lung Transplant 2021

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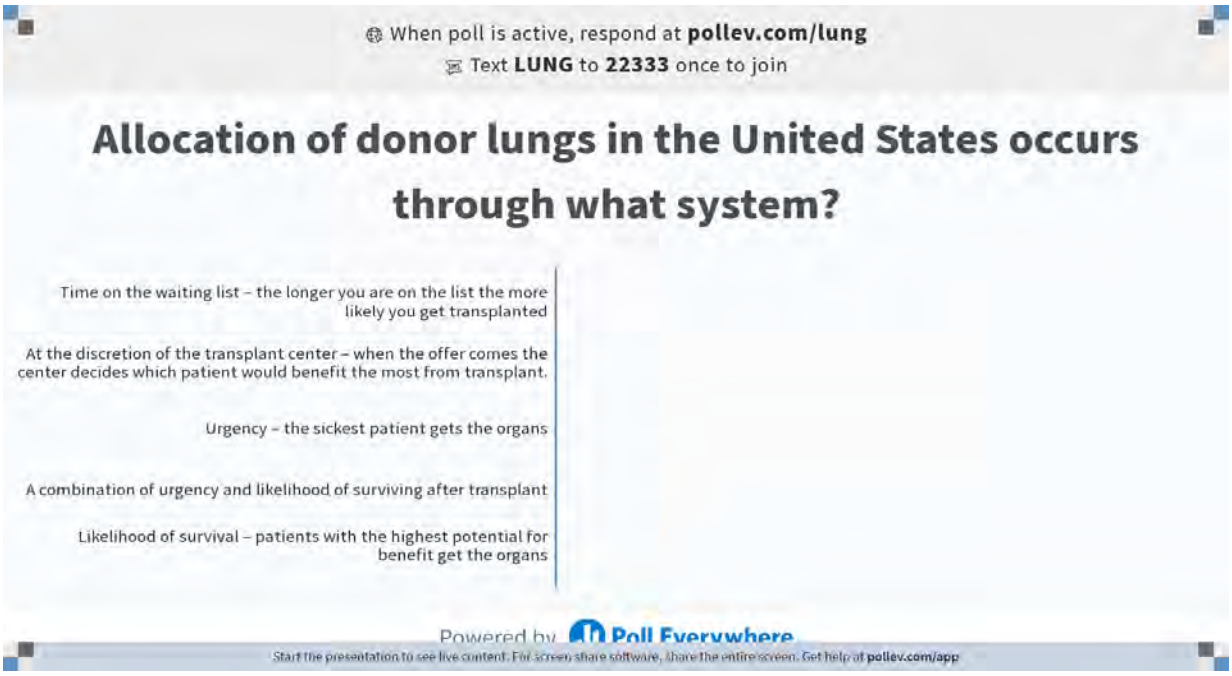

https://pollev.com/lung

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Lung Allocation History

- In United States donor lung allocation occurs through the Organ Procurement and Transplantation Network via the lung allocation score
  - Calculated LAS score by need based on clinical parameters
    - (e.g., PASP, age, 6MWD, oxygen requirements)
- Goal to maximize transplant benefit and minimize risk of wait list death
- Composite LAS Score ranges 0 to 100
- Highest possible score is someone who has a high likelihood of death on the wait list and high likelihood of survival post transplant

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Unique listing for COVID-19

- Not included as a category in LAS until October 2020
- Patients with COVID-19 tend to be very sick so will have a high LAS
- May jump patients with chronic illness

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Interim Summary

- Lung transplantation is a therapeutic option for end stage lung disease
- Extends survival and improves health-related quality of life
- Utility is important in determining candidates
- Organs allocation by system that tries to maximize post-transplant benefit and minimize waitlist death
- Tends to favor sicker patients, like those with COVID-19

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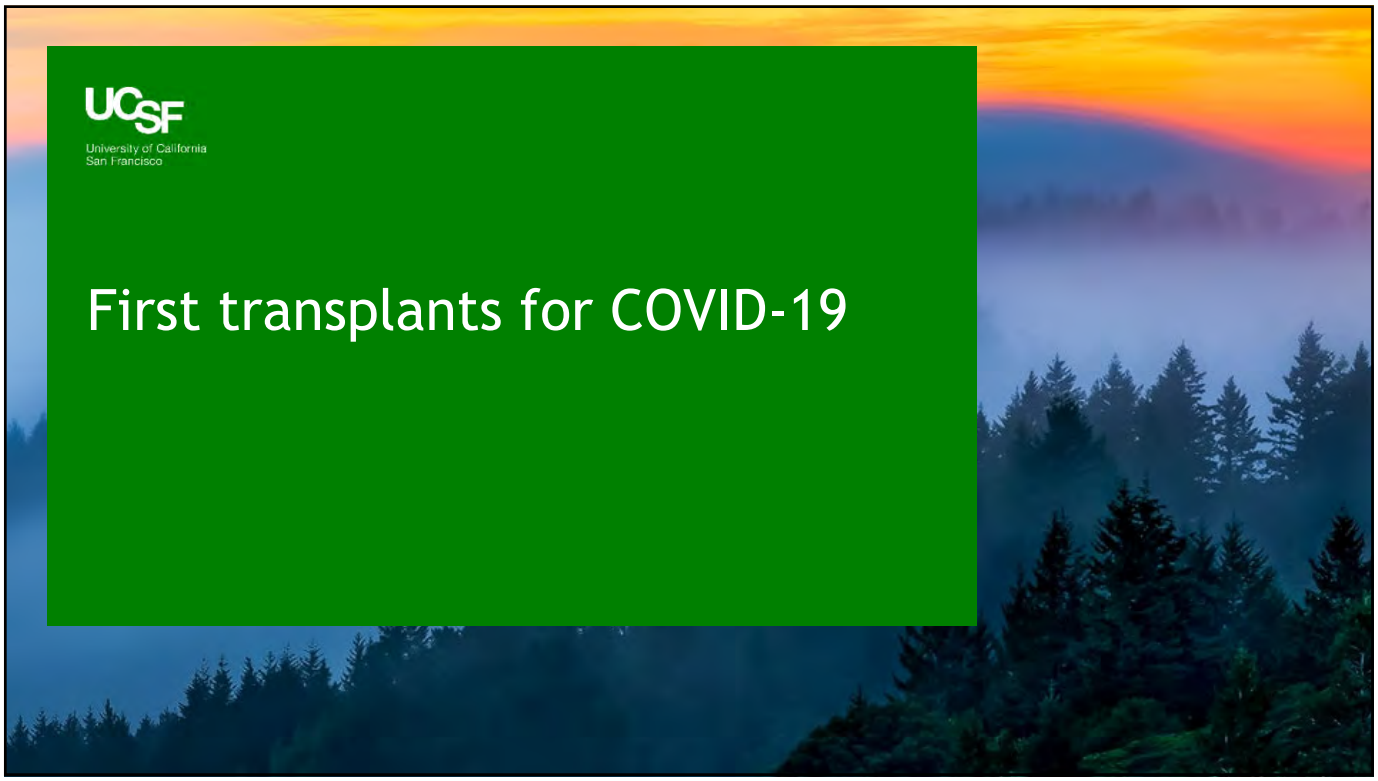
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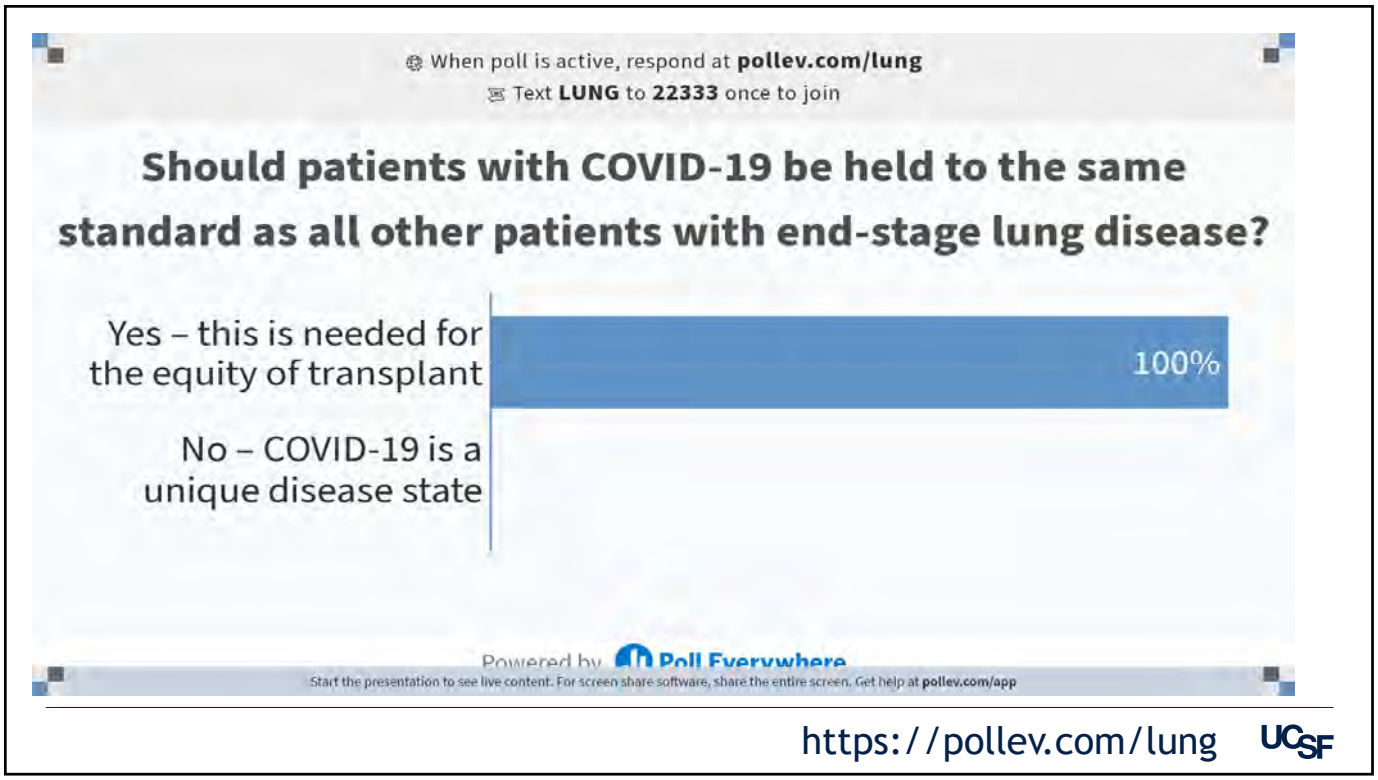
University of California
San Francisco
First transplants for COVID-19

21


When poll is active, respond at pollev.com/lung
Text LUNG to 22333 once to join
Should patients with COVID-19 be held to the same standard as all other patients with end-stage lung disease?
Yes – this is needed for the equity of transplant
100%
No – COVID-19 is a unique disease state
Powered by Poll Everywhere
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app
https://pollev.com/lung
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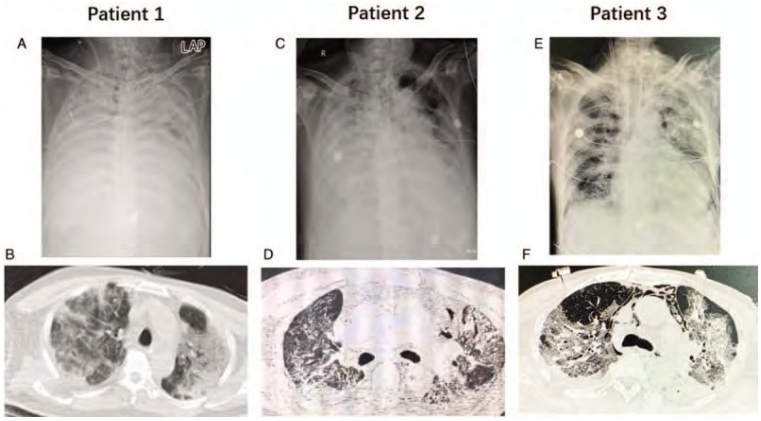
Early days – Chinese Cohort



66 M on VA ECMO
42 days since dx
Died intraoperatively

58 M on VV ECMO
37 days since dx
Alive at POD22

73 M on VV ECMO
44 days since dx
Alive at POD12

Chen et al. Chin Med J (Engl). 2020

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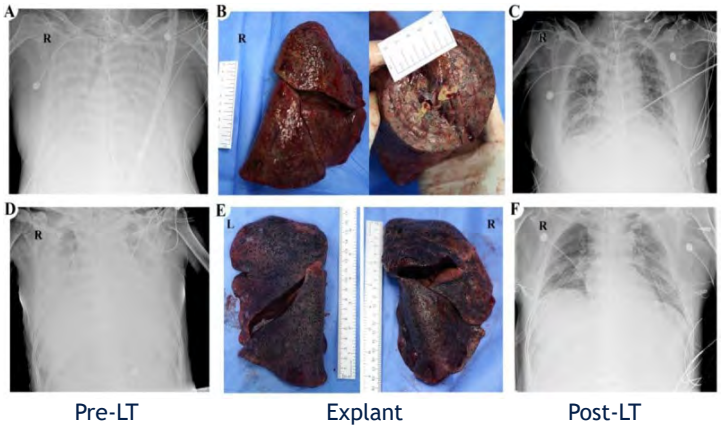
Early days – Chinese Cohort



Pre-LT Explant Post-LT

66 F on VV ECMO
31 days since dx
Alive at POD41

58 M on VV ECMO
35 days since dx
Alive at POD35

Han et al. Ann Surg 2020

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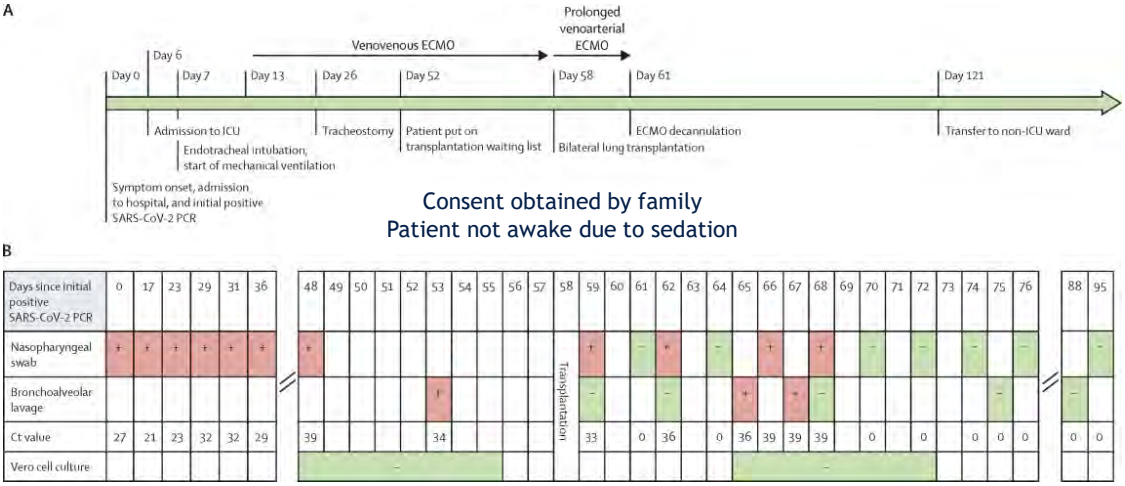
Early days – Europeans report



Consent obtained by family
Patient not awake due to sedation

Lang et al. Lancet Respir Med 2020

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Should the patient be awake and able to give consent for surgery?

Yes – this is necessary so they understand the risks of transplant.

No – family can provide consent. Without family consent these patients will die.

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Early days – Canadians retort

- Age <65
- Single-organ dysfunction
- Sufficient time should be allowed for lung recovery. Flu or ARDS can recover after several weeks to months (recommended 4-6 weeks)
- Radiological evidence of irreversible lung disease
- Awake and able to discuss transplantation
- Able to participate in physical rehabilitation
- Should fulfil the remaining typical criteria for transplantation
- Recent negative SARS-CoV-2 PCR result
- Center should have substantial experience with high-risk transplantation
- Center should have a broad donor pool and low waiting-list mortality

Cypel and Keshavjee Lancet Respir Med 2020

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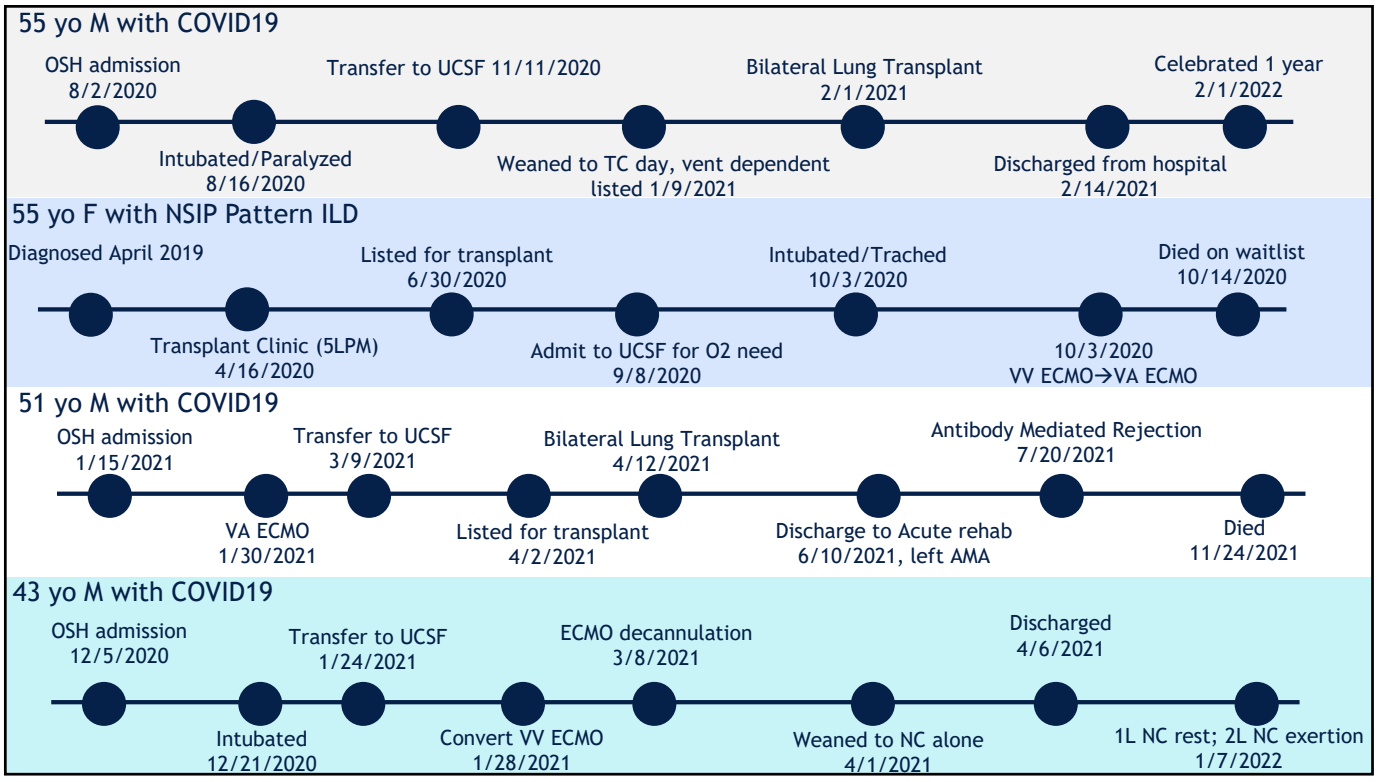

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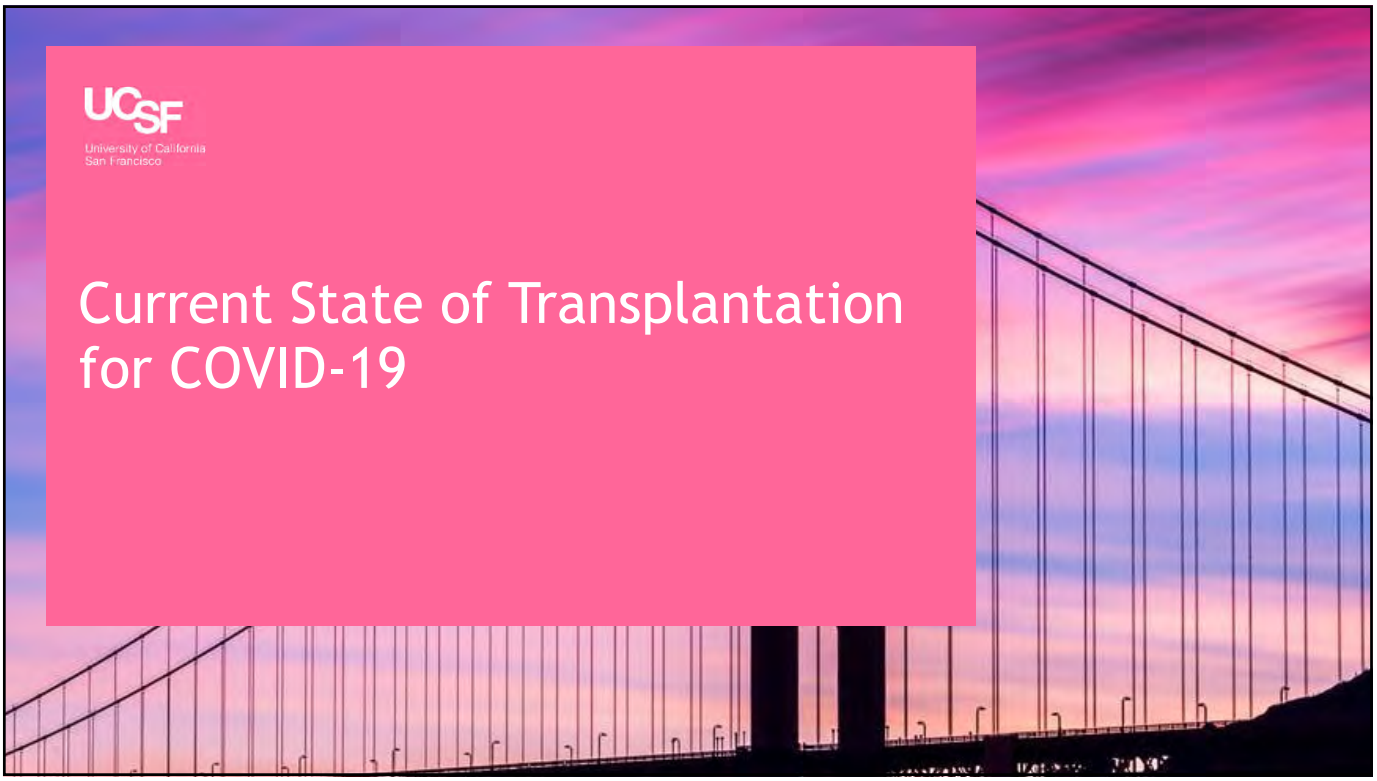
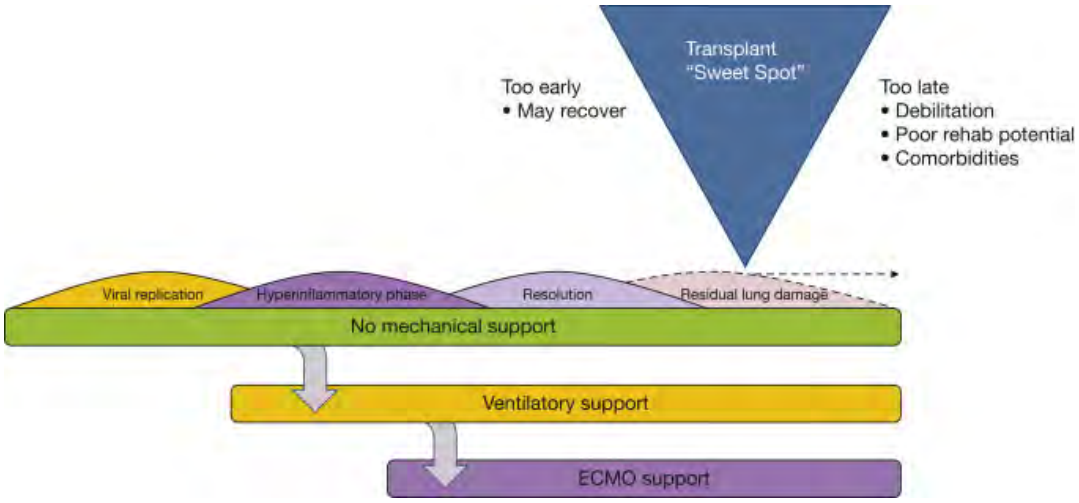


29

Transplant "Sweet Spot"



King et al. Chest 2022

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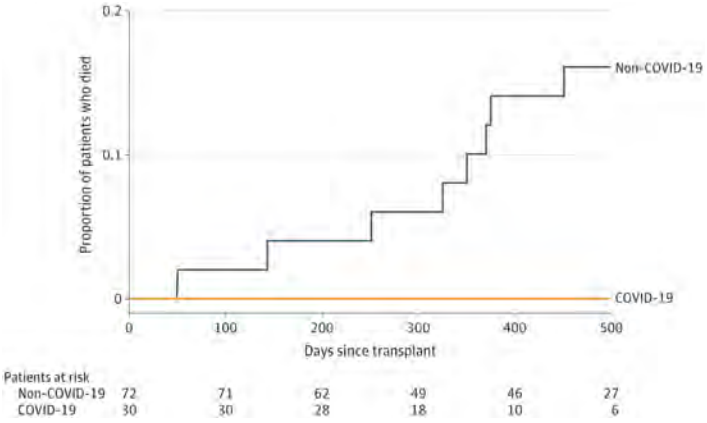
Success of transplantation for COVID19



Report from Northwestern on all transplants between January 21, 2020, and September 30, 2021

Kurihara et al. JAMA 2022

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When poll is active, respond at **pollev.com/lung**
Text **LUNG** to **22333** once to join

Between August 1, 2020 and September 30, 2021 what proportion of all lung transplants in the United States were performed for COVID?

<1%
2%
7%
15%
25%

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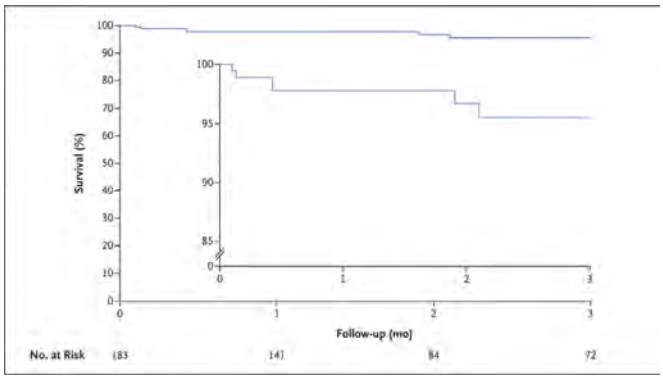
Success of transplantation for COVID-19

- Analysis of UNOS Registry from 8/1/2020-9/30/2021
- 214 of the 3039 US lung transplants performed (7.0%) were performed for Covid-19–related respiratory failure



Roach et al. N Engl J Med 2022

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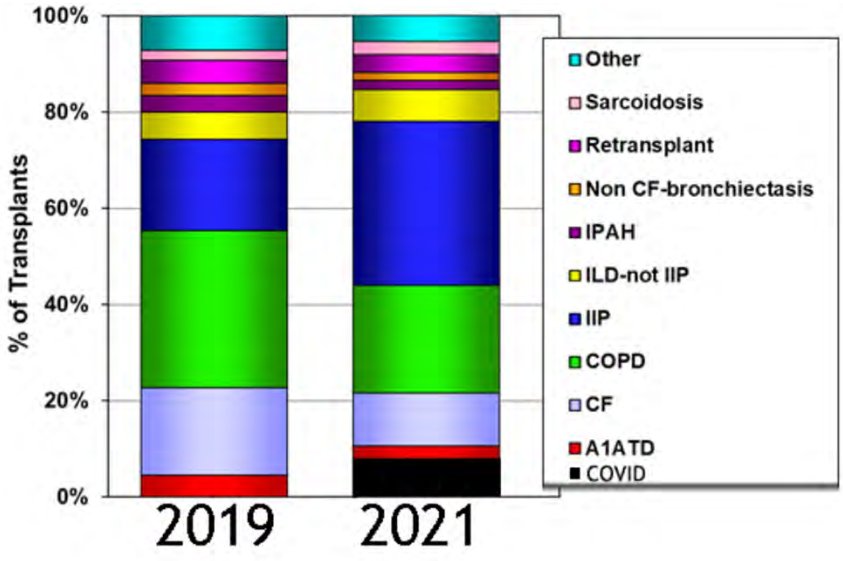
Indications for lung transplantation



ISHLT Registry 2019 and hypothesis of 2021

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Waitlist implications

2019 SRTR Report	UNOS Data
2759 lung transplants performed in the US	~2800 lung transplants performed in the US over 12 month period
Zero transplants for COVID19	214 (7% of all) transplants performed for COVID-19
Waitlist mortality of 14.6%	Waitlist mortality unknown

Roach et al. N Engl J Med 2022
Valapour et al. Am J Transplant 2021

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Interim Summary

- Lung transplantation is a successful option for treatment of COVID19
- Ethical considerations include consent process and transplantation of patients without being able to discuss risks and benefits
- Patients with COVID-19 will have a high allocation score
- Need to find the “sweet spot”
- Concern for increased waitlist mortality in other diagnoses

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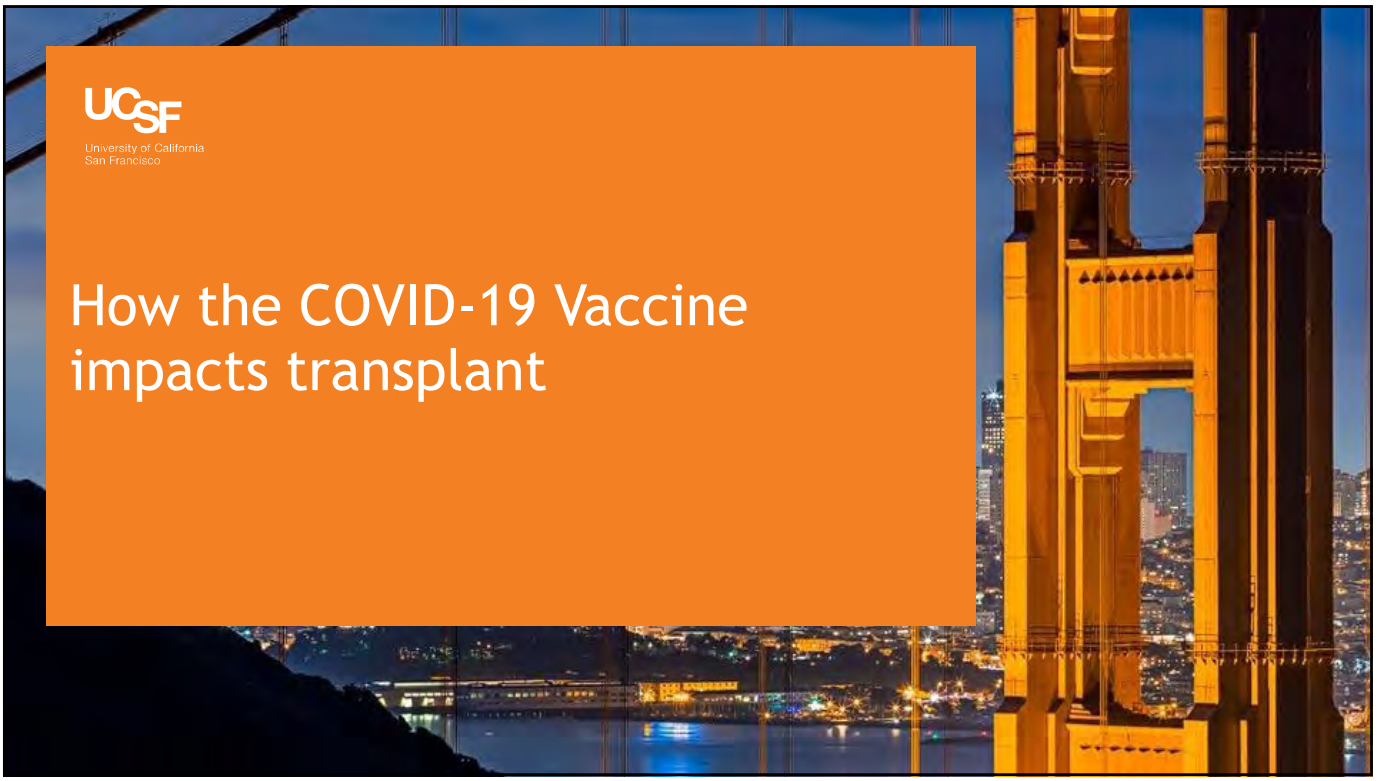

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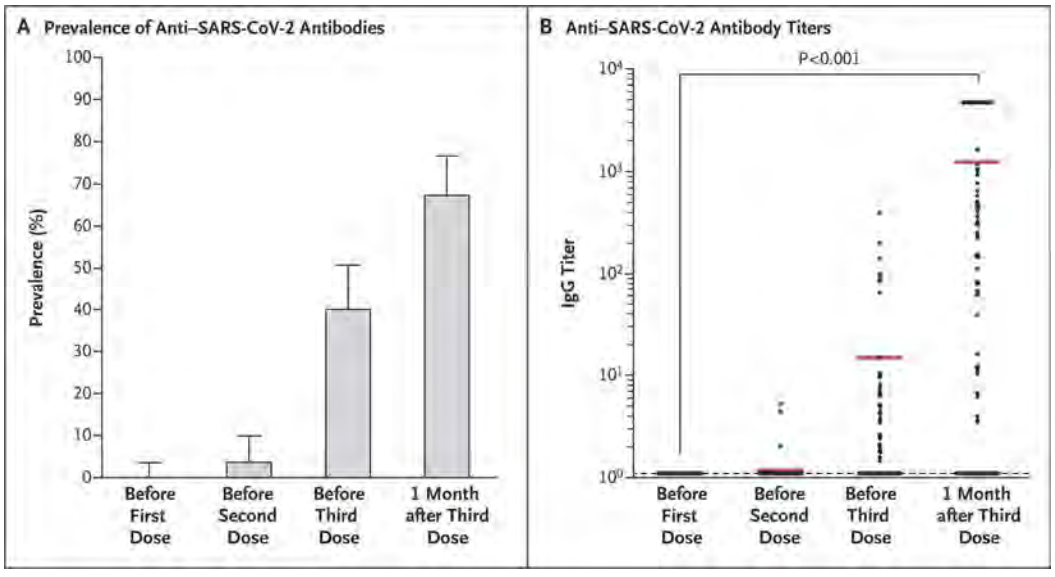

Kamar N Engl J Med 2021

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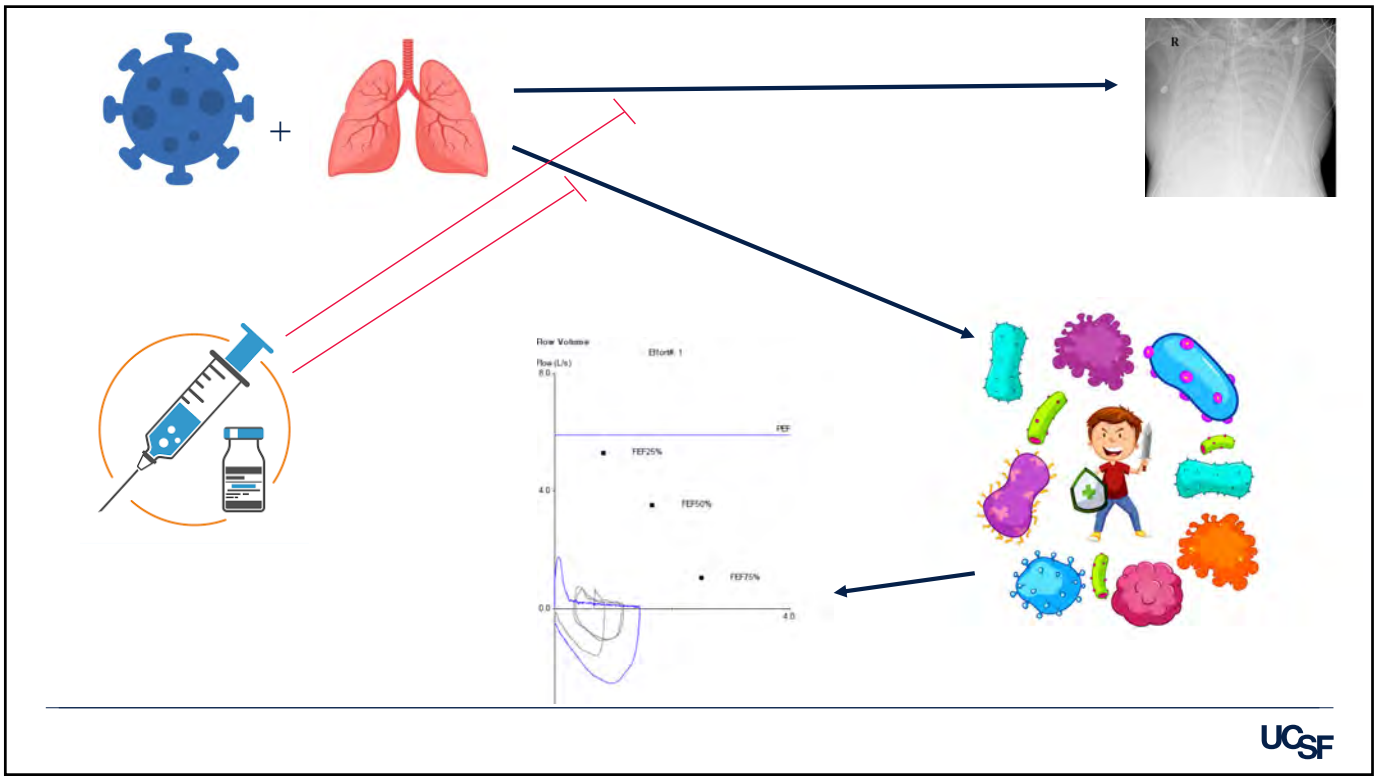

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Should patients with end-stage lung disease be required to obtain the COVID-19 Vaccine prior to listing for transplantation?

Yes - this is a marker of adherence to therapy

No - It is a personal decision that should not influence listing

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https://pollev.com/lung UCSF

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UW Medicine to deny organ transplants to unvaccinated patients

By FOX 13 News Staff | **Published** October 6, 2021 | COVID-19 in Washington | Q13 FOX

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BBC

Unvaccinated man denied heart transplant by Boston hospital

The 31-year-old father-of-two refuses to get the shot, but the hospital says it is following policy.

1 month ago

Medscape

Organ Transplantation: Unvaccinated Need Not Apply

They published a firm stand on transplant candidacy and COVID-19 vaccination

2 weeks ago

Post and Courier

MUSC will remove 23 patients from transplant waiting list for ...

MUSC surgeons perform kidney, heart, lung and liver transplants in ... At MUSC, a COVID-19 vaccine is only

4 weeks ago

Fox News

North Carolina man would rather 'die free' than get vaccine needed for life-saving transplant

North Carolina man says he's willing to "die free" rather than get the coronavirus vaccine in order to receive a kid

1 month ago

Newsweek

Patients Waiting for Life-Saving Organ Transplant to Be Denied Treatment Unless Vaccinated

In Queensland, Australia, patients will have to be vaccinated against the coronavirus in order to receive vital organ transplants.

Dec 6, 2021

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Business Insider

Georgia man, 24, refused COVID-19 vaccine then needed lung transplant

A man who refused a coronavirus vaccine was infected and needed a lung transplant, his mom said. Blake Bargatze, 2

Jul 19, 2021

WebMD

Man Refusing COVID Vaccine Later Needs Lung Transplant

Lung transplants are rare for COVID-19 patients but sometimes necessary for those who dor

Jun 18, 2021

8NewsNow.com

New mom battling COVID needs lung transplant weeks after giving birth

"Like so many pregnant women she held off on getting the vaccine until she got the A-okay from her OB," her sister, Paula ...

Oct 8, 2021

The Courier

Findlay COVID patient receives lung transplant

Kodie Edler intended to get vaccinated against COVID-19. He hadn't gotten around to it yet, but planned to get his shot after returning home...

Sep 11, 2021

43

Should patients with COVID-19 be offered lung transplantation even if they were not vaccinated?

Yes – no vaccine needed	A
Yes – provided they accept the vaccine post-COVID-19 but before listing	B
No – this is a risk factor for non-compliance	C

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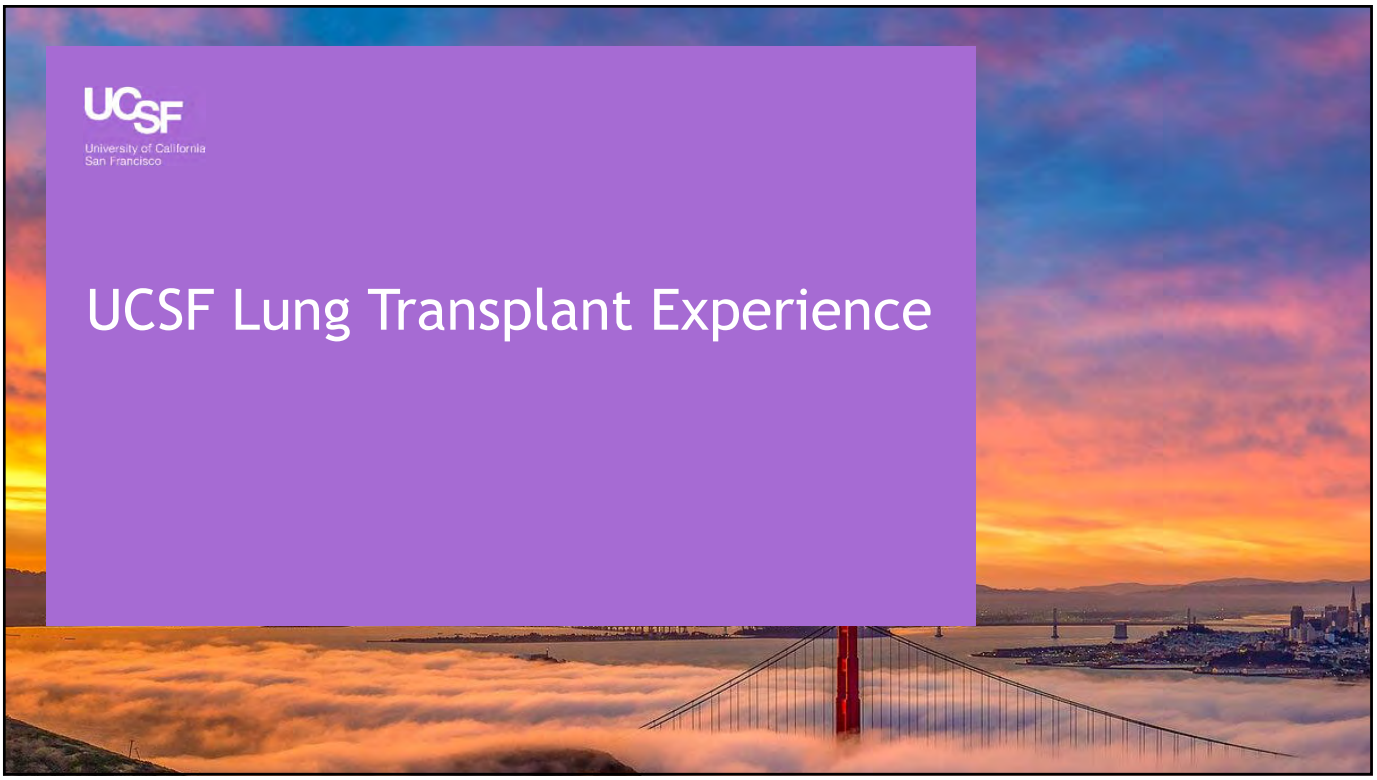
Current State at UCSF

- No mandatory requirement yet, however, this is in the works
- Patients with respiratory failure from COVID-19 will be required to accept vaccine prior to listing once policy is in approved by ethics and legal departments

45



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Lung Transplant Criteria for COVID-19 at UCSF

- Age < 55 years old
- Single organ failure
- BMI < 32
- COVID-19 negative, 2 PCR nasal/BAL one-week apart
- Patient should be awake and able to discuss lung transplantation
- Patient should be able to participate in physical rehabilitation
- At least 8-week from acute illness
- Radiologic evidence of irreversible lung disease

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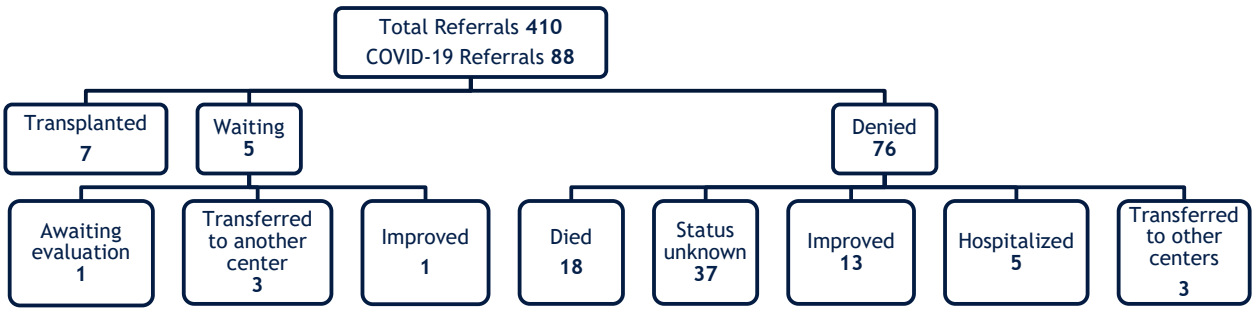
Lung Transplant Referrals



UCSF referrals from January 4, 2021, to February 22, 2022

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Lung Transplant Denials

Denials	76
Age >55	4
More than 1 organ	11
BMI >32	11
COVID-19 positive at time of referral	2
Sedated	19
Acute illness	17
Insurance denial	11
Unknown	1

UCSF referrals from January 4, 2021, to February 22, 2022

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Characteristics of Lung Transplant Recipients

	Characteristics							Medical history				
Patient	Gender	Age	Race	BMI, kg/m^2	Support	Duration	Date LTx	Smoking History	HTN	DM	CKD	Vaccination[a]
1	M	55	Latinx	19.1	No	183	2/1/21	No	No	No	No	No
2	M	51	Caucasian	20.7	ECMO	90	4/12/21	No	No	No	Yes	No
3	M	41	Latinx	20.8	ECMO	172	5/23/21	No	Yes	No	No	No
4	M	52	Latinx	22.0	ECMO	182	5/28/21	No	Yes	No	Yes	No
5	M	47	Latinx	25.6	ECMO	168	6/28/21	No	Yes	Yes	No	No
6	M	48	Latinx	24.4	ECMO	91	7/22/21	No	No	No	No	No
7	F	38	Latinx	23.9	ECMO	164	10/1/21	No	No	No	No	No

[a] All patients were vaccinated after lung transplantation

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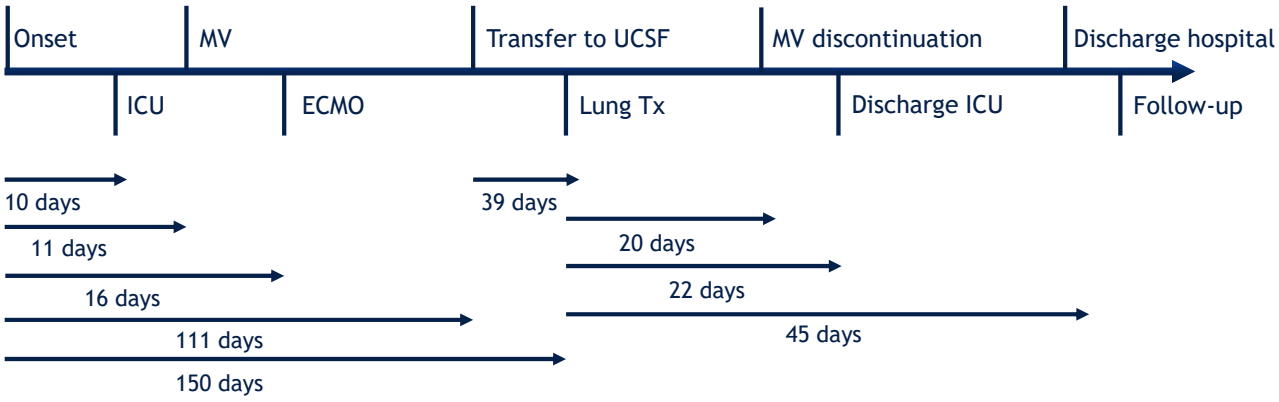
Timeline of Treatment Phases



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Outcomes

Outcomes, n=7		
	Length of MV, days (SD)	20 ± 25
	ICU LOS (SD)	22 ± 18
	Hospital LOS (SD)	45 ± 41
Complications		
	CVVH	2 (29%)
	Bleeding	1 (14%)
	Pneumonia	2 (29%)
	Critical Illness Neuropathy	3 (43%)
	Psychological Symptoms	3 (43%)
	Antibody Mediated Rejection	1 (14%)
Survival		
	Alive	5 (71%)
	Dead	2 (29%)

One death attributed to graft failure
One death from suicide unrelated to graft function

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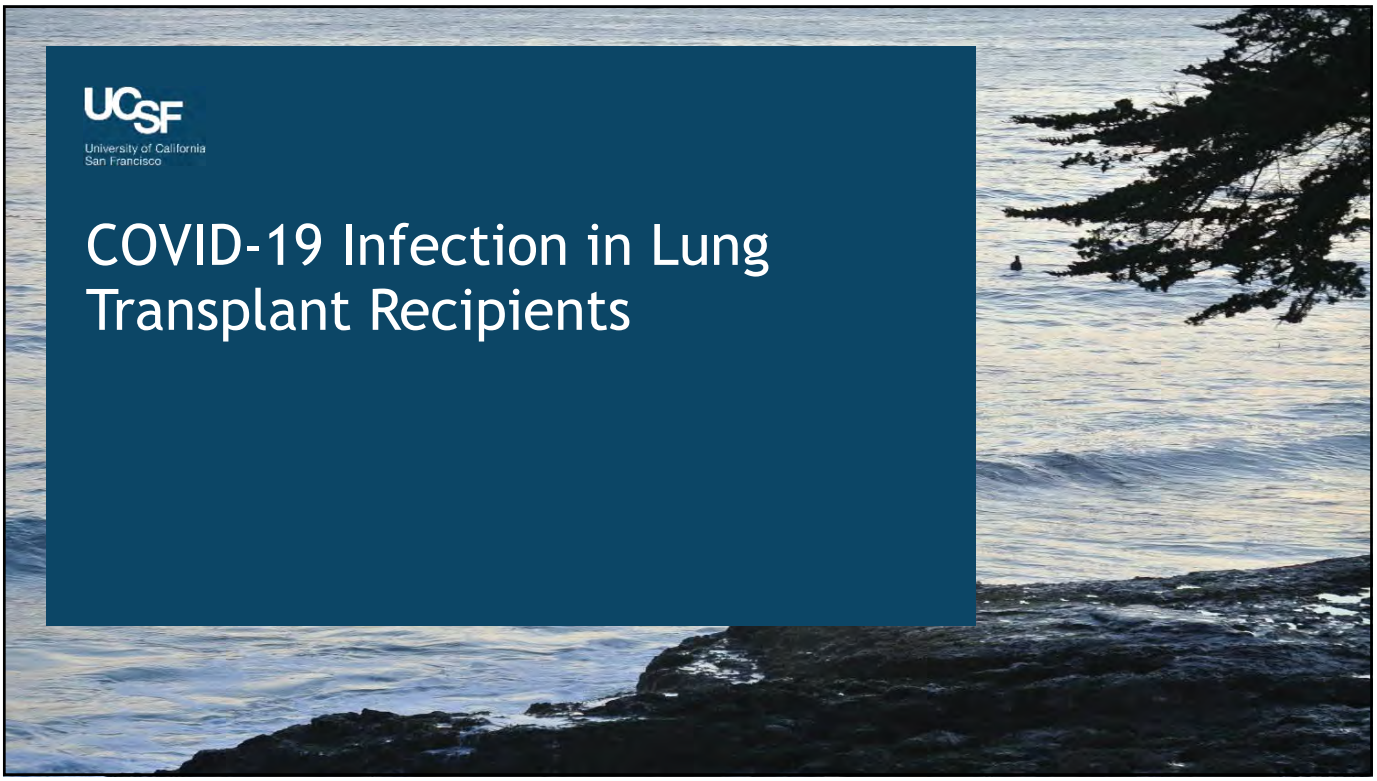

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COVID-19 Infection

- 3/20/2020-12/18/20
  - 18 LTx recipients were diagnosed with COVID-19 infection.
  - 89% of patients had 2 or more comorbidities
  - Clinical presentation ranged from mild to severe, 11% of patients were monitored at home and 89% required hospitalization.
  - Of those hospitalized, 50% were treated in the intensive care unit (ICU).
  - The survival rate of COVID-19 in this population was 94%.

Table 1: Demographics of COVID-19 LTx Population

Age (years)	55.1 (SD ± 3.0)
Male (n, %)	11 (61.1%)
BMI (kg/m^2)	30.8 (SD ± 6.4)
Latinx (n, %)	9 (50%)
Hypertension (n, %)	13 (72.2%)
Diabetes Mellitus (n, %)	11 (61.1%)
CKD (n, %)	7 (38.9%)
Obesity (n, %)	7 (38.9%)

LTx = lung transplant; BMI = body mass index; CKD = chronic kidney disease; SD = standard deviation. Obesity defined as BMI > 30 kg/m^2

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COVID-19 Infection

- 1/3/22-2/7/22
  - 46 patients diagnosed with COVID-19
    - 31 patients received outpatient therapy
      - Sotrovimab
      - Nirmatrelvir-Ritonavir
      - Molnupiravir
    - 12 patients required hospitalization admission

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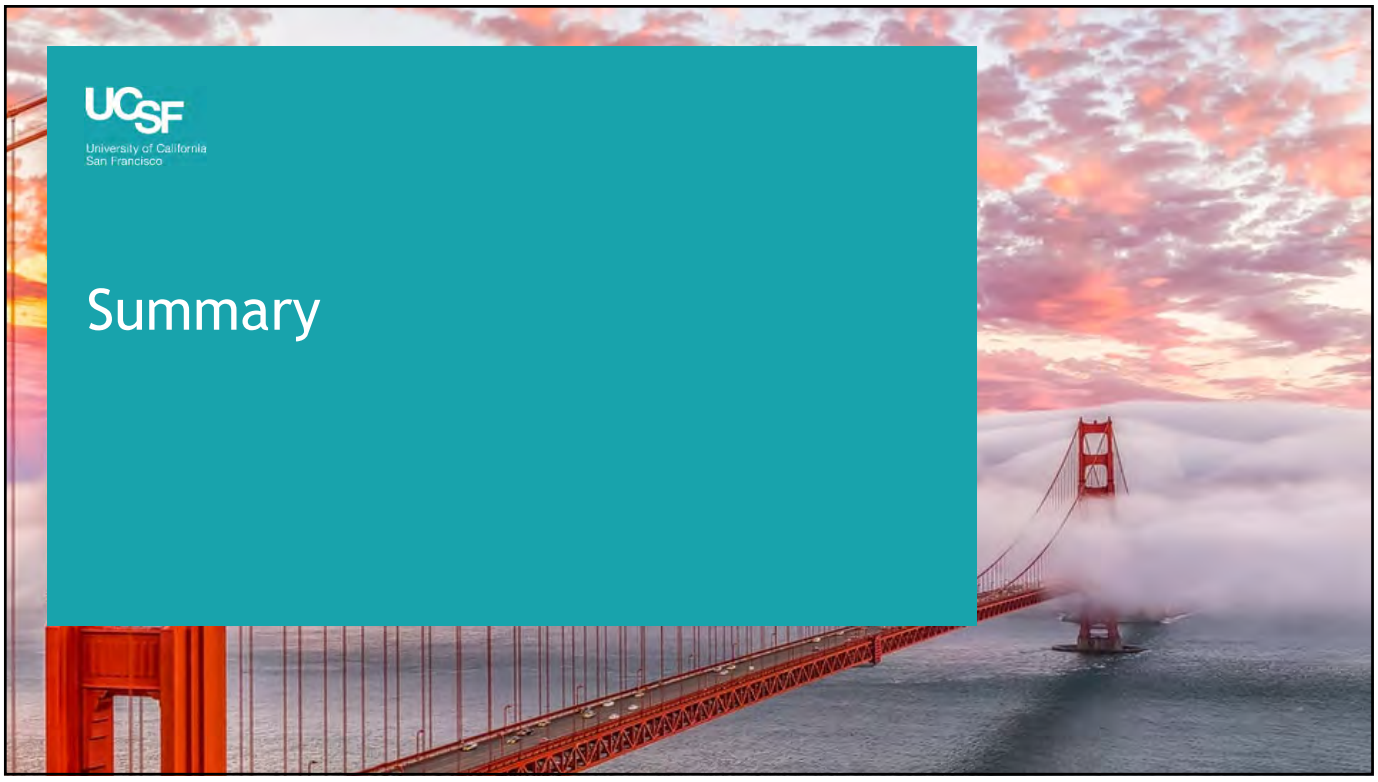

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Summary

- Lung transplantation is a successful option for end-stage lung disease
- Transplantation for COVID-19 should be done in patients who meet similar criteria to others with end-stage lung disease
- Patients face different issues surrounding expectations for life after transplant when the indication is for COVID-19
- Need to find the “sweet spot” between when transplant is done too early and when it is done too late

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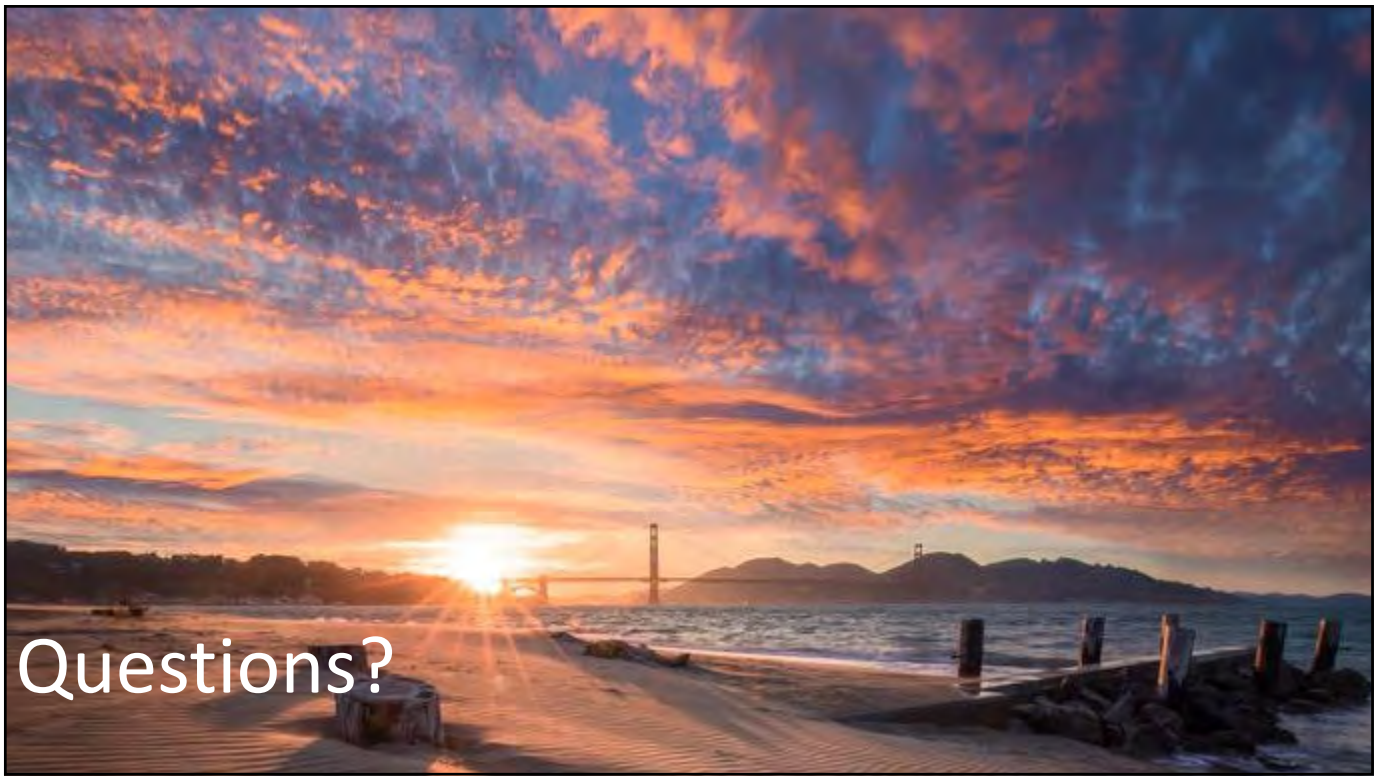

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Long COVID Pulmonary Management: Establishing Post-COVID-19 Models of Care

11:35 a.m. – 12:20 p.m.

LEKSHMI SANTHOSH, MD, MA
UC SAN FRANCISCO

Dr. Lekshmi Santhosh is an Assistant Professor of Pulmonary/Critical Care Medicine and Hospital Medicine and is Associate Program Director of the Pulmonary/Critical Care Fellowship at UCSF. She obtained her Master's in Health Professions Education from UC-Berkeley and her research focuses on graduate medical education. Clinically, she attends in the Medical ICU, the Neuro ICU, and on the Internal Medicine teaching wards, and has clinic in the Pulmonary Outpatient Faculty Practice at UCSF Parnassus.

She is the founder and physician faculty lead of the multidisciplinary post-COVID OPTIMAL Clinic at UCSF Health.

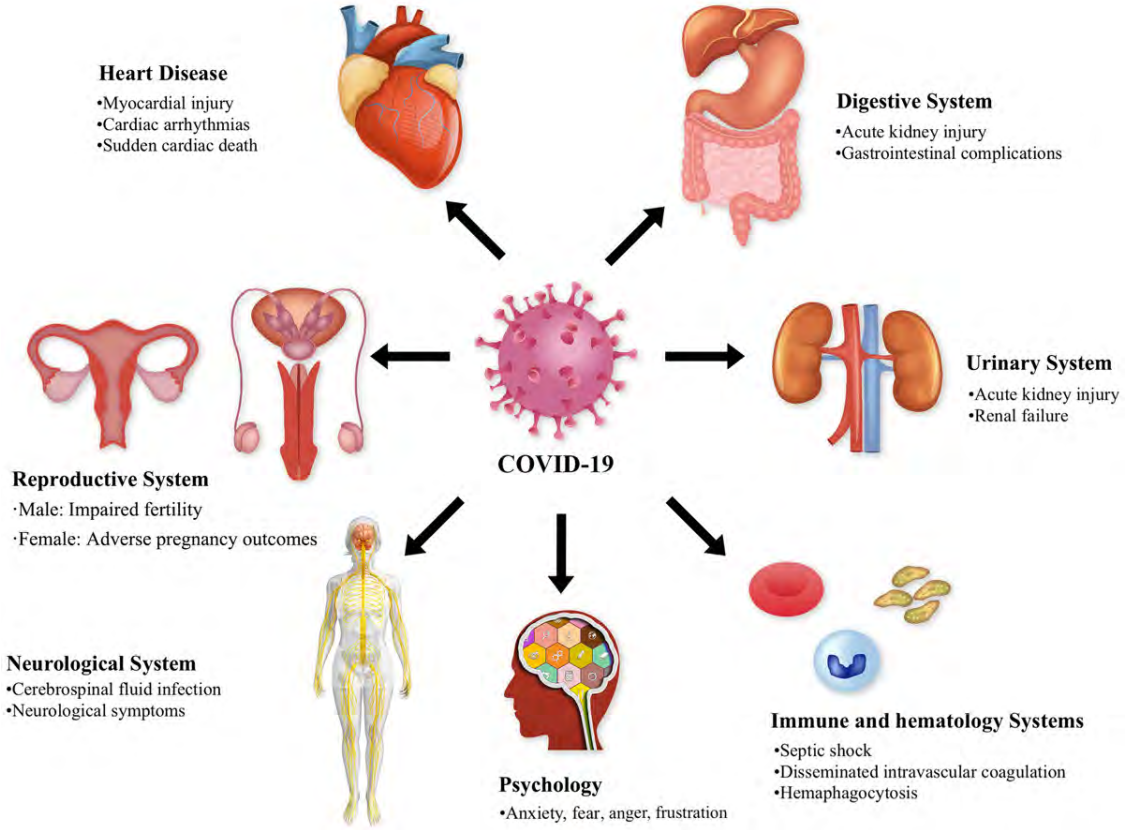
Establishing Post-COVID Care: Lessons Learned from UCSF's OPTIMAL Clinic

Lekshmi Santhosh, MD, MAEd
Assistant Professor, UCSF
Divisions of Pulmonary & Critical Care Medicine & Hospital Medicine
Director, Post-COVID OPTIMAL Clinic
@LekshmiMD

Conflicts of Interest

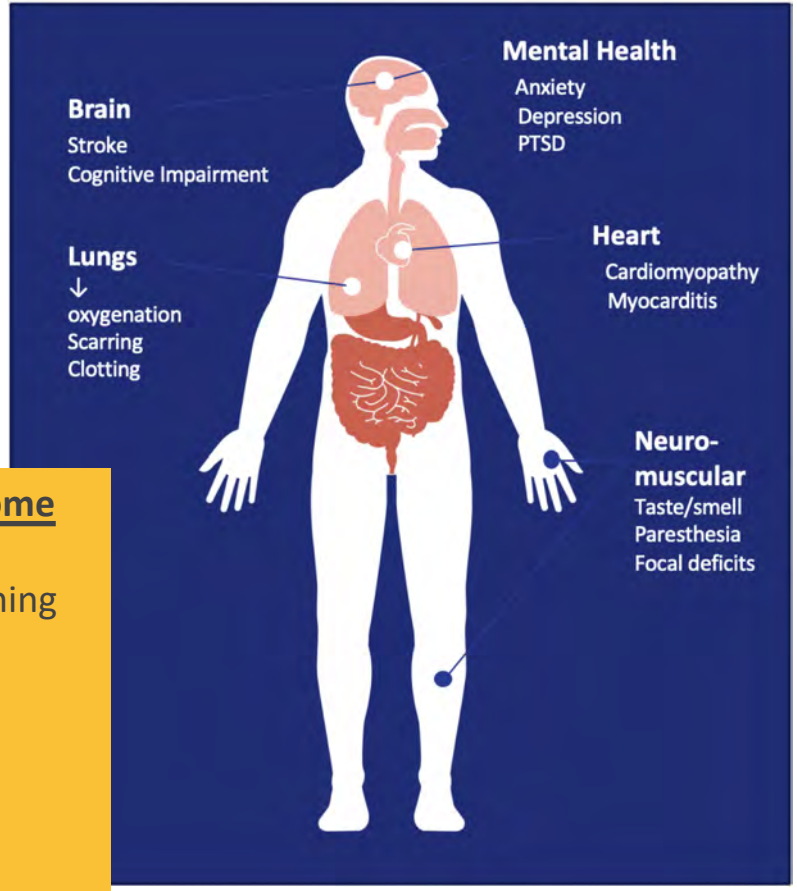
I have no disclosures.

COVID-19 Is A Multi-Organ System Disease Acutely…



Zheng Medical Virology 2020

…And Long(er) Term Outcomes



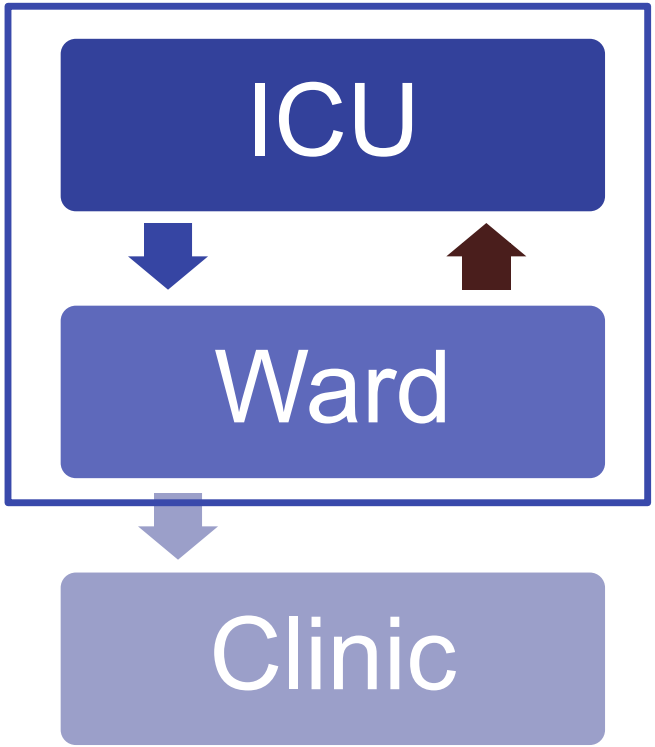
Post-COVID Syndrome
(Long-hauler)

- Waxing and waning
- Fatigue
- Paresthesia
- Cognitive impairment
- Dyspnea
- Palpitations

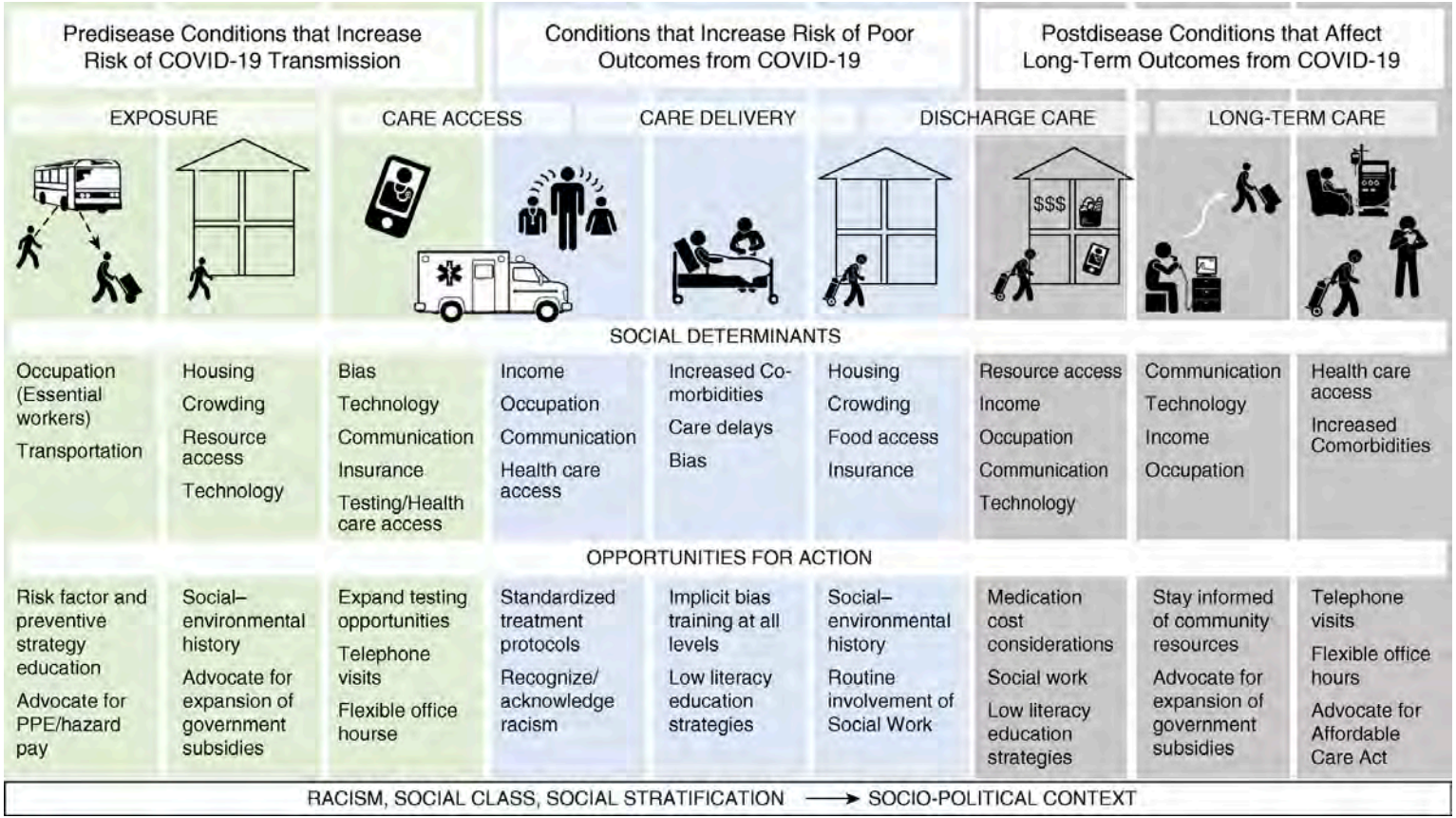
Figure courtesy of
Neeta Thakur MD

Huang Resp Research 2020
Puntmann JAMA 2020

Patients Traverse Multiple Contexts

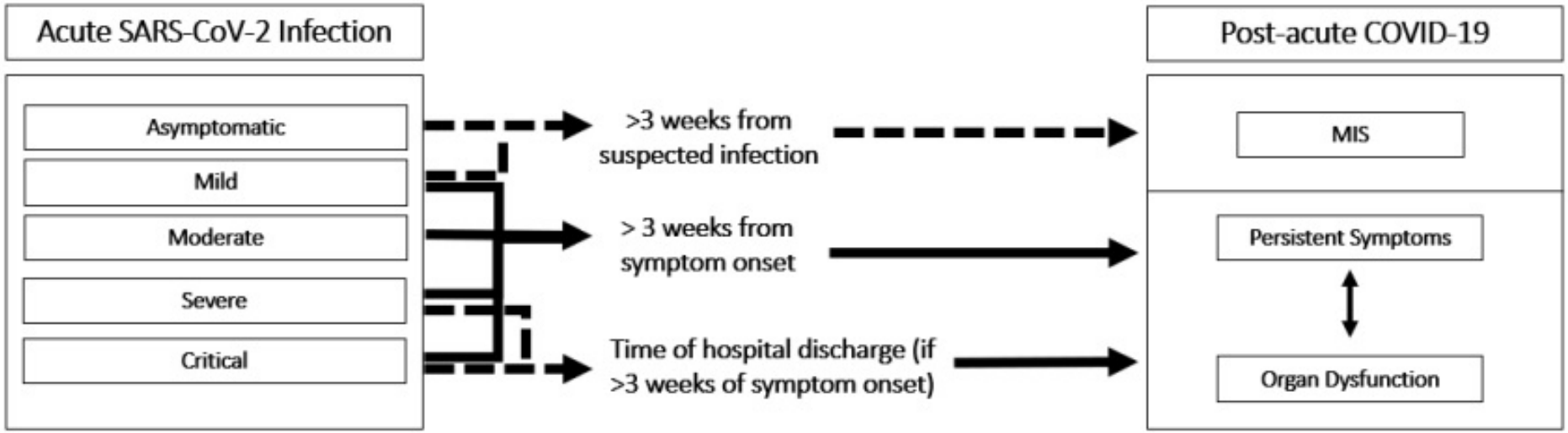


Disparities & Access to COVID-19 Care



Thakur AJRCCM 2020

Symptoms Not Necessarily = Organ Dysfunction



Evaluating and Caring for Patients with Post-COVID Conditions: Interim Guidance

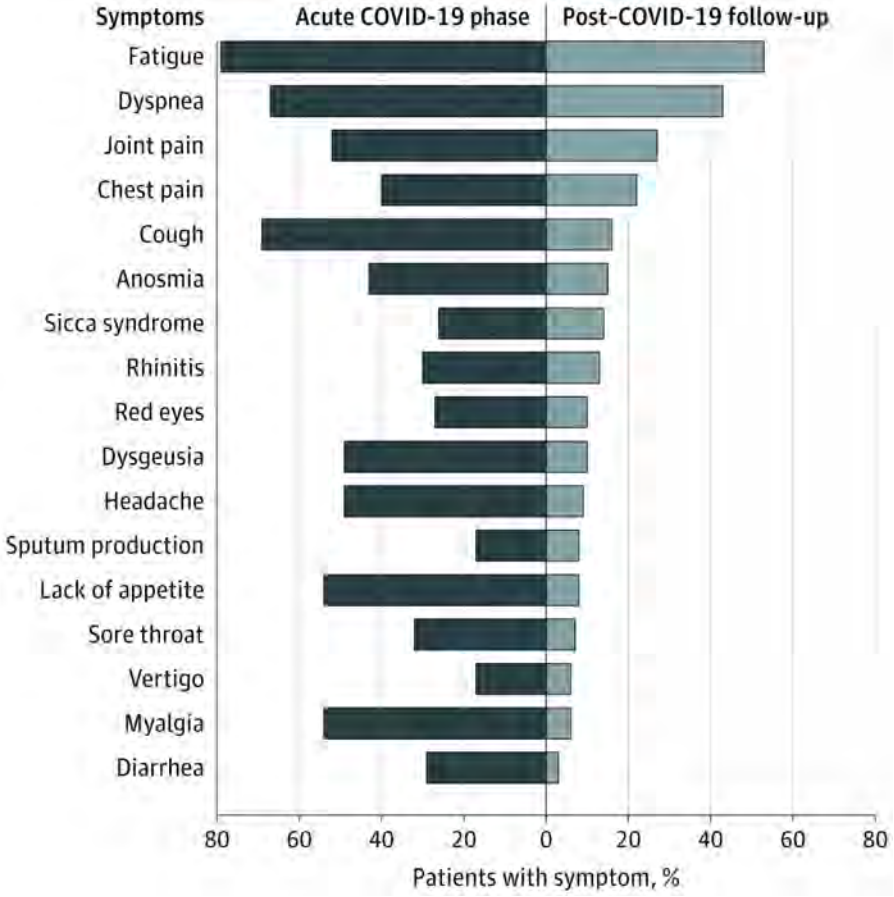
Updated June 14, 2021 Print

- **Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient's well-being; lack of laboratory or imaging abnormalities does not invalidate the existence, severity, or importance of a patient's symptoms or conditions.**
- Healthcare professionals and patients are encouraged to set achievable goals through shared decision-making and to approach treatment by **focusing on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia)**; a comprehensive management plan focusing on improving physical, mental, and social wellbeing may be helpful for some patients.
- Understanding of post-COVID conditions remains **incomplete and guidance for healthcare professionals will likely change** over time as the evidence evolves.

New WHO Case Definition

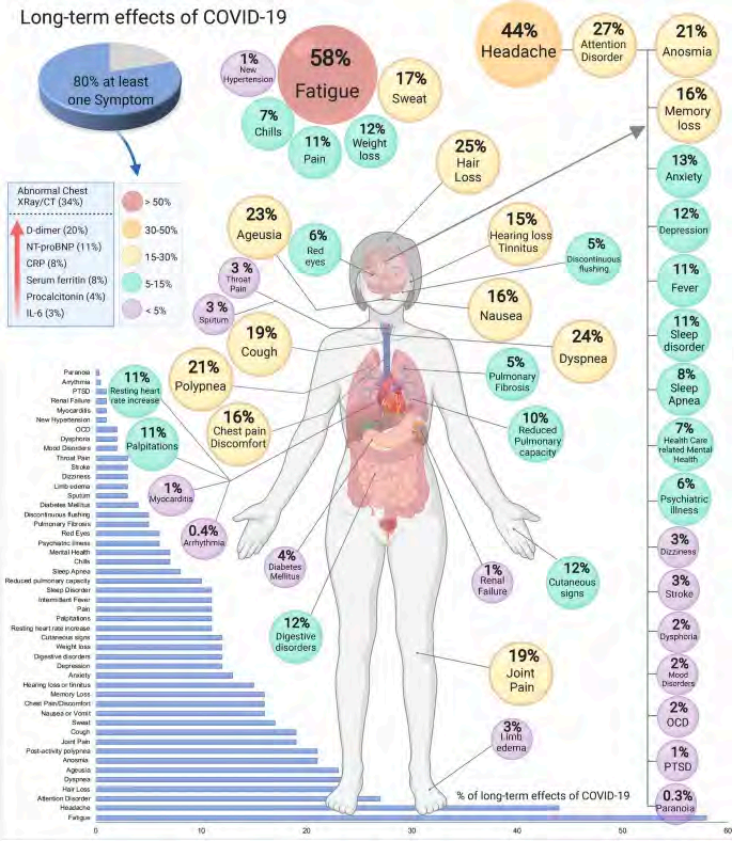
Post COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS-CoV-2** infection, **usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others (see **Table 3** and **Annex 2**) which generally have an **impact on everyday functioning.** Symptoms may be **new onset,** following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time. A separate definition may be applicable for children.

Illness Trajectory: What happens after recovery?

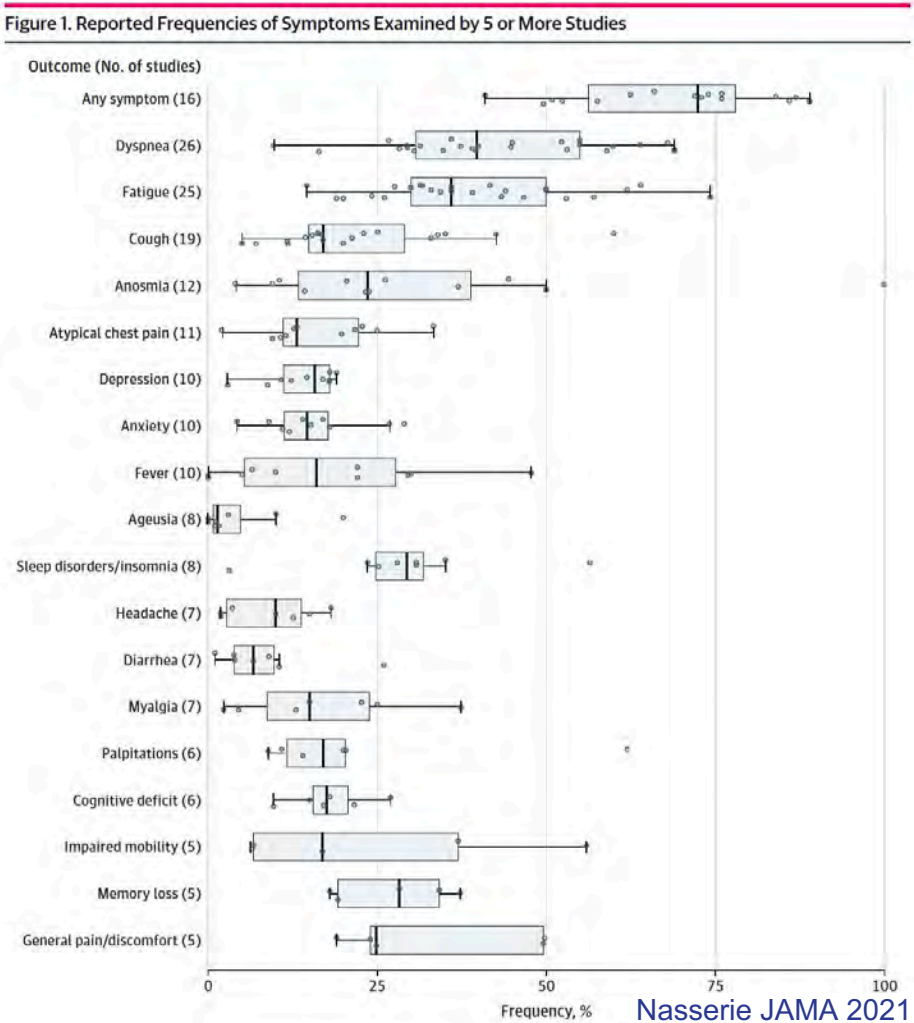


Carfì JAMA 2020

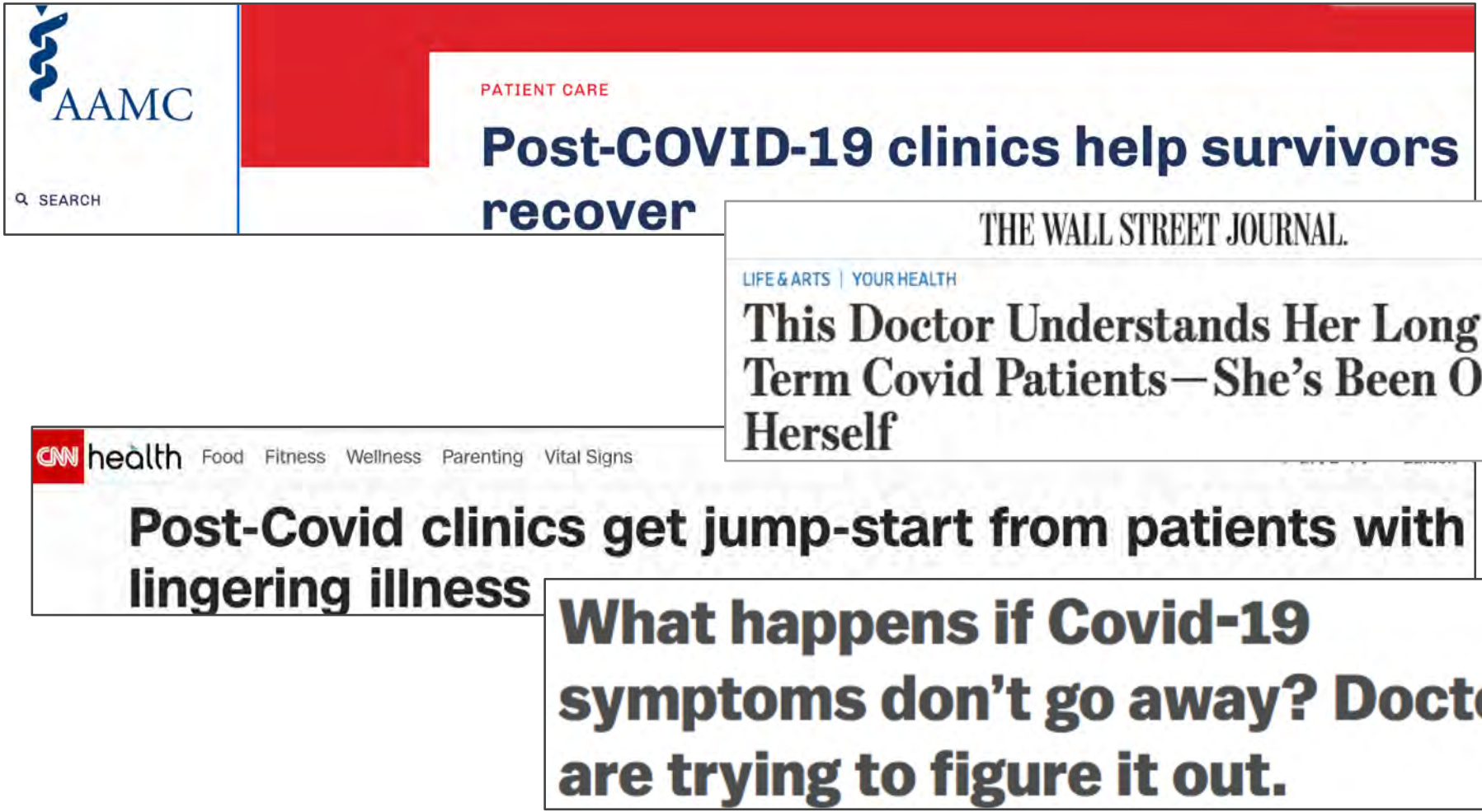
Newer Data Reaffirming



Lopez-Leon 2021

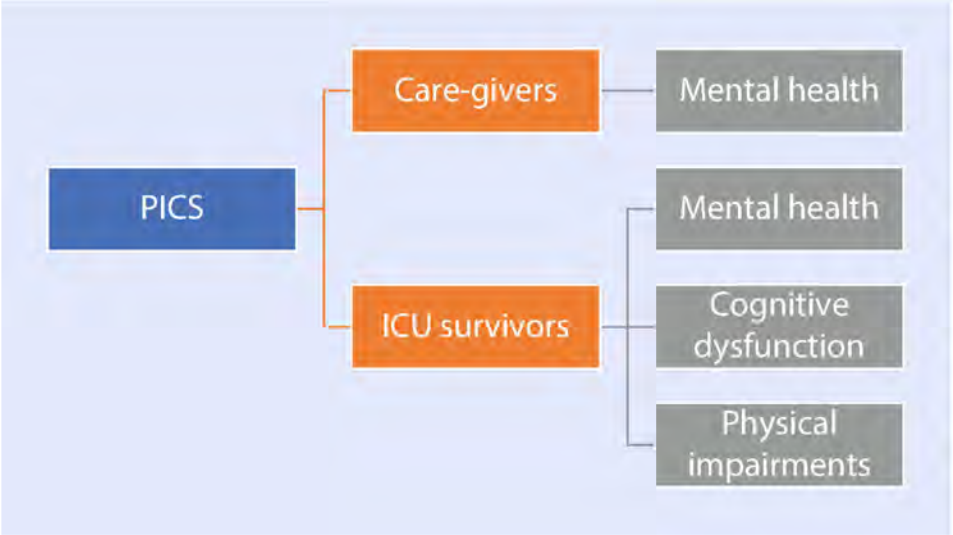


Nasserie JAMA 2021


AAMC
SEARCH
PATIENT CARE
Post-COVID-19 clinics help survivors recover
THE WALL STREET JOURNAL.
LIFE & ARTS | YOUR HEALTH
This Doctor Understands Her Long-Term Covid Patients—She's Been One Herself
CNN health Food Fitness Wellness Parenting Vital Signs
Post-Covid clinics get jump-start from patients with lingering illness
What happens if Covid-19 symptoms don't go away? Doctors are trying to figure it out.
Vox

Post-Intensive Care Syndrome (PICS): Our Framework

- Holistic approach to caregivers & patients - translatable to COVID
  - Pulmonary impairments
  - Physical impairments
  - Cognitive dysfunction
  - Mental Health



Flaaten 2019 PICS

POST-INTENSIVE CARE SYNDROME (PICS)

Critical illness survivors suffer from new or worsening impairments in the physical, cognitive, or behavioral domains.

These unintended consequences of critical care are referred to as PICS.

CHEST®

© 2021 American College of Chest Physicians

Symptoms of PICS

- **Physical Domain**
  - Generalized weakness
  - Fatigue
  - Difficulty walking
- **Cognitive Domain**
  - Memory disturbance/loss
  - Slow mental processing
  - Poor concentration
- **Emotional Domain**
  - Anxiety
  - PTSD
  - Depression

COMMON RISK FACTORS

- ICU length of stay ≥24 hours
- Prolonged immobilization
- Severity of illness
- Older age (≥65)
- Female gender

- Prior psychiatric illnesses
- Prior cognitive impairment
- Lower socioeconomic status
- Exposure to glucocorticoids
- Prolonged use of sedation and/or analgesia drips
- Hyperglycemia

PREVENTION AND SCREENING

Implementation of the ABCDEF bundle

- Spontaneous awakening and breathing trials
- Choice of sedation and analgesics
- Delirium screening and prevention
- Early mobilization
- Family presence at bedside

Use of validated scales to screen and guide targeted treatments

- Delirium screening (CAM-ICU)
- Pain assessment (CPOT, VAS)
- Sedation titration (RASS)

CRITICAL CARE RECOVERY PROGRAMS

Critical care recovery clinics

- Multidisciplinary teams including intensivists, nurses, physical/occupational therapists, pharmacists, spiritual care specialists, palliative care specialists, social workers, and others
- Bridge gaps in transition of care; screen and treat PICS
- Can be conducted in person or via telehealth

Peer-to-peer support groups

- Online or in person

PICS IN CAREGIVERS

- Family and loved ones who provide the needed care and support can also develop some of the same mental and emotional symptoms of PICS; referred to as PICS-family or PICS-F

Learning Objectives

By the end of this lectures, learners will be able to...

- Anticipate the most common residual symptoms following hospitalization for COVID-19 pneumonia in adults, focusing on 4 major symptom domains:
  - Pulmonary
  - Physical Health
  - Cognitive Function
  - Mental Health
- Define strategies for assessing and managing post-COVID-19 hospitalization clinical needs in the outpatient setting

One of my Patients: From COVID ICU to Post-COVID Clinic

Mrs. L is an 83-year-old Spanish-speaking woman recently discharged following hospitalization for COVID-19 pneumonia. She has T2DM, HTN, and hearing loss. She lives with her daughter, who is her DPOA.

She is discharged to subacute rehab at a local skilled nursing facility.

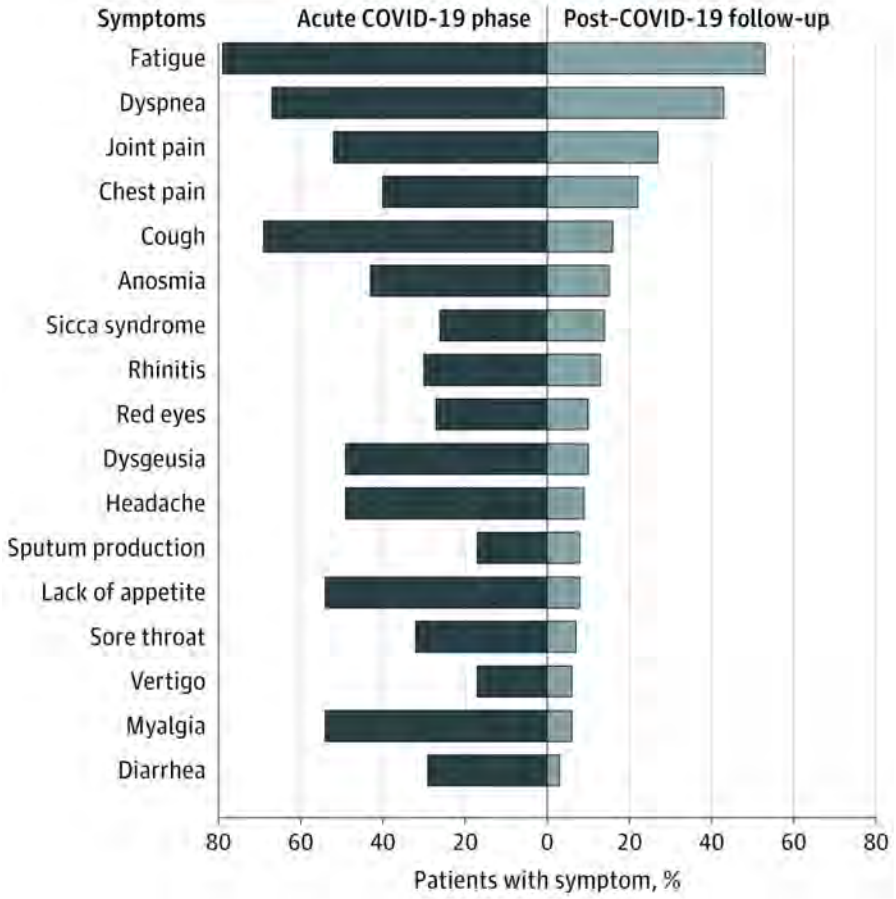
During hospitalization she required HFNC in the ICU. She is discharged home on room air, yet remains breathless, anxious, and socially isolated.

Persistent Pulmonary Sx

ARS Q: For her persistent dyspnea, you should:

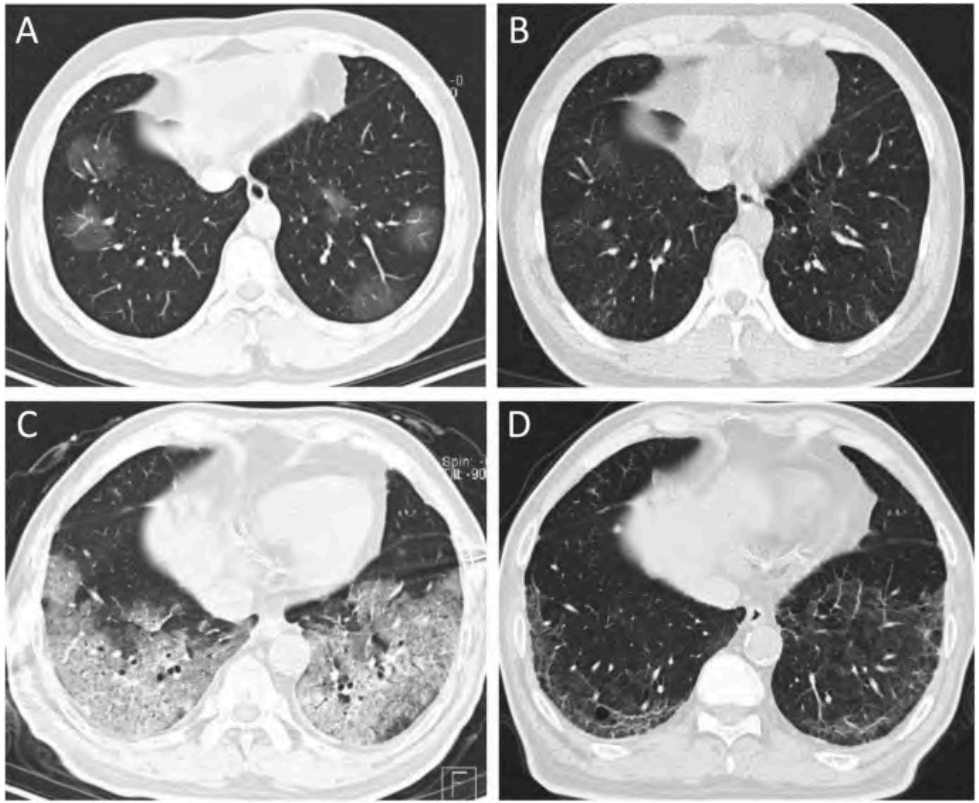
A. Order a Chest CT
B. Order PFTs
C. Order Pulmonary Rehab
D. Schedule 1 month follow-up

Illness Trajectory: What happens after recovery?



Carfì JAMA 2020

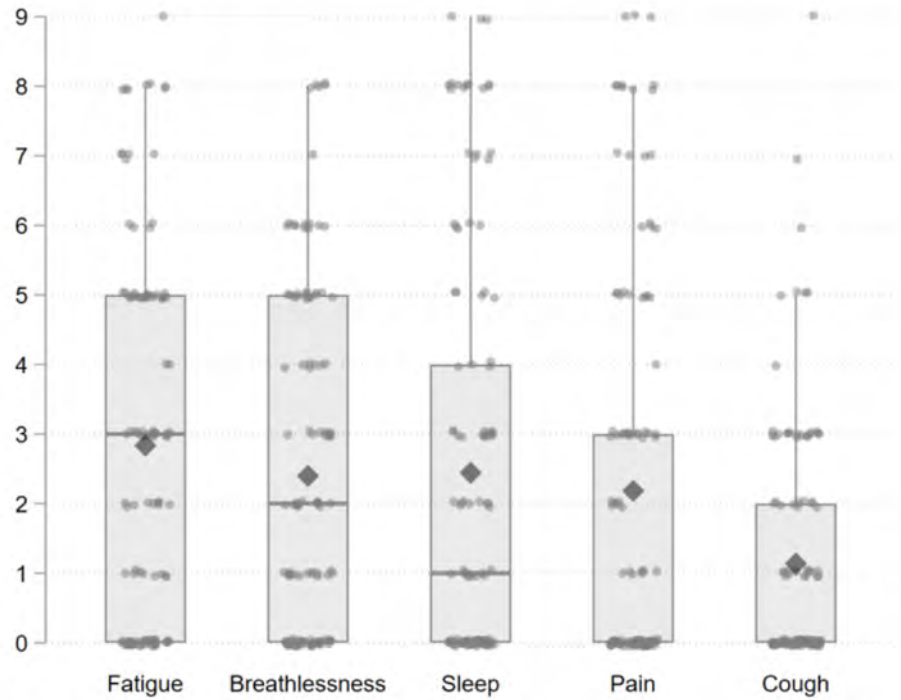
Persistent Pulmonary Issues…But Compared to What?

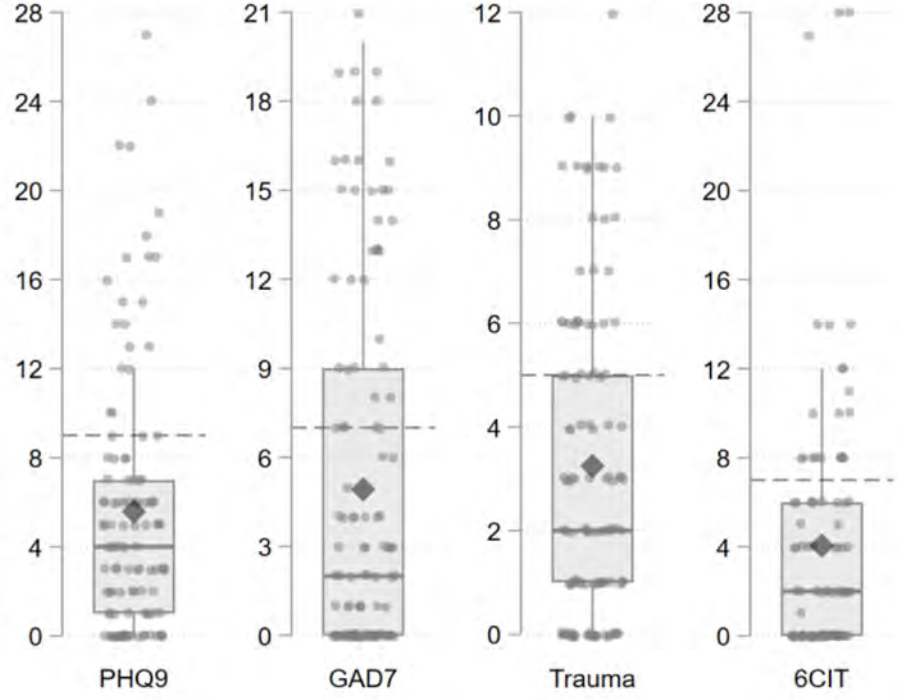


Huang Resp Research 2020

ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia





D'Cruz ERJ 2020

ARDS Survivors Have Persistent PFT Abnormalities

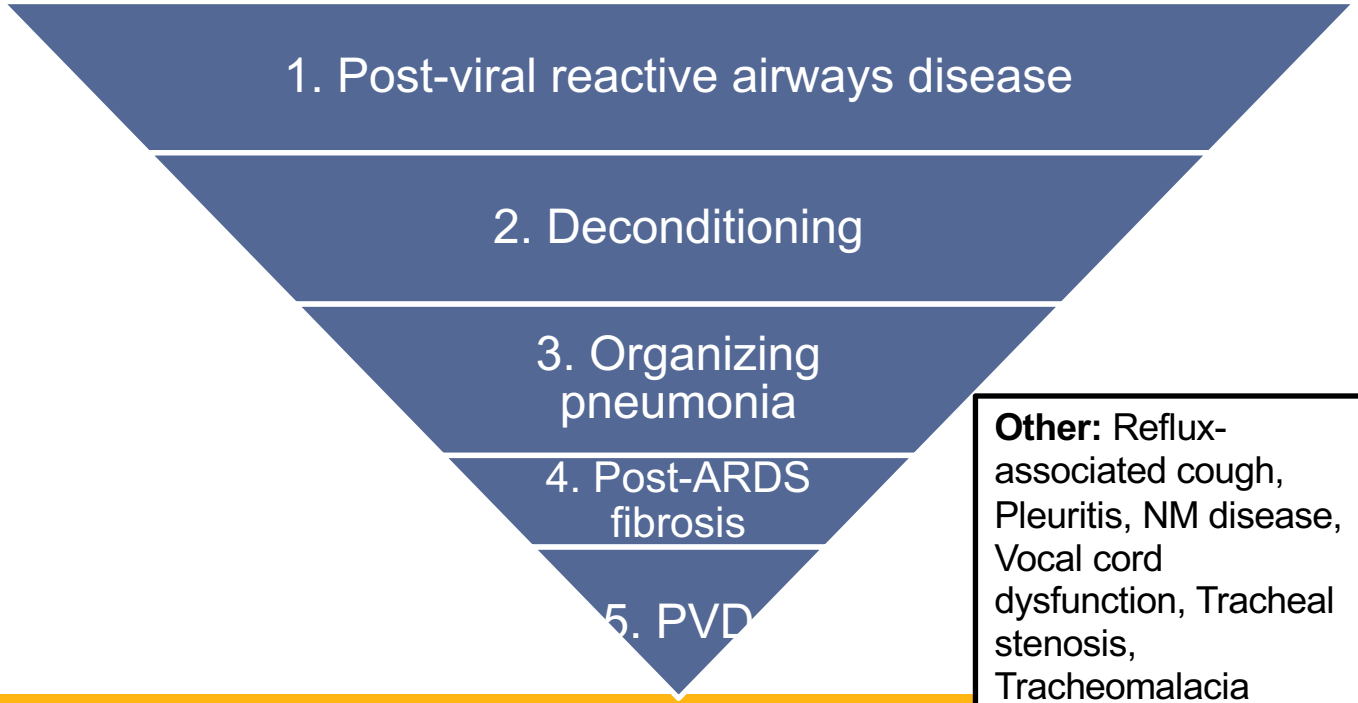
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2011 VOL. 364 NO. 14

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

Differential – Persistent Dyspnea

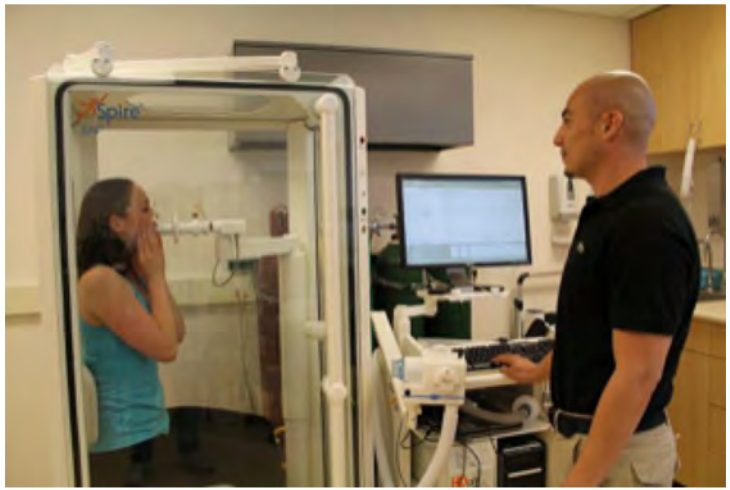


Other: Reflux-associated cough, Pleuritis, NM disease, Vocal cord dysfunction, Tracheal stenosis, Tracheomalacia

Slide Credit: Dr. Kristin Schwab, UCLA

UCSF OPTIMAL Approach to Diagnostics

- Pulmonary Function Tests
    - I like to include 6MWT
- If DLCO is low, consider CT chest
- Also consider TTE
- Labs:
    - CBC w/ diff, ESR/CRP, Thyroid, +/- CPK



Audience Response Question #1

She is reporting persistent dyspnea at the 1-month follow-up visit. Do you:

A. Recommend PFTs
B. Recommend Chest CT
C. Recommend TTE
D. Recommend a 3-mo follow-up visit

Persistent Physical Sx

Back to our Patient: From COVID ICU to Post-COVID Clinic

She remains physically quite deconditioned and weak in addition to her baseline frailty. She reports severe fatigue, worse with exertion.

Audience Response Question #2

For her severe fatigue, do you recommend:

A. Consider physical therapy
B. Recommend graded exercise
C. Short-course of corticosteroids
D. A & B

CHEST

Fatigue Symptoms During the First Year Following ARDS

Karin J. Neufeld, MD, MPH; Jeannie-Marie S. Leoutsakos, PhD, MHS; Haiyuan Yan, PhD; Shihanq Lin, MS; Jeffrey S. Zabinski, MD; Victor D. Dinglas, MPH; Megan M. Hosey, PhD; Ann M. Parker, MD; Ramona O. Hopkins, PhD; and Dale M. Needham, MD, PhD

BACKGROUND: Fatigue is commonly reported by ARDS survivors, but empirical data are scarce.

RESEARCH QUESTION: This study evaluated fatigue prevalence and associated variables in a prospective study of ARDS survivors.

STUDY DESIGN AND METHODS: This analysis is part of the ARDSNet Long-Term Outcomes Study (ALTOS) conducted at 38 US hospitals. Using age- and sex-adjusted, time-averaged random effects regression models, we evaluated associations between the validated Functional Assessment of Chronic Illness Therapy-Fatigue Scale with patient and critical illness variables, and with physical, cognitive, and mental health status at 6 and 12 months following ARDS.

RESULTS: Among ARDS survivors, 501 of 711 (70%) and 436 of 659 (66%) reported clinically significant symptoms of fatigue at 6 and 12 months, respectively, with 41% and 28% reporting clinically important improvement and worsening (n = 638). At 6 months, the prevalence of fatigue (70%) was greater than that of impaired physical functioning (50%), anxiety (42%), and depression (36%); 46% reported both impaired physical function and fatigue, and 27% reported co-existing anxiety, depression, and fatigue. Fatigue was less severe in men and in those employed prior to ARDS. Critical illness variables (eg, illness severity, length of stay) had little association with fatigue symptoms. Worse physical, cognitive, and mental health symptoms were associated with greater fatigue at both the 6- and 12-month follow-up.

INTERPRETATION: During the first year following ARDS, more than two-thirds of survivors reported clinically significant fatigue symptoms. Due to frequent co-occurrence, clinicians should evaluate and manage survivors' physical, cognitive, and mental health status when fatigue is endorsed.

CHEST 2020; 158(3):999-1007

KEY WORDS: acute lung injury; cognitive function; depression; disability; rehabilitation

FOR EDITORIAL COMMENT, SEE PAGE 848

ABBREVIATIONS: APACHE III = Acute Physiology and Chronic Health Evaluation III; FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale; SF-36v2 = Short Form-36 Version 2

AFFILIATIONS: From the Department of Psychiatry and Behavioral Sciences (Drs Neufeld, Leoutsakos, Yan, and Zabinski; and Mr Lin), Division of Pulmonary and Pulmonary and Critical Care Medicine (Mr Dinglas and Drs Parker and Needham), Department of Physical Medicine and Rehabilitation (Drs Hosey and Needham), and Outcomes After Critical Illness and Surgery (OACIS) Group, (Drs Neufeld, Leoutsakos, Hosey, Parker, and Needham, and Mr Dinglas) Johns Hopkins University School of Medicine, Baltimore, MD; Neuroscience Center and Psychology Department (Dr Hopkins), Brigham Young University, Provo, UT; and Pulmonary and Critical Care Medicine (Dr Hopkins), Intermountain Healthcare, and Center for Humanizing Critical Care (Dr Hopkins), Intermountain Medical Center, Murray, UT.

FUNDING/SUPPORT: This research was supported by the National Heart, Lung, and Blood Institute [Grants R24 HL111895, R01HL091760, and R01HL091760-02S1], the Johns Hopkins Institute for Clinical and Translational Research [Grant UL1 TR 000424-06], and the Alliance for Treatment of Acute Lung Injury Trial (ALTA), Early Versus Delayed Enteral Nutrition Trial (EDEN), Omega Nutrition Supplement Trial (OMEGA), and Statins for Acutely Injured Lungs from Sepsis Trial (SAILS) [National Heart, Lung, and Blood Institute contracts HHSN268200536165C to HHSN268200536176C and HHSN268200536179C].

CORRESPONDENCE TO: Karin J. Neufeld, MD, MPH, A4Center, Ste 457, Johns Hopkins Bayview Medical Center, 4940 Eastern Ave, Baltimore, MD 21224; e-mail: kneufel@jhmi.edu

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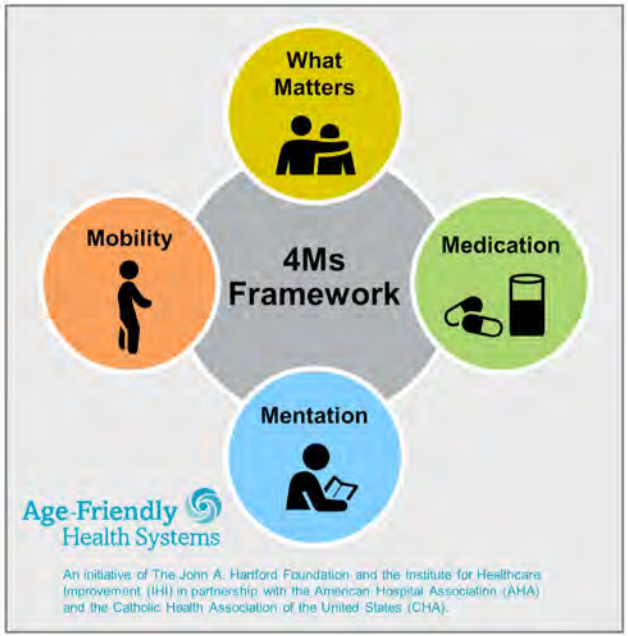
DOI: https://doi.org/10.1016/j.chest.2020.03.489

More than 2/3rds of ARDS survivors reported clinically significant fatigue symptoms 1 year after discharge.

Neufeld CHEST 2020

Post-Hospital syndrome & Older Adults

- Post-hospitalization/ICU risks
  - Weakness/Disability
  - Delirium
  - PTSD
- Critical to assess the 4Ms of Age-Friendly Care:
  - What **M**atters
  - **M**edication
  - **M**entation
  - **M**obility
- Home rehab guide for home exercise, Pulm rehab referral?



What Matters

Know and align care with each older adult's specific health outcome goals and care preferences including, but not limited to, end-of-life care, and across settings of care.

Medication

If medication is necessary, use Age-Friendly medication that does not interfere with What Matters to the older adult, Mobility, or Mentation across settings of care.

Mentation

Prevent, identify, treat, and manage dementia, depression, and delirium across settings of care.

Mobility

Ensure that older adults move safely every day in order to maintain function and do What Matters.

Krumholz NEJM 2013, IHI.org

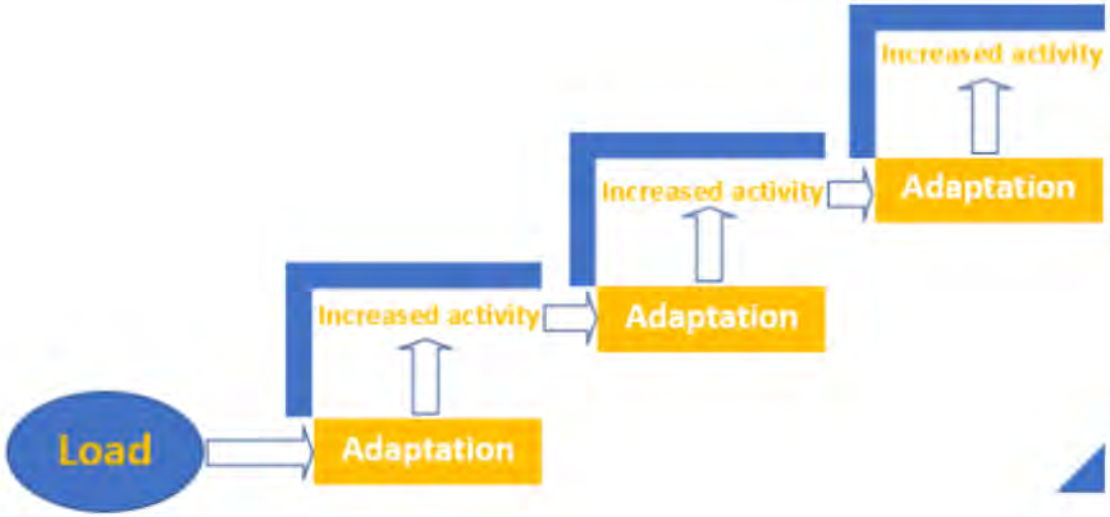


Figure 3: Progressive or graded increase in activity to increase functional capacity

Bouncing Back
From COVID-19

Your Guide to Restoring Movement

Audience Response Question #2

For her severe fatigue, do you recommend:

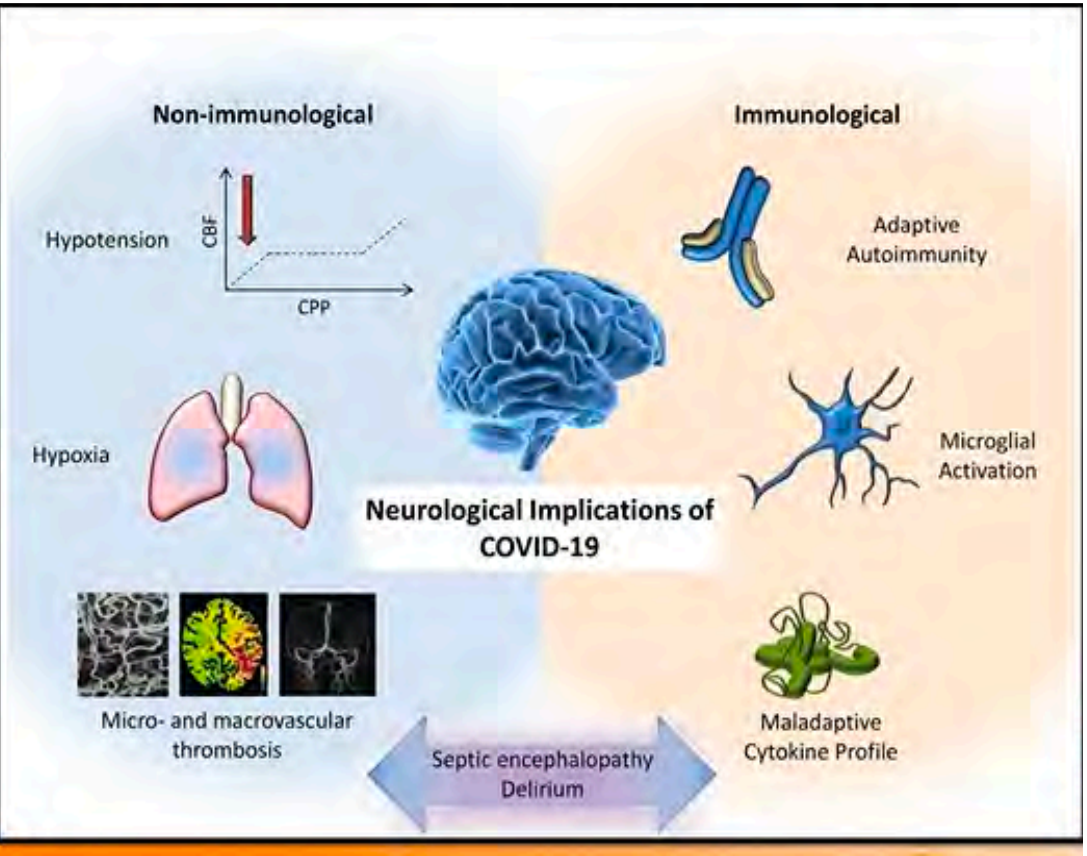
A. Consider physical therapy
B. Recommend graded exercise
C. Short-course of corticosteroids
D. **A & B**

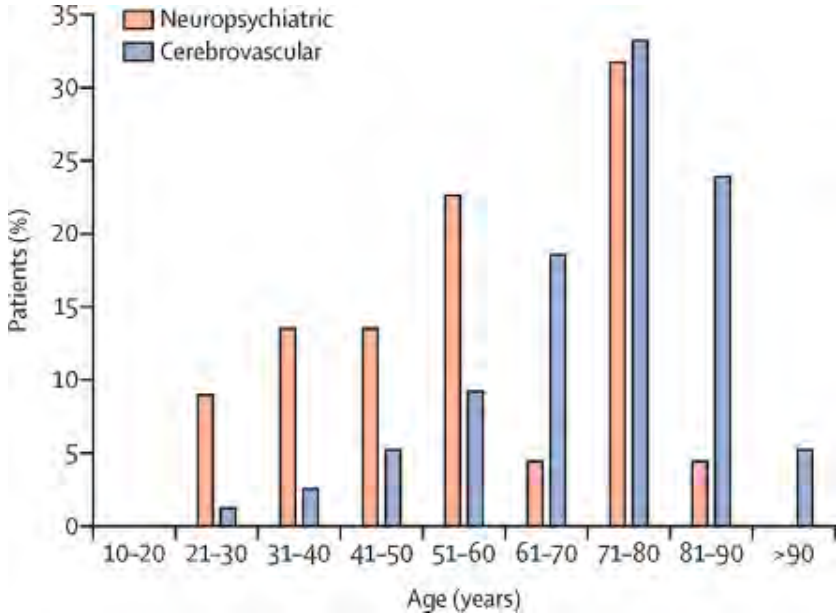
Persistent Cognitive & Mental Health Sx

Back to our Patient: From COVID ICU to Post-COVID Clinic

She reports ongoing anxiety and fears going back to the grocery store because of worries about infecting others or getting re-infected.

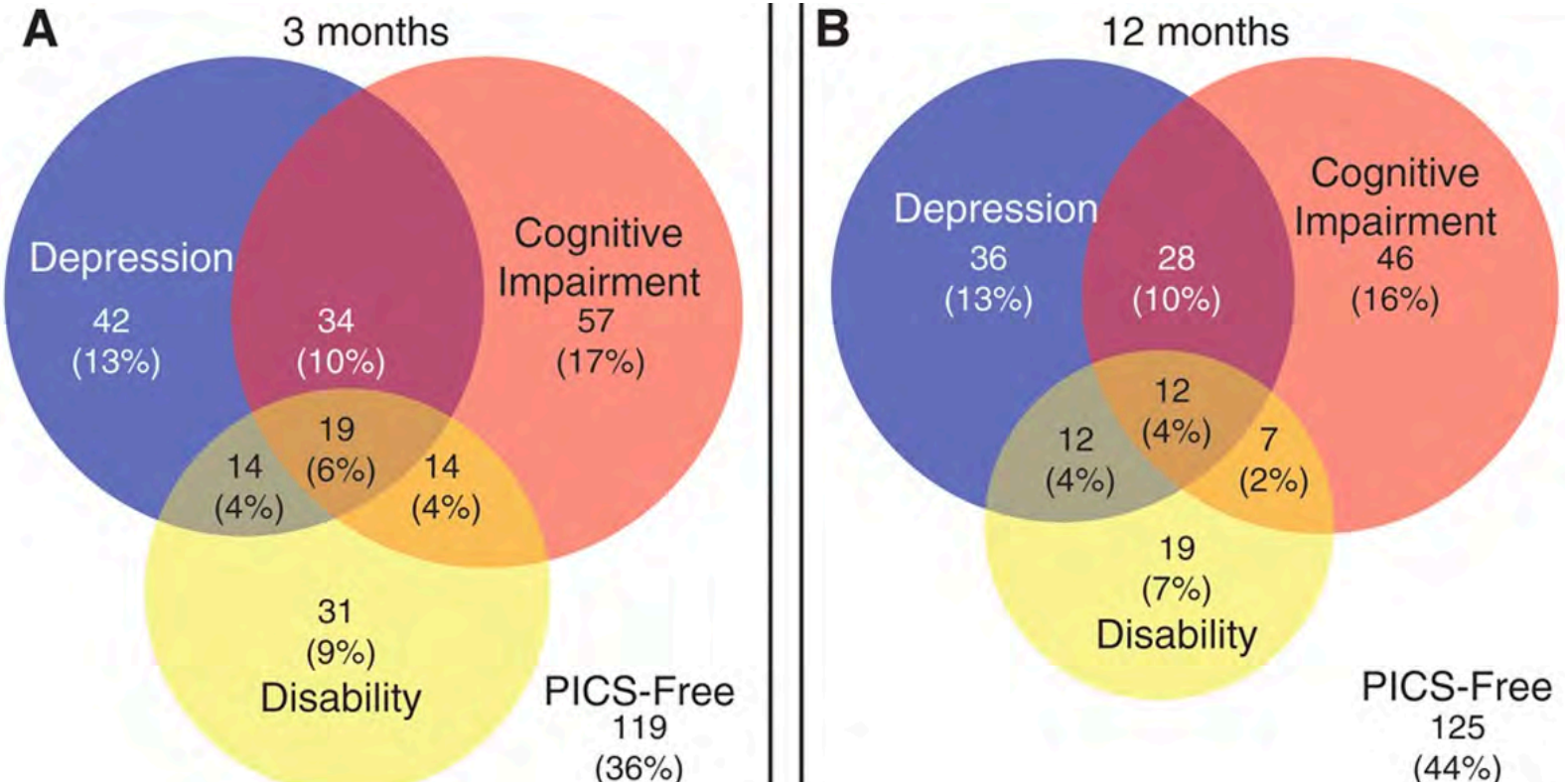
As Many as “1 in 5” Report Persistent Cognitive Sx





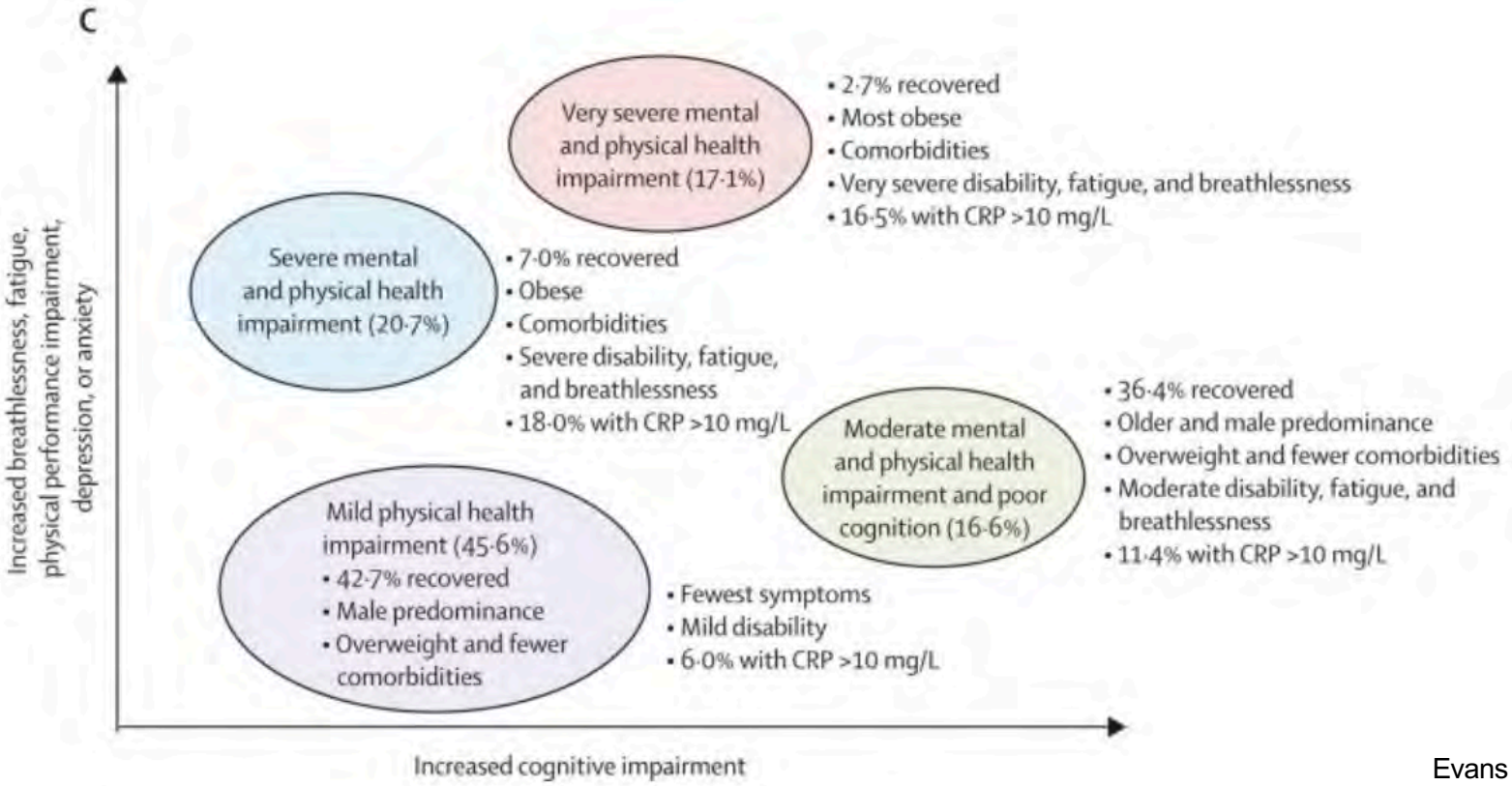
Varatharaj Lancet Psych 2020
Mao JAMA Neurol 2020
Needham Neuro Crit Care 2020
Liotta Annals Clin Transl Neur 2020

Depression, Cog Issues, Disability Are Intertwined



Marra CCM 2018

We See The Same With COVID-19



Evans Lancet Resp Med 2021

A “Delirium Factory”, as Dr. Wes Ely Puts It

The New York Times

Account

‘They Want to Kill Me’: Many Covid Patients Have Terrifying Delirium

Paranoid hallucinations plague many coronavirus patients in I.C.U.s, an experience that can slow recovery and increase risk of depression and cognitive issues.

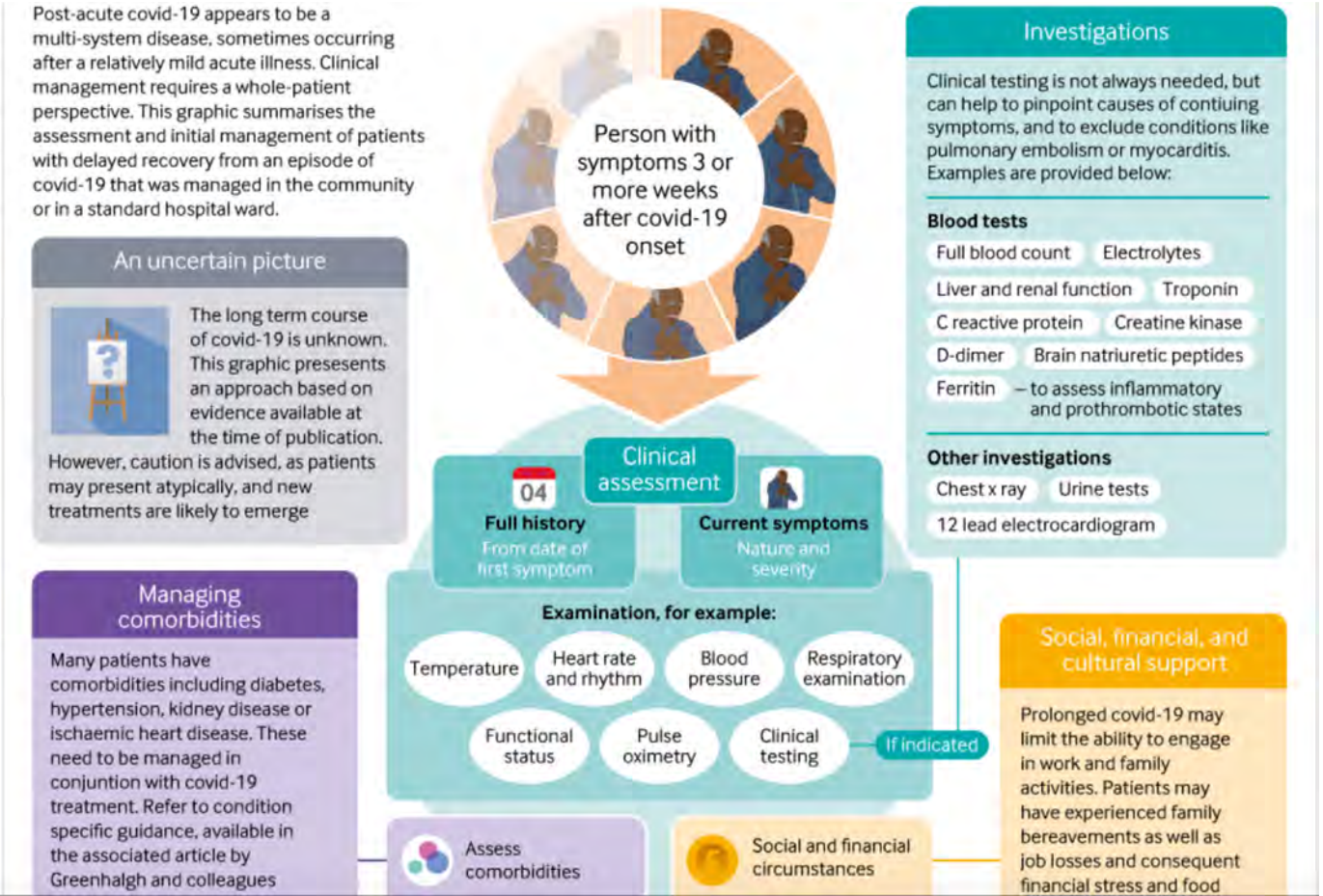
COVID Recovery Resources for Patients: Standard AVS

- **Mental Health:** Reassurance and coping strategies are key, peer support, assess for psych referral/needs for meds

- **Social Isolation/Loneliness:** Older adults and those with many medical problems are at particular risk. Discuss safe socialization and IADL logistics

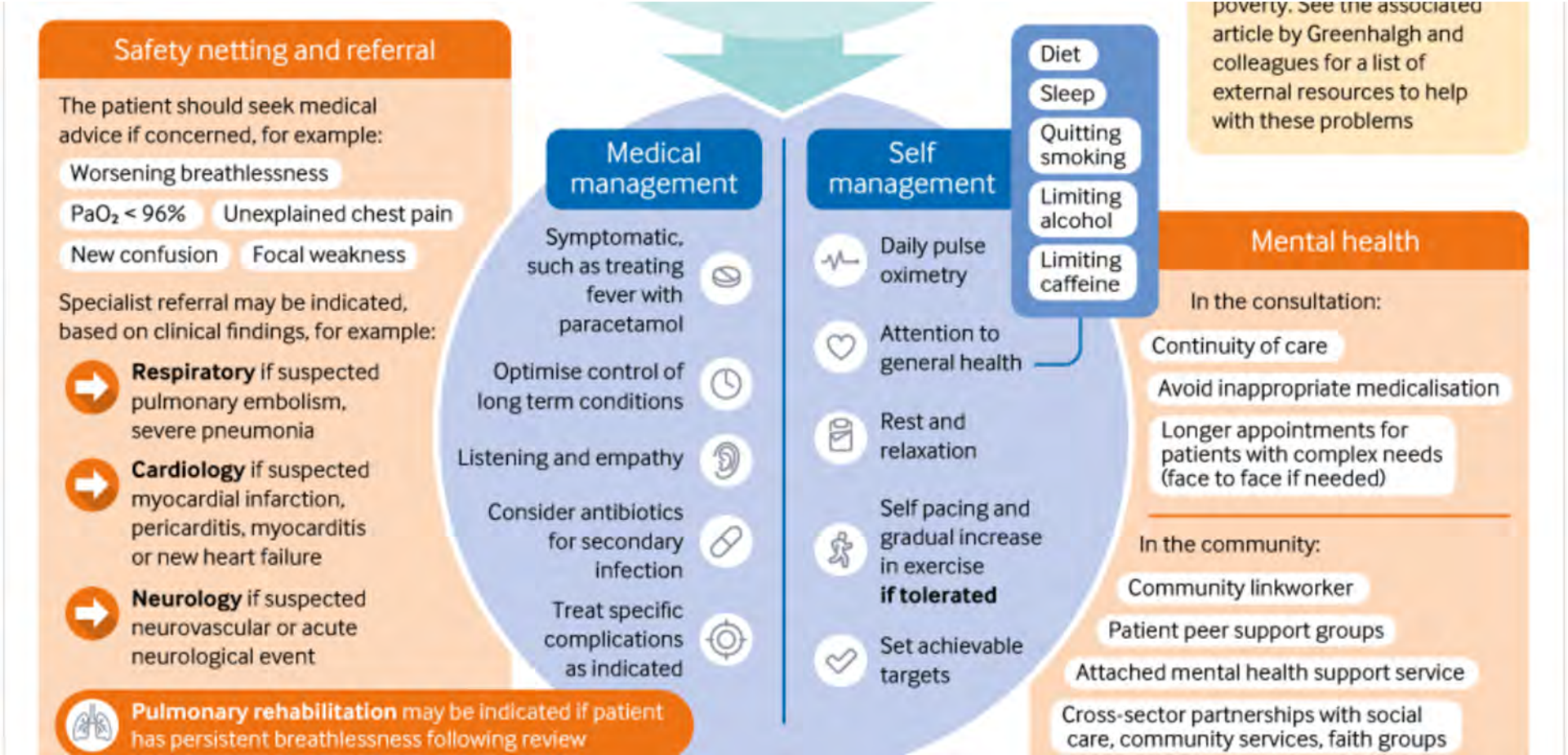
Perissinotto Archives 2012

BMJ Recommendations for PCPs



Greenhalgh BMJ 2020

BMJ Recommendations for PCPs



Post-COVID Clinics

Audience Response Question #3

You decide to refer your patient to a multidisciplinary post-COVID clinic. Is there evidence for such an approach?

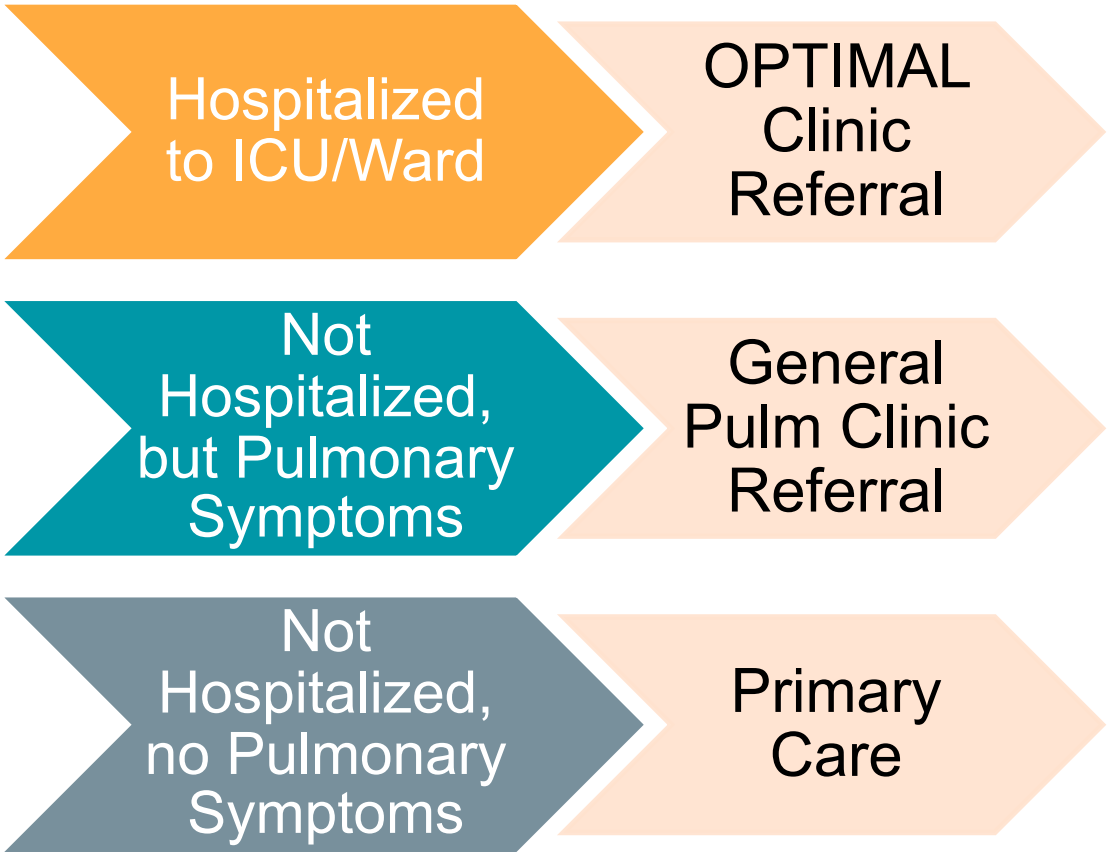
A. Yes
B. No
C. I don’t know, but how does it work?

OPTIMAL Clinic: Ambulatory Follow-Up for COVID

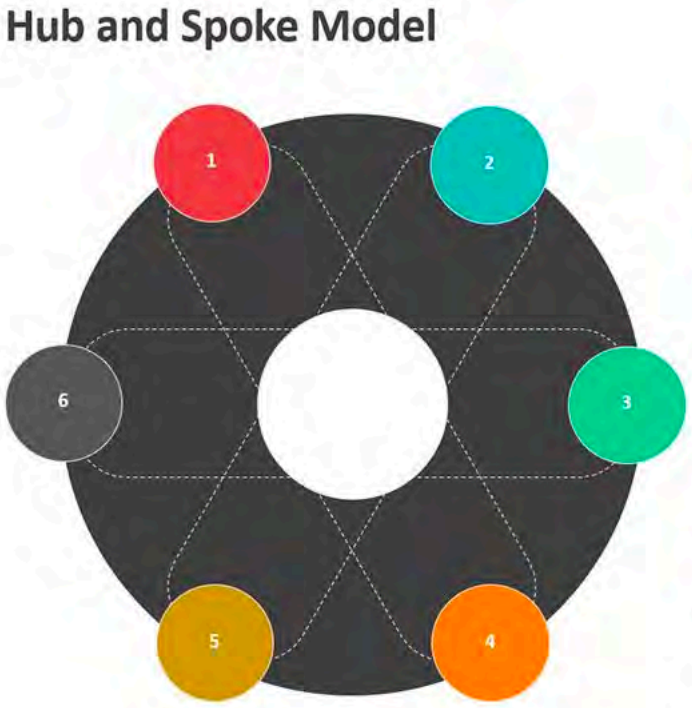
(pOst-covid/PosT-Icu MultidisciplinAry cLinic)

- ❏ At UCSF since May 2020: Multidisciplinary Clinic b/w Pulm, Geriatrics, Pharmacy, PT, Mental Health & faculty champions in other Divisions
- ❏ Coordination w/ research teams at UCSF (LIINC & COMET studies)
- ❏ We see patients ~4 weeks post-discharge (virtual visit), ~3 months, 6 months, 9 months, 12 months post-discharge
- ❏ Please refer any patients who were **admitted to the ward or ICU** with COVID-19 – Also expanded to patients at risk for Post-ICU Syndrome

Referral Pathways for Patients with Sx Post-COVID



Outpatient Follow-Up Structure



OPTIMAL Hub with Collaborations:

- Integrative Medicine
- Cardiology
- Electrophysiology
- Neuro Recovery Clinic
- Pulmonary Rehab
- Virtual Support Groups
- Psychiatry & Behavioral Health
- Infection Control
- Primary Care

Post-hospitalization Outpatient Follow-up Structure

Our experience:

- Trained mental health research assistant administers structured instruments for:
  - Breathlessness (MMRC, BCSS)
  - Anxiety (GAD-7)
  - Depression (PHQ-9)
  - Cognitive function (MOCA)
  - PTSD (PCL-15)
  - Physical function (AMPAC)
  - Lots of options!
  - ?Screening for SDOH?
- Detailed Med Rec By Pharmacists
- Counseling re: Activity
- Reassurance & Linkage to Resources (Psychiatry, Virtual Pulmonary Rehab)

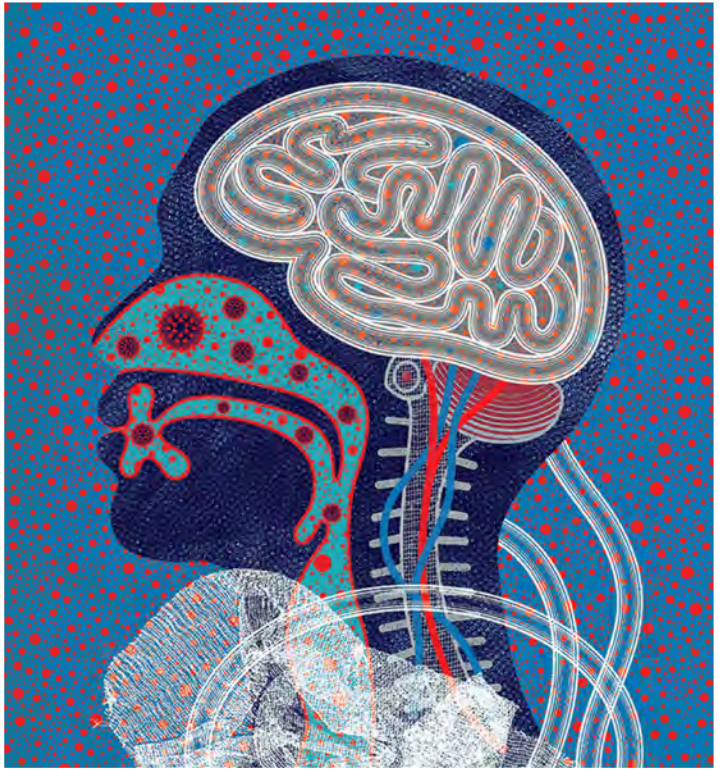


Illustration: Anna & Elena Balbusso, UCSF Magazine

Improving Long-Term Outcomes Research for Acute Respiratory Failure

Core Outcome Set (COS) and Core Outcome Measurement Set (COMS) for Clinical Research in Acute Respiratory Failure

Core Outcome †

Core Outcome Measure ‡
(Recommended Survey/Test if No consensus)

Survival

No Instrument
Recommend collecting date and location of death

HRQOL

EQ-5D
(3L or 5L version)

Optional:
SF-36 v2

Mental Health

HADS

IESR

Pain

EQ-5D Pain Question

Cognition

None
(MoCA BLIND)

Physical Function

None
(6MWT)

Muscle and/or Nerve Function

None
(Manual Muscle Test And Handgrip)

Pulmonary Function

None
(All measures rejected)

† *Crit Care Med.* 2017; 45:1001-1010 ‡ *Am J Resp Crit Care Med.* 2017;196:1122-1130.

This work, created by Dale M. Needham, MD, PhD and the Johns Hopkins University Outcomes After Critical Illness & Surgery (OACIS) Group, was funded by NHLBI R24HL111895, and is licensed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.
To view a copy of this license, visit http://creativecommons.org/licenses/by-nc-sa/4.0/.

OPTIMAL Demographics: > 300 Pts Seen

CHEST

Rapid Design and Implementation of Post-COVID-19 Clinics

Check for updates

Lekshmi Santhosh, MD, MAEd; Brian Block, MD; Soo Yeon Kim, MD; Sarath Raju, MD, MPH; Rupal J. Shah, MD; Neeta Thakur, MD, MPH; Emily Pfeil Brigham, MD, MHS; and Ann Marie Parker, MD, PhD

Survivors of COVID-19 are a vulnerable population, with complex needs because of lingering symptoms and complications across multiple organ systems. Those who required hospitalization or intensive care are also at risk for post-hospital syndrome and post-ICU syndromes, with attendant cognitive, psychological, and physical impairments, and high levels of health care utilization. Effective ambulatory care for COVID-19 survivors requires coordination across multiple subspecialties, which can be burdensome if not well coordinated. With growing recognition of these needs, post-COVID-19 clinics are being created across the country. We describe the design and implementation of multidisciplinary post-COVID-19 clinics at two academic health systems, Johns Hopkins and the University of California-San Francisco. We highlight components of the model which should be replicated across sites, while acknowledging opportunities to tailor offerings to the local institutional context. Our goal is to provide a replicable framework for others to create these much-needed care delivery models for survivors of COVID-19.

CHEST 2021; 160(2):671-677

One of my Patients: From COVID ICU to Post-COVID Clinic

During our OPTIMAL Clinic visit, we assessed Mrs. L & counseled her and her daughter about anticipated recovery. We recommended gradual aerobic exercise, using a home pulse oximeter, & consideration of PRN inhalers. The integrated mental health support of the visit greatly alleviated the patient's stresses & she "felt a lot better after talking to them." We provided reassurance & recommendations for local resources & set f/u appointment for 3 months.

All that “Long-Hauls” is not COVID.

Avoid anchoring & keep ddx broad throughout.

Take Home Points

1. COVID long-term symptoms & complications can affect **multiple organs**
2. Dyspnea **may not correlate** w/ radiographic abnormalities
3. A comprehensive **multidisciplinary** approach is important to address disability, fatigue, neuropsych sx
4. Lots of **uncertainty** remains & further research will help outline best next steps

Gratitude

Dr. Leah Witt, UCSF OPTIMAL
Dr. Brian Block, UCSF OPTIMAL
Dr. Neeta Thakur, ZSFG Pulmonary
Dr. Emily Brigham, JHU PACT Clinic
Dr. Ann Parker, JHU PACT Clinic
My indefatigable ICU RNs & RCPs
My incredible patients & their families

Thank You!
Questions?

Lekshmi.Santhosh@ucsf.edu
@LekshmiMD

LUNCH
EXHIBIT HALL OPEN

12:20 p.m. – 1:20 p.m.

Hands-On Session: ICU Ventilators, Oxygen Delivery Devices, Manual and Self-Proning

1:20 p.m. – 2:20 p.m.

KRYSTAL CRADDOCK
MSRC, RRT, RRT-ACCS, RRT-NPS, AE-C, CCM
UC DAVIS

Krystal Craddock has been a licensed RT since 2007. She received her graduate degree in Respiratory Care in 2020 from Boise State University. Currently Krystal works as the Clinical Operations Manager and COPD Case Management Coordinator at UC Davis Health. She also is adjunct faculty for San Mateo Community College District instructing in the Bachelors of Respiratory Care Program. She also serves as the CTS Liaison for the California Society for Respiratory Care.

JUSTIN PHILLIPS, RCP, RRT-ACCS
UC SAN FRANCISCO - ZUCKERBURG

Justin Phillips is a Adult Critical Care Respiratory Therapist for the University of California San Francisco, Department of Anesthesia at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). There, he currently serves as a bedside therapist and educator. Justin is a lecturer for the Critical Care Residency Program at ZSFG and has spoken nationally at a number of respiratory and critical care conferences. Additionally, he is Adjunct Faculty for the Respiratory Care Program at Ohlone College for Health Sciences and Technology. Justin's clinical interests include enhancing mechanical ventilation delivery through innovation and strategic ventilator practices.

DANIEL STEMEN, MSRS, RCP, RRT-ACCS, ECMOS

UNIVERSITY OF SOUTHERN CALIFORNIA

Daniel Stemen is a respiratory therapist working in teaching facilities for the past 15 years and have been with USC since 2010. I co-authored our curriculum for ECLS and am passionate about providing high fidelity simulation training to our staff. I recently graduated with my masters in regulatory science from our school of pharmacy at USC. I love being a respiratory therapist and all the wonderful physicians and nurses that I work with every day. The passion for patients and their families that I witness from our teams keeps me motivated and proud to work in this field.

BRIAN SMITH, MSRC, RRT
UC DAVIS

Brian Smith is currently a Respiratory care educator at UC Davis, specializing in neonatal and pediatric critical care. I have academic interest and pursuits in mechanical ventilation, transcutaneous C02 monitoring, high frequency modalities, and currently studying the effects of COVID-19 and RT burnount.

EMMA BLACKMON, PHD, RN, CCRN
UC DAVIS

Emma Blackmon received her PhD from UC Davis in 2016. Her work focused on interprofessional communication and teamwork in the adult ICU setting. She has 16 years of experience in caring for ICU patients, specifically in pulmonary and critical care. Currently, she is the Adult Critical Care Educator at UC Davis Health, focusing on the education and training of adult ICU nurses and ancillary staff, serving as a critical care bedside resource and a member of several interdisciplinary teams.

Non-invasive Positive Pressure Ventilation (NIPPV) – Tip Sheet

Noninvasive ventilation (NIV) has been shown to significantly reduce many of the complications associated with conventional mechanical ventilation, including the incidence of ventilator-acquired pneumonia.[1] Commonly we see S/T as the mode of choice for our patients. This tip sheet will give guidance on the use of pressure control and AVAPS modes.

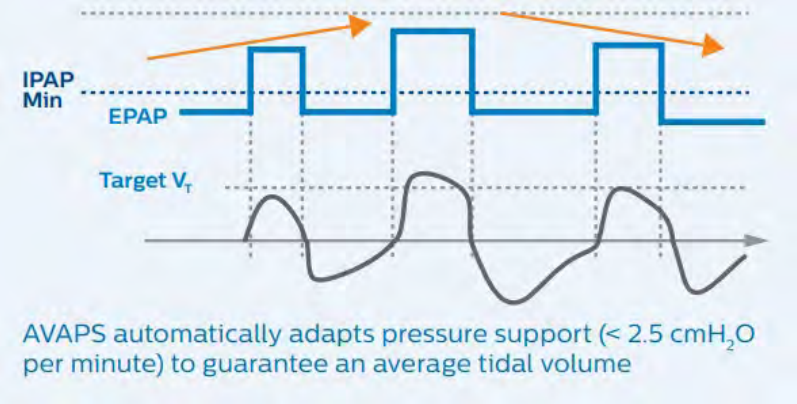
Pressure-controlled ventilation

In pressure-controlled ventilation (PCV), breaths with a user-set IPAP and I-Time are delivered to the patient. The patient can trigger an inspiration and, therefore, control the rate. However, the patient does not control the inspiratory time. Also be aware that any changes in EPAP without an equal change in IPAP will change the pressure support. [2]

AVAPS (average volume-assured pressure support)

AVAPS is a volume-targeted mode and is intended for use with stable chronic patients who do not require rapid pressure support changes to maintain a target VT. At start-up, AVAPS applies an inspiratory pressure equal to one of the following, whichever is greater: [2]

- EPAP + (target volume/60 ml/cmH2O)
- EPAP + 8 cmH2O
- Pmin



Note: when adjusting AVAPS minimum and maximum pressures, remember that IPAP is adjusted to meet the target value. The V60 ventilator will automatically adjust IPAP (up to 2.5 cmH2O per minute), to maintain a tidal volume target.[2]

Remember:

- Because the V60 is intended to augment ventilation in patients who are spontaneously breathing, the rate should be set as a back-up rate in the case of apnea. If the patient fails to trigger a breath through Auto-Trak within the interval determined by the rate setting or cycle time, the ventilator triggers a mandatory breath. [2]
- Setting I-Time adjusts the inspiratory time for a machine triggered breath, therefore influencing the I:E ratio in V60 machine-triggered breaths. Inspiratory time is controlled by the patient in a patient-triggered breath. [2]

References

1. Hill NS, Brennan J, Garpestad E, Nava S. (2007). Noninvasive ventilation in acute respiratory failure. Crit Care Med. Oct;35(10):2402-7.
2. N.A. (2017) V60 Pocket Guide. Accessed from: https://www.usa.philips.com/healthcare/product/HC989805611761/respironics-v60-ventilator#documents

Airway Pressure Release Ventilation (APRV) by Dräger Medical and its industry equivalents (i.e., Bi-Level, BiVent, DuoPAP, etc.) can be classified as non-conventional modes of mechanical ventilation that gained clinical popularity given their ability to provide open-lung ventilation while facilitating spontaneous breathing of mechanically ventilated patients. APRV can be defined as "inverse ratio, pressure controlled, intermittent mandatory ventilation [that allows for] unrestricted spontaneous breathing."[1]

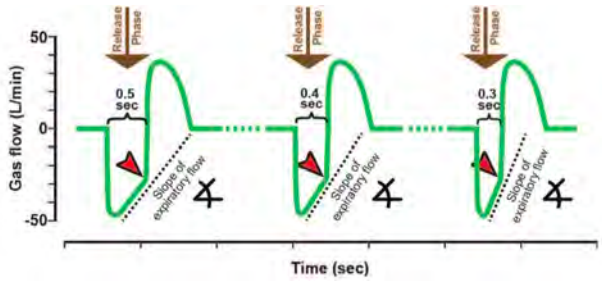
Specific Ventilator Settings

a. P_{HIGH}: xx cmH_2O
b. P_{LOW}: xx cmH_2O
c. T_{HIGH}: xx seconds
d. T_{LOW}: xx seconds
e. Adjust FIO2 to maintain a PaO_2 _____ or S_PO_2 _____%

Recommendations

a. Attempts should be made to minimize release volume to a target of 4 – 8 mL/kg of predicted body weight (PBW)
b. Sedation and analgesia should be titrated to Allow for spontaneous minute ventilation (MV_{SPONT}) to equal approximately thirty percent (30%) of the total minute ventilation (MV_{TOTAL})
c. Once established, avoid adjustments to P_{HIGH} for at least twenty-four (24) hours to maintain optimal "open-lung" ventilation

Setting T_{LOW} in relation to expiratory peak flow



Types of Breaths Observed

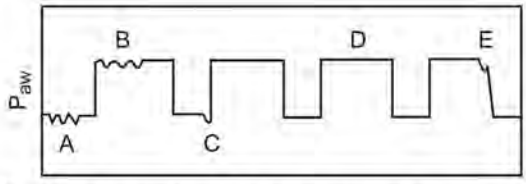


Fig. 1. Breath-type schematic during airway pressure release ventilation. A: Spontaneous breath during low continuous positive airway pressure (CPAP). B: Spontaneous breath during high CPAP. C: Quasi-assisted breath that is synchronized with the ventilator cycling to the high CPAP level. D: Completely passive breath. E: Spontaneous breath that occurs as the ventilator cycles to the lower CPAP level.

References

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2. Zhou Y, Jin X, Lv Y, et al. Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome. Intensive Care Medicine. 2017;43(11):1648-1659. doi:10.1007/s00134-017-4912-z
3. APRV Network. Standard Settings for APRV using the TCAV Method. APRV Network. https://www.aprvnetwork.org/.
4. Kallet RH. Patient-ventilator interaction during acute lung injury, and the role of spontaneous breathing: part 2: airway pressure release ventilation. Respir Care. 2011 Feb;56(2):190-203; discussion 203-6. doi: 10.4187/respcare.00968. PMID: 21333179.

HFNC Cheat Sheet

High Flow Nasal Cannula (HFNC): Is rapidly growing in popularity for patients with acute respiratory failure. Contrary to popular belief it is not just a regular cannula pushing air faster. Works by eliminating dead space associated with anatomical structure of the airway and delivering appropriately humidified oxygen. Eliminates the issue of significant calories/effort in attempting humidify air in acute distress and can reduce airway inflammation.

When to use it: HFNC has been shown to be most effective in patients with hypoxia w/o concomitant hypercarbia

1. HFNC should be considered in acute respiratory failure
2. Patients with elevating oxygenation needs
3. When maintaining appropriate humidification is key
4. Patient unable to tolerate BiPap or unable to remove Bipap when nauseous.

Advantages:

1. More comfortable than BiPap
2. Able to deliver flows 10-60+ lpm
3. Able to deliver & maintain O2 at 37 C with 100% relative humidity (recent literature has demonstrated this to be an important issue in adequate alveolar function & prevention of surfactant loss)
4. Some models are portable
5. Patients with active emesis are less likely to aspirate
6. Breathing treatments are generally deliverable while on HFNC
7. May be able to deliver some PEEP (see below)
8. Minimizes O2 dilution effect.

Disadvantages:

1. Not as effective in CO2 removal as BiPap (and in some pulmonary edema/CHF cases)
2. Non portable models require alternative O2 source during transport.
3. Patients who inspire orally can see diminished effectiveness

Special Considerations:

- Critical to understand model being used. In some HFNC's if operator increases flow rate, fio2 will decrease (washout) & vice versa. Only competent staff should operate to prevent unintended fio2 decrease.
- Literature is mixed regarding whether PEEP is delivered using HFNC. Numerous factors including the mouth being closed, sizing etc. impact PEEP/Dynamic Airway Pressure
- Sizing must be done accurately (manufacturer recommendation) but should be at least 50% of the nare.

Initial Settings:

- 30-55 lpm titrate up/down as necessary
- Patients' acuity will determine ideal Fio2 settings

Manual & Self-Proning Tip Sheet

California Thoracic Society Annual Conference, March 2022

Emma J Blackmon PhD RN CCRN & Brian J Smith MSRC RRT

Manual

- **Pre Prone Check**
  - **Review inclusion criteria**
  - Coordinate/Gather your team(s)
  - Appoint Proning lead
  - Gather Supplies
  - Assess
    - Airway (ETT depth, securement, suction)
    - Skin
    - Sedation/Paralytics
    - Equipment/devices
  - Pre-Oxygenate
  - Protect eyes/mouth/skin
  - Observe tubes/drains
  - Disconnect non-essentials
  - Arrange IVs
  - Procedural Pause
  - Emergency plan

- **Manual Prone**
  - RT leads turn/manages airway
  - Closed loop communication

- **Post Prone Check**
  - Verify patent airway/ETT depth
  - Patient positioning
  - Ensure equipment/lines/drains are not underneath patient
  - Resume all monitoring and re-zero lines
  - Check patency/placement of all lines
  - Resume TF feeding if applicable
  - Ensure HOB flat and patient in Reverse Trendelenberg
  - Check ABG
  - Debrief team/plan for supination

Self-Proning

- **Recommended for:**
  - Patients with persistent hypoxemia despite increased supplemental O2 and for whom endotracheal intubation is not indicated (COVID +)
  - Adjunct, supportive therapy to recruit alveoli and improve gas exchange
- Non-intubated patients who require minimal to no assistance with repositioning
  - Be mindful of contraindications*
- Patient should lie on their abdomen using the arms and pillows for support
- Duration can vary – 30 minutes to 2 hours, 2-4 times a day as tolerated
  - Initial trial ~30 minutes – to assess respiratory/oxygenation requirements
- Consider
  - Hemodynamic or respiratory instability
  - Delirium or confusion
  - Nausea/vomiting
  - Abdominal wounds
  - Advanced pregnancy – consider side lying in discussion with provider
- Monitor for desaturations, clinical worsening or confusion

*Contraindications:

- Facial, pelvic or spinal injuries
- Inability to independently change positions
- Any concern for patient's ability to protect the airway

Advances in Diagnosis and Staging

2:20 p.m. – 3:05 p.m.

HARMEET BEDI, MD
STANFORD UNIVERSITY

Dr. Harmeet Bedi is an Interventional Pulmonologist and Clinical Assistant Professor at Stanford University Medical Center and School of Medicine. He received his medical degree for GMC Patiala (Punjab, India) and completed his Internal Medicine residency and Pulmonary/Critical Care Medicine fellowship from Loma Linda University. He completed an additional fellowship in Interventional Pulmonology from Henry Ford Hospital. His research interests revolve around novel bronchoscopic technologies, lung nodule diagnosis, and lung transplant-related airway complications.

Advances in Diagnosis & Staging

Harmeet Bedi, MD
Clinical Assistant Professor
Director of Interventional Pulmonology & Bronchoscopy

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Disclosures

- No conflicts of interest

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Outline

- Lung Cancer Staging
- Lung Nodule Diagnosis
  - Background
  - Navigation Bronchoscopy
  - Radial Endobronchial Ultrasound (rEBUS)
  - Robotic Bronchoscopy
  - Cryobiopsy
  - Cone-Beam CT-guided Bronchoscopy

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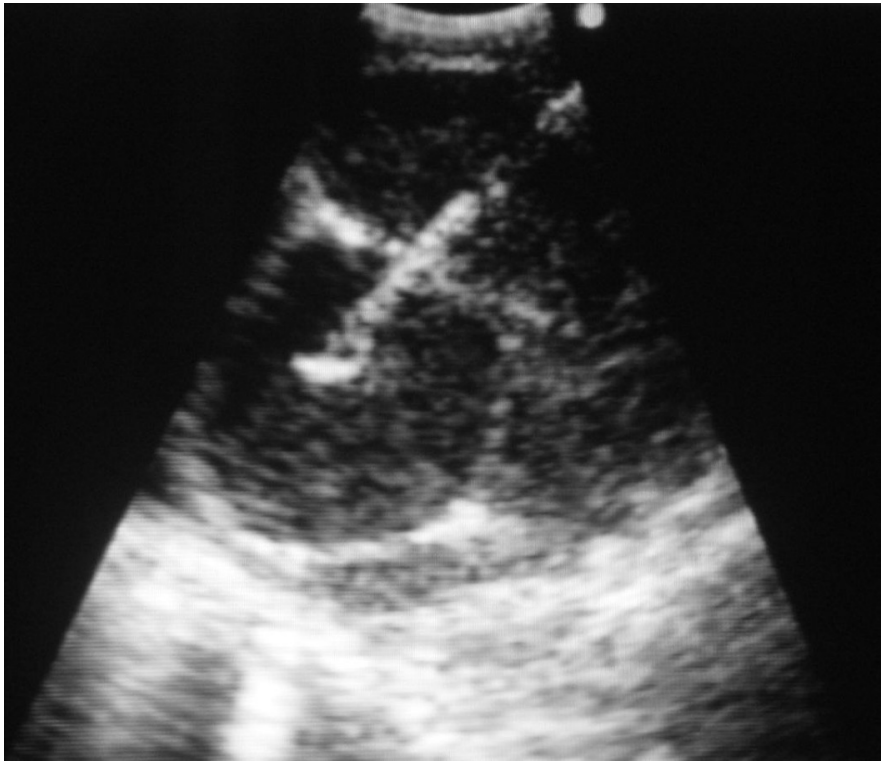
Staging - Endobronchial Ultrasound (EBUS)



- Multiple systematic reviews and meta-analyses
- Pooled sensitivity for EBUS & lung cancer staging: 88-93%
- EBUS-TBNA equivalent to mediastinoscopy
  - Sensitivity
  - Specificity
  - NPV
  - Diagnostic Accuracy

GuP. et al. EurJ Ca. 2009
Adams K. et al. Throax. 2009
Zhang R. et al. EurJ Ca. 2013
Ge, X., Guan, W., Han, F. et al. Lung 2015

*and Hojoong Kim, MD, PhD**

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CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Methods for Staging Non-small Cell Lung Cancer

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Gerard A. Silvestri, MD, FCCP; Anne V. Gonzalez, MD; Michael A. Jantz, MD, FCCP; Mitchell L. Margolis, MD, FCCP; Michael K. Gould, MD, FCCP; Lynn T. Tanoue, MD, FCCP; Loren J. Harris, MD, FCCP; and Frank C. Detterbeck, MD, FCCP

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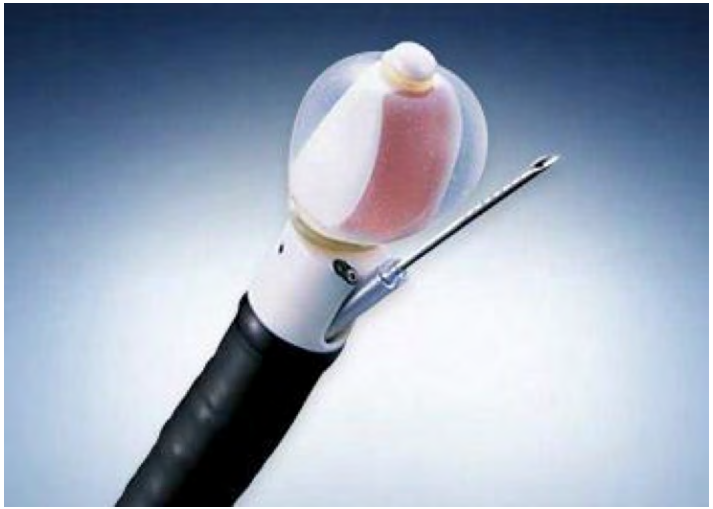
4.4.4.3. In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B)**.**

Remark: This recommendation is based on the availability of these technologies (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) and the appropriate experience and skill of the operator.

Remark: In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (eg, mediastinoscopy, video-assisted thoracic surgery [VATS], etc) should be performed.

Remark: The reliability of mediastinal staging may be more dependent on the thoroughness with which the procedure is performed than by which test is used.

4.4.6.2. In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B)**.**



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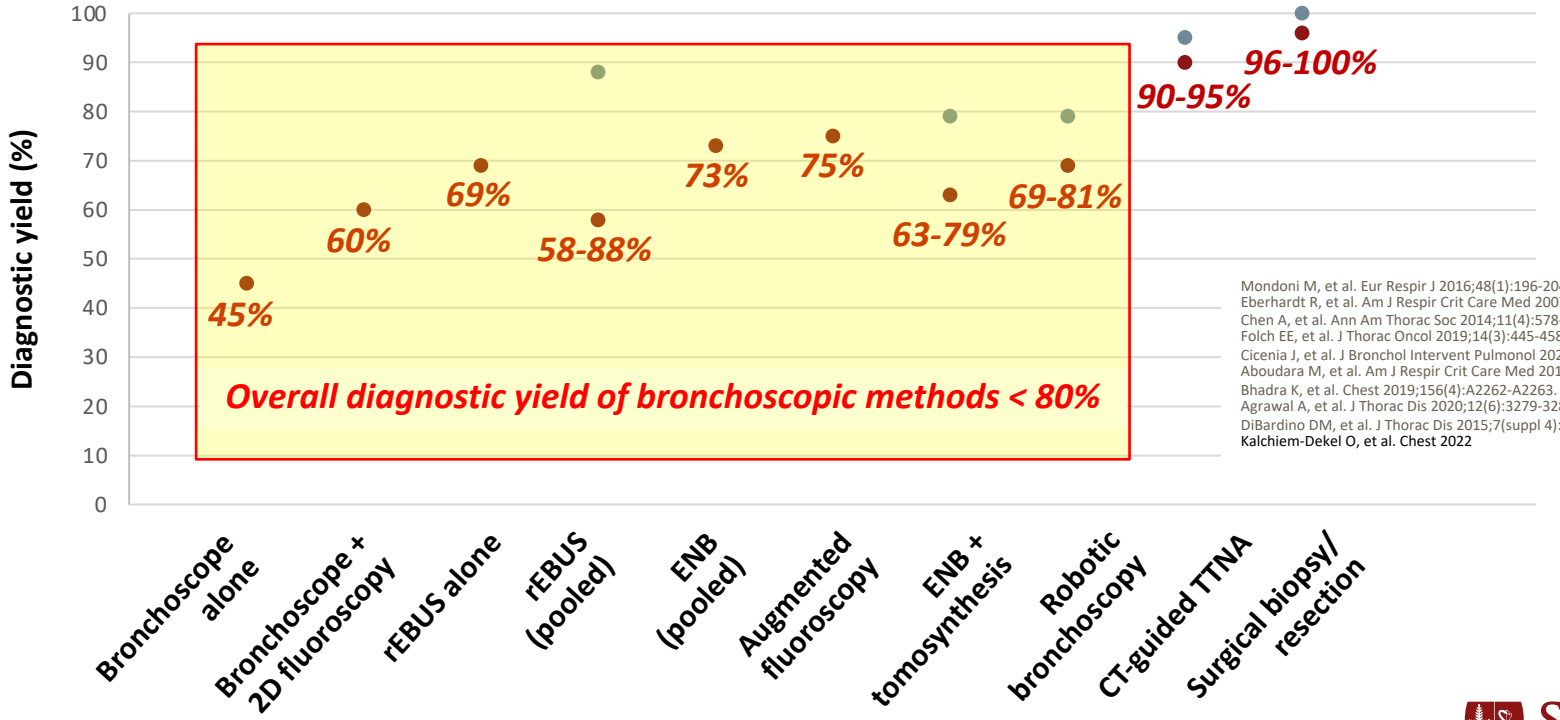
Lung Nodule Diagnosis



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Cicenia J, et al. J Bronchol Intervent Pulmonol 2020 (Online ahead of print).
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Bhadra K, et al. Chest 2019;156(4):A2262-A2263.
Agrawal A, et al. J Thorac Dis 2020;12(6):3279-3286.
DiBardino DM, et al. J Thorac Dis 2015;7(suppl 4):S306-S316.
Kalchiem-Dekel O, et al. Chest 2022

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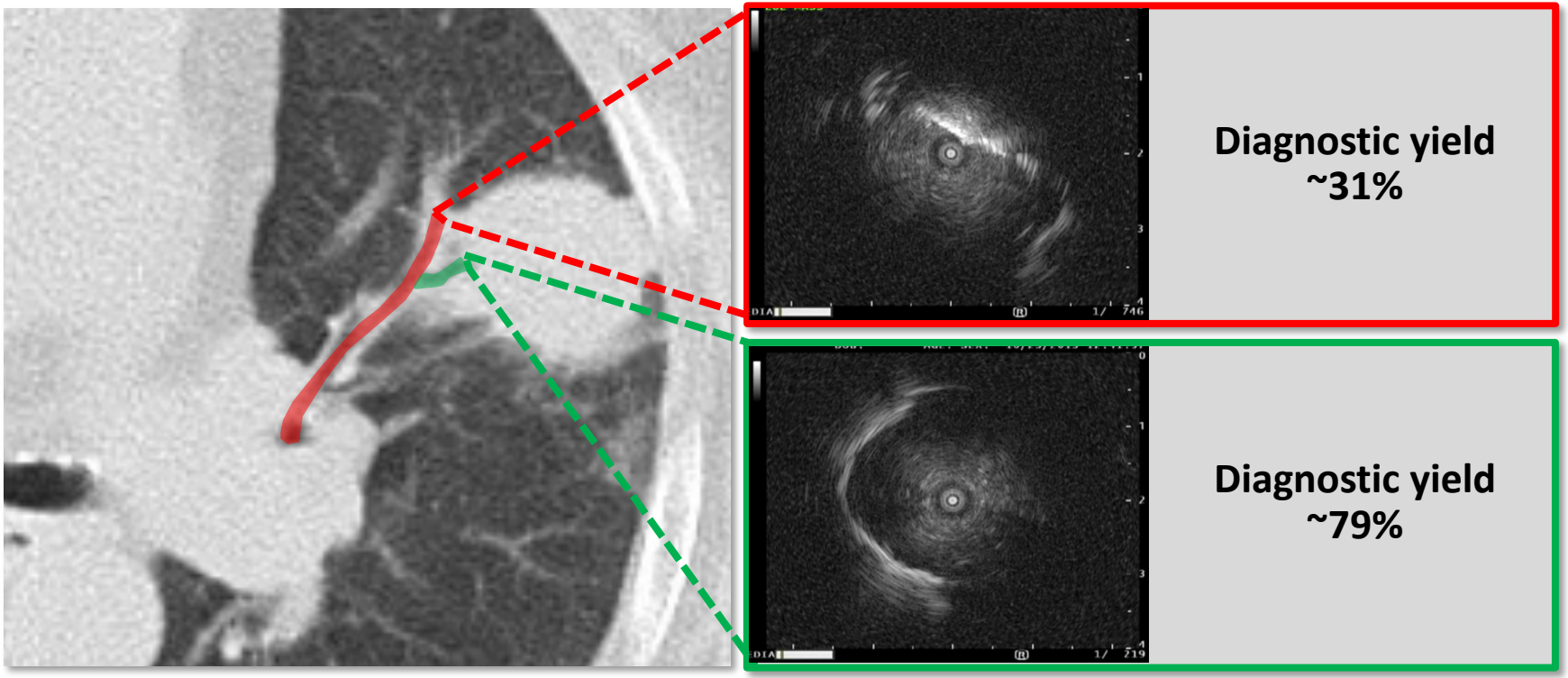
Limitations of Bronchoscopic Methods

- Many nodules invisible on 2D fluoroscopy (*~40% in NAVIGATE*)
- Absence of "bronchus sign" negatively impacts yield
- Nodule-specific factors (size, location, density) affect procedural success
- Reliance on historical imaging and "virtual" guidance (*e.g.*, EMN)
- CT-to-body divergence thwarts all techniques

Seijo LM, et al. Chest 2010;138(6):1316-1321.
Folch EE, et al. J Thorac Oncol 2019;14(3):445-458.
Shaller BD, et al. Exp Rev Respir Med 2020;14(7):655-669.
Pritchett MA, et al. J Thorac Dis 2020;12(4):1595-1611.

Limitations of Bronchoscopic Methods

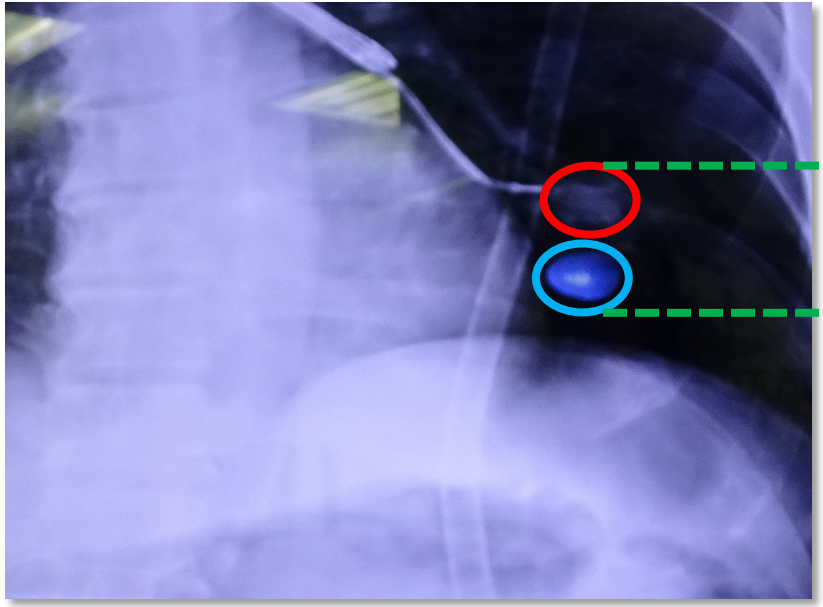
An illustrative example:



Shaller BD, et al. Exp Rev Respir Med 2020;14(7):655-669.

Seijo LM, et al. Chest 2010;138(6):1316-1321.

Limitations of Bronchoscopic Methods



= fluoroscopically visible nodule

= nodule as marked on planning CT < 5 min prior

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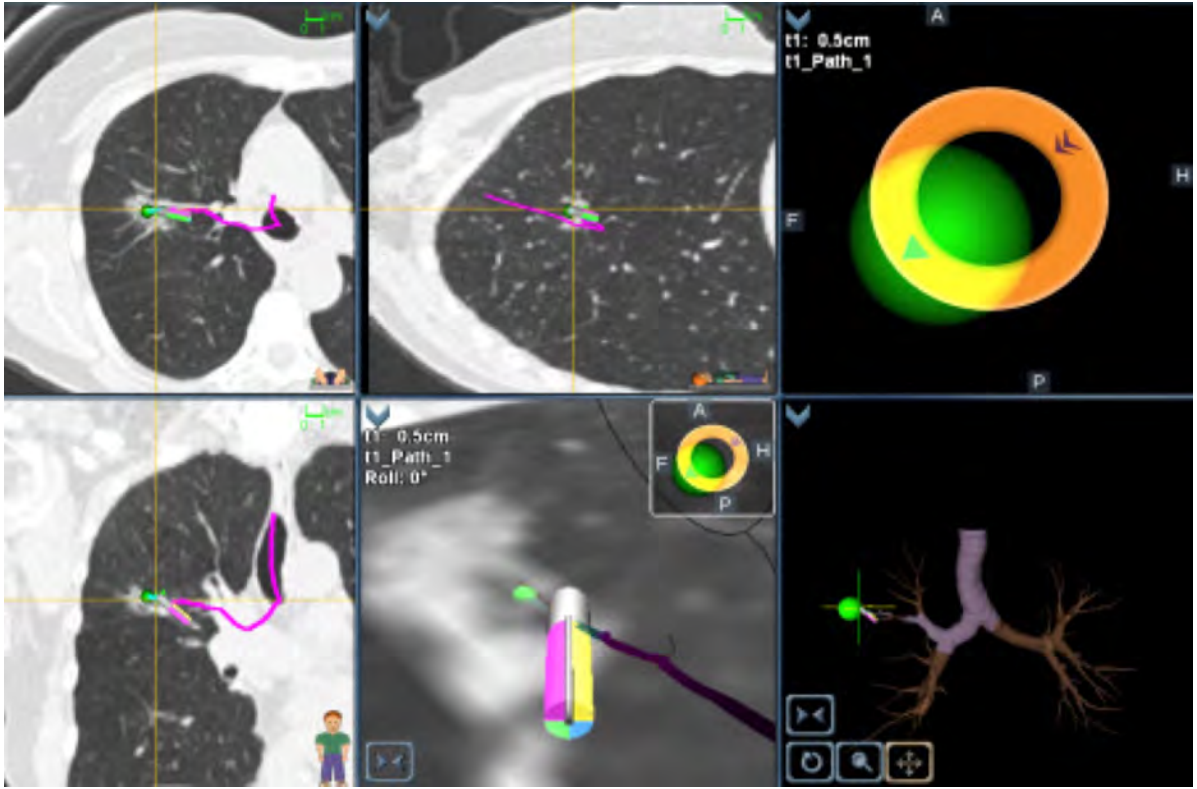
General Considerations

- The following approaches are in the context of solitary pulmonary nodules (SPNs)
- Biopsy approach decision should be based upon local resources and expertise
- Positive result: malignancy OR definitive benign diagnosis (i.e. sarcoidosis, interstitial lung disease, infection)
- NORMAL lung tissue on biopsy = NON-Diagnostic
- IF there is any suspicion for metastatic disease, then the procedure (technique) chosen should be capable of simultaneously diagnosing AND staging during the same procedure
- Getting a diagnosis is not enough
- Era of MOLECULAR MARKERS

Lung Nodules – Navigation Bronchoscopy



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Lung Nodules – Radial Endobronchial Ultrasound (rEBUS)

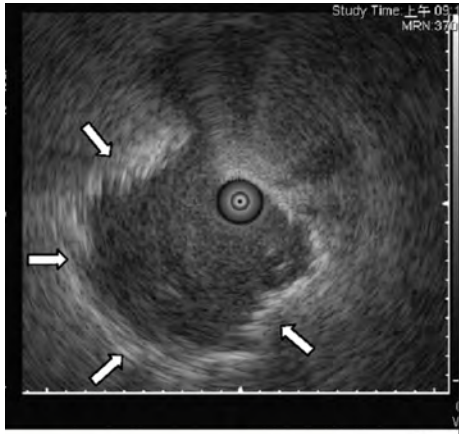

Table 2—*Inverse Weighted Diagnostic Yield Overall and by Modality*

Technology	Studies, No.	Weighted Proportion, %	95% CI	Q Statistic	Q *P* Value
VB	10	72.0	(65.7-78.4)	21.0	.01
ENB	11	67.0	(62.6-71.4)	13.3	.21
GS	10	73.2	(64.4-81.9)	63.8	<.0001
U	11	70.0	(65.0-75.1)	15.2	.12
R-EBUS	20	71.1	(66.5-75.7)	84.2	<.0001
All	39	70.0	(67.1-72.9)	119.4	<.0001

CHEST Original Research
PULMONARY PROCEDURES
Meta-analysis of Guided Bronchoscopy for the Evaluation of the Pulmonary Nodule
Jessica S. Wang Memoli, MD; Paul J. Nietert, PhD; and Gerard A. Silvestri, MD, FCCP

Lung Nodule Diagnosis

Lesions > 20 mm			Lesions ≤ 20 mm		
Lesions, No.	Diagnoses Made, No.	Yield, %	Lesions, No.	Diagnoses Made, No.	Yield, %
9	6	66.7	15	8	53.3
69	57	82.6	81	59	72.8
12	11	91.7	18	8	44.4
11	8	72.7	2	1	50
23	17	73.9	31	23	74.1
12	10	83.3	26	21	80.8
39	32	82.1	11	2	18.2
20	15	75	20	10	50
30	20	66.7	9	7	77.8
19	18	94.7	77	42	54.5
86	78	90.7	37	28	75.7
57	40	70.2	35	22	62.9
84	65	77.4	74	41	55.4
17	16	94.1	15	11	73.3
75	55	73.3	23	13	56.5
9	7	77.8	4	3	75
0	0		100	46	46
46	37	80.4	7	3	42.9
57	44	77.2	14	5	35.7
92	74	80.4	30	22	73.3
Weighted Dx Yield:		**82.5%**			**60.9%**

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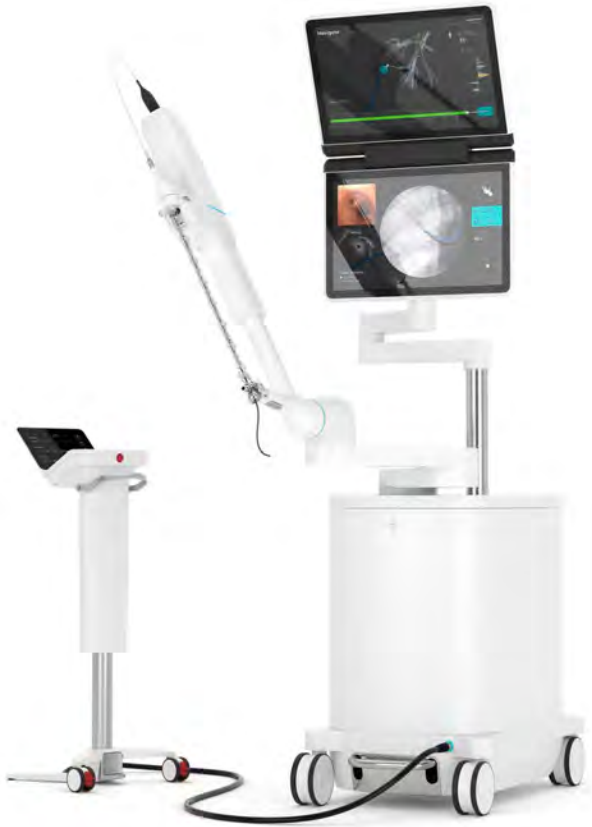
Lung Nodules – Robotic Bronchoscopy



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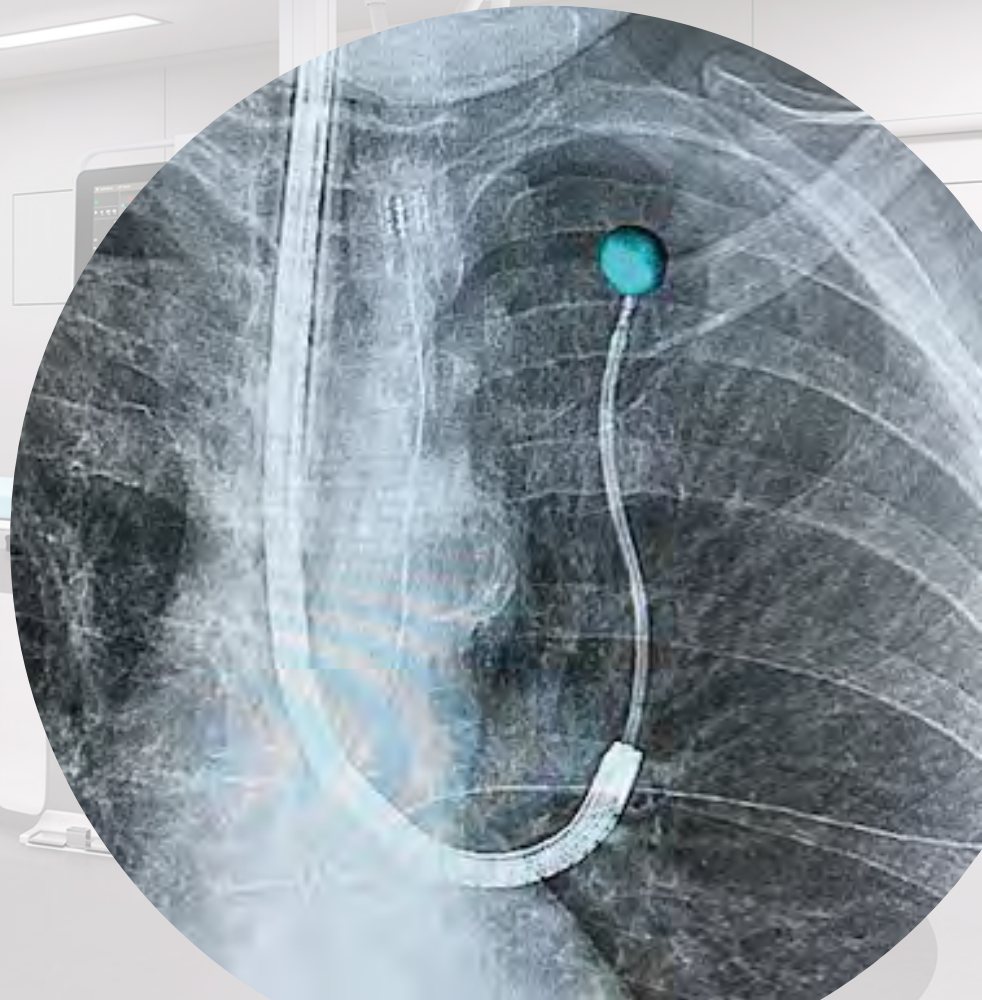
Lung Nodules – Robotic Bronchoscopy

- Fine-movement, reticulating bronchoscopic catheter
- Ability to go "hands-free" with reliable stability
- Synergy with cone-beam CT-guided bronchoscopy
- Potential for therapeutic delivery
- Limited data, but numerous ongoing studies
  - Thus far, diagnostic yield: 77% - 82%

Agrawall A, et al. Ann Thoracic 2022
Kalchiem-Dekel O, et al. Chest 2022
Chen AC, et al. Chest 2021

CBCT-Guided Bronchoscopy



Lung Nodules – Cone-Beam CT-Guided (CBCT) Bronchoscopy

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CBCT-Guided Bronchoscopy

- Intraprocedural fluoroscopy + CT capabilities
- CTs can be used to produce augmented fluoroscopy
  - Augmented fluoroscopy: ability to take information from a CT and project it onto a fluoroscopic x-ray
  - Philips: LungSuite, Siemens: iGuide
- Converts bronchoscopy into a true **"image-guided procedure"**
- Philips (Allura and Azurion), Siemens (Zee, Zeego, Pheno, & CIOs), GE (OEC 3D)

Studies	Design	Procedural modalities	CBCT used	Overall diagnostic yield	Lesions	Nodule size	Radiation information
Pritchett *et al.*	Retrospective study	CBCT + ENB + AF	Allura Xper FD20; Philips	83%	93	Median nodule size 20 (range, 7–55) mm	2.0 mSv per CBCT run, average 1.5 runs, 3.5 mSv
Sobieszczyk *et al.*	Retrospective study	CBCT + ENB + R-EBUS + TBAT	Not reported	77.2%	22	Median nodule size 21 (range, 7–52) mm	Not reported
Casal *et al.*	Prospective observational cohort study	CBCT + R-EBUS + Ultrathin Bronchoscope	Not reported	70%	20	Median nodule size 21 (range, 11–30) mm	Estimated to range between 8.6 to 23 mSv, average fluoroscopy time 8.6 minutes (range, 5–15.4 minutes)
Bowling *et al.*	Retrospective study	CBCT + ENB + TBAT	Artis Zeego; Siemens	71%	14	Median nodule size of 18 (range, 9–30) mm	4.3 mSv (range, 3 to 5 mSv), and the average fluoroscopic time was 17 minutes (range, 2 to 44 minutes)
Ali *et al.*	Prospective study	CBCT + VBN + Ultrathin Bronchoscope	Artis Zeego; Siemens	90%	40	Median nodule size 20 (range, 9–30) mm	Not reported

Cheng GZ, Liu L, Nobari M, Miller R, Wahidi M. Cone beam navigation bronchoscopy: the next frontier. J Thorac Dis 2020;12(6):3272-3278.

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Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules

Michael A. Pritchett, DO, MPH,† Stéphanie Schampaert, PhD,‡ Joris A.H. de Groot, PhD,‡ Charles C. Schirmer, MD,§ and Imramsjah van der Bom, PhD‡*

- Lesion size (median, mm): 16.0mm
- Bronchus sign: 39%
- Lesions ≤ 20.0mm: 65/92 (71%)
- Lesions ≤ 10.0mm: 19/92 (21%)
- Overall DY: 83.7%
- Overall diagnostic accuracy: 93.5%

TABLE 3. Diagnostic Performance of ENB and CBCT With Augmented Fluoroscopy

Diagnostic Performance	Diagnostic Yield (95% CI)	Diagnostic Accuracy (95% CI)*
All lesions (n = 92) (mm)	83.7% (74.8%-89.9%)	93.5% (86.5%-97.0%)
Lesions ≤ 10 (n = 19)	84.2% (62.4%-94.5%)	89.5% (68.6%-97.1%)
Lesions ≤ 20 (n = 65)	83.1% (72.2%-90.3%)	90.8% (81.3%-95.7%)
Lesions > 20 (n = 27)	96.3% (81.7%-99.8%)	100% (87.5%-100%)
Minimum sensitivity for malignancy†	91.3% (82.3%-96.0%)	
Maximum sensitivity for malignancy‡	95.5% (87.5%-98.4%)	
Minimum prevalence of malignancy‡	71.7% (61.8%-79.9%)	
Maximum prevalence of malignancy†	75.0% (65.3%-82.7%)	
Minimum negative predictive value	79.3% (61.6%-90.2%)	
Maximum negative predictive value	89.7% (73.6%-96.4%)	

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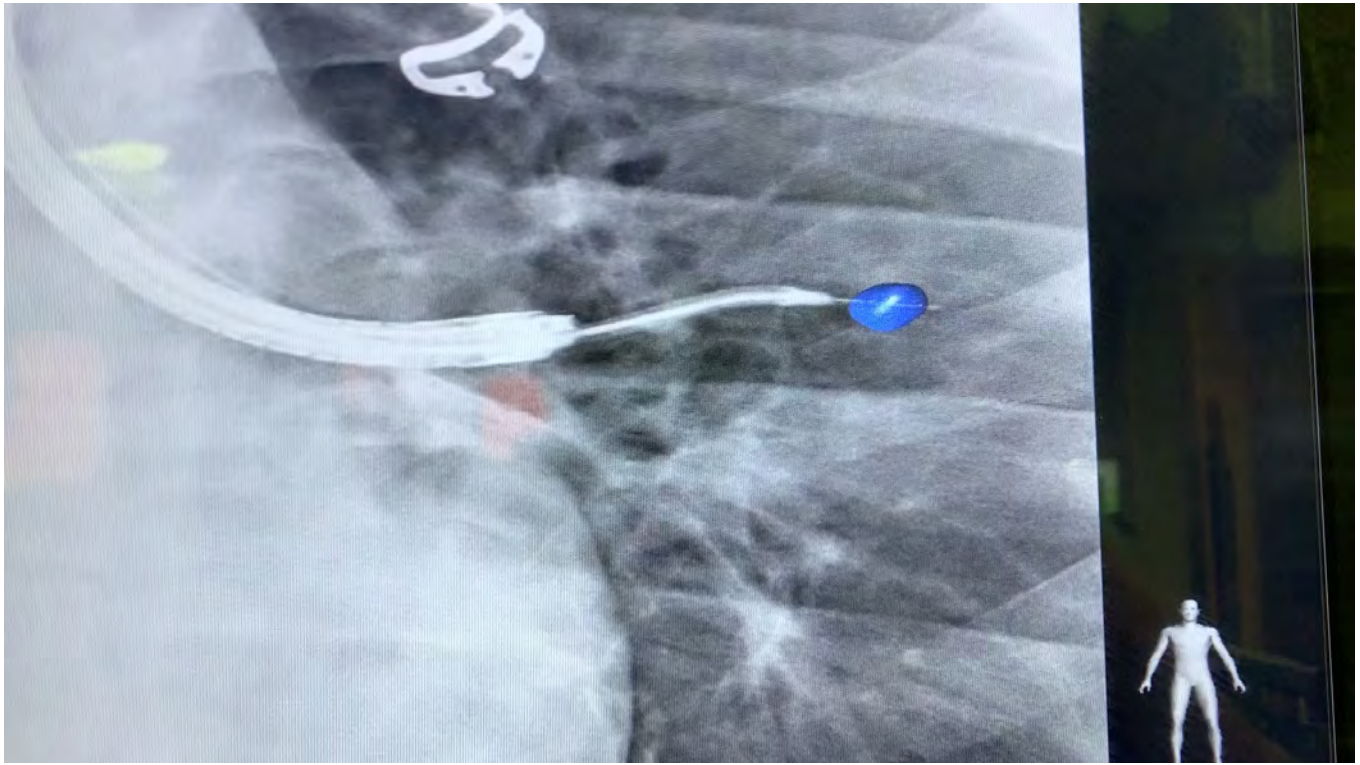
Lung Nodules – Cone-Beam CT-Guided (CBCT) Bronchoscopy



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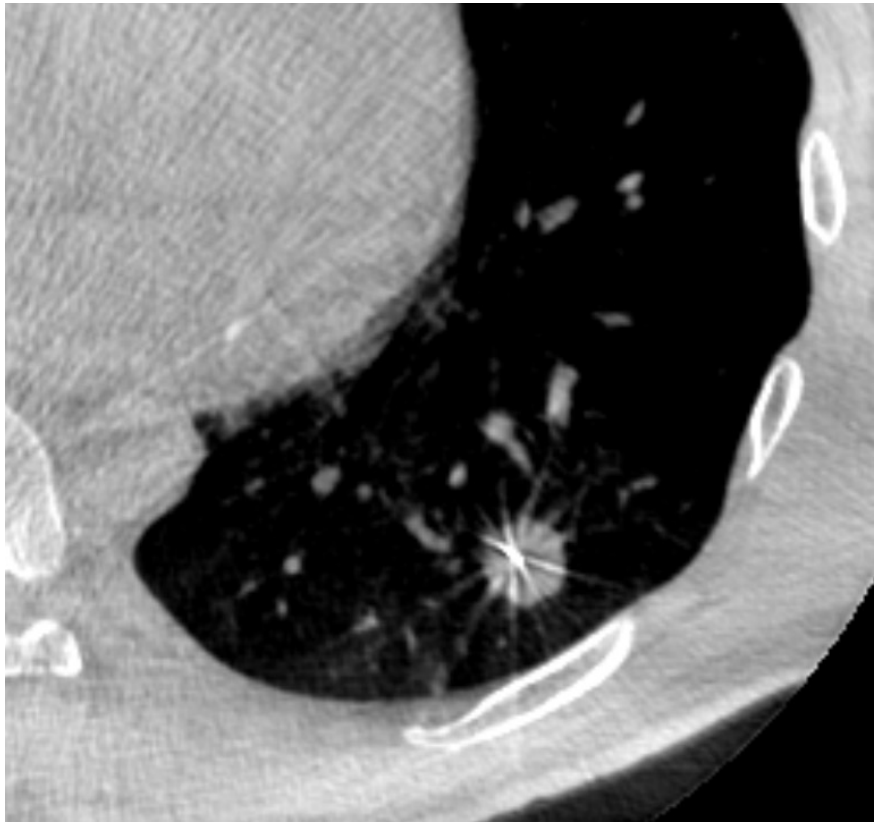
Lung Nodules – Cone-Beam CT-Guided (CBCT) Bronchoscopy



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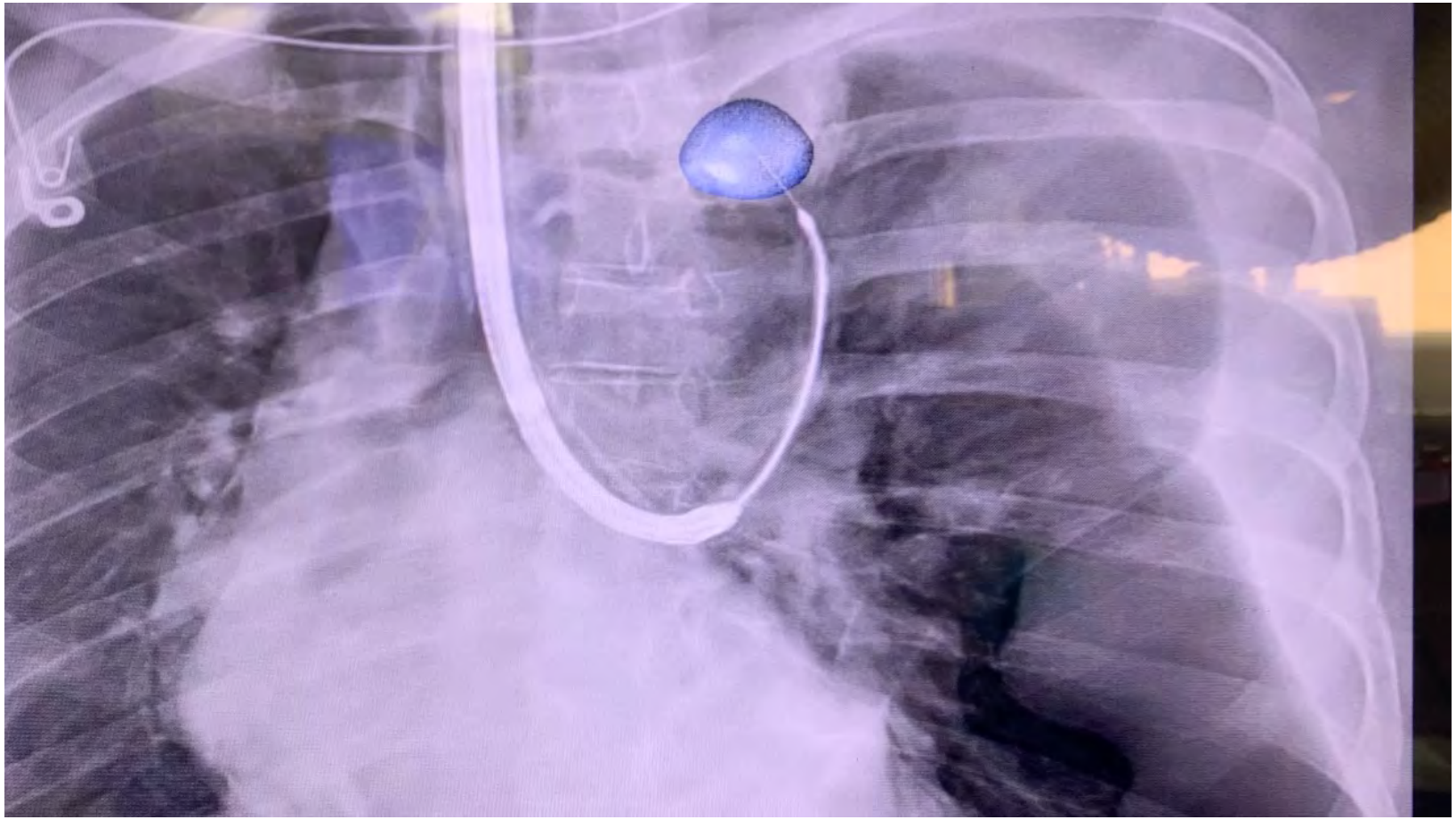

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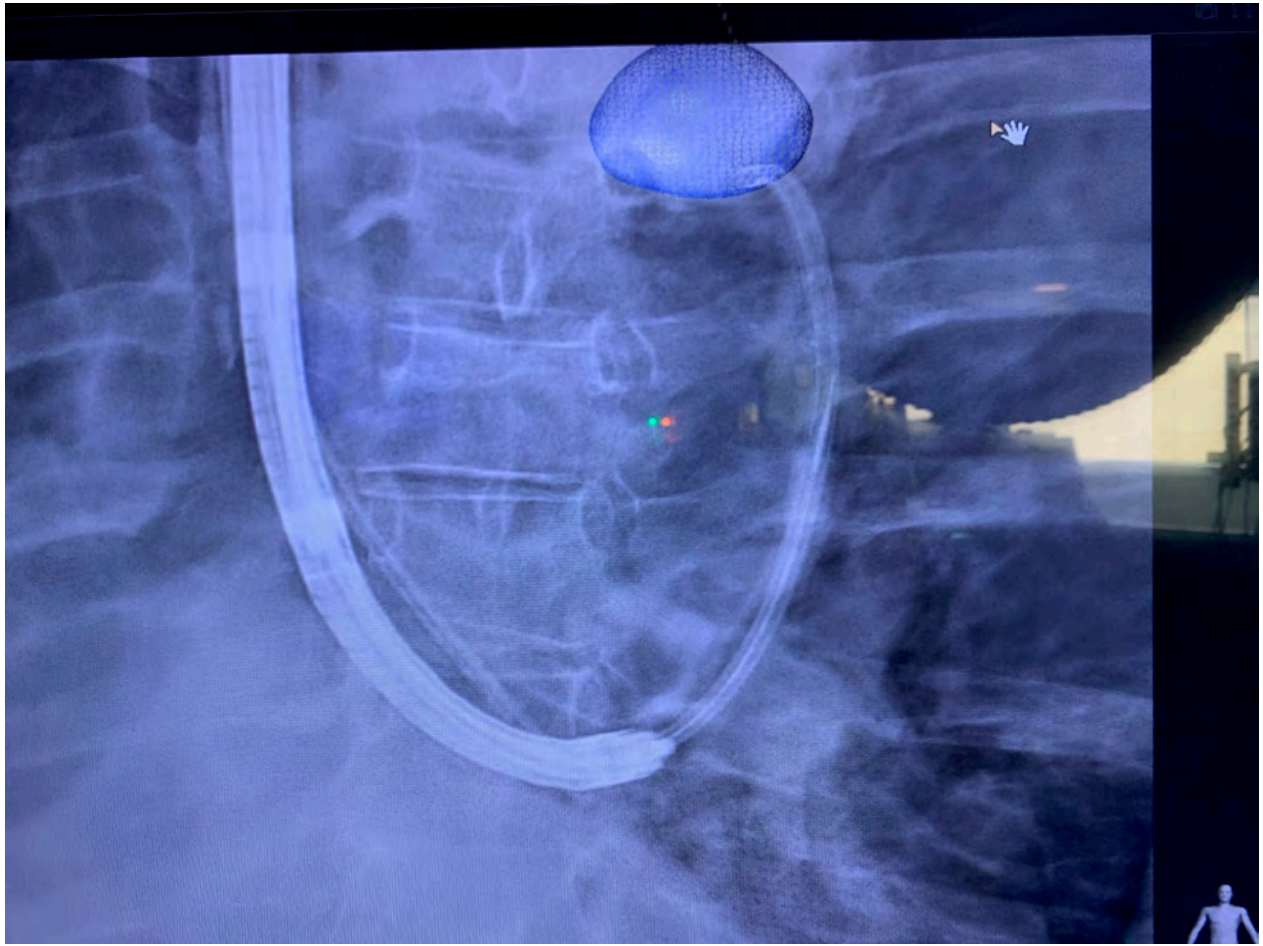

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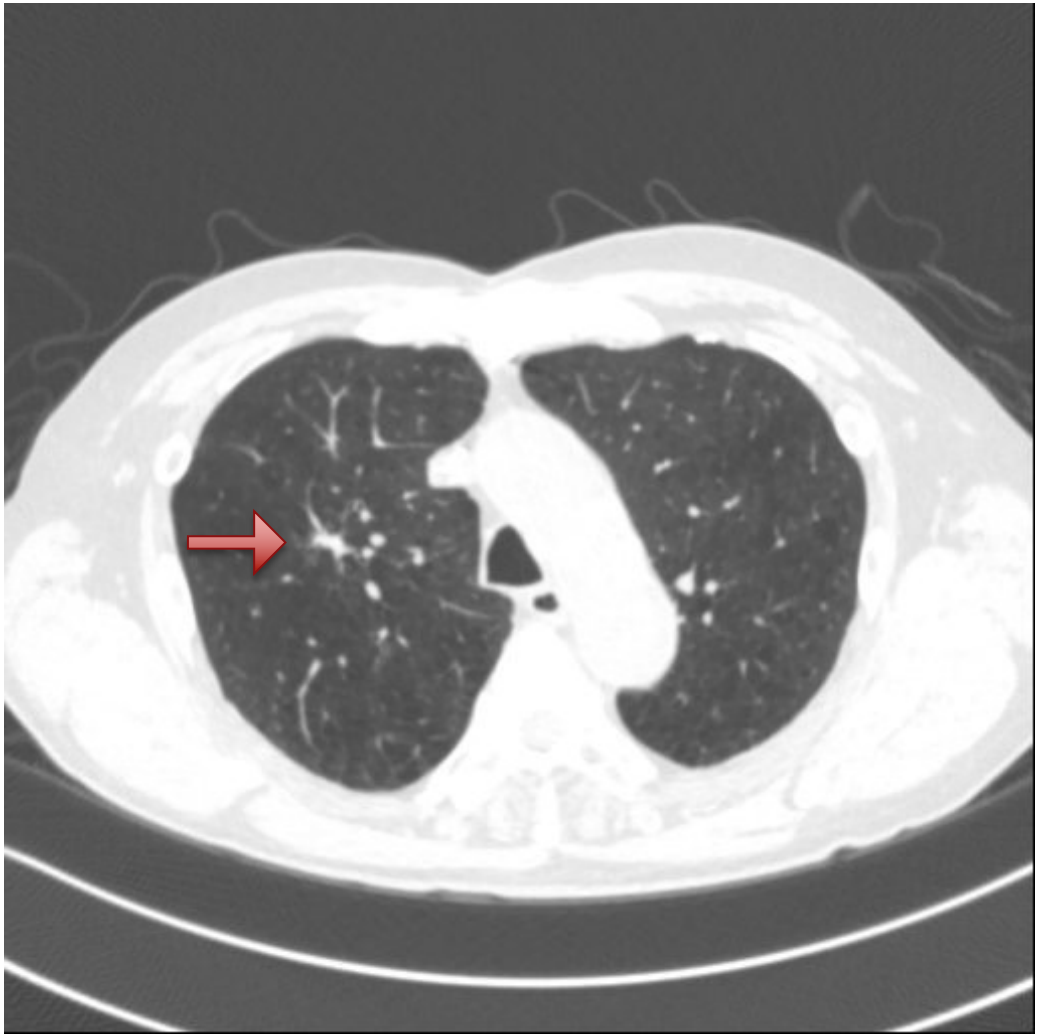

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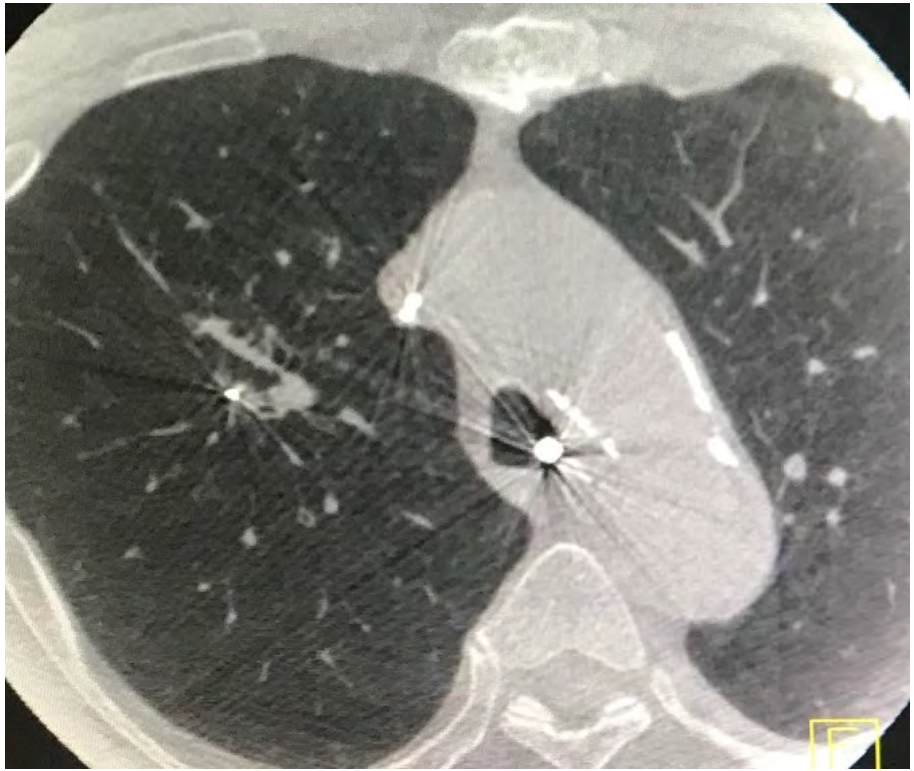

Dx: Invasive lung adenocarcinoma

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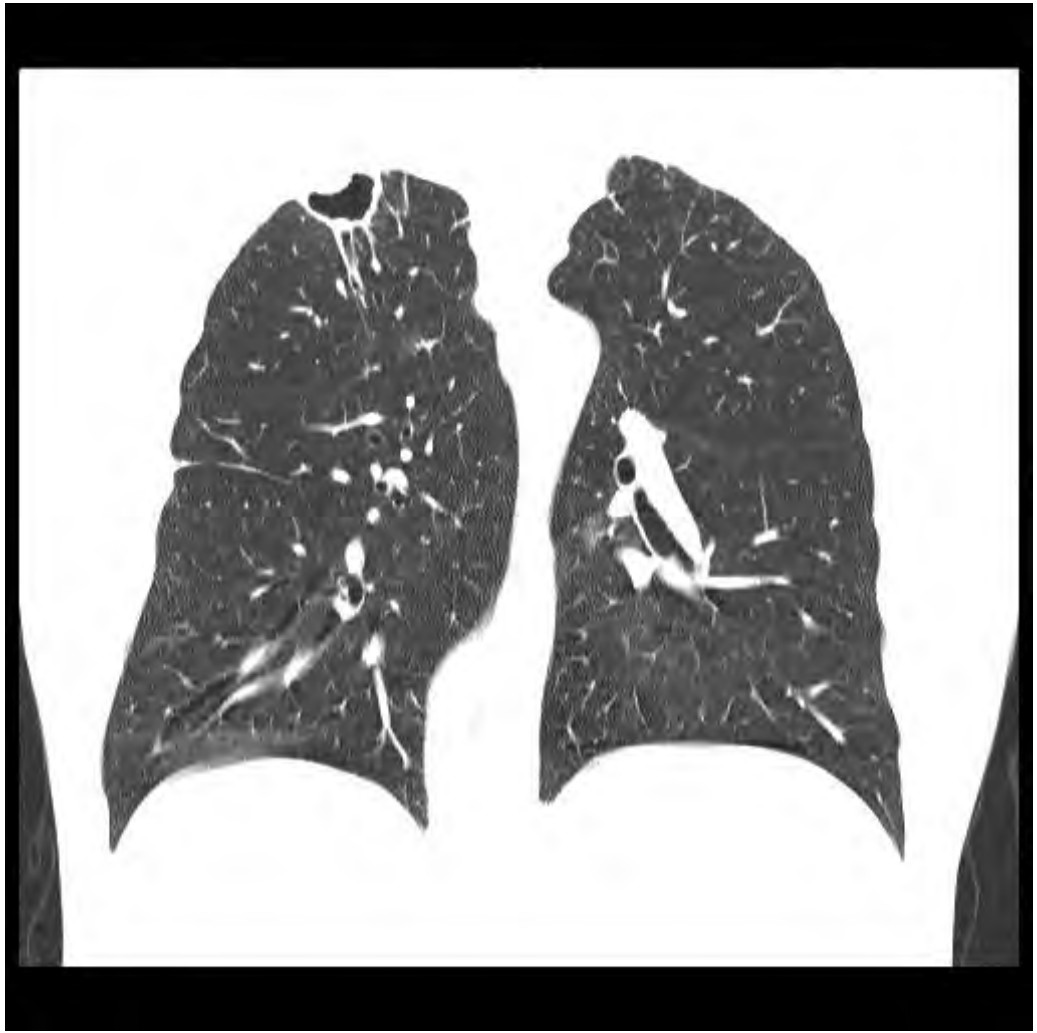

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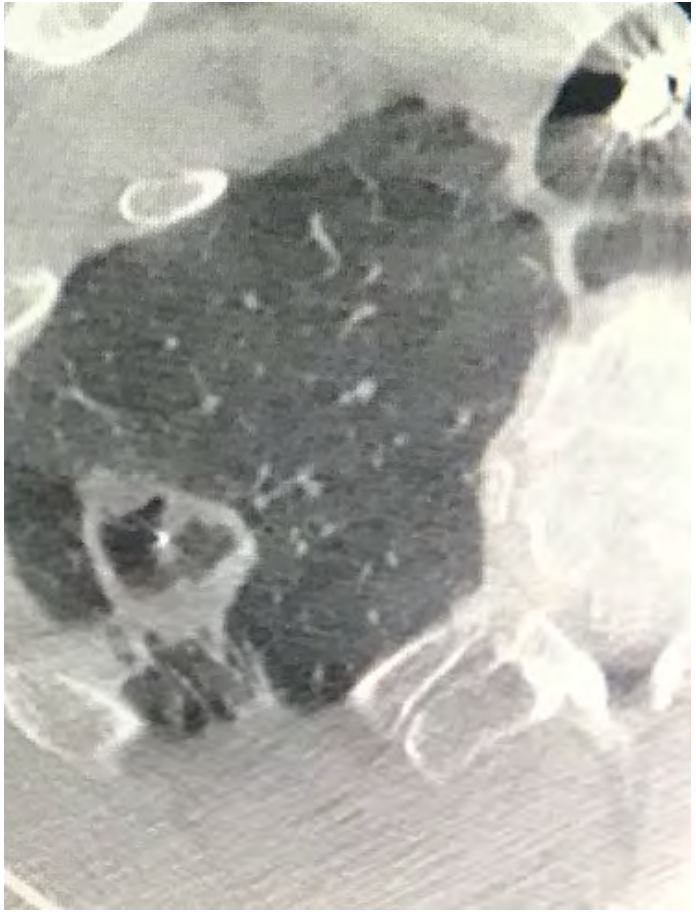

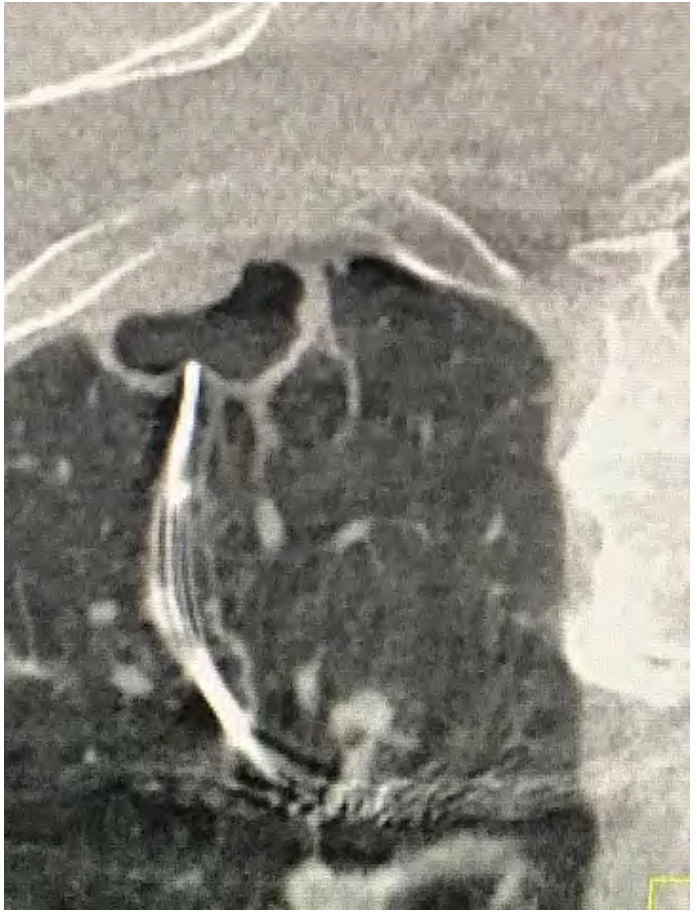

Dx: Mycobacterium xenopi

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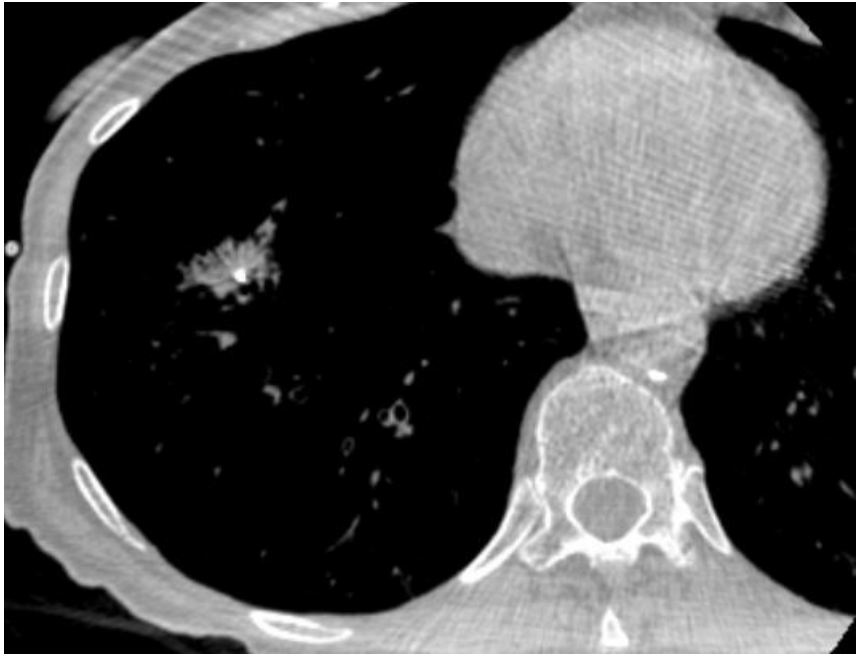
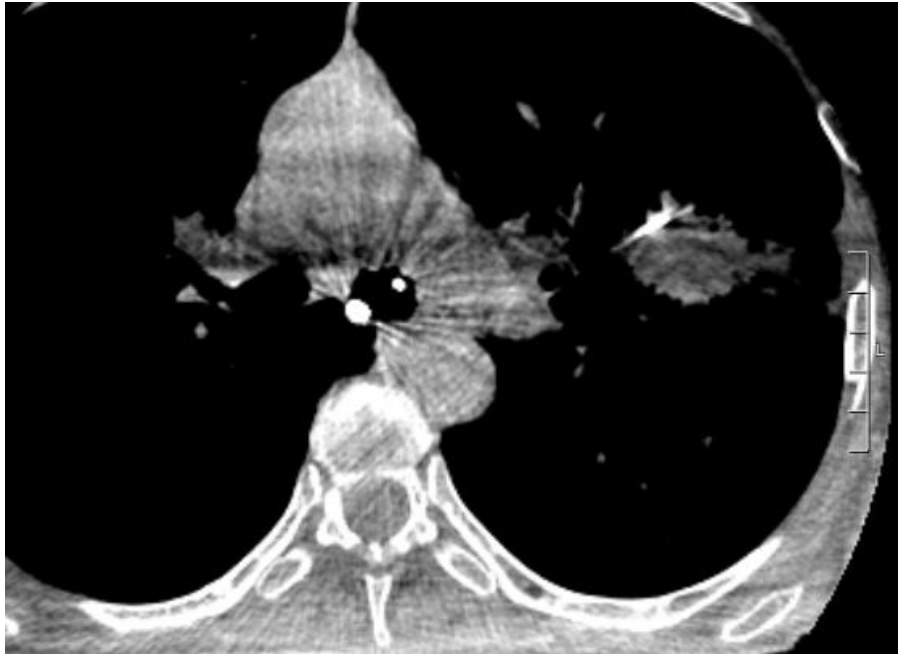


Dx: Adenocarinoma



Dx: Squamous cell carcinoma

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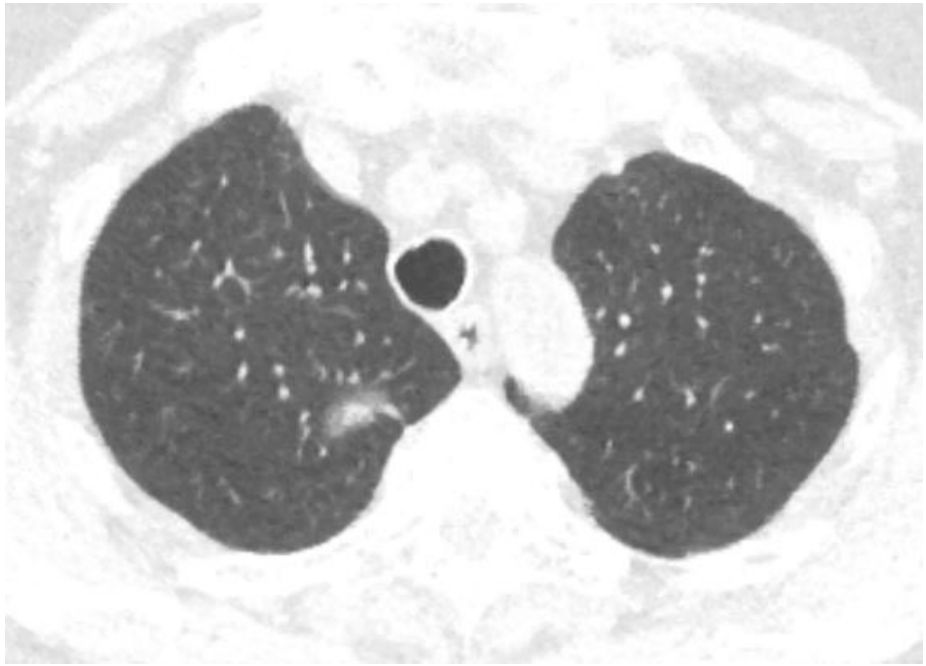

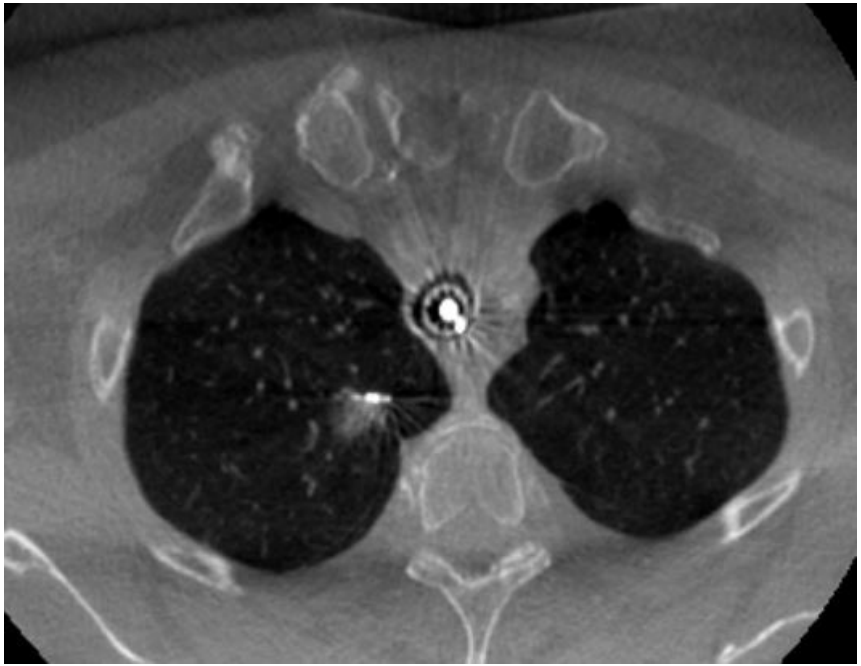

Dx: Well-differentiated adenocarcinoma

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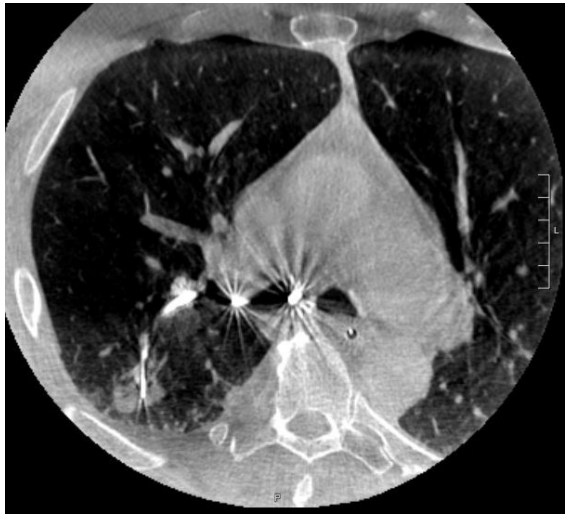

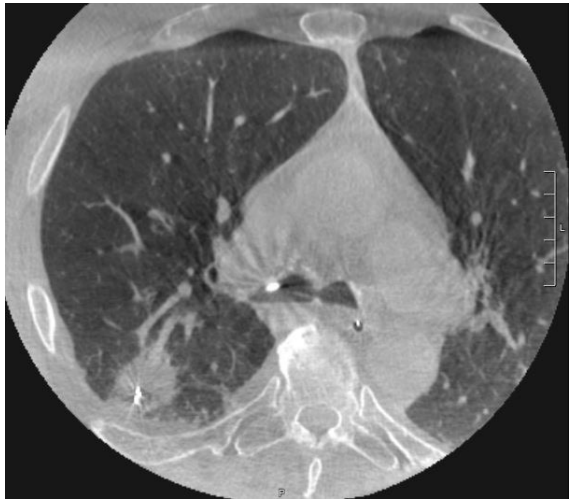

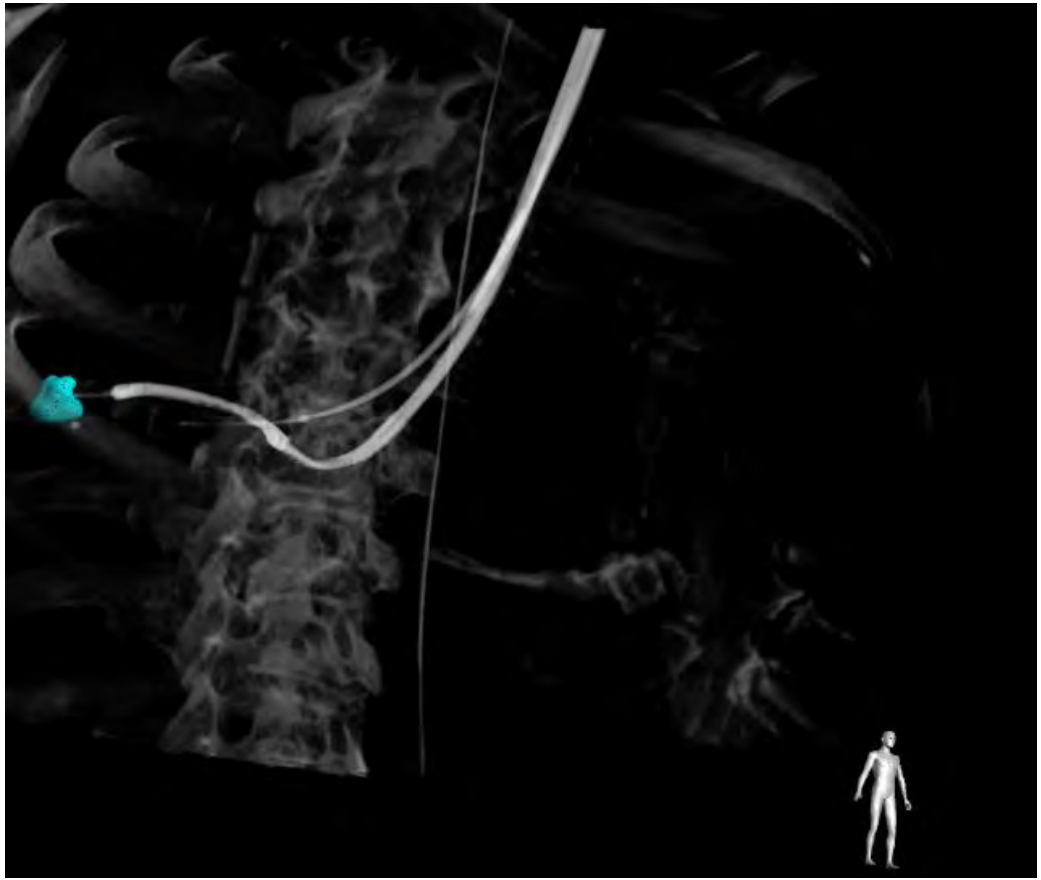

Dx: Invasive adenocarinoma

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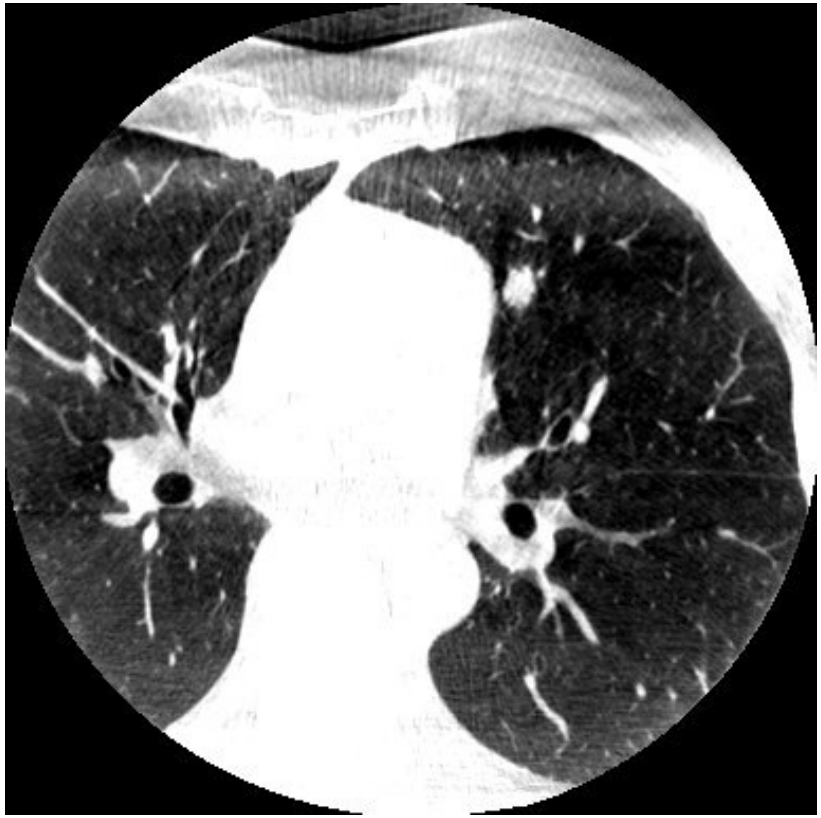

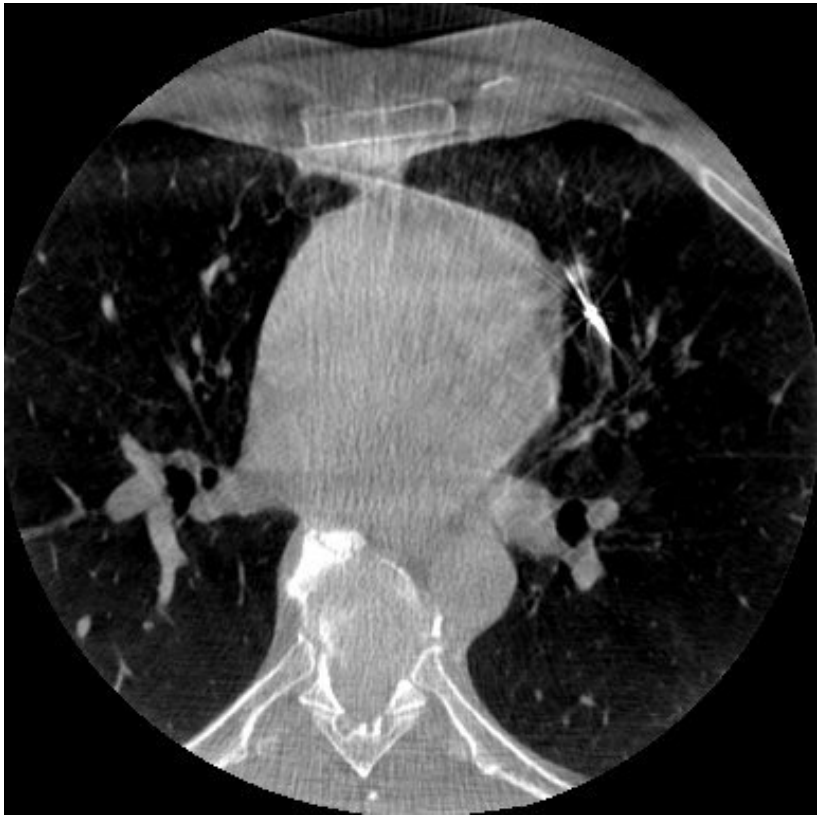

Dx: Squamous cell carcinoma

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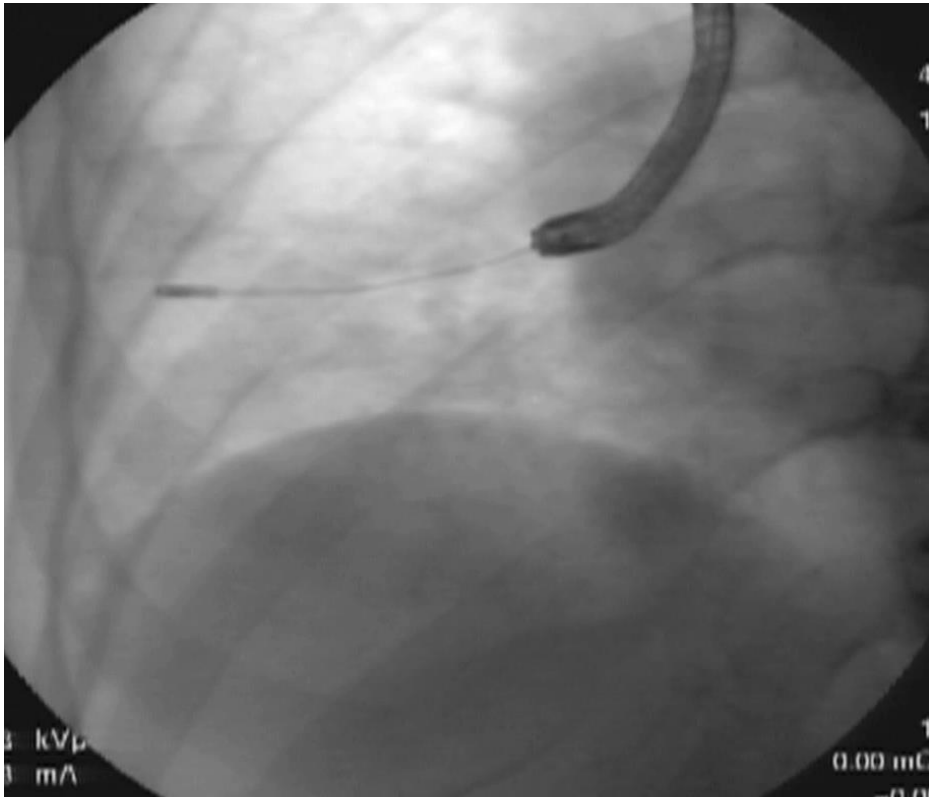
Cryobiopsy For Lung Nodule Diagnosis



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Role of Transbronchial Cryobiopsy

- Flexible cryoprobe for freezing and extracting larger biopsy specimens
  - Reusable (1.9 mm, 2.4 mm) or disposable (1.1 mm, 1.7 mm, 2.4 mm)
  - Disposable 1.1mm and 1.7mm cryoprobes will work with therapeutic/robotic bronchoscopes

Benefits:

- Large, histopathologic specimen
- No crush artifact (*vs* forceps)
- Sample tissue adjacent to probe tip
- High diagnostic yield
- Greater detection of EGFR mutations?

Risks:

- Bleeding (central lesions)
  - *Prophylactic balloon blocker*
- Pneumothorax (subpleural lesions)
  - *CBCT to check distance to pleura and adjust accordingly*

Schuhmann M, et al. Eur Respir J 2014;43(1):233-239.
Taton O, et al. Pulm Med 2018:6032974 (eCollection).
Kho SS, et al. ERJ Open Res 2019;5(4):00135-2019.
Torky M, et al. Clin Respir J 2020 (Online ahead of print).
Haentschel M, et al. Lung Cancer 2020;141:56-63.

- Carbon dioxide gas
- Disposable cryoprobes (1.1, 1.7, and 2.4mm)
- Increased reproducibility for freezing time/power
- Lightweight cryoprobes (no metal kinking)
- Increase length (compatible with all navigation-based catheters/robots)
- Cryotherapy unit can be stacked within APC stand/unit
- 1.1mm cryoprobe
  - Less catheter deflection
  - Ability to pull specimen through working channel

ORIGINAL ARTICLE

WILEY

The LungVision navigational platform for peripheral lung nodule biopsy and the added value of cryobiopsy

Barak Pertzov[1,2] | Evgeni Gershman[1,2] | Shimon Izhakian[1,2] | Moshe Heching[1,2] | Shai Moshe Amor[1,2] | Dror Rosengarten[1,2] | Mordechai Reuven Kramer[1,2]

ORIGINAL ARTICLE

Efficacy of Radial Endobronchial Ultrasound (R-EBUS) guided transbronchial cryobiopsy for peripheral pulmonary lesions (PPL's): A systematic review and meta-analysis

P.B. Sryma[a], S. Mittal[a], N.K. Madan[b], P. Tiwari[a], V. Hadda[a], A. Mohan[a], R. Guleria[a], K. Madan[a,*]

Original Article

A pilot study of the ultrathin cryoprobe in the diagnosis of peripheral pulmonary ground-glass opacity lesions

Simin Jiang[1,2,3#], Xiaojun Liu[1,2,4#], Junxiang Chen[1,2,3], Haifeng Ma[5], Fangfang Xie[1,2,3], Jiayuan Sun[1,2,3]

7 pages

Research Article

Diagnostic Yield of Combined Pulmonary Cryobiopsies and Electromagnetic Navigation in Small Pulmonary Nodules

Olivier Taton,[1] Benjamin Bondue,[1] Pierre Alain Gevenois,[2] Myriam Remmelink,[3] and Dimitri Leduc[1]

Median size: 25.0mm, 63 patients
Diagnostic yield: 81.8% (for <20mm: 72.2%)
9/63 patients had ONLY diagnostic Cryobiopsy
Majority underwent 2.4mm cryoprobe (3 seconds)
1 PTX

Pooled cryo diagnostic yield: 77%
Pooled TBBx diagnostic yield: 72%
No significant difference

23 GGOs (12 pure GGNs, 11 part-solid), ultrathin scope
Mean size: 21.58mm
Diagnostic yield: 82.6%
1.1mm cryoprobe (3-5 seconds)
0 PTX

32 patients, ENB guided
Mean diameter: 16mm
TBLC diagnostic yield: 69%
TBBx diagnostic yield: 38%
1.9mm cryoprobe (7-8 seconds)
1 PTX

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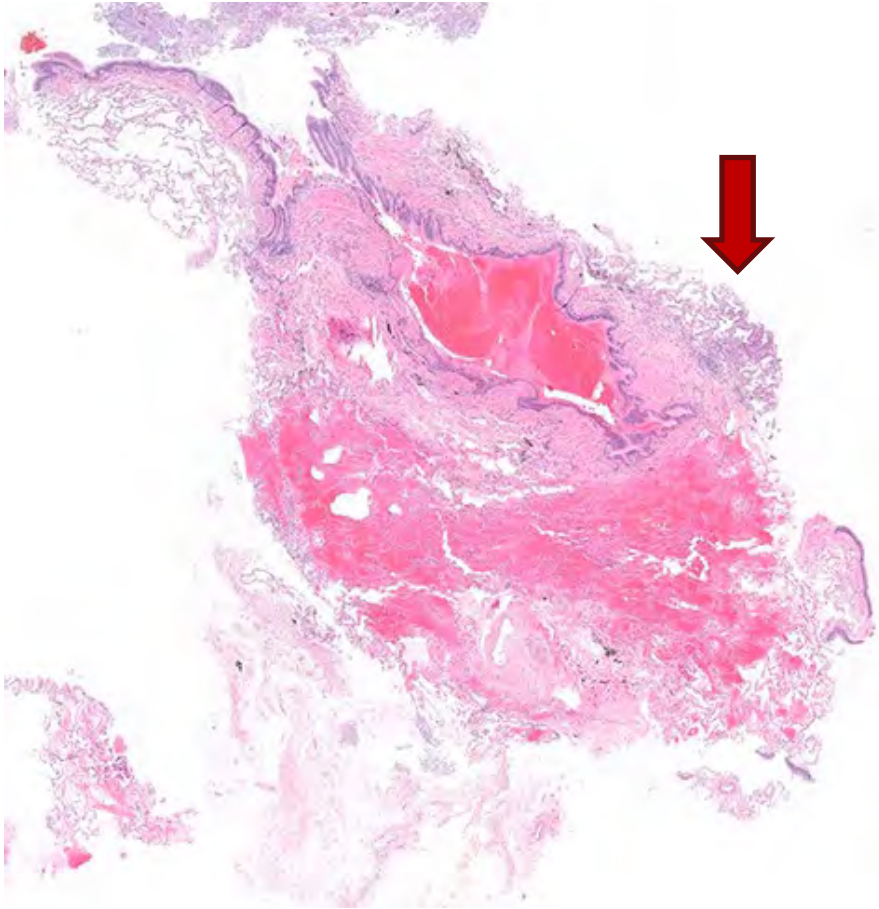
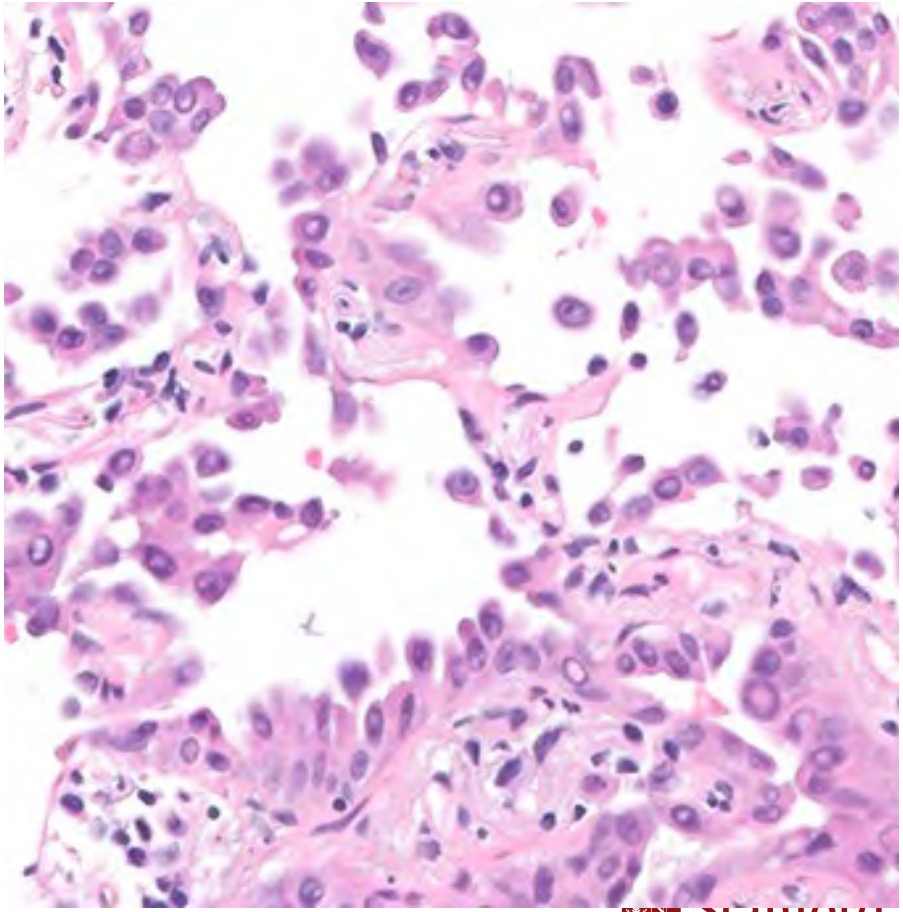
CBCT-Guided Cryobiopsy and Why?

- Interstitial lung disease evaluation
  - Target specific regions of disease (when ILD process is less diffuse)
  - Ability to sample regions that have a less advantageous fluoroscopic view (i.e. disease that is straight anterior, medial, or posterior vs lateral directionality)
  - Ensure position of cryoprobe in relation to pleura (or critical structures) prior to biopsy (potential for less PTX?)
  - Provide intra-procedural CT imaging of sampled sites for ILD MDDs

- Peripheral lung lesions
  - Potential role in sub-solid lung lesions (pure GGN/part-solid)
  - Ability to sample beyond the bronchus (and to the surrounding alveolar tissue/nodule)
  - Any advantage when sampling the edge of a lesion (eccentric lesions)?
  - Decrease overall number of biopsies/samples collected?





Diagnosis: Adenocarcinoma

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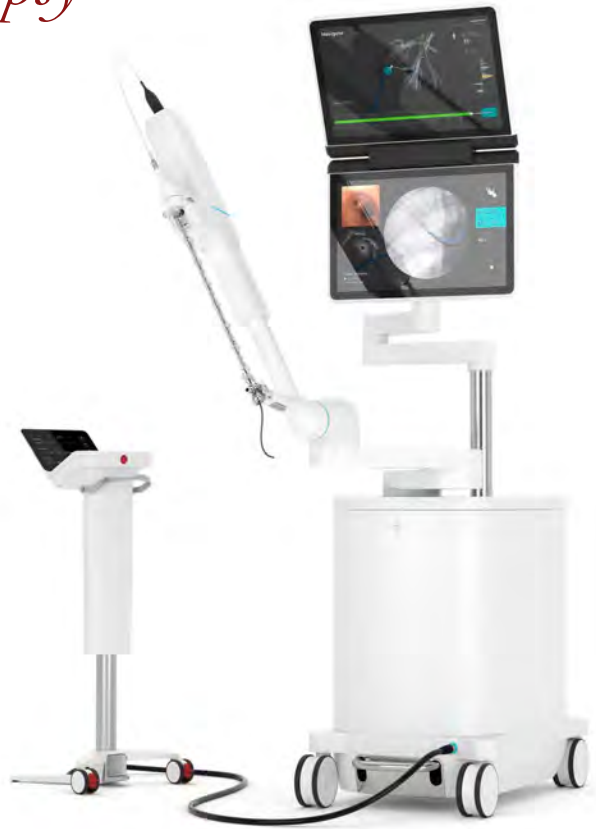
New Frontier: CBCT, Robotics, and Cryobiopsy



Lung (2021) 199:177–186
https://doi.org/10.1007/s00408-021-00421-1

INTERVENTIONAL PULMONOLOGY

Robotic-Assisted Navigation Bronchoscopy as a Paradigm Shift in Peripheral Lung Access

Bryan S. Benn[1] · Arthur O. Romero[2,3] · Mendy Lum[4] · Ganesh Krishna[2,4,5]

CBCT + Intuitive iON Robot
Lesion size, axial (mean, mm): 19.6mm
Bronchus sign ABSENT: 54%
Tissue diagnosis: 83%
Diagnostic yield: 86%
Malignancy sensitivity: 84%

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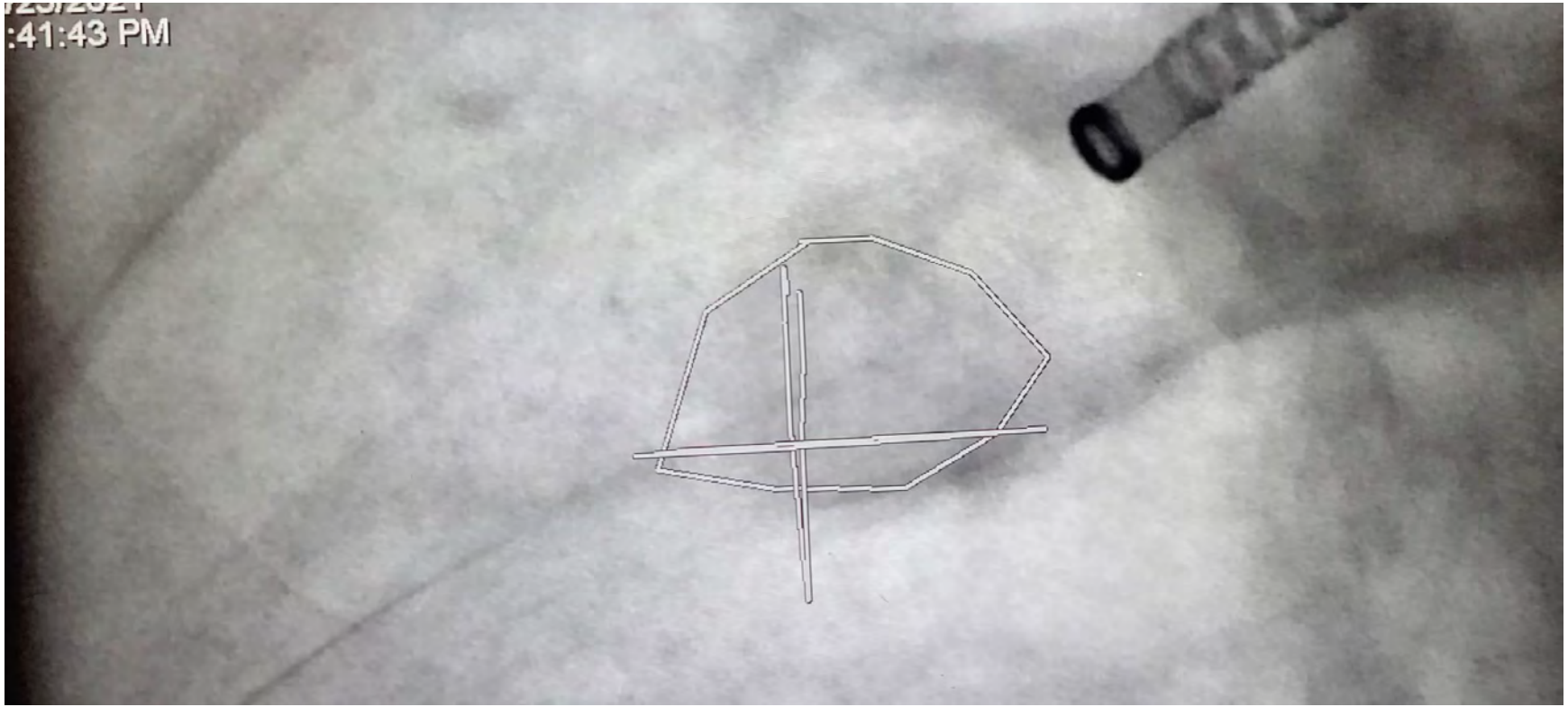

1.1mm Cryoprobe

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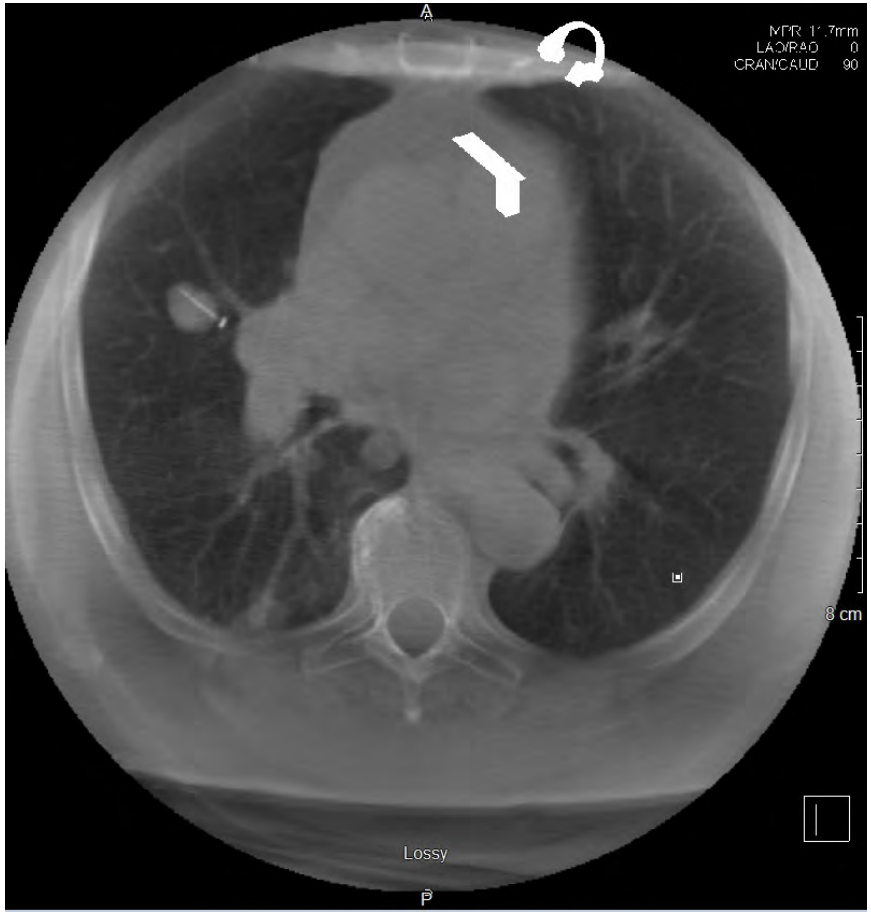
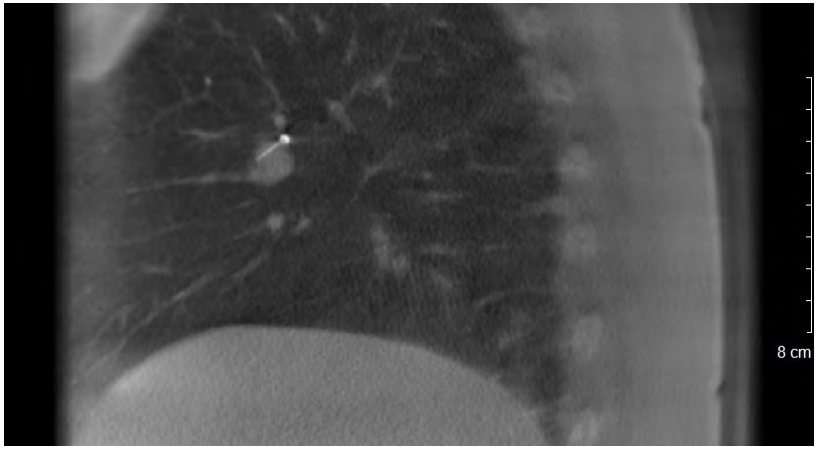
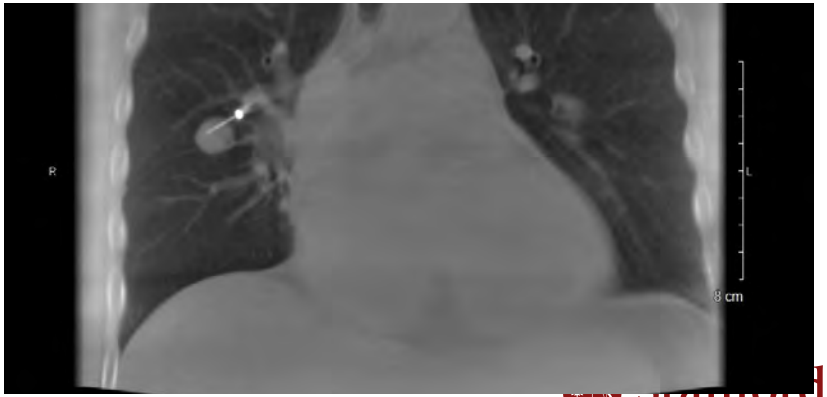
Lung Nodule Diagnosis







Courtesy of Krish Bhadra (CHI Memorial)

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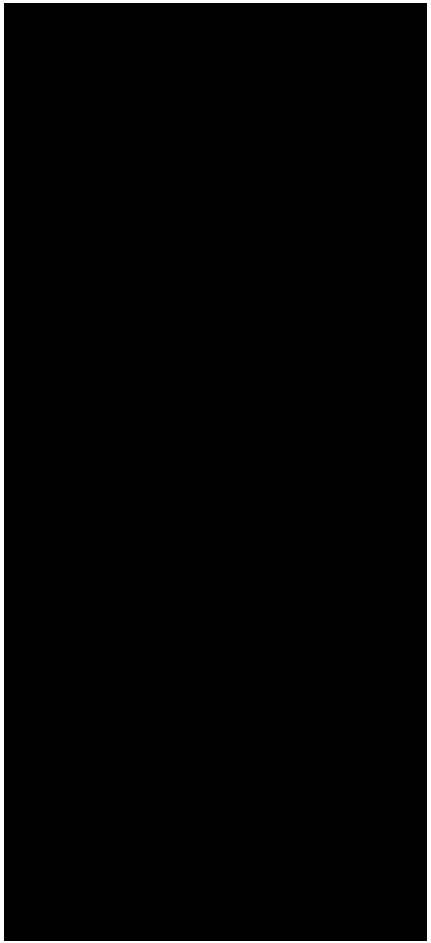
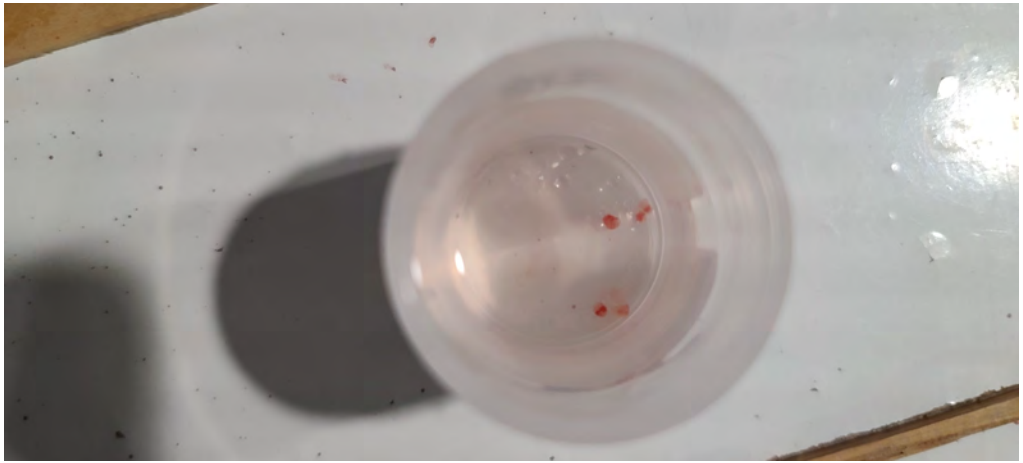
Lung Nodule Diagnosis



Diagnosis: Malignant Melanoma



Courtesy of Krish Bhadra (CHI Memorial)

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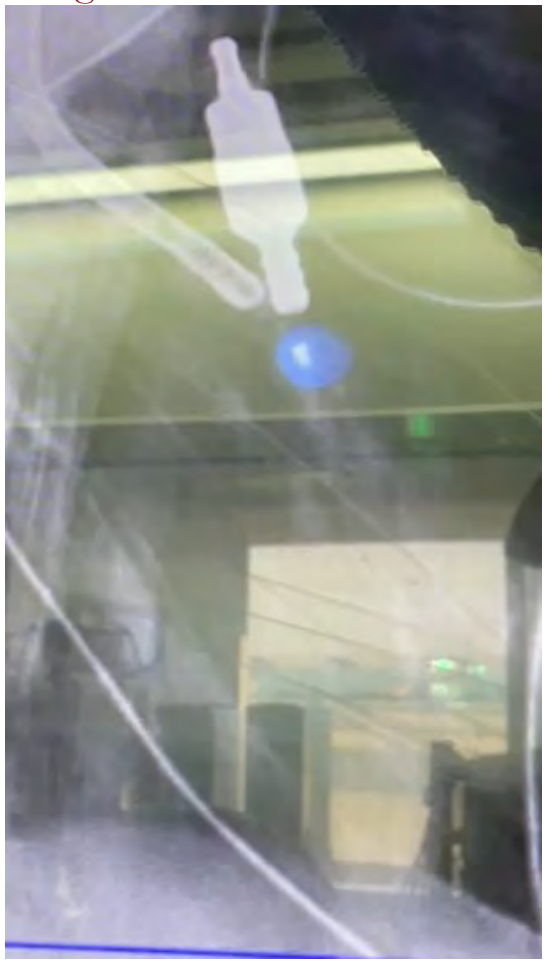

1.1mm Cryoprobe

1.7mm Cryoprobe

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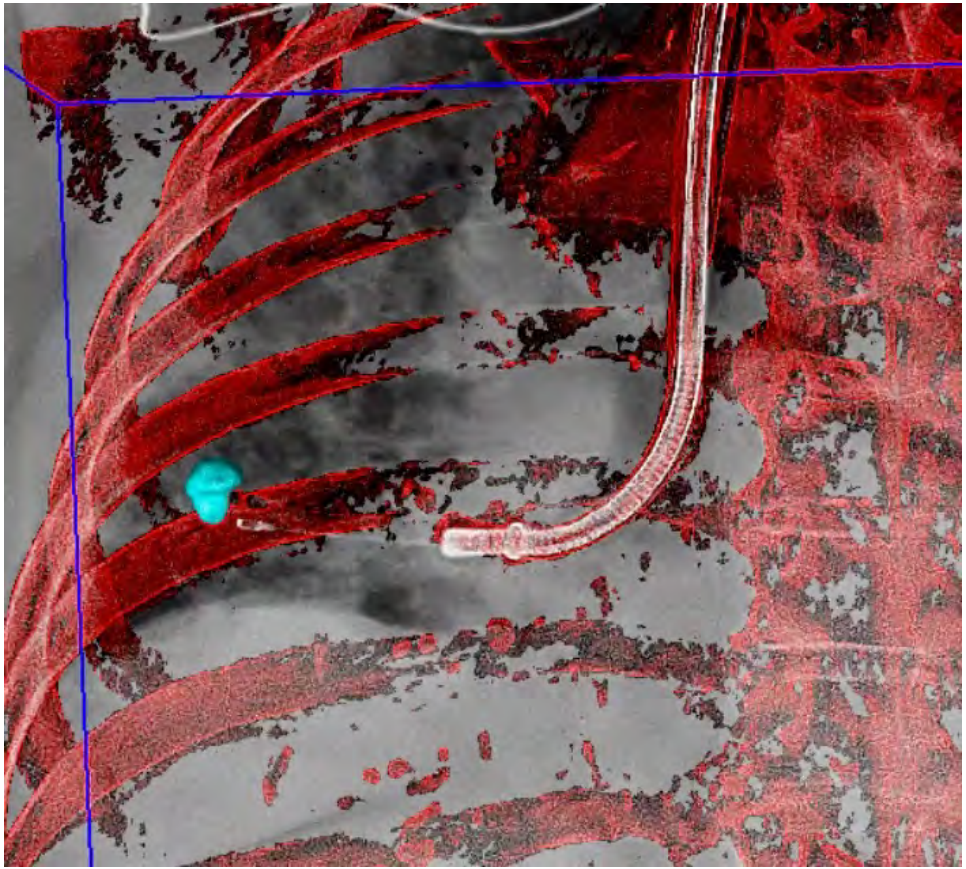
Lung Nodule Diagnosis



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Thank You!
Questions?

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Harmeet Bedi
hbedi@stanford.edu

Molecular Testing and Targeted Therapies

3:05 p.m. – 3:50 p.m.

MILLIE DAS, MD
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Dr. Millie Das received her medical degree from the University of Massachusetts in Worcester, MA. She completed her residency in internal medicine and her fellowship in hematology/oncology at Stanford University. She is a practicing thoracic oncologist, seeing patients both at the VA in Palo Alto, CA and at Stanford University. She has a strong interest in clinical research and serves as a principal investigator on several clinical and translational clinical trials in lung cancer at the Palo Alto VA. Currently she is Chief of Oncology at the VA in Palo Alto, CA and also serves as an Associate Professor of Medicine at Stanford University.

Molecular Testing and Targeted Therapies

Millie Das, MD
Clinical Associate Professor, Stanford University
Chief, Oncology, VA Palo Alto Health Care System

1

Disclosures

- Consulting/Advisory board: Astra Zeneca, Beigene, Sanofi, Jazz Pharmaceuticals, Genentech (uncompensated)
- Research: Novartis, Abbvie, United Therapeutics, CellSight, Varian, Verily

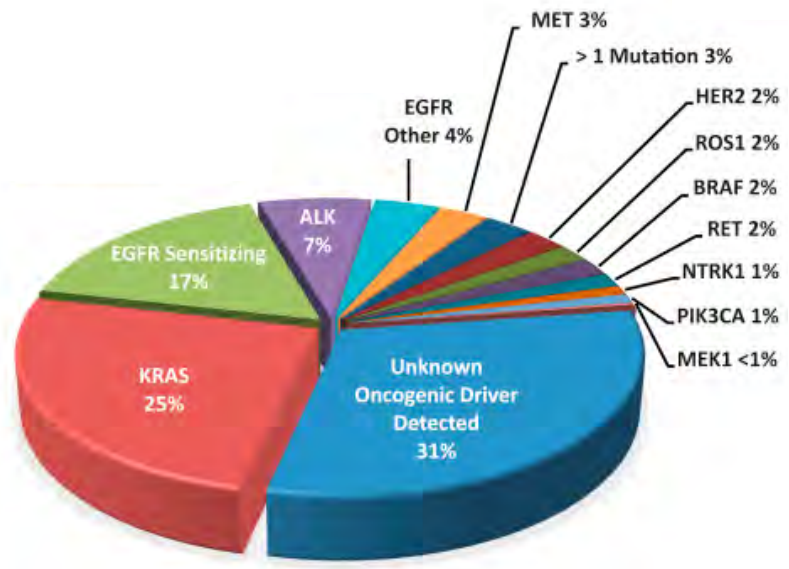
2

Agenda

- Role of biomarkers in therapy selection for lung cancer
- Molecular testing recommendations in NSCLC
- Updated data for therapy selection
  - -EGFR
  - -ALK
  - -ROS1
  - -MET
  - -Kras
  - -HER2
  - -NTRK
  - -RET

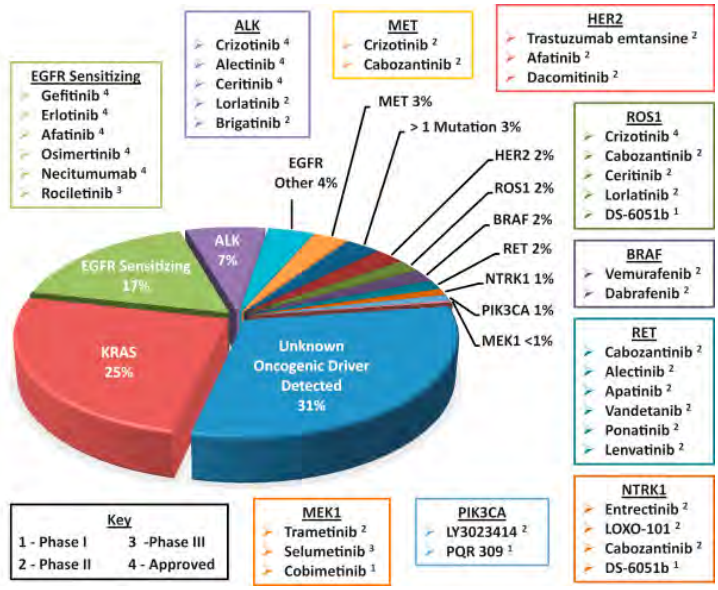
3

Identification of driver mutations leads to treatment with targeted therapies in metastatic NSCLC



4

Identification of driver mutations leads to treatment with targeted therapies in metastatic NSCLC



5

Treatment Options: Overview

- Targeted therapies in the metastatic setting result in robust responses and prolonged disease control for NSCLC but cannot cure- RESISTANCE IS INEVITABLE
- For patients without a targetable mutation, standard firstline treatment recommendation is chemotherapy + IO, regardless of PDL-1 status
- Immunotherapy alone can be considered for patients with PDL-1>=50%

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Treatment considerations

Who should get molecular testing?

- All patients with metastatic non-squamous NSCLC
- Patients with never/light smoking history and metastatic squamous NSCLC

Timing of Treatment

- Wait for rapid molecular testing (EGFR, ALK, ROS1, PDL-1) results prior to treatment initiation (usually 1 week)

7

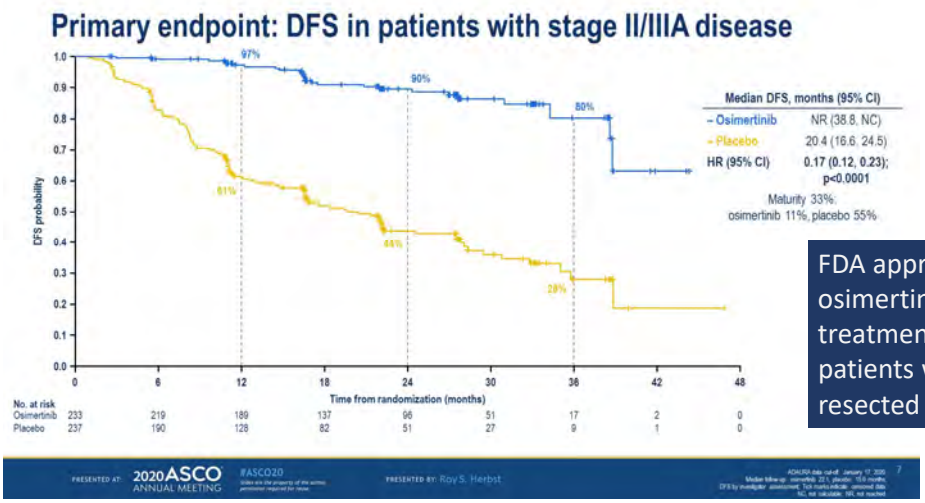
EGFR Mutations

- 15-20% of NSCLC
  - More frequently seen in Asian, never or light smokers
- Most common sensitizing mutations are exon 19 del and L858R
- Firstline treatment with osimertinib in stage IV (FLAURA)
- Brain metastases seen commonly with good CNS penetration of osimertinib
- Exon 20 insertions are generally resistant to classical TKIs with some variant exceptions
- Resistance to EGFR TKIs is common

8

ADAURA TRIAL:

Adjuvant osimertinib improves DFS in early stage II/IIIA EGFR+ NSCLC



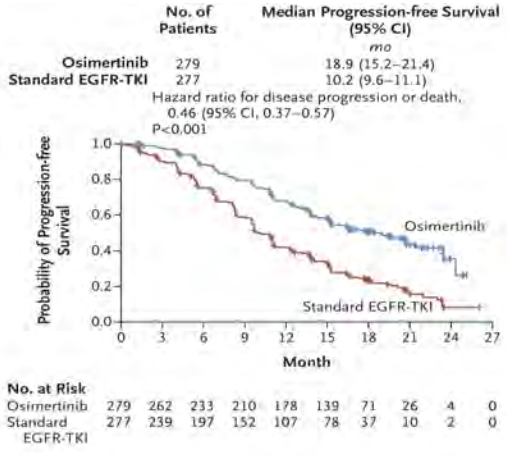
FDA approved osimertinib as adjuvant treatment in Dec 2020 in patients with early stage resected EGFR+ NSCLC

9

FLAURA TRIAL:

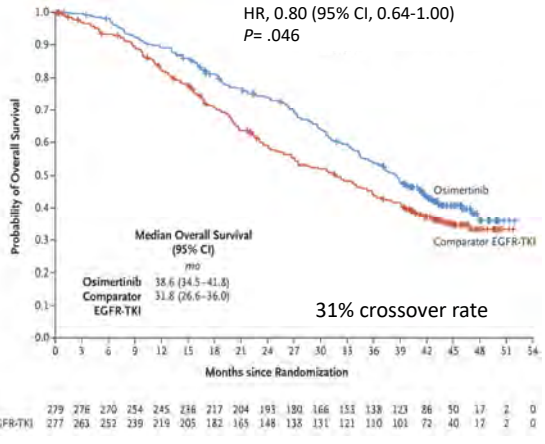
Osimertinib Improves PFS & OS Compared to Older Generation EGFR TKIs in Stage IV EGFR+ NSCLC

PFS



Soria JC et al. *N Engl J Med*. 2018;378(2):113-125.

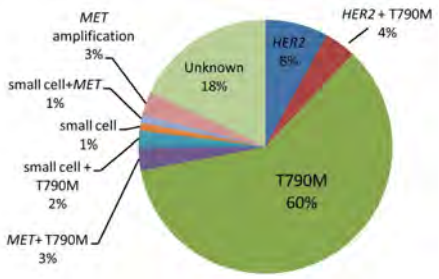
OS



Ramalingam S, et al. *N Engl J Med*. 2020;382(1):41-50.

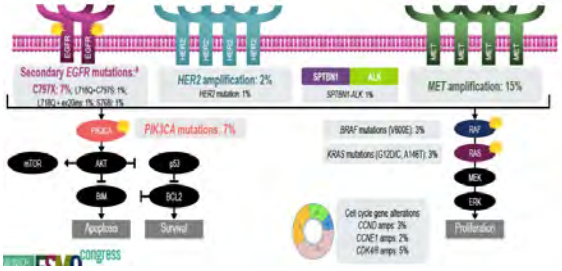
10

Resistance to targeted therapy inevitable & resistance mechanisms more challenging with next generation drugs



Dominant mechanism of resistance for 1st generation EGFR TKIs erlotinib or gefitinib

Yu H et al. Clin Cancer Res. 2013 Apr 15;19(8):2240-7.



Heterogeneous & multiple simultaneous mechanisms of resistance to 3rd generation EGFR TKI osimertinib

Ramalingam SS et al. ESMO 2018, Munich

11

CHRYSALIS TRIAL:

Osimertinib ineffective in EGFR Exon 20 insertion, but Amivantamab shows promise

Response	Efficacy Population (n = 81)
ORR, % (95% CI)	40 (29-51)
CBR,* % (95% CI)	74 (63-83)
Best response, n (%)	
• CR	3 (4)
• PR	29 (36)
• SD	39 (48)
• PD	8 (10)
• NE	1 (1)
Median DoR, mos (95% CI)	11.1 (6.9-NR)

*CBR = CR, PR, of SD at ≥ 2 disease assessments.
†Does not include 9 patients with race not reported and multiple race.

FDA approved amivantamab for patients with NSCLC who harbor EGFR exon 20 insertion mutation and whose disease has progressed on or after platinum-based chemotherapy in May 2021

Sabari. WCLC 2020. Abstr OA04.04. NCT02609776.

12

EGFR Targeted Therapy: Summary

- Recent ADAURA trial is practice changing
  - **Test all early stage patients for EGFR!**
- Strategies in development to delay or overcome resistance to osimertinib
- Usually chemotherapy is administered after resistance to osimertinib develops
- Identifying specific resistance mutations in each patient's tumor (i.e., tissue biopsy, liquid biopsy) and tailoring subsequent approach
- Newly approved drugs for EGFR exon 20 ins
  - Amivantanab
  - Mobocertinib

13

ALK Targeted Therapy

3-5% of NSCLC

- More frequent in males
- More frequent in never or light smokers
- Brain metastases commonly seen

Frontline treatment options

- Alectinib
- Brigatinib (approved May 2020)
- Lorlatinib (approved March 2021)

Other ALK inhibitors

- Ceritinib, Crizotinib

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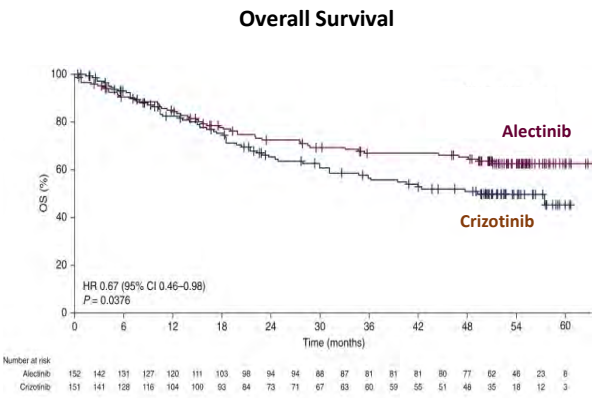
ALEX Phase III TRIAL:

Alectinib superior to Crizotinib in Untreated *ALK*-Positive NSCLC



Name	Level	Log-rank *P* value	Hazard ratio	95% CI	Interaction test *P* value (likelihood ratio)
All	n/a	0.0609	0.70	(0.48–1.02)	
Age group (years)	< 65	0.1481	0.73	(0.48–1.12)	0.6768
	≥ 65	0.2189	0.63	(0.30–1.33)	
Sex	Female	0.3020	0.76	(0.45–1.28)	0.6923
	Male	0.1155	0.66	(0.39–1.11)	
Race	Asian	0.3298	0.74	(0.40–1.36)	0.8575
	Non-Asian	0.1161	0.69	(0.43–1.10)	
Smoking status	*n* = 17 Active smoker	0.4126	1.97	(0.38–10.20)	0.5471
	Non-smoker	0.1181	0.68	(0.42–1.11)	
	Past smoker	0.1339	0.62	(0.33–1.17)	
ECOG PS	0	0.1266	0.52	(0.22–1.22)	0.4636
	1	0.0960	0.68	(0.44–1.07)	
	n = 20 2	0.6440	1.30	(0.43–3.90)	

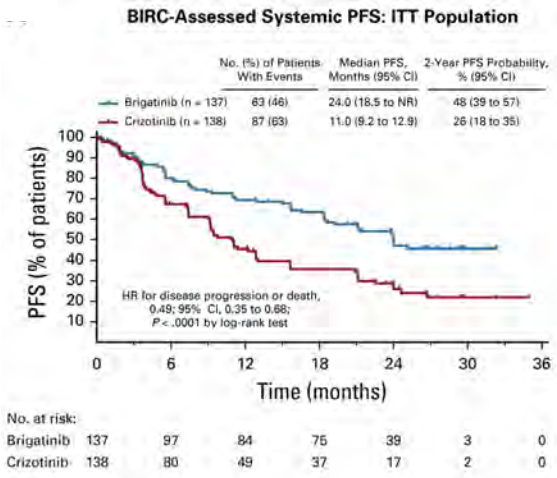
FDA approved alectinib in the first line for patients with ALK-positive NSCLC in November 2017

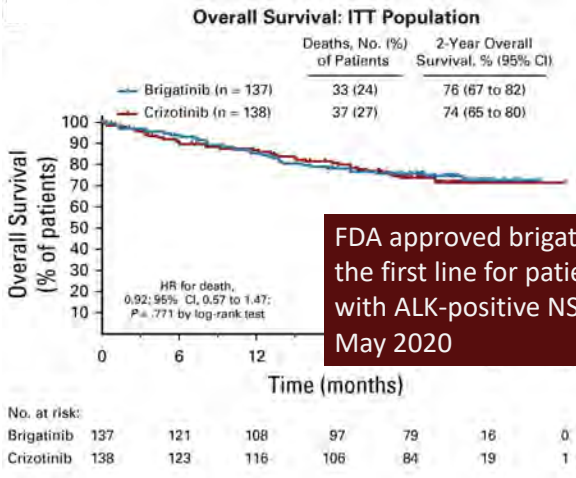
Peters S, et al.. *J Clin Oncol*. 2020;38(15):9518. Mok T, et al. *Ann Oncol*. 2020;31(8):1056-1064.

15

ALTA-1L Phase III TRIAL:

Brigatinib superior to Crizotinib in Untreated *ALK*-Rearranged NSCLC





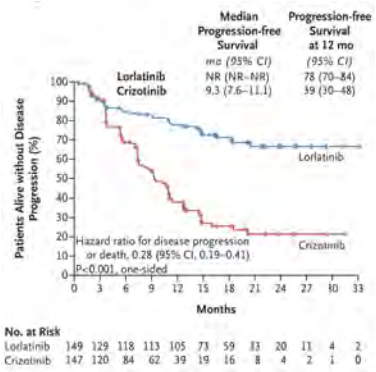
FDA approved brigatinib in the first line for patients with ALK-positive NSCLC in May 2020

Camidge DR, et al. *J Clin Oncol*. 2020;38(31):3592-3603.

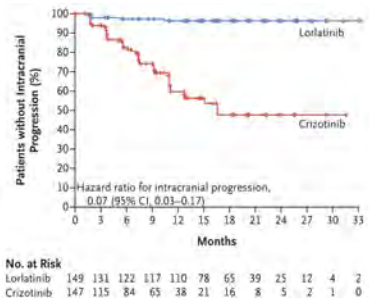
16

CROWN Phase III TRIAL:
Lorlatinib superior to Crizotinib in Advanced *ALK*-Positive NSCLC

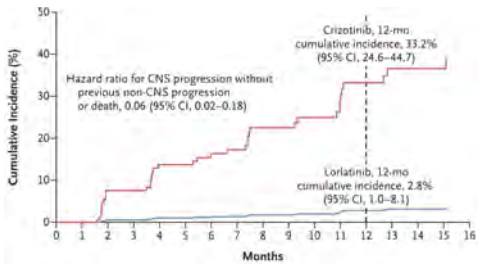
Progression Free Survival



Time to Intracranial Progression



Cumulative Incidence of CNS Progression as the First Event



FDA approved lorlatinib for patients with NSCLC whose tumors are *ALK*-positive in March 2021

Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018-2029.

17

ALK Targeted Therapy: Summary

- Multiple first line FDA approved ALK TKI options
- Alectinib is generally preferred first line given favorable side effect profile and high CNS penetration
- Resistance to ALK TKIs occurs
- Can use other ALK TKIs at the time of disease resistance (brigatinib, lorlatinib)

18

ROS1 Targeted Therapy

Found in 1% of NSCLC

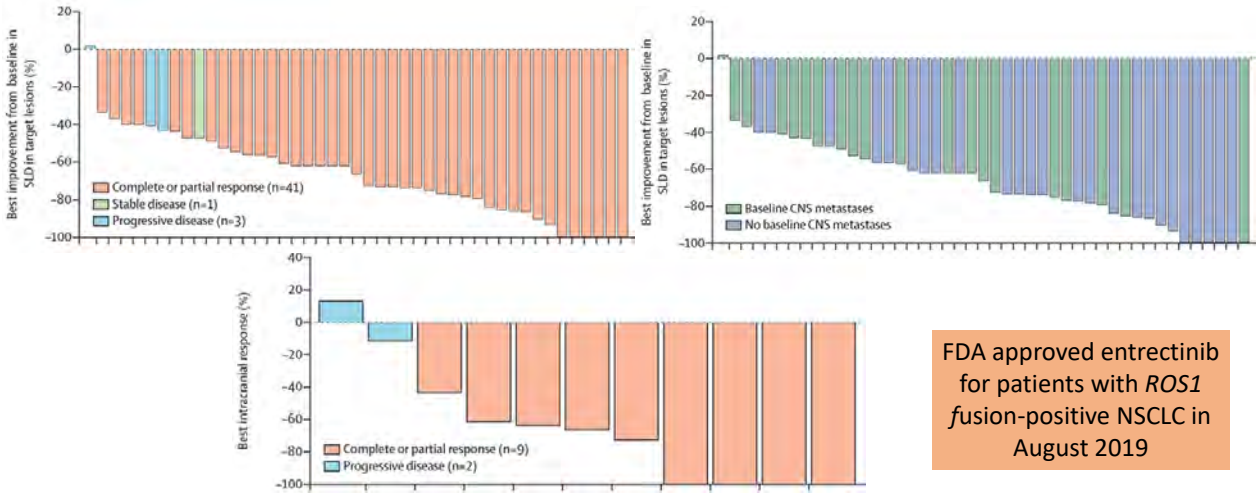
- More common in light or never smokers
- Longer median OS of patients

Targeted therapies

- Crizotinib
- Entrectinib (approved Aug 2019)
- Ceritinib

19

Entrectinib in *ROS1* Fusion-positive NSCLC
Integrated Analysis of 3 Phase I/II Trials (STARTRK-1, ALKA, STARTRK-2)



FDA approved entrectinib for patients with *ROS1* fusion-positive NSCLC in August 2019

Drilon A, et al. *Lancet Oncol*. 2020;21(2):261-270.

20

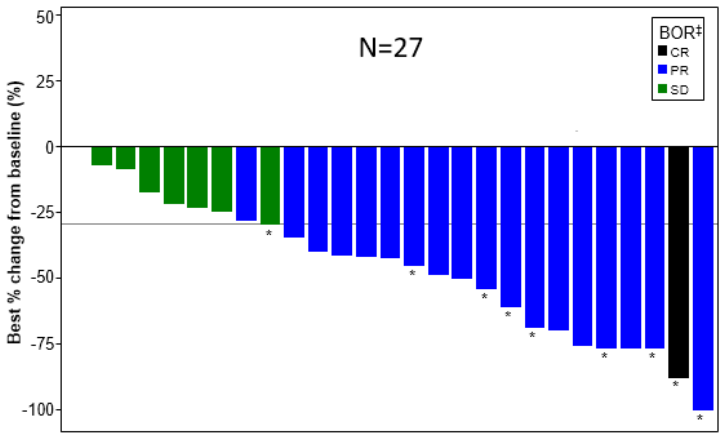
MET Targeted Therapy

- MET alterations occur is many solid malignancies, including NSCLC (gene amplification and exon 14 skipping mutations)
- MET antibodies and TKIs being investigated
- MET amplification seen in cases of EGFR-TKI resistance
- Capmatinib and tepotinib are FDA approved first line treatment options for patients MET exon 14 skipping mutations

21

GEOMETRY mono-1 TRIAL:

1st line Capmatinib effective in *MET*ex14—mutated NSCLC



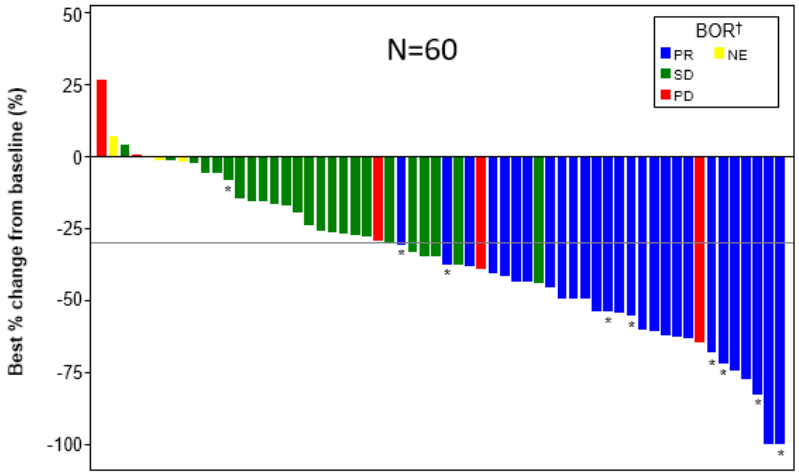
	Response-evaluable patients N=28
ORR	67.9%
mDoR	11.1 mos
mPFS	9.69 mos

Garon EB, et al. Presented at: 2020 American Association for Cancer Research Virtual Annual Meeting I: Virtual; April 27-28, 2020. Abstract CT082.

22

GEOMETRY mono-1 TRIAL:

Subsequent line Capmatinib effective in *MET*ex14—mutated NSCLC



	Subsequent line Capmatinib N=69
ORR	40.6%
mDoR	9.7 mos
mPFS	5.4 mos

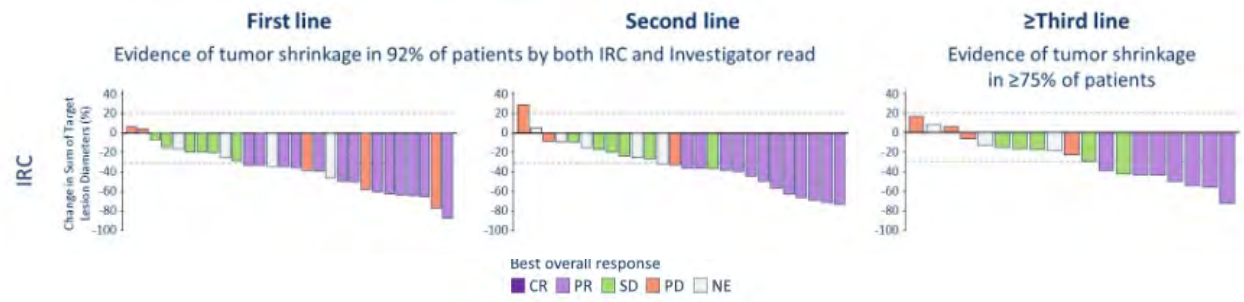
FDA approved capmatinib for patients with METex14—mutated NSCLC in May 2020

Garon EB, et al. Presented at: 2020 American Association for Cancer Research Virtual Annual Meeting I: Virtual; April 27-28, 2020. Abstract CT082.

23

VISION TRIAL:

Tepotinib targets MET Exon 14 skipping mutations



	Tepotinib N=87
ORR	45%
mDoR	1.7mos

In February 2021, FDA granted accelerated approval for tepotinib in patients with mNSCLC harboring MET exon 14 skipping alterations.

Paik, et al. *J Clin Oncol*. 2019;37915_suppl0: 9005-9005

24

MET Targeted Therapy: Summary

- Capmatinib and tepotinib are standard of care 1st line treatment for MET exon 14 skipping mutations
- Other MET targeted drugs are in clinical development

25

KRAS targeted therapy

- KRAS is the common mutation in lung adenoCA (25%)
- KRAS G12C mutations found in 13% of lung adenoCA
- Up until recently, KRAS mutations were not felt to be targetable in lung cancer

26

Sotorasib (AMG 510)

- Phase 1 dose escalation study (N = 129; n=59 with NSCLC)
  - Efficacy in NSCLC
    - CR/PR: 32.2% (n=19)
    - Disease control (CR/PR/SD): 88.1% (n=52)
    - mPFS: 6.3 months
  - Safety
    - Most common AEs: diarrhea, fatigue, and nausea
    - Grade ≥3 AEs: 52.7% (n=68)
    - No DLTs or grade 4 or serious TEAEs

In May 2021, sotorasib was FDA approved for KRAS G12C-mutated NSCLC for patients who have received at least one prior systemic therapy

27

Adagrasib

- Phase I/II study (N=110; n = 79 with NSCLC [51 evaluable])
  - Efficacy in NSCLC
    - CR/PR: 45% of NSCLC
    - Disease control (CR/PR/SD): 96%
  - Safety
    - Most common AEs: nausea, diarrhea, vomiting, fatigue, and increased liver enzymes
    - Grade ≥3 AEs: 30%
    - 2 deaths (pneumonitis, cardiac failure)

In June 2021, adagrasib earned a breakthrough therapy designation from the FDA for patients with KRAS G12C–mutant NSCLC

28

KRAS targeted therapy: Summary

- Sotorasib is a viable second line therapy option with KRAS G12 mutated NSCLC (chemo+IO still firstline)
- No targeted treatment options for other KRAS non-G12C mutations

29

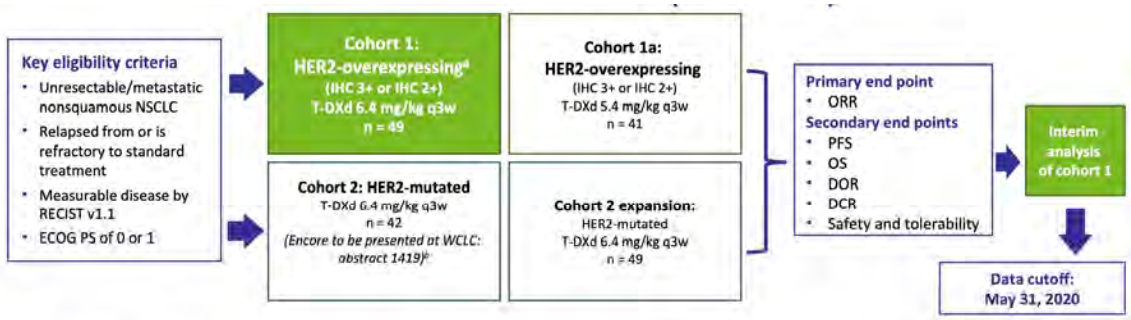
HER2 (ERBB2) Targeted Therapy

- Currently no standard therapies targeting HER2 pathway in NSCLC
  - Approved therapies in HER2+ gastric and breast cancers
- No clear correlation between HER2 overexpression, amplification, or mutation (not mutually exclusive)
  - HER2 mutations in 2-4% (most exon 20 ins)
  - HER2 amplification in 10-20%
  - HER2 overexpression in 2.4-38%
- HER2 alterations can represent primary driver or mechanism of acquired resistance

Jebbink et al. Cancer Treat Rev 2020;86:101996
Rolfo et al. Cancer Discov 2020 May 10(50):643-645

30

DESTINY Lung-01 TRIAL:
Trastuzumab deruxtecan (HER2 Targeted Therapy)

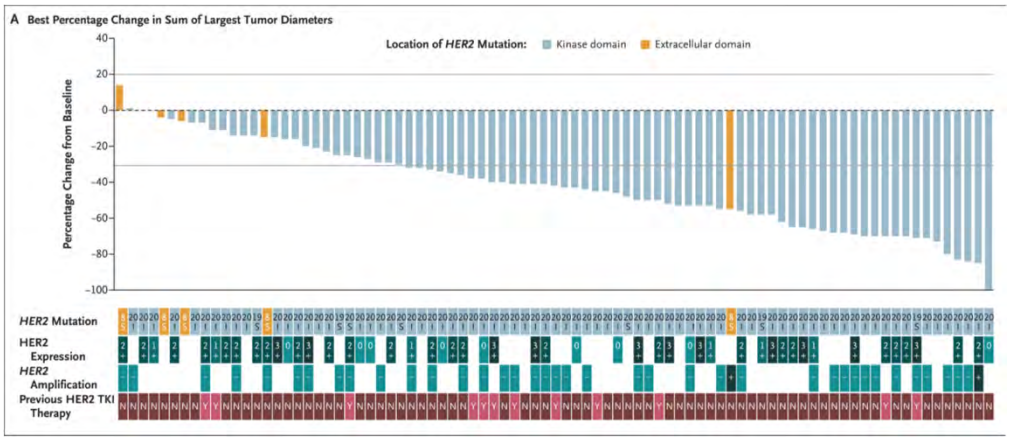


- In cohort 1, 11 patients remained on treatment, and 38 patients had discontinued treatment primarily because of PD (n = 22) or AEs (n = 9)[c]
- Median treatment duration was 18.0 weeks (range, 3.0-57.1 weeks)

Nakagawa K et al. Presented at: 2020 World Conference on Lung Cancer Singapore; January 28-31; Virtual. Abstract OA04.05

31

DESTINY Lung-01 TRIAL:
Trastuzumab deruxtecan shows response in HER2-mutant NSCLC



Li BT et al. NEJM. 2022; 20;386(3):241-251

32

HER2 Targeted Therapy

	First author	Overall response rate *HER2* mutation	Overall response rate *HER2* amplification
Dacomitinib	Kris	3/26 (12%)	0/4 (0%)
Neratinib	Hyman	1/26 (4%)	NA
Neratinib	Gandhi	0/17 (0%)	NA
Neratinib + temsirolimus	Gandhi	8/43 (19%)	NA
Afatinib	Smit	0/13 (0%)	NA
Afatinib	Lai	3/22 (14%)	NA
Trastuzumab	Gatzemeier	NA	NA*

* Negative randomized phase 2 trial cisplatin/gemcitabine ± trastuzumab in HER2 IHC2+/3+ lung cancers.

- TKIs are minimally effective with overall low response rates
- Poziotinib, a more potent inhibitor of EGFR and HER2 exon 20 mutations, being studied in phase II trial

Jebbink et al. Cancer Treat Rev 2020;86:101996

33

HER2 Targeted Therapy: Poziotinib

IASLC 2020 World Conference on Lung Cancer Singapore

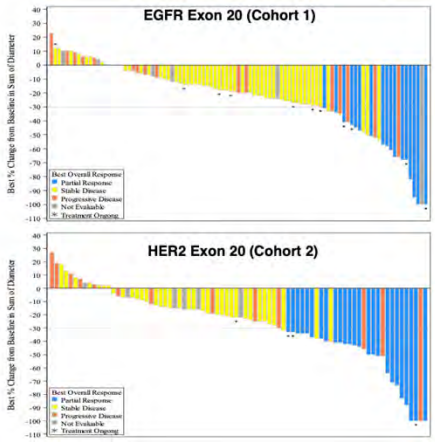
wclc2020.IASLC.com | #WCLC20

CONQUERING THORACIC CANCERS WORLDWIDE

Primary Efficacy and Safety

- Cohort 2 (2L HER2 exon 20) primary endpoint was met
- Median age 61yrs; median prior therapy = 2 (1-9); 66% females; 67% non-smokers; 13% stable brain metastases at entry
- Common Grade 3 TRAEs: Diarrhea (26%), Rash (29%), mucosal inflammation (10%)

	2L EGFR Exon 20 (N=115)	2L HER2 Exon 20 (N=90)
ORR (n), [95% CI]	**14.8%** (17) [8.9, 22.6%]	**27.8%** (25) [18.9, 38.2%]
Unconfirmed ORR (n), [95% CI]	**19.1%** (22) [12.4, 27.5%]	**31.1%** (28) [21.8, 41.7%]
DCR (n), [95% CI]	**68.7%** (79) [59.4, 77.0%]	**70.0%** (63) [59.4, 79.2%]
DoR, median (months), [95% CI]	**7.4** [3.7, 9.7]	**5.1** [4.2, 5.5]
PFS, median (months), [95% CI]	**4.2** [3.7, 6.6]	**5.5** [3.9, 5.8]



Cornelissen R et al. Presented at: 2020 World Conference on Lung Cancer Singapore; January 28-31; Virtual Abstract MA11.04

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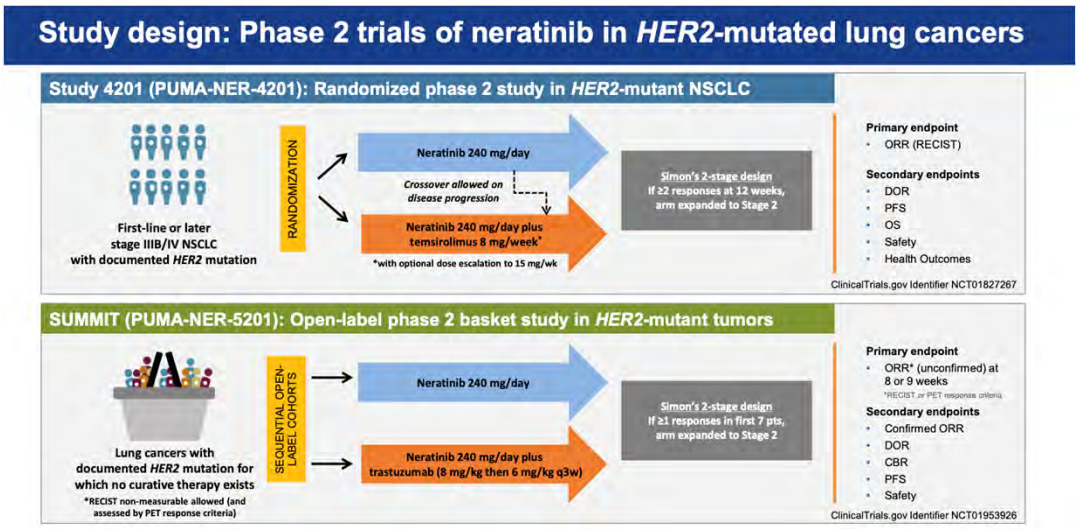
HER2 Targeted Therapy: Neratinib



Li B et al. Presented at 2020 World Conference on Lung Cancer Singapore; January 28-31; Virtual Abstract FP14.15

35

HER2 Targeted Therapy: Summary

- Potential role for antibody-drug conjugates T-DM1 and trastuzumab-deruxtecan (FDA breakthrough designation)
- Existing and emerging small molecule TKIs are only modestly active
- Poziotinib demonstrates increased activity against HER2 mutated NSCLC compared to other TKIs

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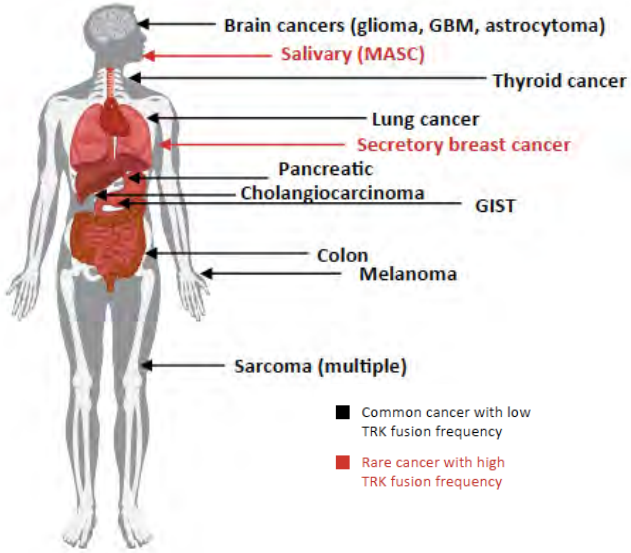
Other less common actionable targets: NTRK, RET

37

NTRK Targeted Therapy



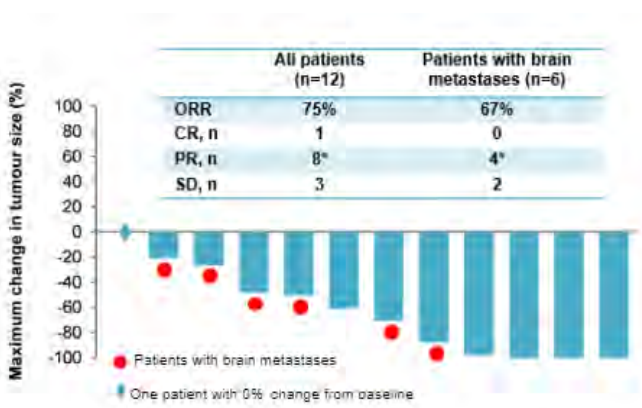
NTRK fusions are found across multiple cancer histologies

1500-5000 patients in United States annually

Hyman American Society of Clinical Oncology Annual Meeting 2017

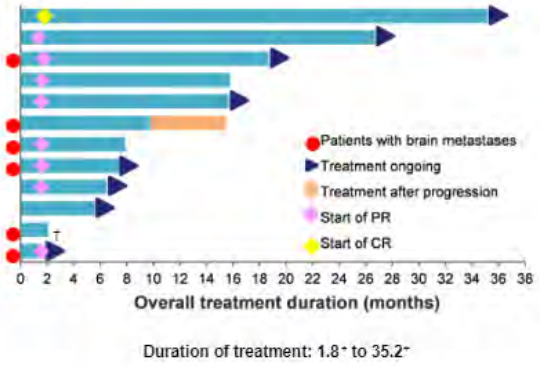
38

LOXO-TRK-14001/SCOUT/NAVIGATE TRIALS:
Larotrectinib with efficacy in solid tumors with NTRK gene fusion



	All patients (n=12)	Patients with brain metastases (n=6)
ORR	75%	67%
CR, n	1	0
PR, n	8*	4*
SD, n	3	2

Median duration of response not reached (range 3.9+ to 25.9+ months)
(median follow-up of 12.8 months)



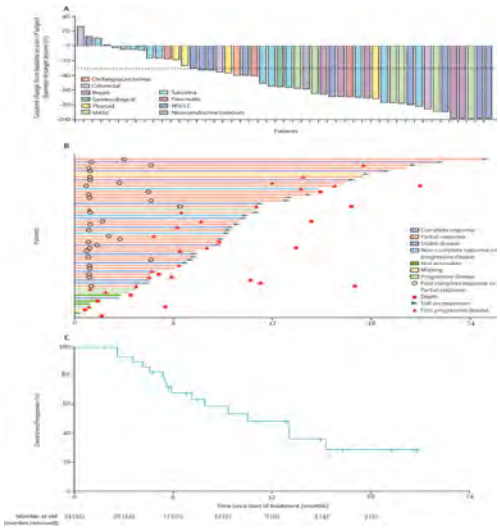
Duration of treatment: 1.8+ to 35.2+

Larotrectinib was FDA approved in November 2018 for solid tumors harboring NTRK gene fusion

Farago et al World Conference on Lung Cancer 2019

39

ALKA-372-001/STARTRK-1/STARTRK-2 TRIALS:
Entrectinib with efficacy in solid tumors with NTRK gene fusion



- Pooled analysis of 3 phase I/II trials
- 10 different tumor types
- 31 of 54 patients had objective response
  - 7% CR
  - 50% PR
- Most common AEs
  - Increased weight
  - Anemia
  - Cognitive disorder

Entrectinib was FDA approved in August 2019 for solid tumors harboring NTRK gene fusion

Doebele et al Lancet Oncol 2020;21(2):271-282

40

NTRK Targeted Therapies: Summary

- NTRK is an uncommon mutation in NSCLC (<0.5%)
- NTRK inhibitors larotrectinib and entrectinib are FDA approved for NTRK positive solid tumors, including NSCLC
- High response rates (>70%) and generally well tolerated

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RET Alterations

- Seen mostly in lung and thyroid cancers
- Multi-kinase inhibitors target various kinases and other receptors (including RET)
  - Sunitinib, sorafenib, vandetanib, cabozantinib, regorafenib, lenvatinib, alectinib
    - Limited clinical benefit
    - Dose-limiting off target toxic effects
- Recent FDA approvals of selpercatinib and pralsetinib

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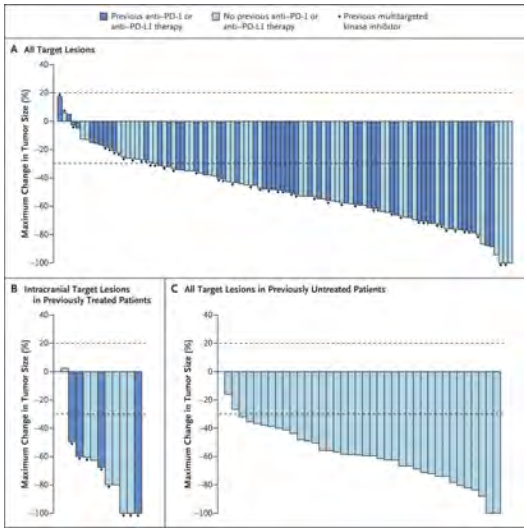
LIBRETTO-001 TRIAL:

Selpercatinib effective in *RET*-fusion-positive NSCLC



- 105 patients with RET positive NSCLC
- ORR= 64%
- Intracranial response: 91%
  - Noted in 10/11 patients with CNS mets
- Most common AEs
  - HTN
  - Increased AST

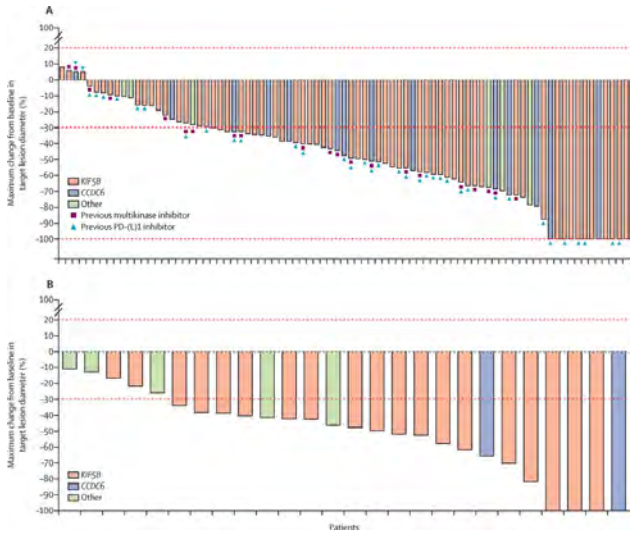
In May 2020, selpercatinib was FDA approved for patients with RET+ NSCLC

Drillon et al NEJM 2020;383:813-834

43

ARROW TRIAL:

Pralsetinib effective in *RET*-fusion-positive NSCLC



- Phase I/II study
- 233 patients with RET positive NSCLC
  - 92 patients with prior platinum-based chemo (ORR= 61%)
  - 29 patients were treatment naïve (ORR= 70%)
- Most common AEs
  - Neutropenia
  - HTN
  - Anemia

In December 2020, pralsetinib was FDA approved for patients with RET+ NSCLC

Gainor et al. Lancet Oncol 2021;22(7):959-969

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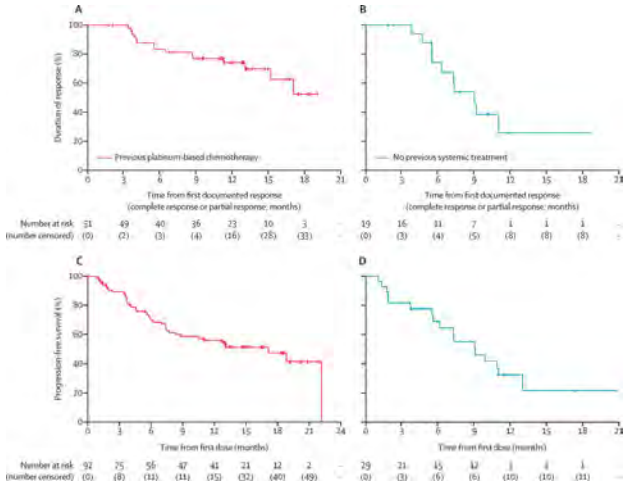
Pralsetinib



- Shrinkage of CNS mets noted in all 9 patients with measurable intracranial metastases
  - 5/9 patients had intracranial response (with 3 CRs)

Gainor et al. Lancet Oncol 2021;22(7):959-969

45

RET Targeted Therapy: Summary

- RET fusions seen in 1-2% of NSCLC
- Associated with high risk of CNS metastases
- Selpercatinib and pralsetinib are newly FDA approved options for RET-rearranged NSCLC

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Conclusions

- Obtain sufficient tissue for molecular testing, even in early stage patients
- Driver mutations (even rare subsets) are being identified on NGS panels in NSCLC tumor specimens
- Novel targeted therapeutics offer better outcomes with many recent FDA approvals
- Cancer Moonshot initiative
  - Accelerate research, making more therapies available through precision oncology
  - Bench to bedside

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BREAK
EXHIBIT HALL OPEN

3:50 p.m. – 4:05 p.m.

Palliation Therapies (Stents, Laser Therapy, Indwelling Pleural Catheters)

4:05 a.m. – 4:50 a.m.

GEORGE CHAUX, MD, FCCP
CEDARS-SINAI MEDICAL CENTER

Dr. George E. Chaux is Medical Director of Interventional Pulmonology and Associate Medical Director of the Lung Transplant Program at Cedars-Sinai Medical Center. He has achieved the rank of Professor in Clinical Medicine at Cedars-Sinai and UCLA School of Medicine. Residency and fellowship in internal medicine, pulmonary and critical care medicine completed at UCSD Medical Center in 1997.

Palliation Therapy (Stents, Laser, Indwelling Pleural Catheters)

George Chaux, MD

Professor of Medicine

Cedars-Sinai Medical Center

Cedars Sinai

cedars-sinai.org

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1

Disclosures

Cedars Sinai

2

2

Objectives

- Palliative therapy in lung cancer
- Airway interventions for CAO
  - Dilation
  - Debridement: laser, cryo-, argon plasma
  - Stents
  - Photodynamic therapy
- Pleural interventions
  - Pleurodesis
  - Indwelling pleural catheters

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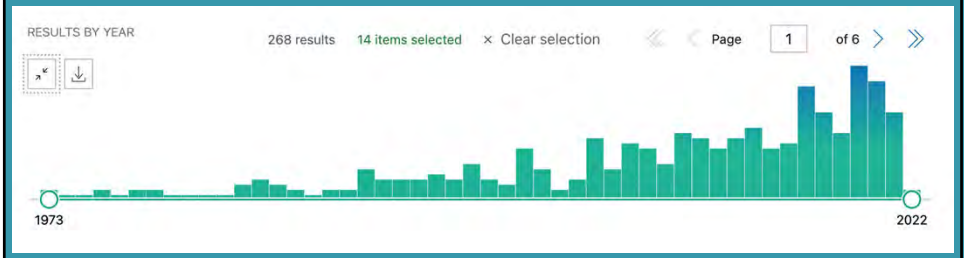
3

3

Literature on Lung Cancer and CAO



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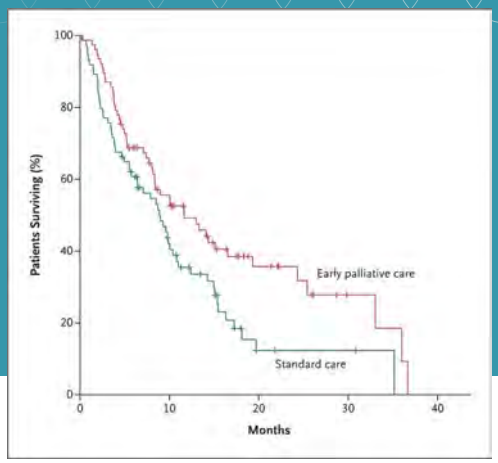
4

Benefit of Palliative Care in Advanced Lung Cancer

- Improved patient reported outcomes
  - Quality of life
  - Mood
- Improved health care delivery
  - Hospice utilization
  - Less aggressive care
- Improved survival

N Engl J Med 2010; 363:733-742



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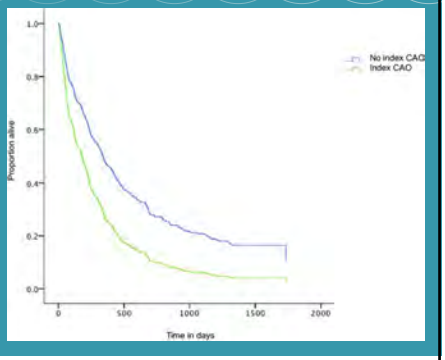
5

Prevalence and Outcome of Central Airway Obstruction in Patients with Lung Cancer

- BMJ 2019 Sep 24;6(1)
- Single Center CT study of 342 patients
- Prevalence 15%, 5% incidence
  - Missed on index CT in 31%
- CAO associated with worse outcome
  - Median survival of 94 days
  - Risk of death: HR = 2.48, p=0.001



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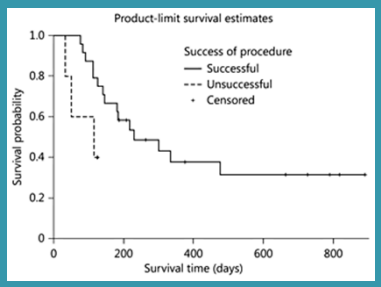
6

6

Airway Patency Associated with Better Outcomes

- Therapeutic bronchoscopy improves spirometry, quality of life, and survival in central airway obstruction. *Mahmood K, Wahidi MM, Thomas S, Argento AC, Ninan NA, Smathers EC, Shofer SL. Respiration. 2015; 89(5):404-13.*
  - 53 patients with CAO
    - *Successful bronchoscopic intervention*
    - *Various interventions used*
    - *Significant improvement in*
      - *FVC*
      - *FEV1*
      - *SOBQ score*
      - *SF-36 domains*
    - *Patients in whom airway patency could not be achieved had worse survival*



- **Similar survival compared to patients without CAO**
  Chhajed PN er al, Chest 2006 Dec;130(6):1803-7

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7

7

NCCN NSCLC Guidelines Approach to CAO

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Non-Small Cell Lung Cancer

THERAPY FOR RECURRENCE AND METASTASIS

Locoregional recurrence

- Endobronchial obstruction → Any combination of the following:
  - Laser/stent/other surgery[k]
  - External-beam RT or brachytherapy[l]
  - Photodynamic therapy
- Resectable recurrence → Reresection (preferred)[k] / External-beam RT or SABR[l,m]
- Mediastinal lymph node recurrence
  - No prior RT → Concurrent chemoradiation[l,q]
  - Prior RT → Systemic therapy (NSCL-17)
- Superior vena cava (SVC) obstruction → Concurrent chemoradiation[l,q] (if not previously given) / External-beam RT[l] / SVC stent
- Severe hemoptysis → External-beam RT or brachytherapy[l] / Laser or photodynamic therapy or embolization / Surgery

All → Chest CT with contrast; Brain MRI with contrast; PET/CT

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8

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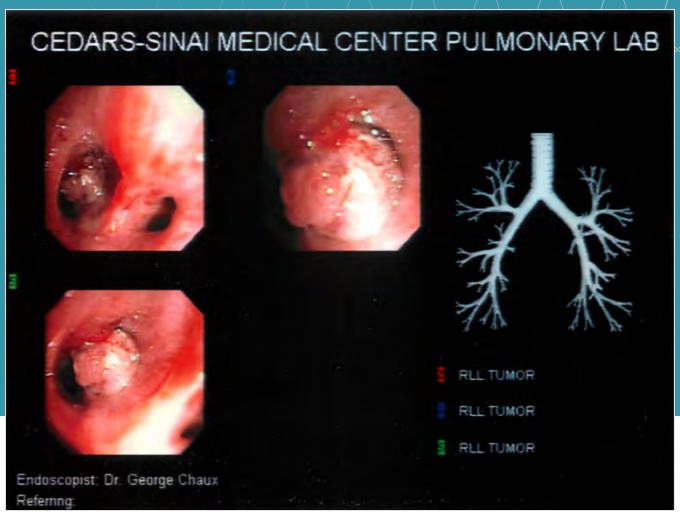
Endobronchial Tumor



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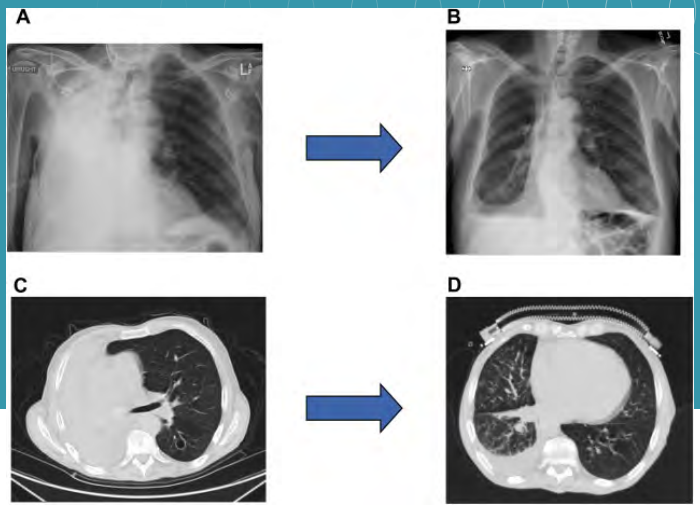
Atelectasis due to CAO



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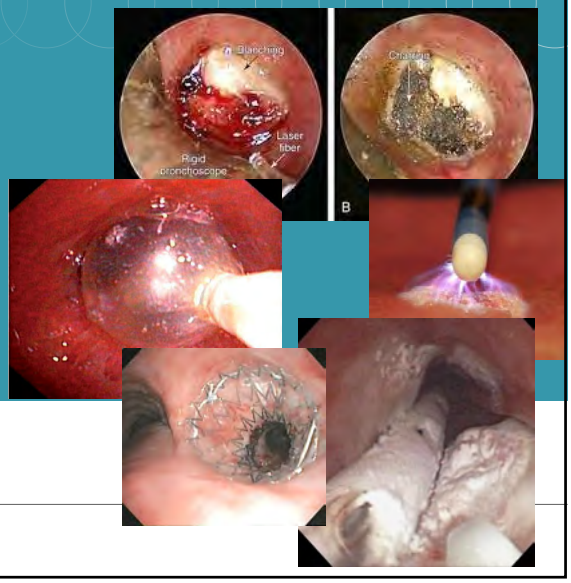
10

10

Airway Interventions for Bronchogenic and Metastatic Carcinoma of the Lung

- Dilation
- Debridement
  - laser
  - cryo-
  - argon plasma
- Stents
- Photodynamic therapy



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Hot versus Cold Therapies

Hot

- Laser
  - KTP
  - Nd:YAG
- Argon plasma photocoagulation
- Electrocautery

Cold

- Balloon dilation
- Cryo-ablation
- Photodynamic therapy
- Brachytherapy
- Stents

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Rigid versus Flexible Bronchoscopy

- Rigid bronchoscopy
  - Traditionally used
  - Special skill
  - Advantages
    - Airway stabilization
    - Ventilation
    - Mechanical dilation/debridement
    - Better for bleeding and secretions?
  - Disadvantages
    - Airway/laryngeal injury
    - Not as versatile
    - Image quality
- Flexible Bronchoscopy
  - Easier to handle
  - Great visibility
  - More versatile
  - Disadvantages
    - Intubation
    - Scope damage

FLEXIBLE FIBEROPTIC BRONCHOSCOPE

RIGID METAL BRONCHOSCOPE

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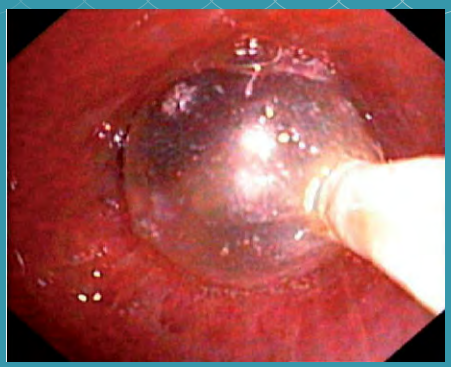
Airway Interventions: Balloon Dilation

- Relatively less invasive
- Relatively safe
- Temporizing
- Risks
  - Bleeding
  - Airway perforation



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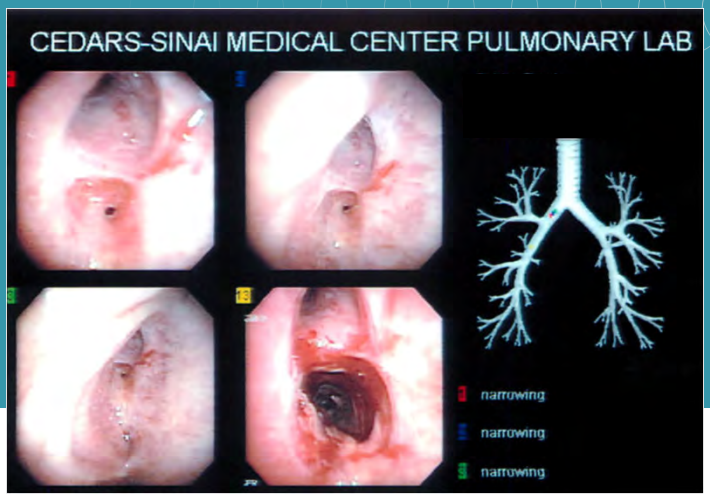
Balloon Dilation



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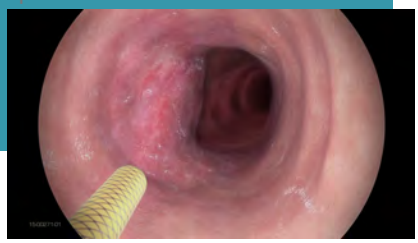
Liquid Nitrogen Spray Cryotherapy

- Liquid Nitrogen -196 degree C
- Rapid freezing and thawing causes apoptosis
- Low pressure spray < 3 psi
- No risk of fire
- Risk of pneumothorax and pneumomediastinum



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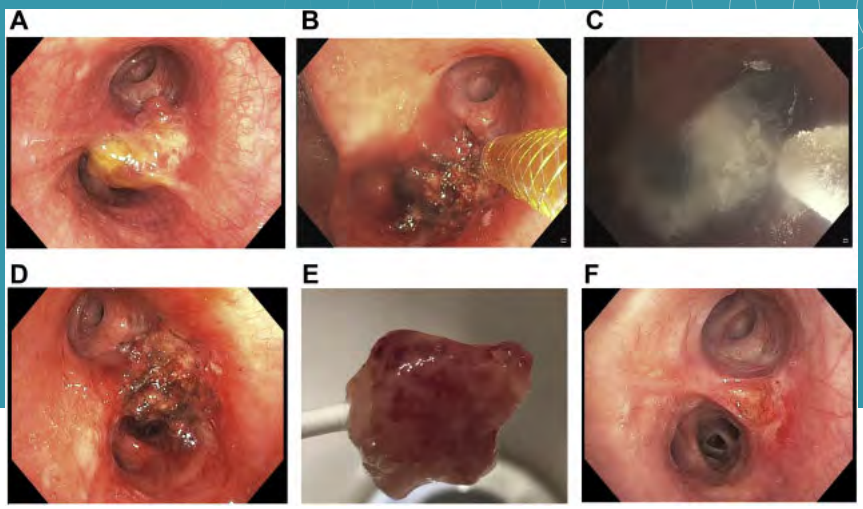
SCT Treatment of Endobronchial Carcinoid



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Aboudara, M et al. Clinics in Chest Med Feb 29, 2020; 41(1):145-160

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Laser Therapy for CAO

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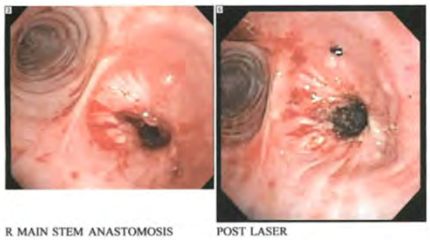
Bronchoscopy Exam Images

Patient:
Patient ID:
Attending Physician: George Chaux M.D.
Exam Date: 05/18/2010



R MAIN STEM ANASTOMOSIS

POST LASER

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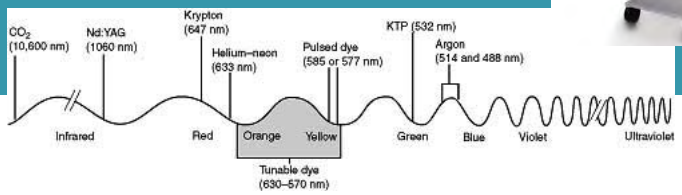
Laser Therapy for CAO

Laser options

- Nd:YAG – neodymium:yttrium-aluminum-garnet
- ND:YAP – neodymium:yttrium-aluminum-perovskite
- KTP – potassium titanyl phosphate
- CO2 - carbon dioxide
- Holmium

Laser alternatives

- APC – argon plasma coagulation
- Electrocautery



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Laser Characteristics

*(**L**ight **A**mplification by **S**timulated **E**mission of **R**adiation)*

Laser light is monochromatic, bright, unidirectional and coherent

Monochromatic

- Light emitted at the same wavelength and energy
- Allows for precise targeting of tissue with sparing of adjacent structures

Brilliancy

- Intense and well centered
- Allows for peak power

Coherency

- Photons emitted vibrate in phase, a measure of precision of the waveform
- Allows for precise focusing

Directionality

- All photons travel in a single direction
- Allows for focusing on a small spot

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Laser-Tissue Interaction

Laser beam that encounters tissue is absorbed, reflected, scattered or transmitted

Photons interact with matter only by transferring energy so only absorbed photons can have a tissue effect

A Chromophore is required for photon absorption
- A material in tissue that absorbs wavelengths depending on its absorption coefficient
- Hgb, water, proteins, amino acids, nucleic acids and bilirubin

The aim of medical grade lasers is to increase absorption and minimize transmission, scatter and reflection
- Absorbed photos produce thermal, mechanical and chemical changes in tissue
- High energy photons are typically delivered in ultrashort pulses of nanoseconds

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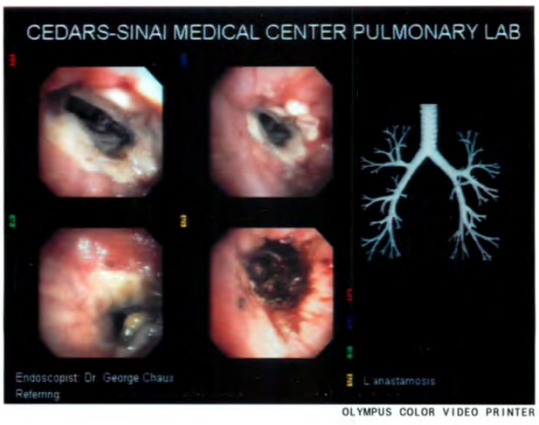
Laser Debridement – Anastomotic Stricture



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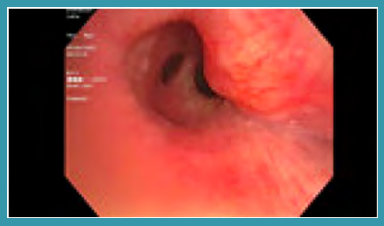
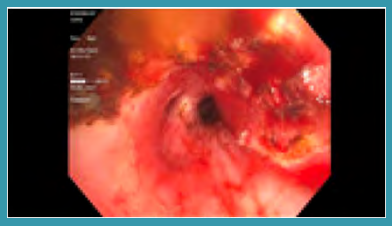
Laser Debridement – Airway Tumor

Pre-KTP Laser



Post-KTP Laser



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Does Laser Debridement Affect Outcomes in Lung Cancer?

- Han C.C., Praselyo D., Wright C.M.: Endobronchial palliation using Nd-YAG laser is associated with improved survival when combined with multimodal adjuvant treatments. *J Thorac Oncol 2007; 2: pp. 59-64*
- Retrospective
- 110 patients who underwent 153 laser treatments
- Nd:YAG laser
- Two groups
  - Laser alone: 30
  - Laser plus multimodality therapy: 66 (stenting, chemo, radiation)
- Results in median survival
  - Multimodality 6.99 months vs. 3.77 months (P=0.002) for all malignancies
  - Multimodality 7.17 months vs. 2.27 months (P<0.001) for NSCLC

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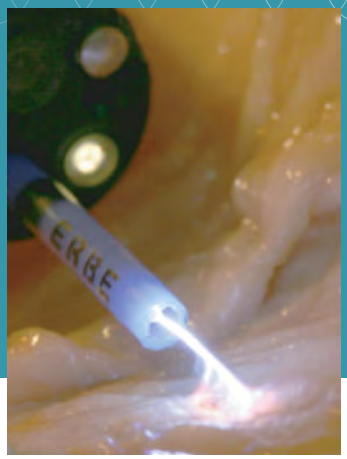
Argon Plasma Coagulation

- Electrosurgery = application of an alternating current to tissues in order to induce a thermal effect
- Temperatures above 60 degrees C cause coagulation and cell death
- APC
  - Electrical current is used to ignite Argon gas discharged from the tube surrounding the active electrode
  - Biochemically inert and inexpensive
  - Penetration depth is a few millimeters
  - Establishes hemostasis and tissue debridement
  - Applications in general surgery, urology, ENT, GI and bronchoscopy
  - Generally, very safe



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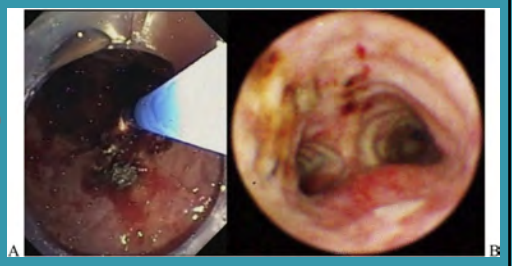
Clinical efficacy of argon plasma coagulation combined with cryotherapy for central airway stenosis caused by lung cancer
Wang Z, Wang W, Wu G.
J Cardiothorac Surg. 2019 Aug 28;14(1):155

- Retrospective analysis
- 177 patients with CAO
  - 43 received cryotherapy alone
  - 134 received cryotherapy plus APC
- Improvements noted in the APC group
  - Karnofsky score
  - Oxygenation
  - Ventilation ($PaCO_2$)
  - Bleeding, fever and arrhythmia
  - 72% vs. 51% survival



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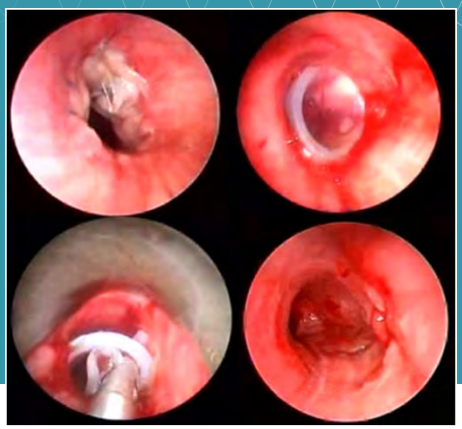
Stenting for Central Airway Obstruction

- Silicone
- Metal
- Hybrid



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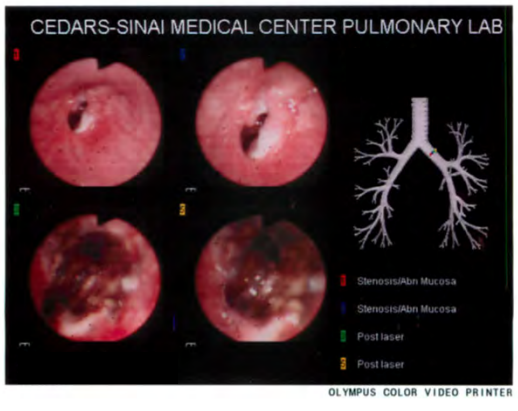
Laser and Stent



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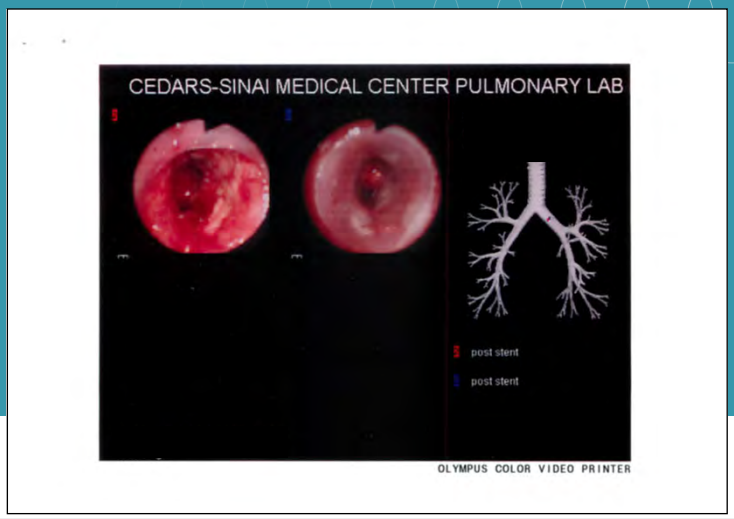
Laser and Stent



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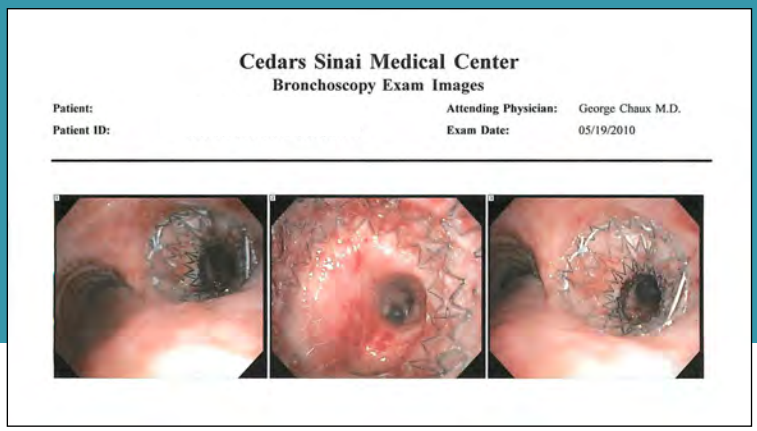
Bronchial Stent for Benign Stricture



Cedars Sinai Medical Center
Bronchoscopy Exam Images

Patient: **Attending Physician:** George Chaux M.D.
Patient ID: **Exam Date:** 05/19/2010

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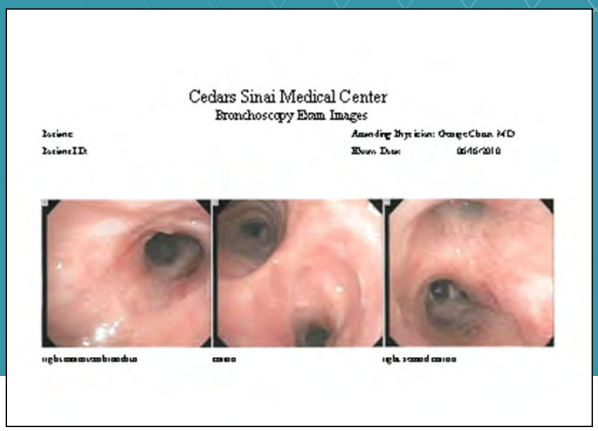
Benign Stricture post Stent Removal



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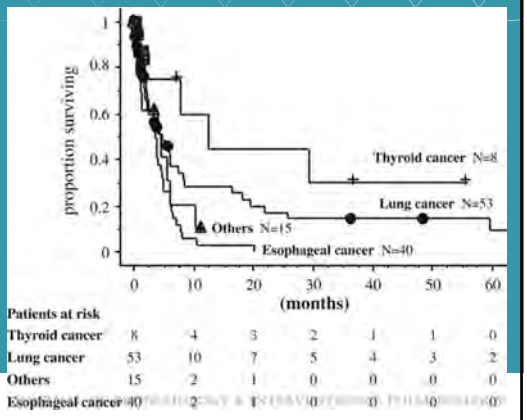
Contributions of Airway Stent for Long-term Outcome in Patients with Malignant Central Airway Stenosis or Obstruction

Iyoda A, Azuma Y, Sano A, Sakai T, Koezuka S, Otsuka H, Tochigi N, Isobe K, Sakamoto S, Takagi K.
J Bronchology Interv Pulmonol. 2021 Jul 1;28(3):228-234

- Retrospective analysis
- 116 patients at a single center in Japan
- All had stenting of CAO or stenosis over 10 yrs
  - 53 lung cancer
  - 40 esophageal cancer
  - 8 thyroid cancer
  - 15 others
- Best prognosis: thyroid followed by lung cancer especially with chemo/rad
- Worse prognosis: esophageal cancer
- Most complications: thyroid cancer



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Impact of Silicone Stent Placement in Symptomatic Airway Obstruction due to Non-Small Cell Lung Cancer – A French Multicenter Randomized Controlled Study. The SPOC Trial
Dutau H, Di Palma F, Thibout Y, Febvre M, Cellerin L, Naudin F, Hermant C, Vallerand H, Lachkar S, Fournier C, Laroumagne S, Quiot JJ, Vergnon JM; SPOC Investigators.
Respiration. 2020;99(4):344-352

- First RCT investigating the benefit of silicone stent insertion after successful therapeutic bronchoscopy in symptomatic malignant airway obstruction without extrinsic compression
- Underpowered
- Did not meet primary endpoint of 1-year survival rate
- Demonstrated benefit at 1-year
  - Dyspnea score
  - Obstruction recurrence
  - Need for additional bronchoscopic intervention

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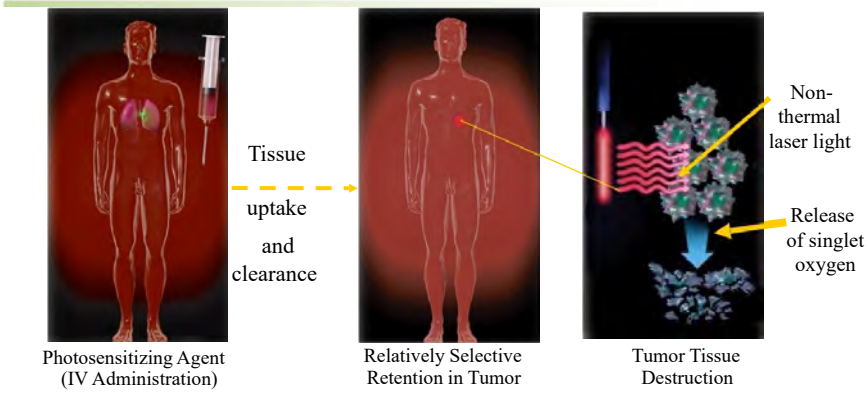
Photodynamic Therapy (PDT): Overview



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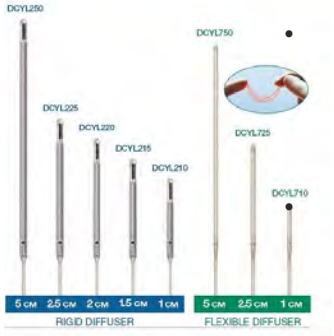
Light Dosimetry



A range of quartz optical rigid and flexible fibers fitted with cylinder diffuser tips: 1.0cm to 5.0cm (Optiguide® Fiber Optic)

200J/cm for interstitial therapy, or intraluminal therapy, over 8 minutes and 20 seconds

DIOMED 630 PDT Laser

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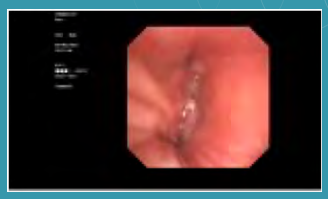
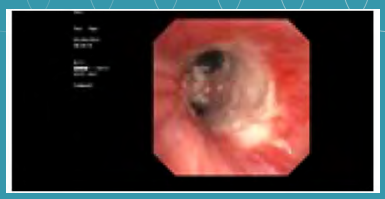
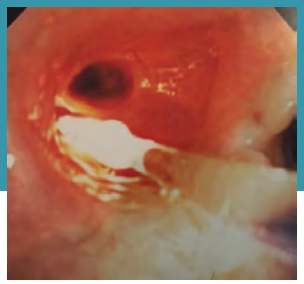
Pre- and Post-PDT







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Outcomes of patients with advanced non-small cell lung cancer and airway obstruction treated with photodynamic therapy and non-photodynamic therapy ablation modalities

Jayadevappa R, Chhatre S, Soukiasian HJ, Murgu S.
J Thorac Dis. 2019 Oct;11(10):4389-4399

- SEER Medicare database
- Stage III and IV NSCLC patients from 2000 - 2011
- Three treatment groups:
  - PDT + rad +/- chemo
  - Non-PDT ablation + rad +/- chemo
  - Rad/chemo
- All-cause and cause-specific mortality
  - Similar HR of mortality in PDT c/t Rad/chemo
  - Non-PDT ablation group had higher mortality c/t Rad/chemo

Association between treatment type and mortality

Covariates	All-cause mortality OR	All-cause mortality 95% CI	Lung cancer-specific mortality OR	Lung cancer-specific mortality 95% CI
Treatment group				
PDT*	1.03	0.73–1.45	1.04	0.71–1.51
Non-PDT ablation**	1.22	1.13–1.33	1.10	1.01–1.20
Radiation + chemo (reference)	–	–	–	–
Age at diagnosis	1.01	1.01–1.04	1.00	1.00–1.01
Race and ethnicity				
White	1.13	1.09–1.15	1.04	1.01–1.07
Other (reference)	–	–	–	–
Marital status				
Married	0.91	0.89–0.93	1.00	0.98–1.03
Other (reference)	–	–	–	–
Gender				
Male	1.28	1.26–1.31	1.03	1.01–1.05
Female (reference)	–	–	–	–
Geographic region				
Metro	0.94	0.92–0.97	0.99	0.97–1.02
Non-metro (reference)	–	–	–	–
Commodity score				
Comorbidity ≥1	1.19	1.17–1.22	0.99	0.97–1.01
Zero comorbidity (reference)	–	–	–	–
Stage				
Stage III	0.64	0.62–0.65	0.90	0.88–0.92
Stage IV (reference)	–	–	–	–

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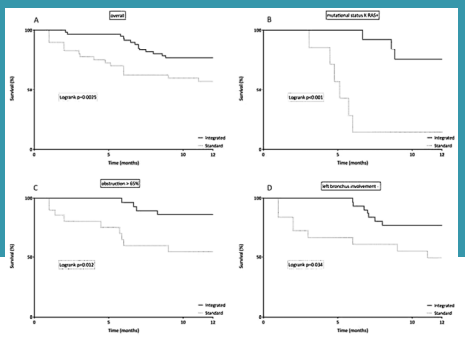
EVERMORE Trial

Integrated intErventional bronchoscopy in the treatment of locally advanced non-small lung cancER with central Malignant airway Obstructions: a multicentric, REtrospective study (EVERMORE). Marchioni A, Andrisani D, Tonelli R, Piro R, Andreani A, Cappiello GF, Meschiari E, Dominici M, Bavieri M, Barbieri F, Taddei S, Casalini E, Falco F, Gozzi F, Bruzzi G, Fantini R, Tabbì L, Castaniere I, Facciolongo N, Clini E; EVERMORE Study group. *Lung Cancer. 2020 Oct;148:40-47.*

- Retrospective cohort study conducted at two teaching hospitals
- 60 patients received interventional bronchoscopy plus chemo/rad; 40 patients received chemo/rad
- Improved 1-year survival
- Reduced new hospitalizations, increased symptom free interval and prevented atelectasis



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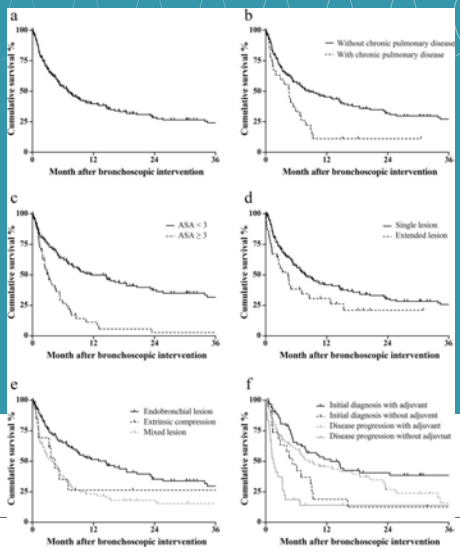
Prognostic factors for survival after bronchoscopic intervention in patients with airway obstruction due to primary pulmonary malignancy
Kim BG, Shin B, Chang B, Kim H, Jeong BH.
BMC Pulm Med. 2020 Feb 27;20(1):54.

- Single center
- Retrospective study
- 224 patients with CAO due to primary lung cancer
- Median survival: 7 months
- One- and two-year survival: 39.7% and 28.3%
- Poor survival in
  - Chronic pulmonary disease
  - Poor performance status
  - Extended lesion
  - Extrinsic or mixed lesion
  - CAO due to disease progression
  - No adjuvant treatment



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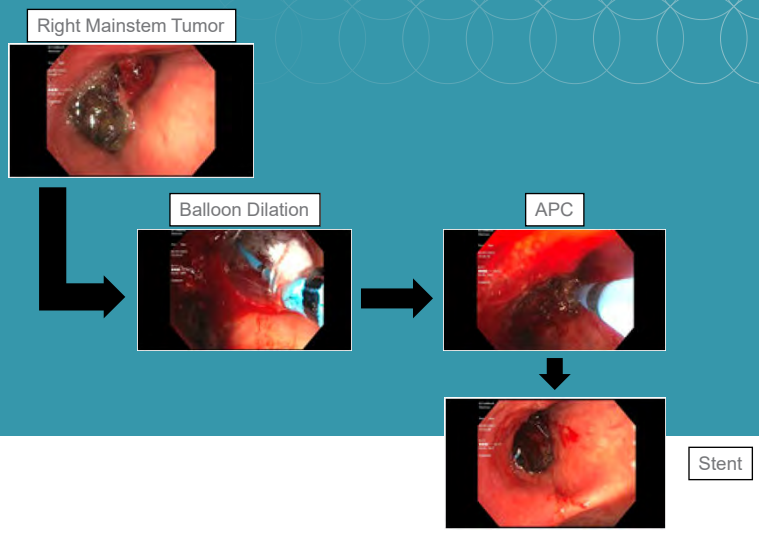
Multimodality Approach to CAO



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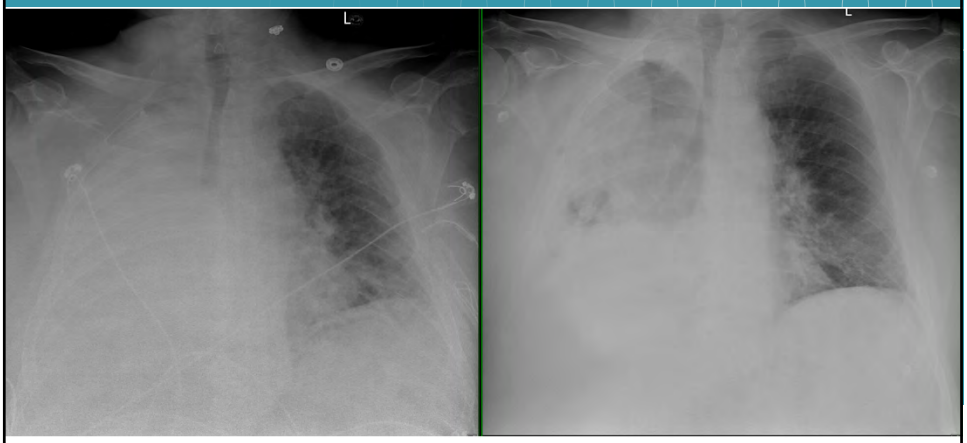
Multimodality Approach



Pre-CXR

Pre-CXR

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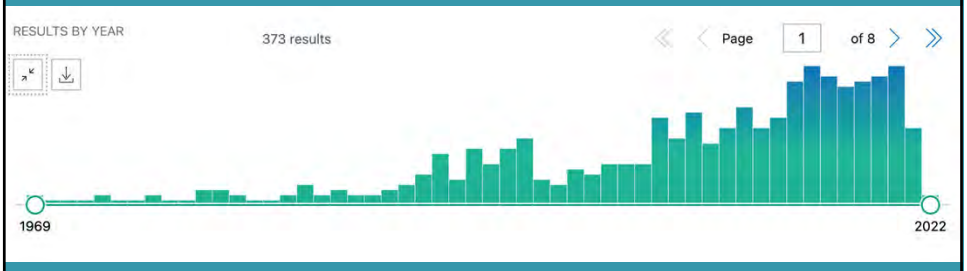
Literature on Pleurodesis for Lung Cancer



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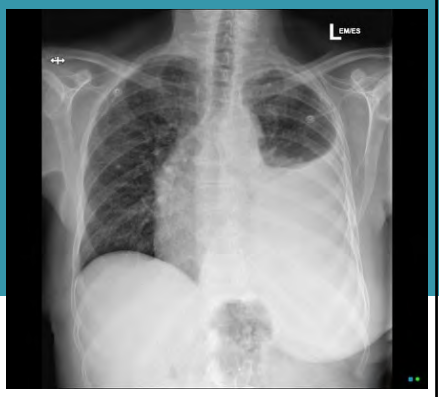
Palliative Interventions for Pleural Disease

- **Incidence**
  - 22% of all pleural effusions diagnosed in the USA – 150,000 (Junaid Akram et al., 2020)
  - In 2012 – 126,825 patients with MPE were admitted to hospital in the US (Vertis et al., 2021)
- **Morbidity and mortality**
  - Median survival of 3 to 24 months (Feller-Kopman et al., 2018)
  - Dyspnea and chest pain
- **Approaches to palliation**
  - Pleurodesis
    - Talc
    - Hypertonic glucose
    - Autologous blood
    - Iodopovidone
    - Minocycline
    - Mechanical
  - Indwelling pleural drainage



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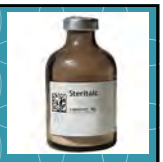
Talc Pleurodesis



- **2015 Cochrane meta-analysis** – *Clive AO et al., Cochrane Database Syst Rev 2015;5*
  - 62 RCTs
  - Talc is likely the most efficacious agent
  - Best administered by VATS
- **Talc Poudrage vs. Slurry** – *Bhatnagar R et al., Health Technology Assessment 2020 Jun;24(26):1-90*
  - 330 adults at 17 NHS hospitals in the UK
  - Randomized to thoracoscopy with 4 gm Talc poudrage versus chest tube and 4 gm Talc slurry
  - Primary outcome: pleurodesis failure at 90 days
    - No difference – 22% vs. 24% failure rate
    - No difference in adverse events, hospital days and all-cause mortality (40% vs. 42% at 180 days)

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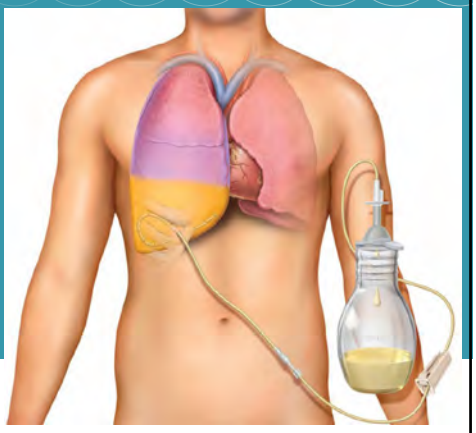
Indwelling Pleural Catheters

- Narrow, soft silicone catheter with a one-way valve
- Tunneled insertion
- Allow for home drainage
- Improvement in symptoms – 89 to 100% (Wrenta et al., 2019)
- Outpatient procedure
- Decreased need to hospitalization and access the healthcare system (Fysler Kocman et al., 2019)
- Infections rare (Chalchob et al., 2015)
- Allows for pleurodesis
- Cost savings
  - $42,376 for a median 5.5-day hospital stay for MPE (Taghizadeh et al. (2017)
  - Potential savings of $7,705/day



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Talc versus IPC for Malignant Pleura Effusion

Interventions for the management of malignant pleural effusions: a network meta-analysis.
Dipper A, Jones HE, Bhatnagar R, Preston NJ, Maskell N, Clive AO.
Cochrane Database Syst Rev. 2020 Apr 21;4(4):CD010529.

- Meta-analysis of 80 RCTs
- Fewer failure rates with Talc
- IPC associated with inferior definitive pleurodesis rates
- Comparable control of breathlessness
- Lower rate of requiring repeat pleural interventions with IPC
- Conclusion: "*Local availability, global experience of agents and adverse events (which may not be identified in randomized trials) and patient preference must be considered when selecting an intervention.*"

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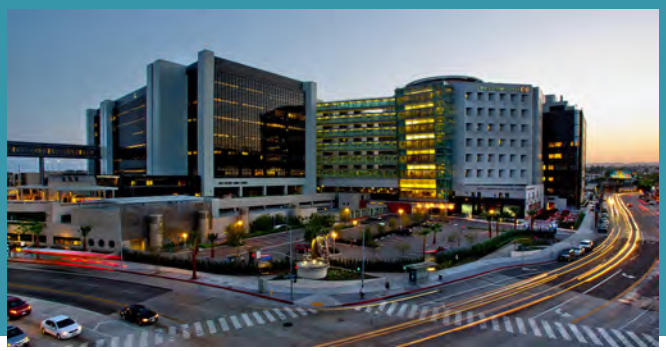
Thank You



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Post-Test and Adjourn

4:50 p.m. – 5:00 p.m.

KRISTINA KUDELKO, MD
STANFORD UNIVERSITY

GAURAV SINGH, MD, MPH
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Trainee Poster Session (NON-CME)

5:30 p.m. – 7:30 p.m.