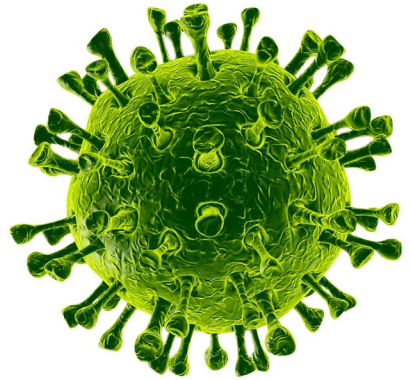
CAS Town Hall Webinar

COVID-19 Diagnosis and Ventilator Management Strategies



MODERATOR:
Dr Daniel Bainbridge

Dr Niall Ferguson

Dr John Granton

Dr Linda Hoang

COVID-19 Virus Testing:

A Primer for Anesthesiologists

CAS Webinar April 19, 2020

Linda M. N. Hoang MD, MSc, DTM&H, FRCPC

Associate Director, BCCDC Public Health Laboratory

Program Head, BCCDC Public Health Advanced Bacteriology & Mycology Lab

Clinical Associate Professor, Department of Pathology and Laboratory Medicine

The University of British Columbia, Vancouver, BC

COVID-19

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Outline

- Evolution of COVID-19 RT-PCR test at BCCDC Public Health Lab
- Analytical performance and attributes of test
- Interpretation of results
- Clinical performance and attributes of test
- Interpretation of reported epidemiological data
- Serology
- Test utilization and role of perioperative testing

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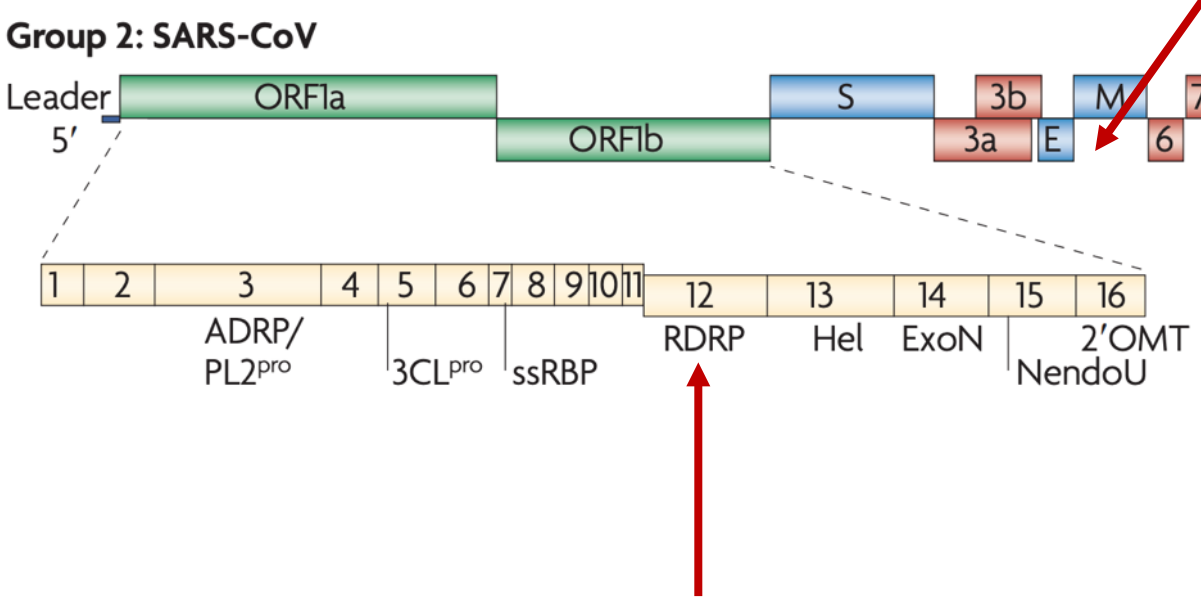
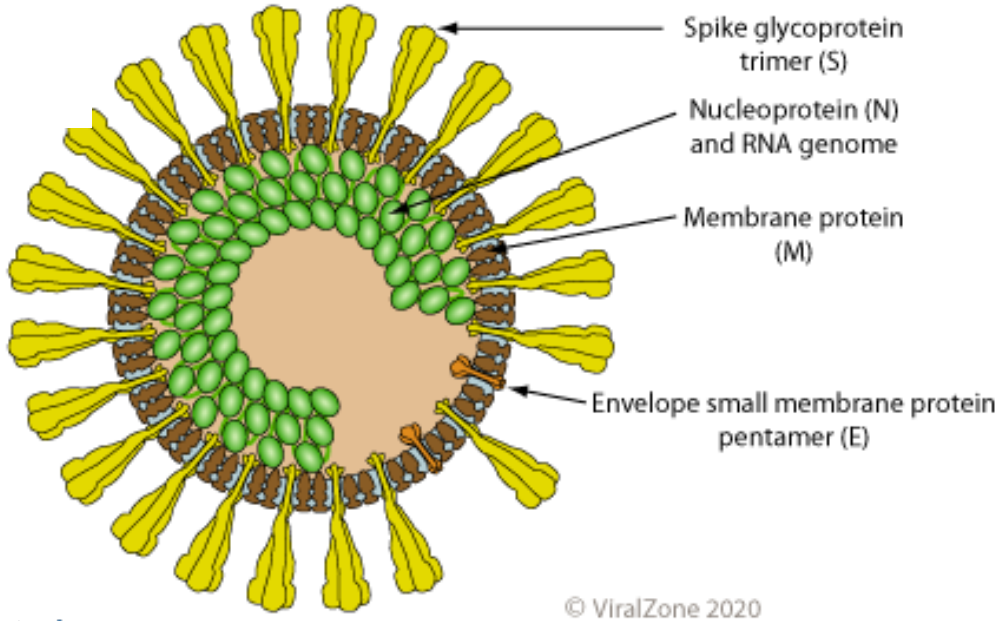
Coronavirus Genome: PCR and Sequencing Targets

Envelope (E) gene

Nucleoprotein (N) gene



RNA dependent RNA Polymerase



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Timeline of SARS-CoV-2 Assay Development in BC

Dec 2019
Pneumonia of unknown cause in Wuhan

Dec 31, 2019
Pneumonia of unknown cause reported to WHO

Jan 02, 2020
Lab confirmation of 2019-nCoV in 41 patients

Jan 10, 2020
1st 2019-nCoV genome released publicly

Jan 13, 2020
BCCDC designs qPCR assays; order primers

Jan 14, 2020
1st qPCR assay released on WHO website

Jan 20, 2020
BCCDC qPCR assay developed; undergoing validation

Jan 23, 2020
1st BC person under investigation (PUI) tested

Jan 27, 2020
1st positive sample from PUI

Feb 2, 2020
151 samples tested, 1 positive

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Courtesy of Dr. Natalie Prystajecky

No COVID-19 viruses were harmed in the making of this assay……

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Analytical Performance

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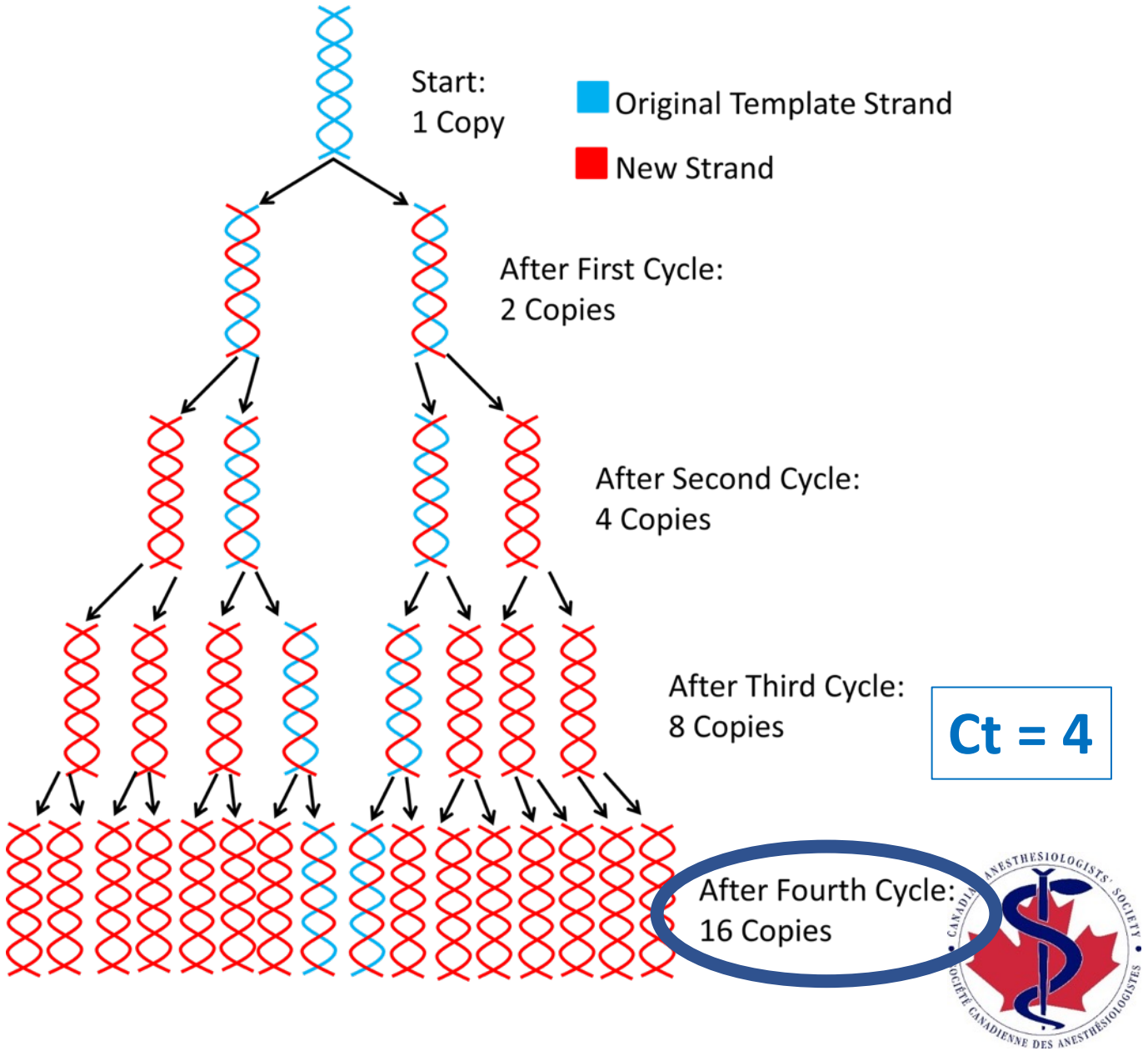
What is the Test?

RNA→ DNA
DNA amplification

Target 2 different COVID-19 genes:
RdRP and E-genes
AND internal sample control

Quantification: # cycles to reach the detection threshold.

The fewer the cycle the larger the viral load



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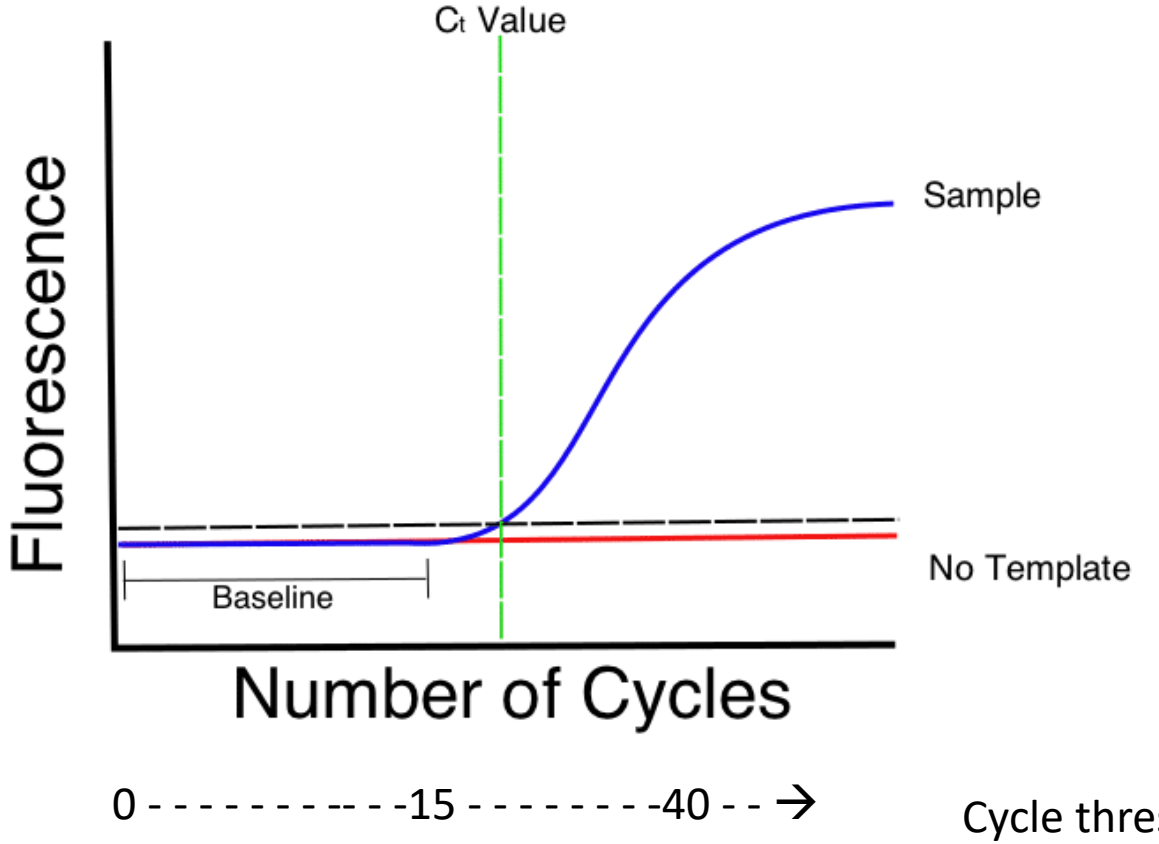

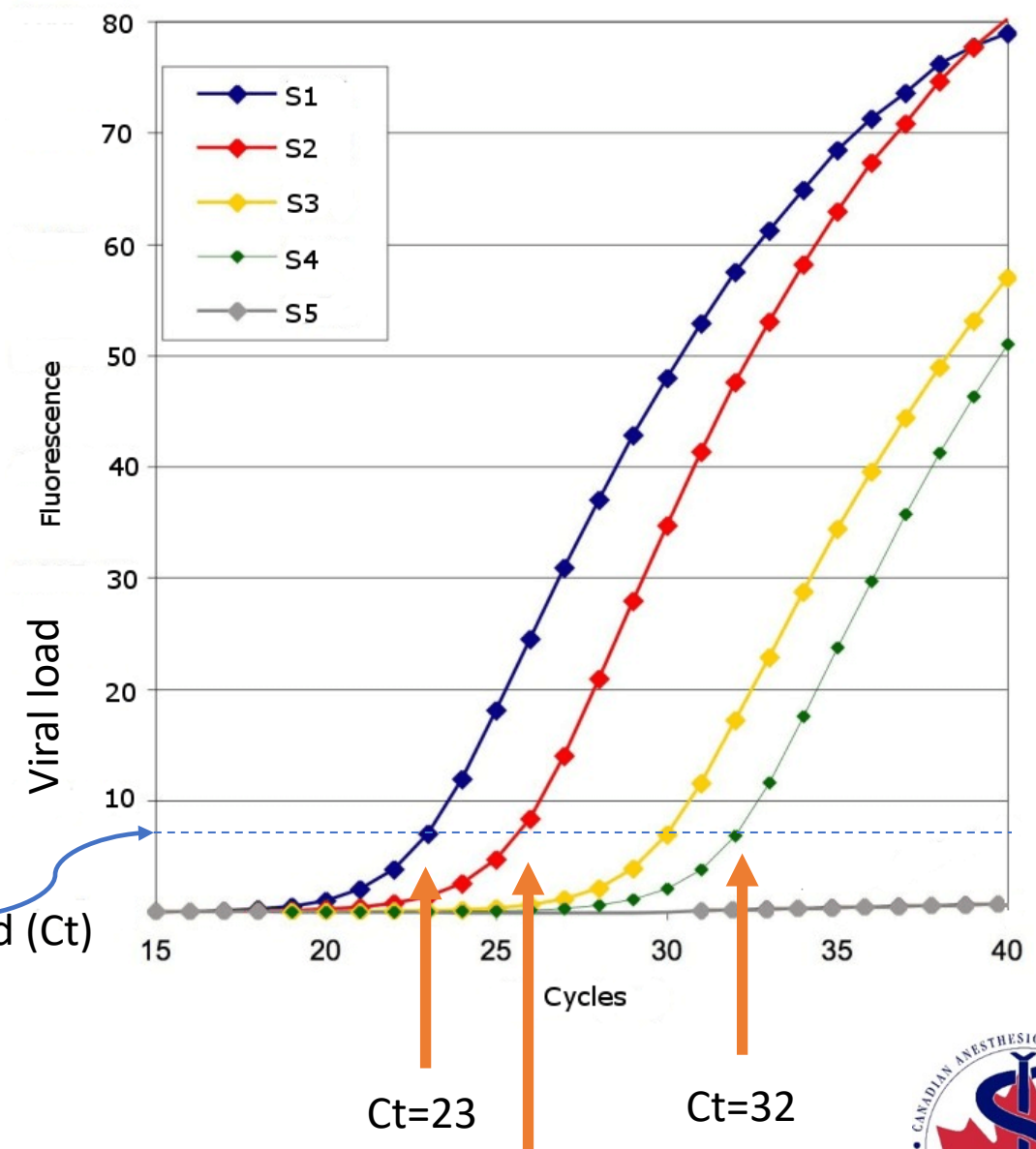

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COVID-19 Assay Attributes

Limit of detection: <10 RNA copies/mL sample

Alignment: with existing workflow, can be handled in CL2

Multiple targets: RdRP gene, E-gene, RNAseP (internal control)

Sample type: nasopharyngeal sample, throat swabs, throat to nose, etc

Analytical Sensitivity: 100% sensitive, 100% specific

Positive result: Cycle threshold (Ct) = <35

Indeterminate result = Ct 35-40

Negative result = Ct >40

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Negative and positive results

- If Ct is > 40 or not generated AND internal control is good

→ report as NEGATIVE for COVID-19

- If Ct is <35 AND internal control is good

→ report as POSITIVE for COVID-19

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Indeterminate results

- Variable terminology: inconclusive, indeterminate, undetermined, etc
- If Ct is not generated BUT internal control is not generated

  → Indeterminate, poor sample quality

- If Ct 35-40 AND internal control is good

  → Indeterminate,

  - Low level positive either in early or late disease
    - RNA is at the level of assay detection
  - Contamination

    → "Recollect if clinically indicated"

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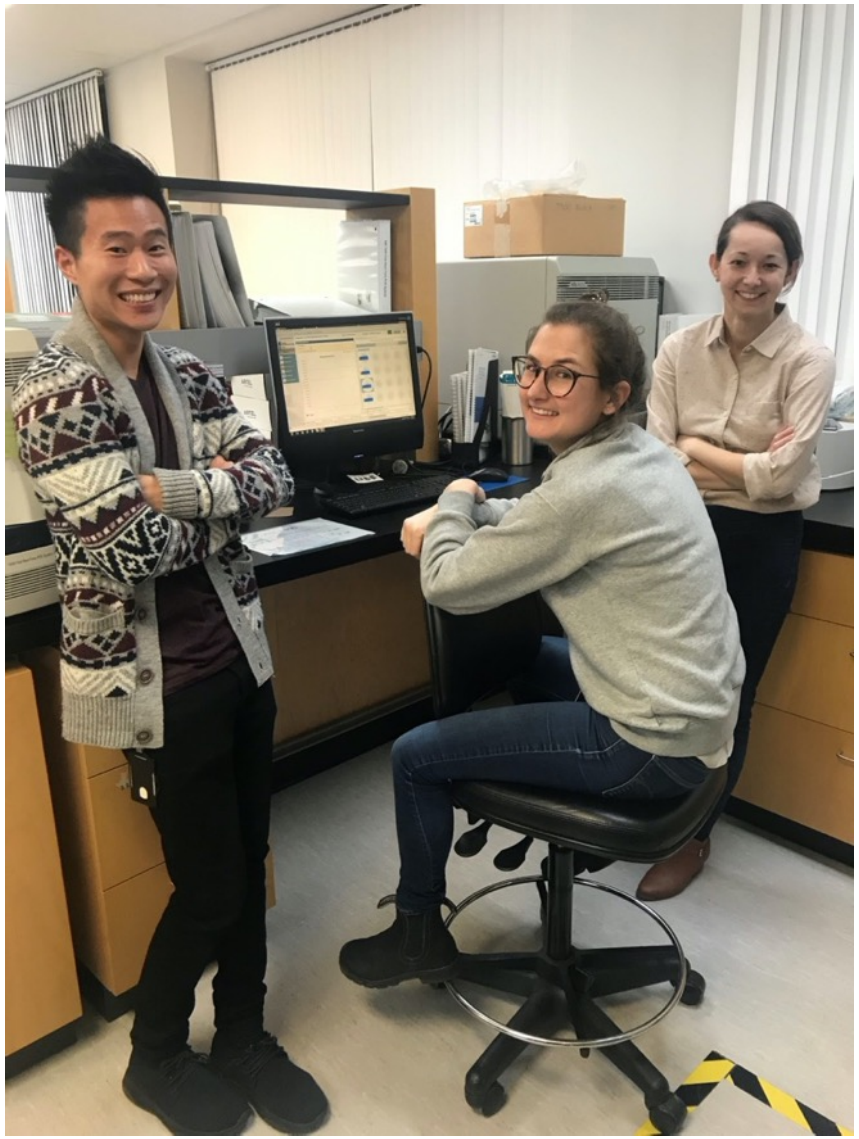
January 27, 2020

BC’s first case of confirmed COVID-19



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Challenges with Supply Chain

- Swab shortages
  - COPAN factory in Northern Italy
- Reagents for PCR test in short supply, contamination issues
  - Stockpiled provincially and nationally
  - Worldwide competition
  - No commercial flights
  - Border closures

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Challenges

B.C. has tested more people for COVID-19 than the entire United States, premier says

BY SIMON LITTLE · GLOBAL NEWS

Posted February 28, 2020 6:16 pm
Updated March 2, 2020 8:00 pm

- Exponential increase in volume
  - Routine capacity for respiratory virus PCR ~200 tests/day
  - →1500 tests per day
  - BCCDC PHL only lab in BC testing

➢Automation and commercial systems with high throughput

➢Decentralized testing to hospital and community laboratories

➢Implemented multiple assays as backup plans A, B and C….

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Clinical Performance

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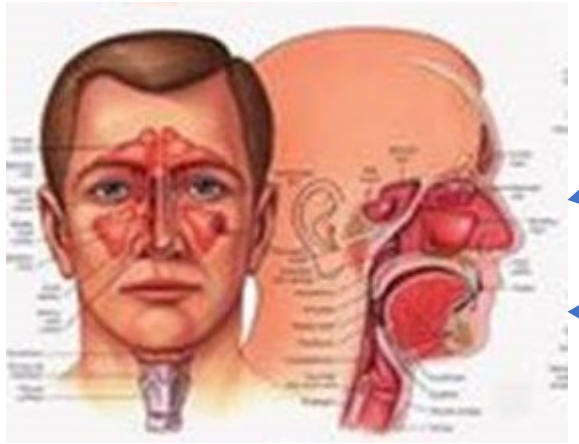
Determinants of Clinical Assay Performance

1) Operator

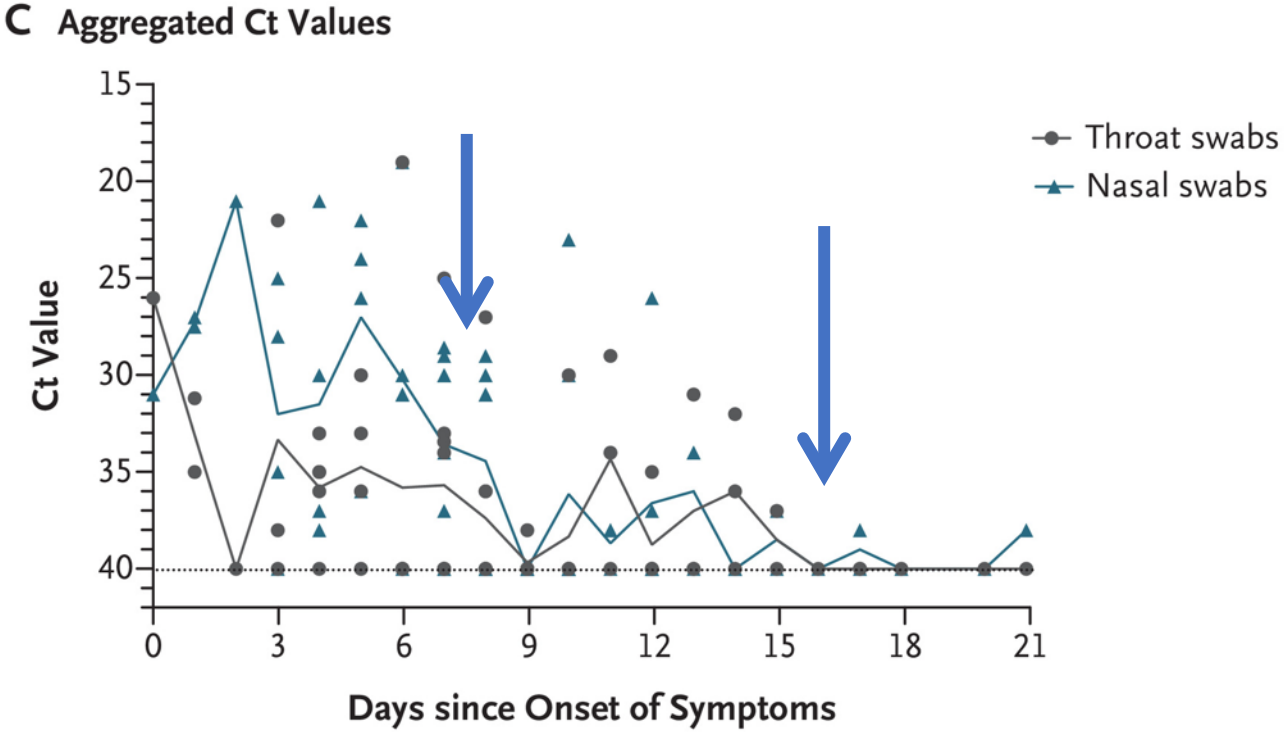


2) Site sampled

Nasal, NP

Throat

3) Time of sampling during course of illness



(Zou *et al.*, NEJM March 19, 2020)

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1) Operator

- Was the right swab used?
- Was the test collected correctly?
- Could there have been a mix-up?
- Is the sample kept in the appropriate conditions?
- Was the sample transported to the testing site within the acceptable time frame?
- etc

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2) Which Site(s) Should Be Tested?

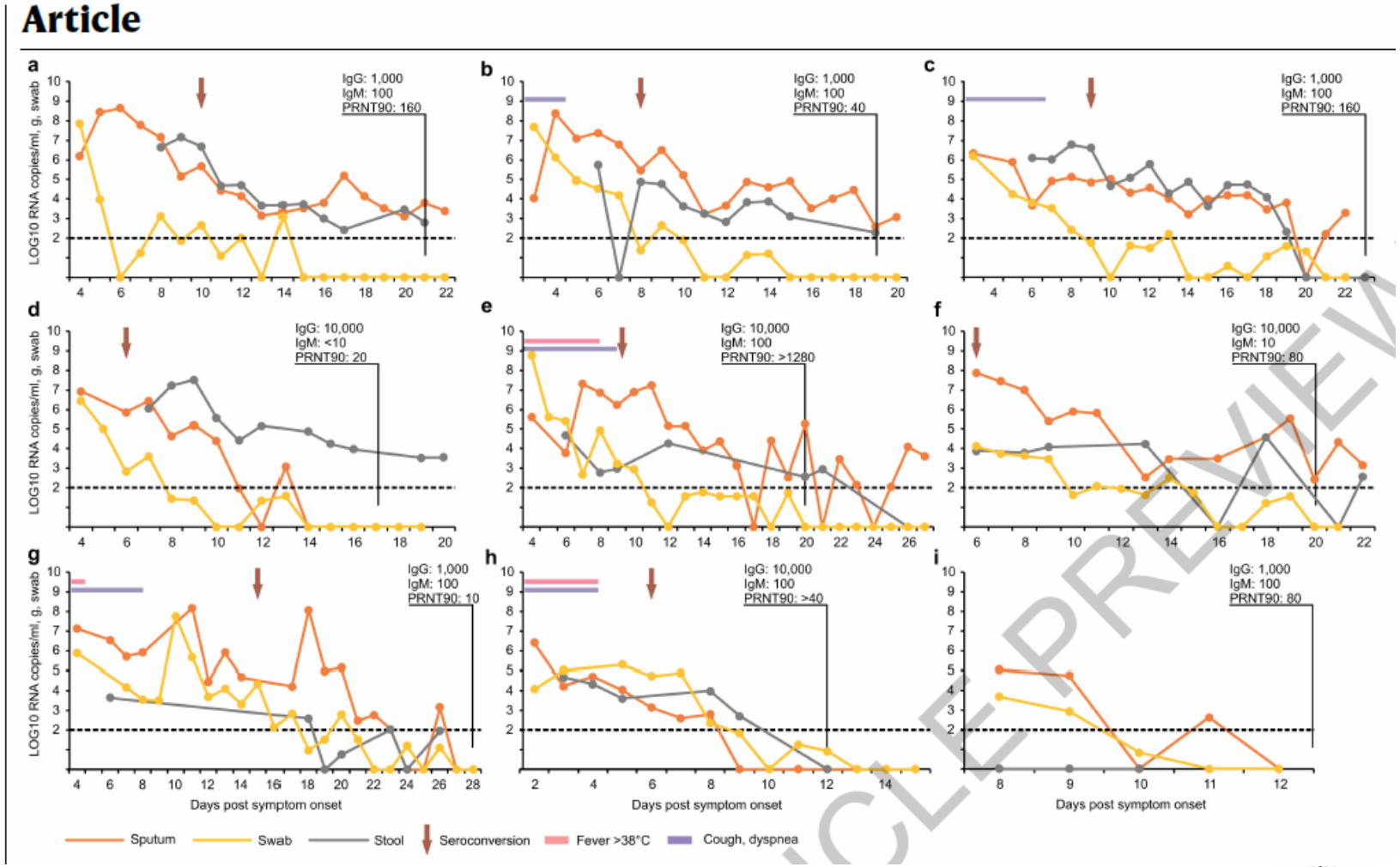
Nasopharyngeal & throat swabs

Sputum

Stool

~~**Serum**~~

~~**Urine**~~



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Wölfel *et al.*, Nature April 1, 2020
https://doi.org/10.1038/s41586-020-2196-x

2) Site Sampled Affects Viral RNA Detection

- Live virus most likely shed during the first week of symptoms
  - RNA load highest during the 1st week, then decreases
  - RNA shedding occurs ~3 weeks , up to 37 weeks
  - Undetectable live viral shedding 8 d post symptom onset, despite high RNA load
- NP swabs more sensitive than throat swabs
- Sputum specimens from patients with lower respiratory tract disease remain positive for longer duration
- Likely asymptomatic shedding, but limited data

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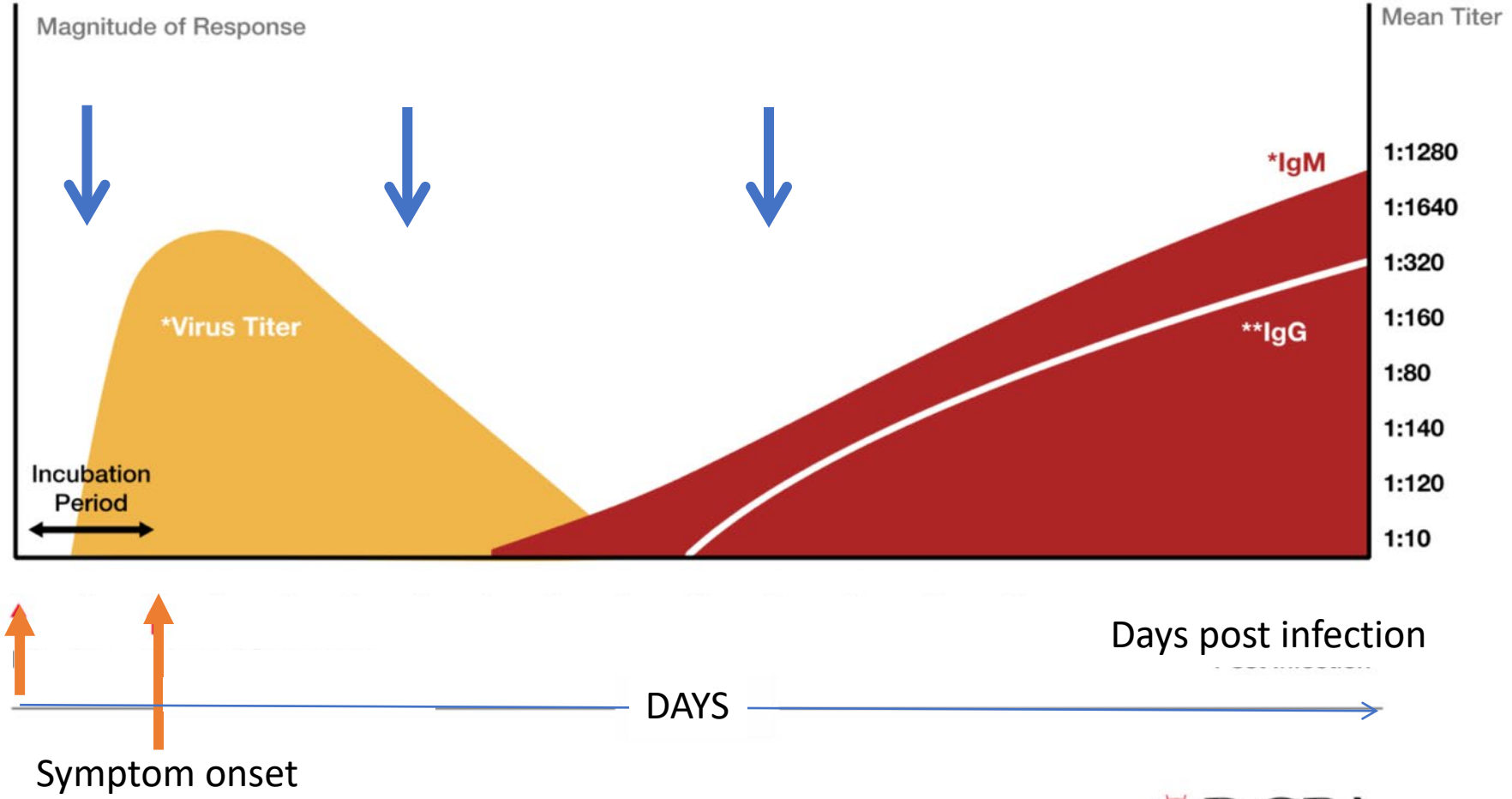
3) Time of Sampling During Course of Illness

- Upper respiratory tract viral load highest in first 5 days
- Lower respiratory tract likely starts later and extends for longer with lung involvement



The timing and level of antibodies is uncertain after SARS-COV-2 infection, and varies between patient populations. This graphic depicts one scenario based on the limited published evidence.

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The Royal College of Pathologists of Australasia

COVID-19

Why Can't You Tell Us What the Sensitivity of the Test Is?

To determine CLINICAL performance, one needs to do a "clinical trial"

BUT

No "clinical gold standard" for COVID-19 positive and negative cases, therefore unable to assess true clinical performance of PCR assay

- *The only studies that report PCR assay performance used CT Chest as "clinical gold standard" for identifying COVID-19 positive or negative cases*

References:

1) Huang P, Liu T, Huang L, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology 2020.

2) Xu J, Wu R, Huang H, et al. Computed Tomographic Imaging of 3 Patients With Coronavirus Disease 2019 Pneumonia With Negative Virus Real-time Reverse-Transcription Polymerase Chain Reaction Test. Clin Infect Dis. 2020;ciaa207.

3) Wu J, Liu J, Zhao X, et al. Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. Clin Infect Dis. 2020;ciaa199.

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Calculations

Sensitivity = 95%
Specificity = 98%

Disease prevalence	PPV	NPV
70%	99.08%	89.63%
50%	97.88%	95.28%
20%	92.02%	98.78%
5%	70.83%	99.74%
1%	31.79%	99.95%

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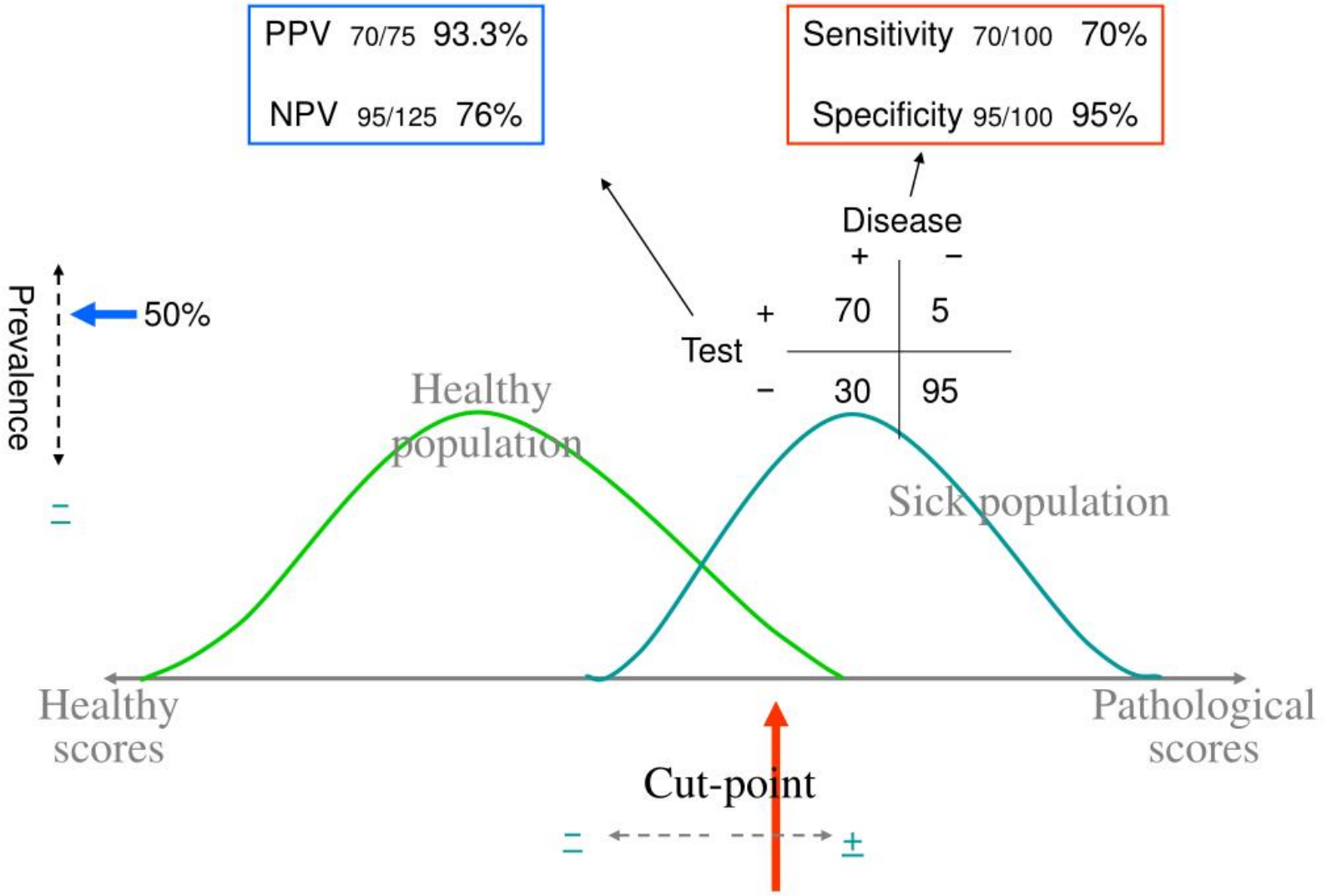

Multiple Factors Affecting Interpretation of Results

- Was the sample properly collected, were there any errors in handling and testing?
- What type of sample was collected?
- Where was the patient in the course of illness when the sample was collected?
- What is the prevalence of disease of the patient's population, at the time of sample collection?

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“Blood test”
AKA Serology

PCR tests detect the presence of COVID-19 virus RNA

Serology tests detect the immune response to COVID-19 infection

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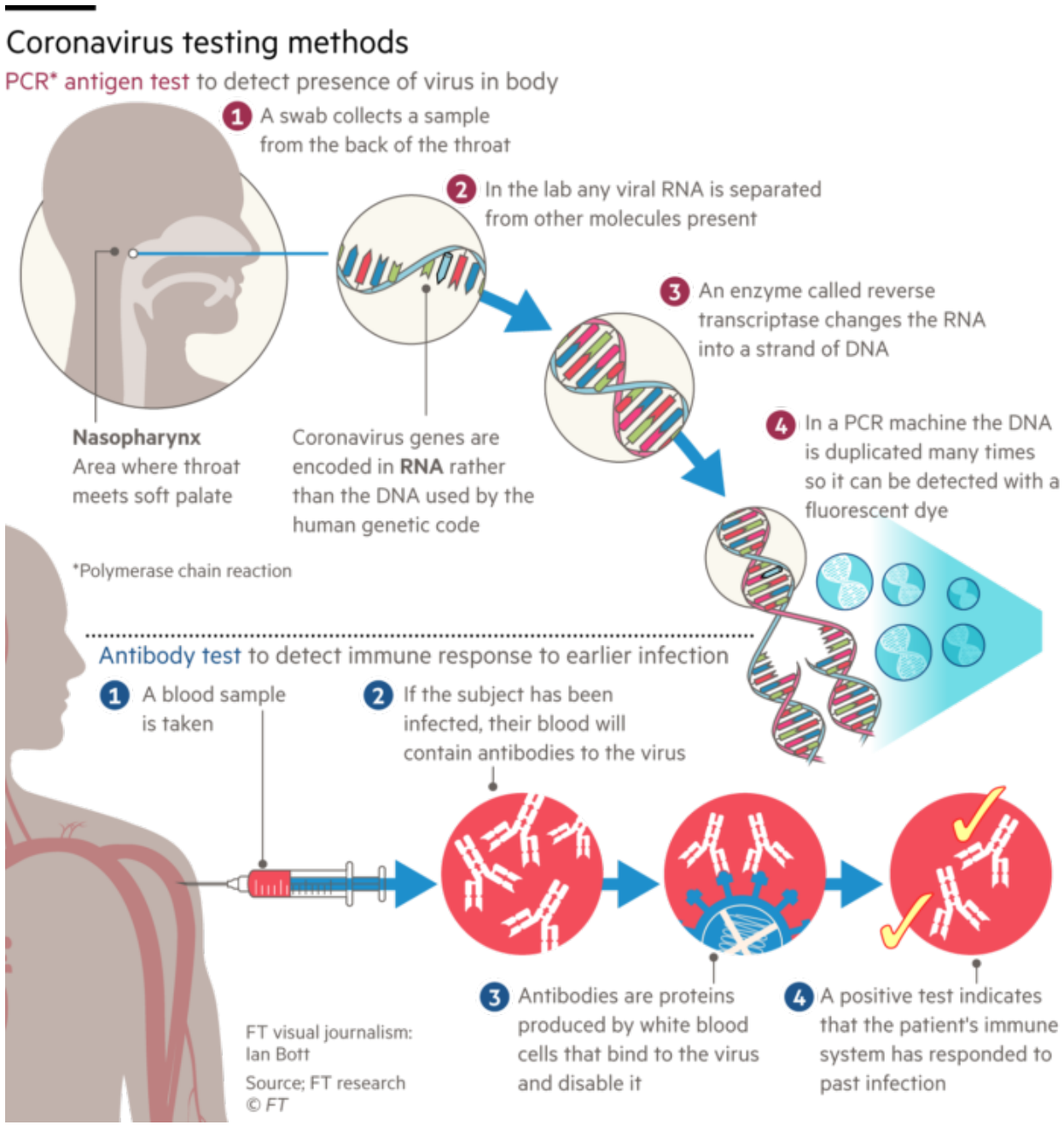
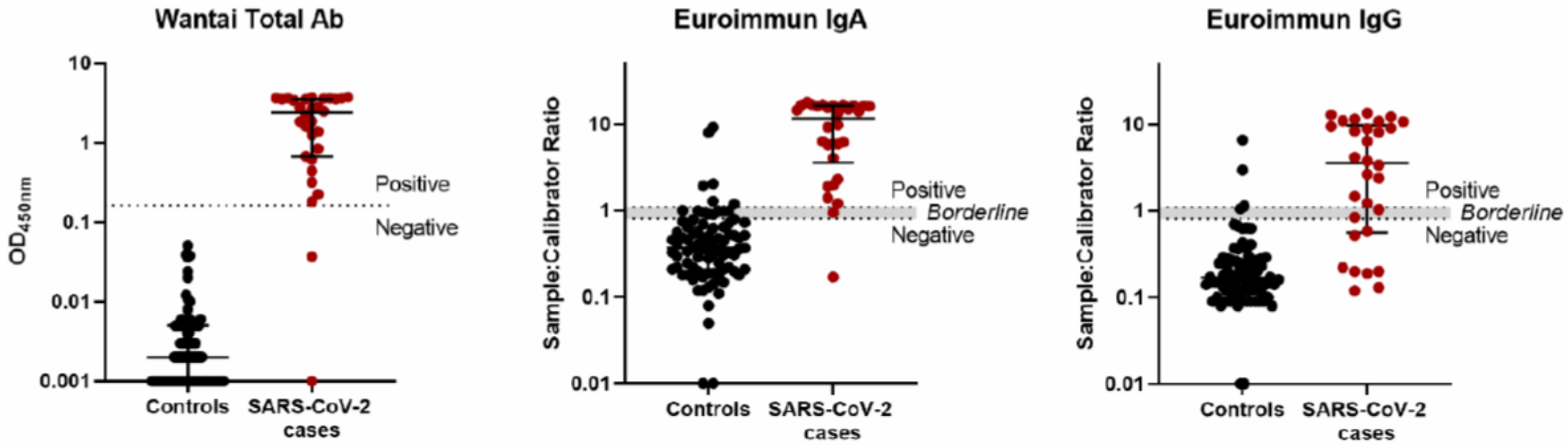


SARS-CoV-2 Antibody ELISA Performance

A



COVID-19

Lassaunière *et al.*, medRxiv https://doi.org/10.1101/2020.04.09.20056325

Comparison of COVID-19 Virus Antibody Detection

TABLE 1. Analytical sensitivities, specificities, and predictive values for SARS-CoV-2 antibody detection

Assay	Number (%) of serum samples		PPV (%)	NPV (%)
	Case sera testing positive	Control sera testing negative		
ELISA				
Wantai Total Ab	28/30 (93)	82/82(100)	28/28 (100)	82/84 (98)
Euroimmun IgA[a]	28/30 (93)	76/82 (93)	28/34 (82)	76/78 (97)
Euroimmun IgG[a]	20/30 (67)	79/82 (96)	20/23 (87)	79/89 (89)
Point-of-care test				
Dynamiker	27/30 (90)	32/32 (100)	27/27 (100)	32/36 (89)
CTK Biotech	27/30 (90)	32/32 (100)	27/27 (100)	32/36 (89)
AutoBio Diagnostics	28/30 (93)	32/32 (100)	28/28 (100)	32/25 (91)
Artron Laboratories	25/30 (83)	17/17 (100)	25/25 (100)	17/23 (74)
Acro Biotech	4/5 (80)[b]	12/15 (80)	4/7 (57)	12/13 (92)
Alltest Biotech	1/1 (100)[b]	13/15 (87)	Too few tested	Too few tested

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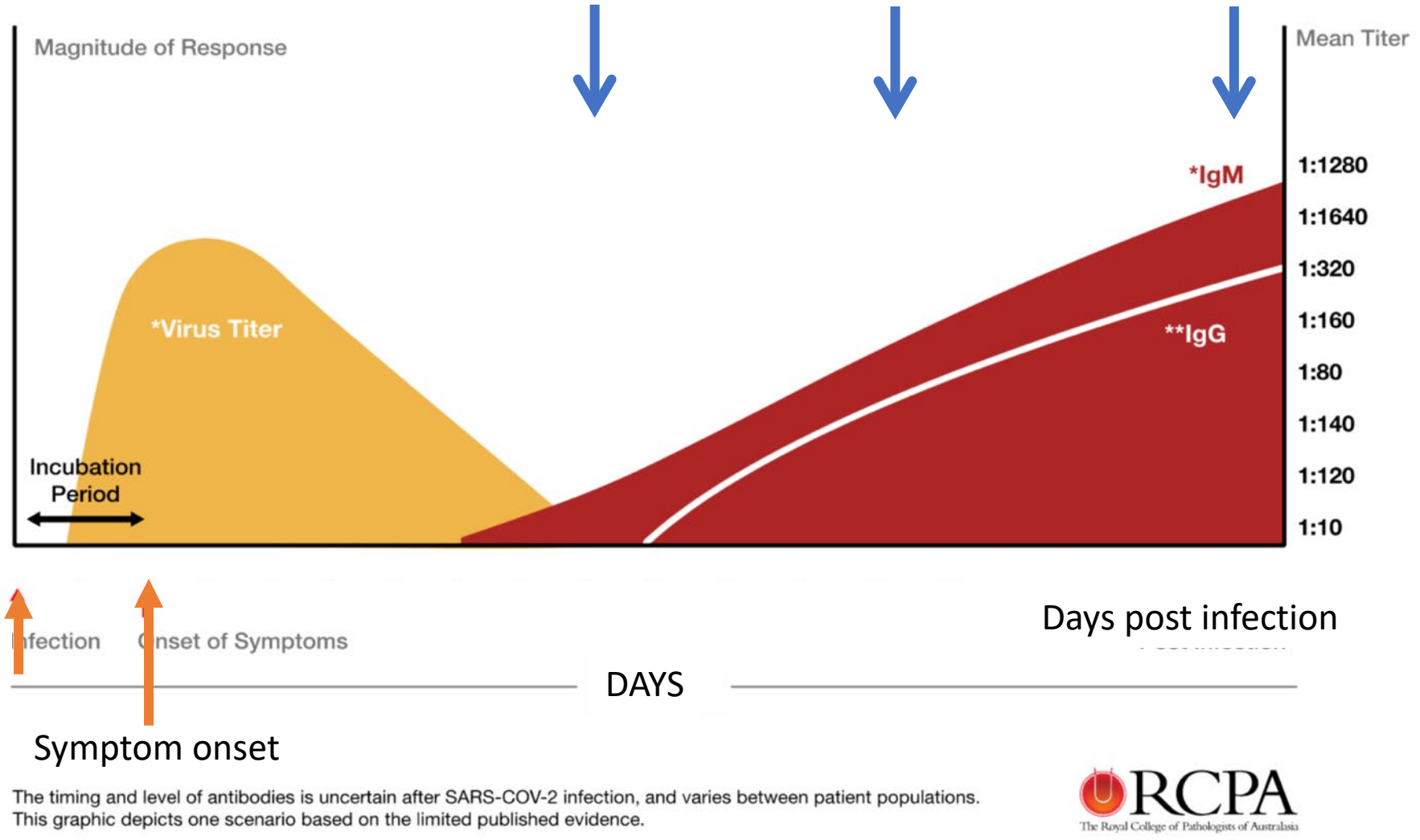
COVID-19 Disease and Reaction Time

- IgM/IgG rise
  ~ 2 weeks after illness onset
- Serology not for acute disease diagnosis
- For seroprevalence determination



The timing and level of antibodies is uncertain after SARS-COV-2 infection, and varies between patient populations. This graphic depicts one scenario based on the limited published evidence.

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The Royal College of Pathologists of Australasia

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Ability to Detect COVID-19: Foundational Component of Canada's Containment and Mitigation Strategy

- **Mitigation**
  - Population-based testing for surveillance, case detection and transmission prevention
- **Containment**
  - Hospitalized patients with severe respiratory or flu-like illnesses
  - Symptomatic healthcare workers
  - Where testing modifies patient management
    (e.g. infection control, patient diagnosis and treatment)
  - Outbreak detection and management – including HCW and pts in acute care
  - Surveillance

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Perioperative Criteria in BC

- Pre-operative screening
  - At the discretion of the surgeon/anesthesiologist
  - For patients with compromised cardiopulmonary systems, may consider screening, and if positive, reschedule until resolution of disease
  - Asymptomatic vs symptomatic
  - Can inform post-op IPAC management
  - Limitations
    - Turnaround time of test
    - Life and limb
    - Negative test does not rule out disease

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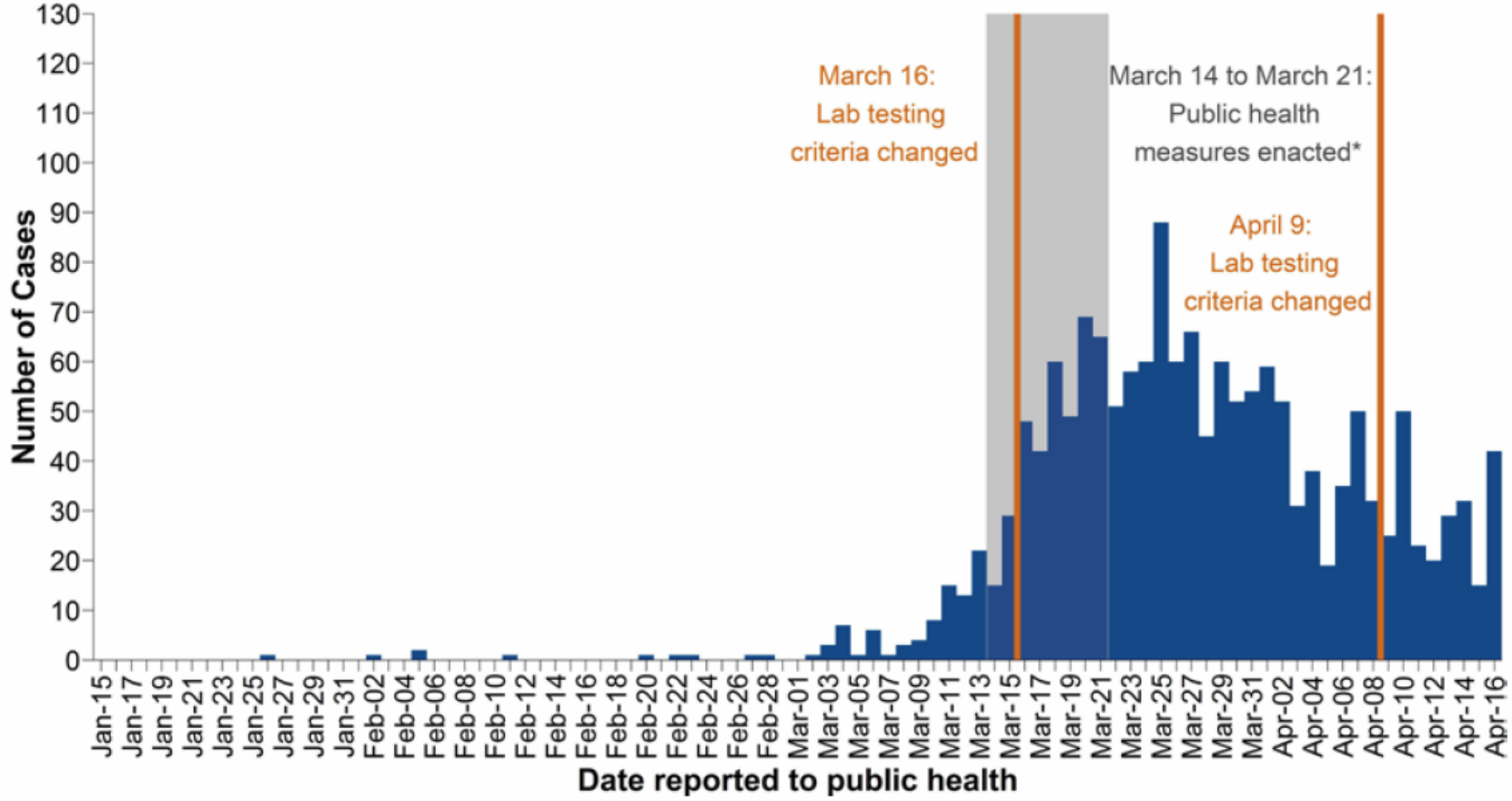
Testing Criteria Vary Across and Within Provinces

Figure 3: Epidemic curve, confirmed COVID-19 cases in BC by reported date January 1-April 16, 2020 **(N=1,617‡)**



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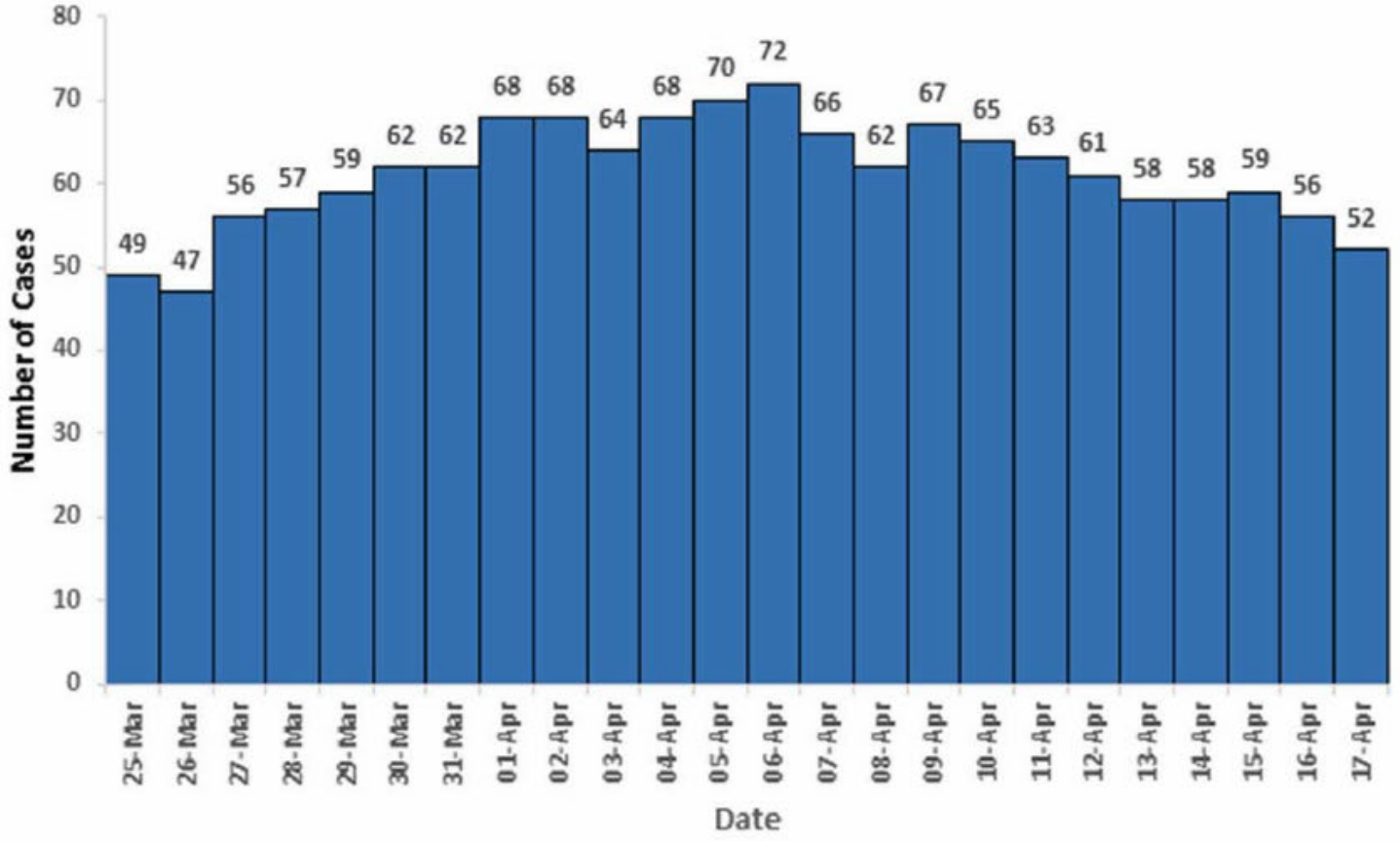
Provincial Health Services Authority

BC Centre for Disease Control
Provincial Health Services Authority

Figure 7: Total positive COVID-19 cases in critical care by day, BC, March 25- April 17, 2020



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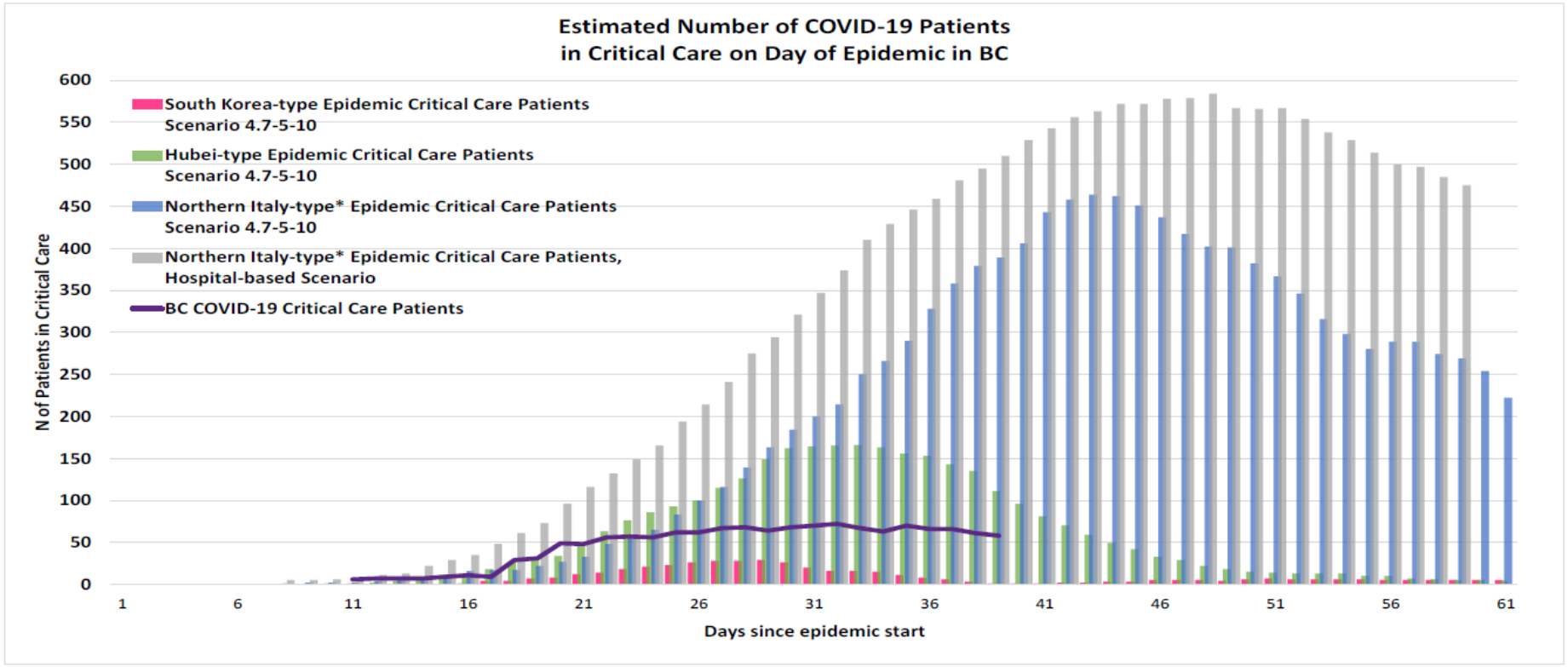
BC actual critical care cases compared to updated modelled cases from other jurisdictions data



Scenario 4.7-5-10 assumes that 4.7% of all COVID-19 cases will be admitted to critical care. Critical care admissions will commence 5 days (range 4-7 days) after symptom onset; ALOS in Critical Care will be 10 days (range 7-14 days). Note: Italian epidemic in progress and did not reach the peak.

COVID-19 IN BC

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What's Next

- Combination of targeted PCR and serology tests to inform patient care, IPAC and public health response
- Decentralize testing
- Operationalise up to 24 hr turn around time
- Ensure ongoing supply of test reagents
- Maintain healthy laboratory environment to ensure ongoing testing capacity
- Automation where possible
- Genomics!!!

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UHN ECLS PROGRAM

critical care canada FORUM
leading science, leading practice

ARDS: MECHANICAL VENTILATION FOR COVID-19

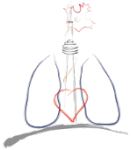
UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex

Niall D. Ferguson, MD, FRCPC, MSc
Head of Critical Care Medicine
University Health Network & Mount Sinai Hospital

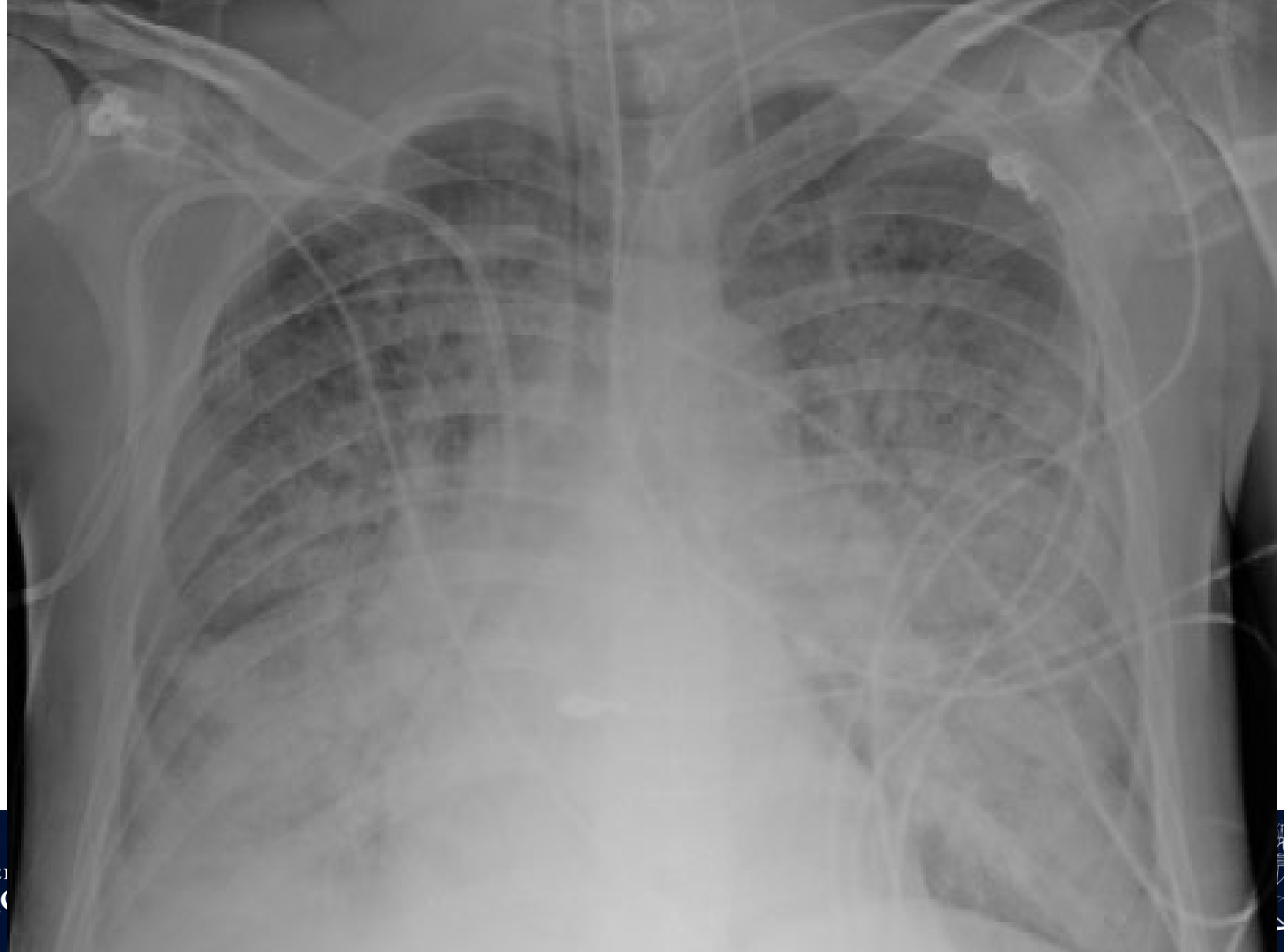
Professor, Departments of Medicine & Physiology,
Institute of Health Policy, Management and Evaluation
Interdepartmental Division of Critical Care Medicine
University of Toronto

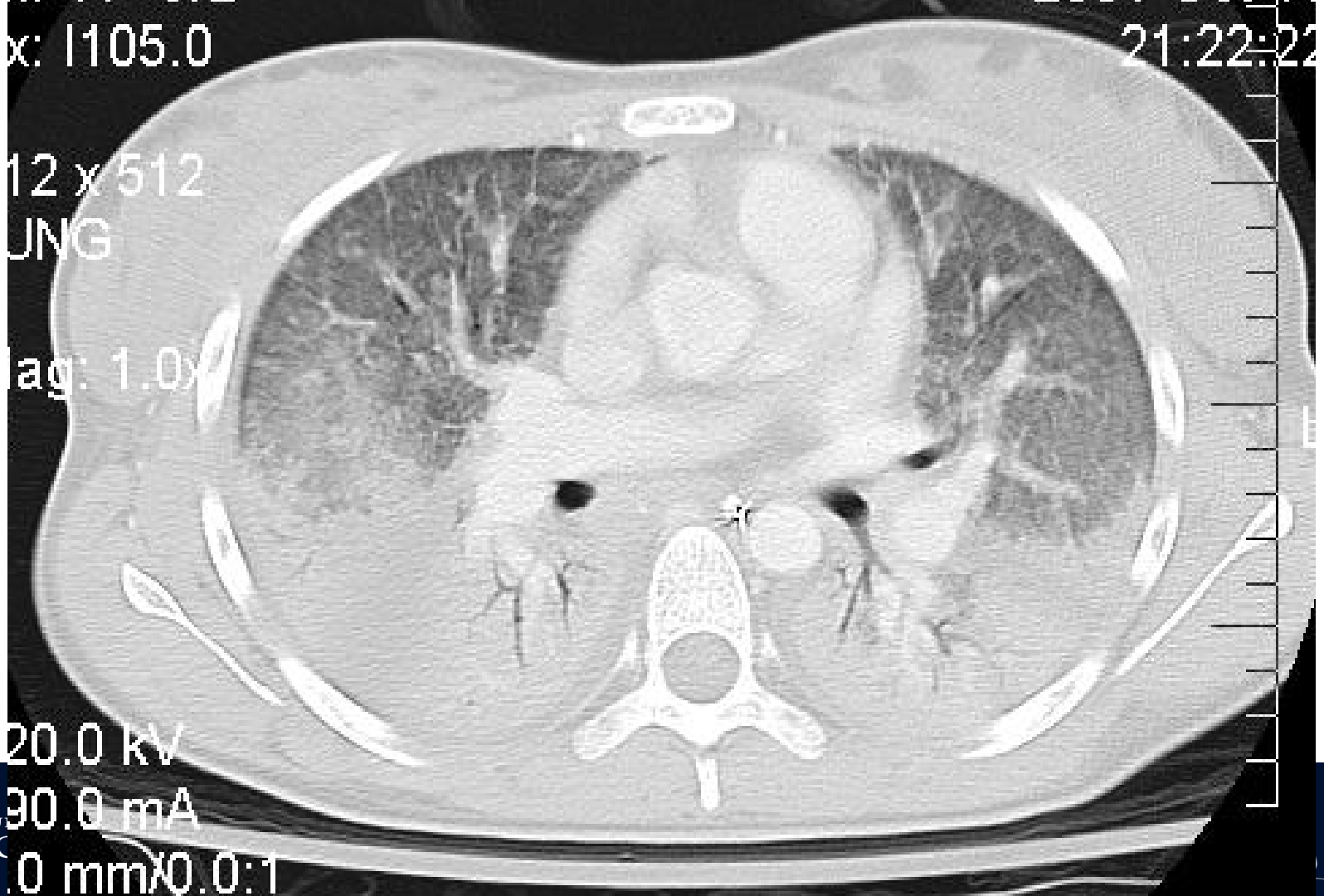
UNIVERSITY OF TORONTO | Interdepartmental Division of Critical Care Medicine



Disclosures

- Consultant for Xenios
- Speaker fees from Getinge




x: 1105.0
21:22:22
12 x 512
UNG
lag: 1.0x
20.0 kV
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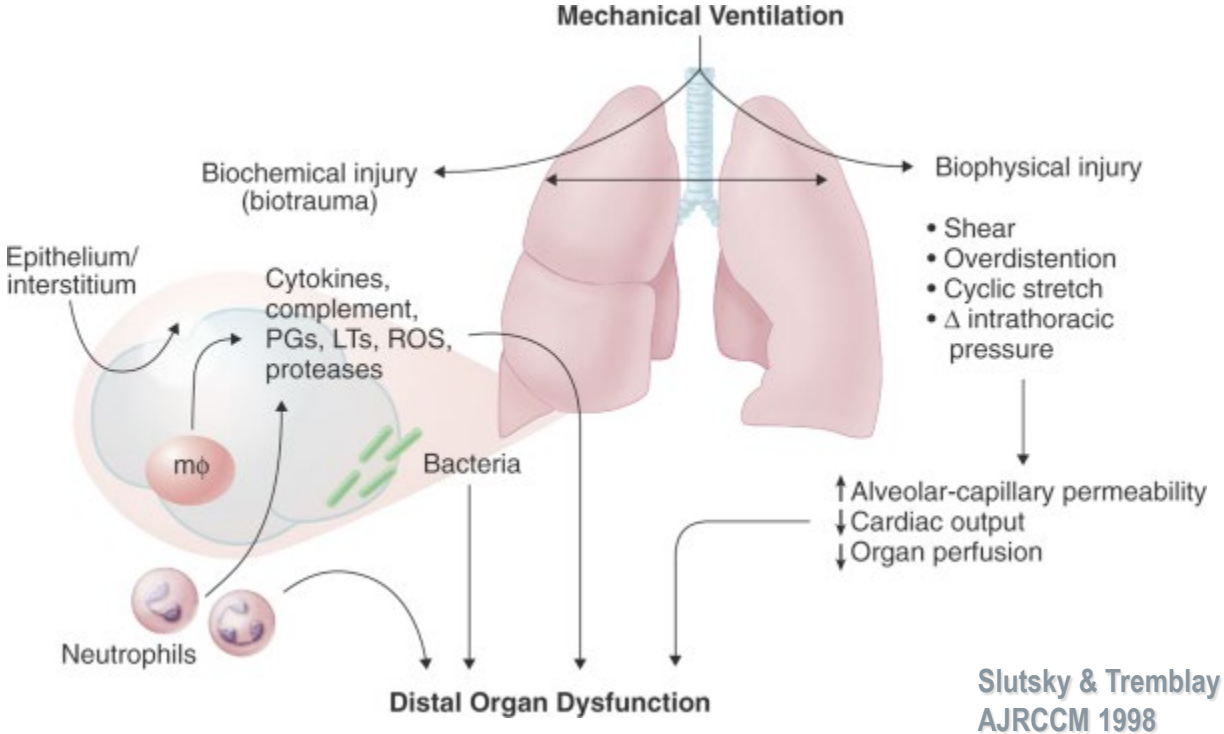
Ventilator-Induced Lung Injury



Slutsky & Tremblay
AJRCCM 1998

VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

High Stretch

- V_T: 11.8
- P_{PLAT}: 32-34
- RR: 18
- V_{MIN}: 13
- PEEP: 8

Low Stretch

- V_T: 6.2 ml/kg
- P_{PLAT}: 25 cm H_2O
- RR: 29
- V_{MIN}: 13 L/min
- PEEP: 9 cm H_2O

Mortality 40%

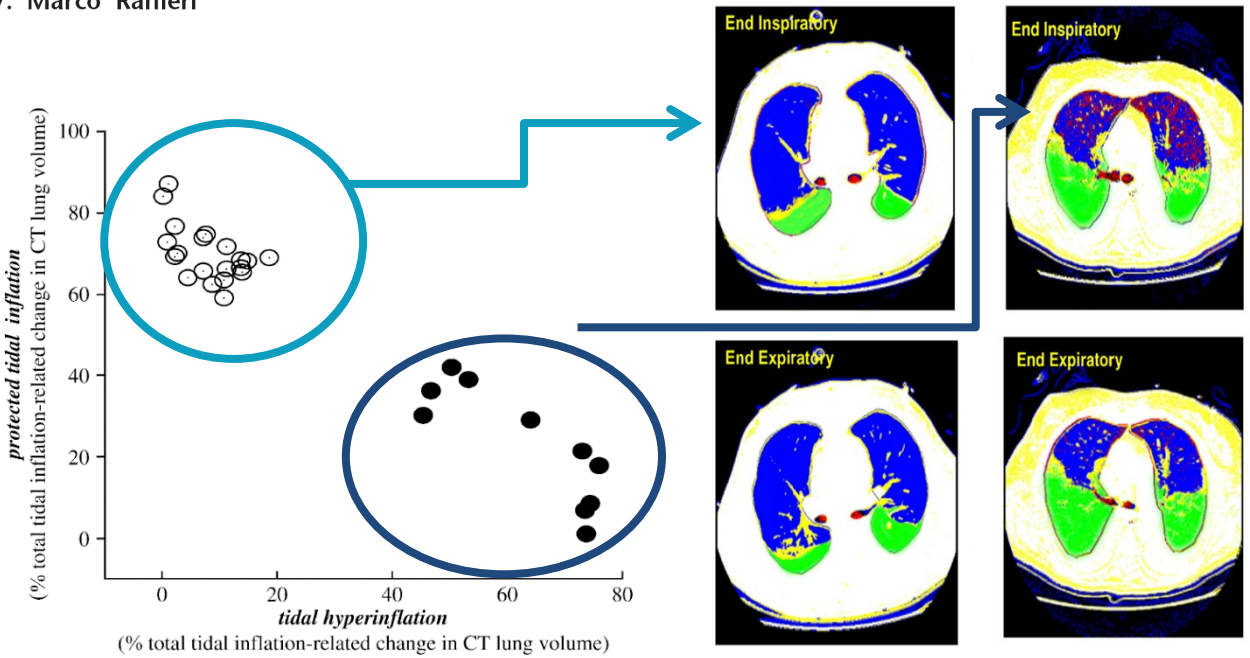
Mortality 31%*

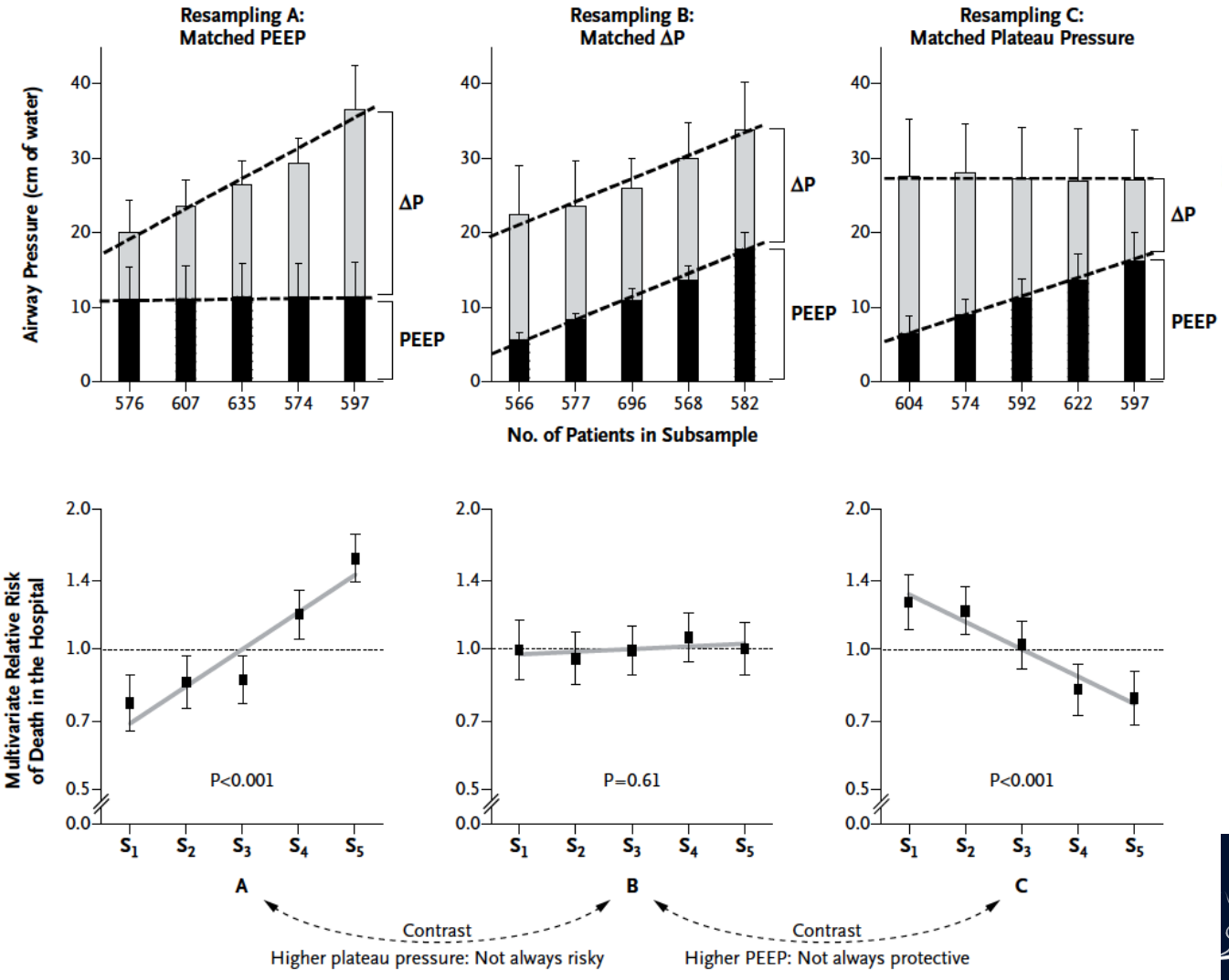
*p=0.005

Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome

Am J Respir Crit Care Med Vol 175. pp 160–166, 2007

Pier Paolo Terragni, Giulio Rosboch, Andrea Tealdi, Eleonora Corno, Eleonora Menaldo, Ottavio Davini, Giovanni Gandini, Peter Herrmann, Luciana Mascia, Michel Quintel, Arthur S. Slutsky, Luciano Gattinoni, and V. Marco Ranieri




Resampling A:
Matched PEEP
Resampling B:
Matched ΔP
Resampling C:
Matched Plateau Pressure
Airway Pressure (cm of water)
ΔP
PEEP
576 607 635 574 597
566 577 696 568 582
604 574 592 622 597
No. of Patients in Subsample
Multivariate Relative Risk of Death in the Hospital
P<0.001
P=0.61
P<0.001
A
B
C
Contrast
Higher plateau pressure: Not always risky
Contrast
Higher PEEP: Not always protective

Prone Positioning in Severe Acute Respiratory Distress Syndrome

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ABSTRACT

BACKGROUND

Previous trials involving patients with the acute respiratory distress syndrome (ARDS) have failed to show a beneficial effect of prone positioning during mechanical ventilatory support on outcomes. We evaluated the effect of early application of prone positioning on outcomes in patients with severe ARDS.

METHODS

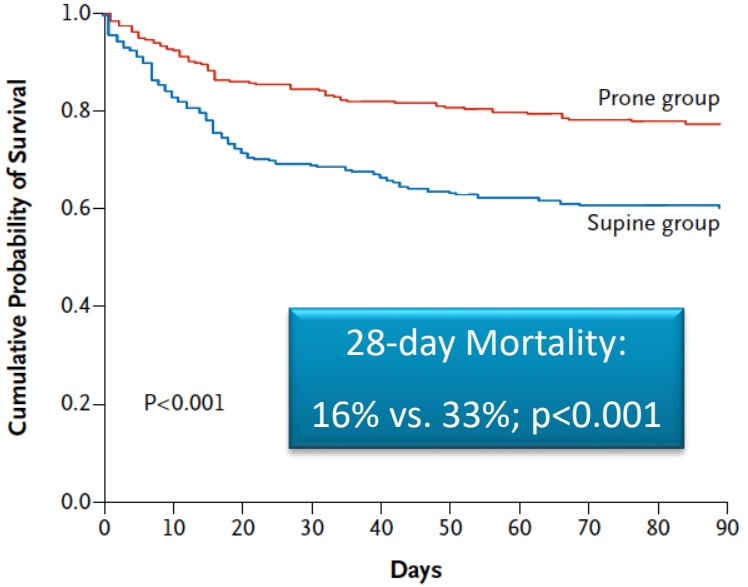
In this multicenter, prospective, randomized, controlled trial, we randomly assigned 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 hours or to be left in the supine position. Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2/Fio_2) of less than 150 mm Hg, with an Fio_2 of at least 0.6, a positive end-expiratory pressure of at least 5 cm of water, and a tidal volume close to 6 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died from any cause within 28 days after inclusion.

RESULTS

A total of 237 patients were assigned to the prone group, and 229 patients were assigned to the supine group. The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group (P<0.001). The hazard ratio for death with prone positioning was 0.39 (95% confidence interval [CI], 0.25 to 0.63). Unadjusted 90-day mortality rates were 23.6% in the prone group and 41.0% in the supine group (P=0.001), with a hazard ratio of 0.64 (95% CI, 0.39 to 0.67). The incidence of complications did not differ significantly between the groups, except for the incidence of cardiac arrests, which was higher in the supine group.

CONCLUSIONS

In patients with severe ARDS, early application of prolonged prone positioning sessions significantly decreased 28-day and 90-day mortality. (Funded by the Programme Hospitalier de Recherche Clinique National 2006 and 2010 of the French Ministry of Health; PROSEVA ClinicalTrials.gov number, NCT00527813.)



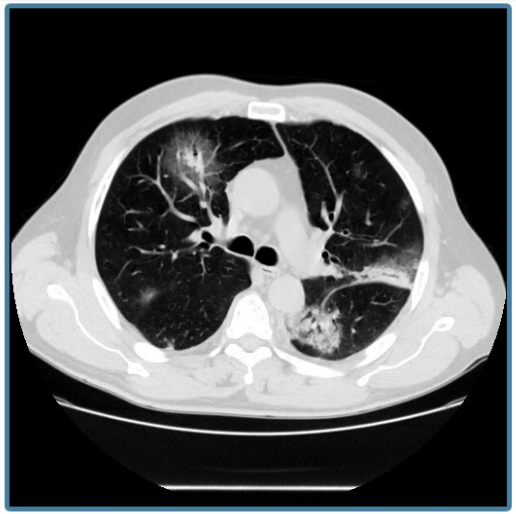
No. at Risk

Prone group	237	202	191	186	182
Supine group	229	163	150	139	136

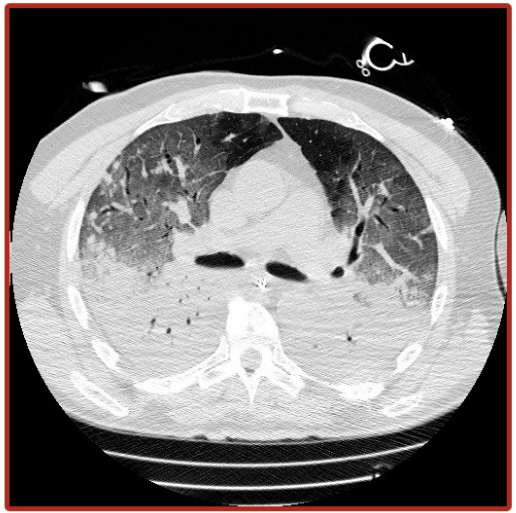
N Engl J Med 2013.
DOI: 10.1056/NEJMoa1214103

COVID-19 pneumonia: different respiratory treatment for different phenotypes?

L. Gattinoni[1], D. Chiumello[2], P. Caironi[3], M. Busana[1], F. Romitti[1], L. Brazzi[4], L. Camporota[5]



PaO_2/FiO_2
95 mmHg



PaO_2/FiO_2
84 mmHg

Basing Respiratory Management of Coronavirus on Physiological Principles

Martin J. Tobin MD,

Division of Pulmonary and Critical Care Medicine,

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

World

Ventilators are being overused on COVID-19 patients, world-renowned critical care specialist says

Italian experts say many patients fare poorly on ventilators; Toronto expert says more data needed

Megan Williams · CBC News · Posted: Apr 17, 2020 4:00 AM ET | Last Updated: April 17

Some Doctors Moving Away From Ventilators for Virus Patients

By The Associated Press

Published April 8, 2020 Updated April 12, 2020

NEW YORK — As health officials around the world push to get more ventilators to treat coronavirus patients, some doctors are moving away from using the breathing machines when they can.

What is the right amount of PEEP?

Everything we know about the ARDS clinical phenotype we learned in 1967

TABLE III—EFFECT OF POSITIVE END-EXPIRATORY PRESSURE IN PATIENT 11 WITH VIRAL PNEUMONIA

—	No retard (30 l./min.)	Retard (15 l./min.)
P_{IO_2} (mm. Hg)	560 (mm. Hg)	560 (mm. Hg)
P_{aO_2} (mm. Hg)	42 (mm. Hg)	141·5 (mm. Hg)
S_{aO_2} (%)	78 (74)	98 (98)
P_{aCO_2} (mm. Hg)	31 (33)	39·5 (35)
pH	7·436 (7·435)	7·370 (7·405)
Blood-pressure (mm. Hg)	120/ ? (mm. Hg)	120/84 (mm. Hg)
Time (min.)	0 (55 min.)	30 min. (65 min.)

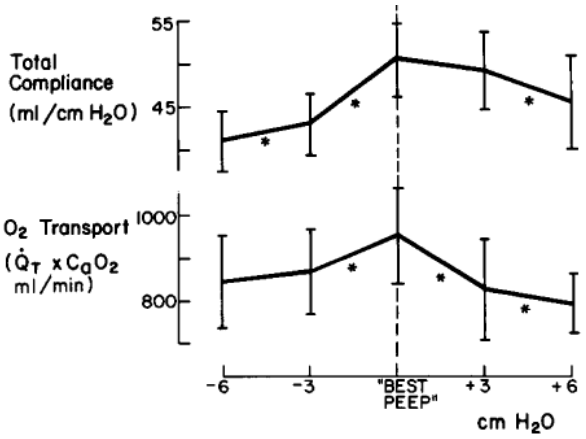
Oxygenation improvement with PEEP

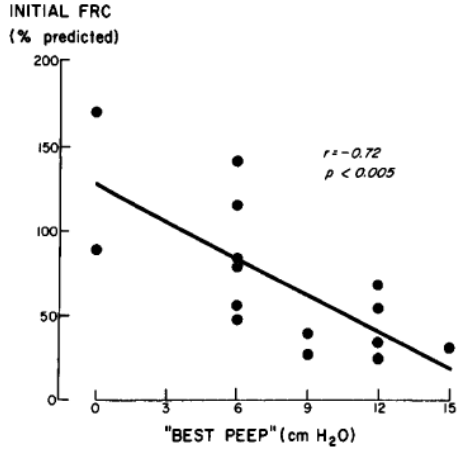
OPTIMUM END-EXPIRATORY AIRWAY PRESSURE IN PATIENTS WITH ACUTE PULMONARY FAILURE

PETER M. SUTER, M.D., H. BARRIE FAIRLEY, M.B., B.S., F.F.A.R.C.S., AND MICHAEL D. ISENBERG, M.D.

Abstract To determine whether in the management of pulmonary failure, the maximum compliance produced by positive end-expiratory pressure coincides with optimum lung function, 15 normovolemic patients requiring mechanical ventilation for acute pulmonary failure were studied. The end-expiratory pressure resulting in maximum oxygen transport (cardiac output times arterial oxygen content) and the lowest dead-space fraction both resulted in the greatest total static compliance. This end-expiratory pressure varied between 0 and 15 cm of water and correlated inversely with functional residual capacity at zero end-expiratory pressure ($r = -0.72$, $p < 0.005$). Mixed venous oxygen tension increased between zero end-expiratory pressure and the end-expiratory pressure resulting in maximum oxygen transport, but then decreased at higher end-expiratory pressures.

When measurements of cardiac output or of true mixed venous blood are not available, compliance may be used to indicate the end-expiratory pressure likely to result in optimum cardiopulmonary function. (N Engl J Med 292:284-289, 1975)





Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

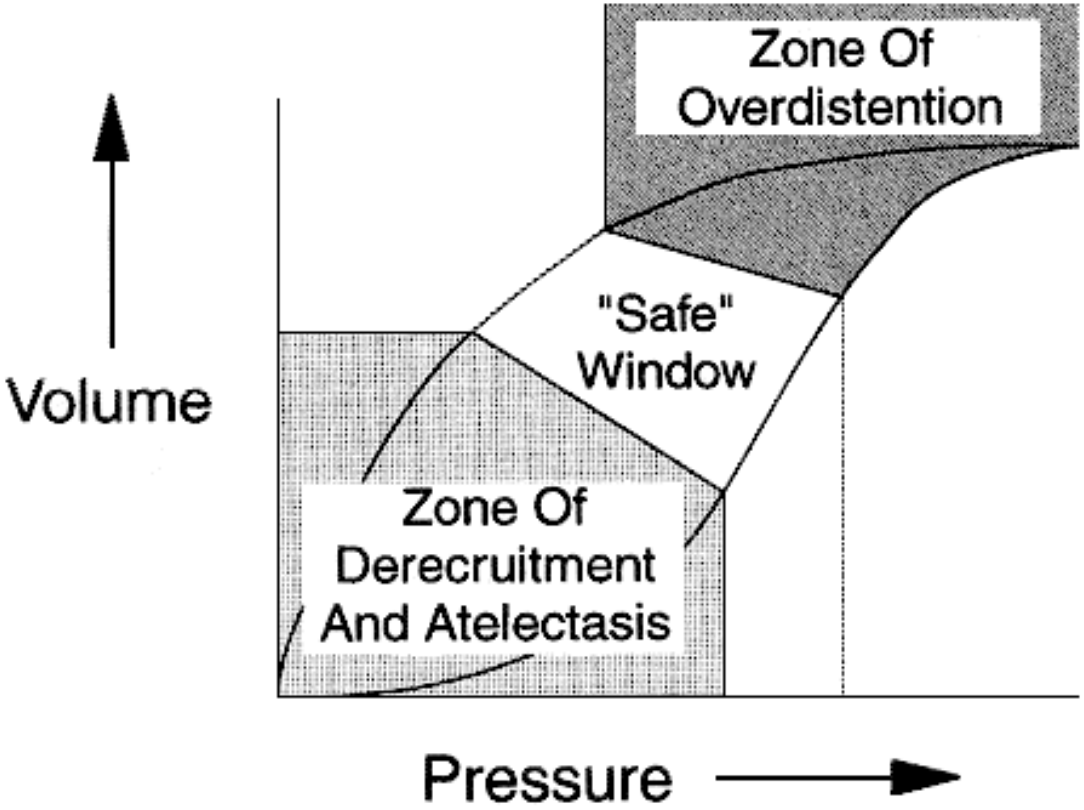
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

JAMA February 23, 2016 Volume 315, Number 8

Giacomo Bellani, MD, PhD; Luciano Gattinoni, MD, FR Gordon Rubenfeld, MD, M for the LUNG SAFE Investi; Andres Esteban, MD, PhD; Marco Ranieri, MD; ASc; Antonio Pesenti, MD;

Table 3. Baseline Characteristics of Patients With Acute Respiratory Distress Syndrome Treated With Invasive Ventilation by Severity Category at Diagnosis

Parameter	All (N = 2377)	Mild (n = 714)	Moderate (n = 1106)	Severe (n = 557)	*P* Value[a]
Age, median (IQR), y	61 (61-62)	61 (60-63)	62 (62-63)	57 (55-58)	<.001
No longer meet ARDS criteria after 24 h, No. (%) [95% CI]	486 (17.3) [15.9-18.7]	190 (26.6) [23.4-30.0]	152 (13.7) [11.8-15.9]	71 (12.8) [10.1-15.8]	<.001
Severity of illness, mean (95% CI), SOFA score[b]					
Day 1	10.1 (9.9-10.2)	8.8 (8.6-9.1)	10.2 (9.9-10.4)	11.4 (11.1-11.8)	<.001
Day 1 nonpulmonary[c]	6.9 (6.7-7.0)	6.7 (6.4-7.0)	6.9 (6.7-7.1)	7.0 (6.7-7.4)	.34
Worst	11.1 (10.9-11.3)	10.3 (10.0-10.6)	11.8 (11.5-12.0)	13.0 (12.6-13.3)	<.001
Worst nonpulmonary	8.0 (7.8-8.2)	8.0 (7.7-8.3)	8.7 (8.4-8.9)	9.0 (8.4-8.9)	<.001
Ventilator settings, first day of ARDS					
Set PEEP	8.4	7.4	8.3	10.1	
Total respiratory rate, mean (95% CI), 1/min	20.8 (21.5-21.2)	19.5 (19.0-19.9)	20.7 (20.3-21.1)	22.7 (21.5-23.8)	<.001
VT, mean (95% CI), mL/kg PBW	7.6 (7.5-7.7)	7.8 (7.6-7.9	7.6 (7.5-7.7)	7.5 (7.3-7.6)	.02
Control vent mode	7.5 (7.4-7.6)	7.6 (7.5-7.8)	7.4 (7.3-7.6)	7.4 (7.2-7.6)	.06
Spontaneous vent mode	7.9 (7.8-8.1)	7.9 (7.7-8.2)	8.0 (7.7-8.2)	7.7 (7.4-8.1)	.55
P value (control vs spont mode)	<.001	.049	<.001	.053	
Set PEEP, mean (95% CI), cm H_2O	8.4 (8.3-8.6)	7.4 (7.2-7.6)	8.3 (8.1-8.5)	10.1 (9.8-10.4)	<.001
Peak pressure, mean (95% CI), cm H_2O[d]	27.0 (26.7-27.4)	24.7 (24.1-25.4)	26.9 (26.5-27.4)	30.3 (29.6-30.9)	<.001
Patients in whom P_{PLAT} measured, No. (%)					
Among all invasively ventilated patients, No. (%) [95% CI]	954 (40.1) [38.2-42.1]	260 (36.4) [32.9-40.1]	463 (41.9) [38.9-44.8]	231 (41.5) [37.3-45.7]	.05
Among patients with controlled ventilation, No. (%) [95% CI]	756 (48.5) [46.0-51.0]	198 (46.1) [41.3-51.0]	363 (49.8) [46.1-53.5]	195 (48.5) [43.5-53.5]	.49
P_{PLAT}, mean (95% CI), cm H_2O[e]	23.2 (22.6-23.7)	20.5 (19.8-21.3)	23.1 (22.6-23.7)	26.2 (25.2-27.1)	<.001
Standardized minute ventilation, mean (95% CI), l/min[f]	10.8 (10.6-11.0)	9.3 (9.1-9.6)	10.7 (10.5-11.0)	12.8 (12.3-13.3)	<.001
Spontaneous ventilation, No. (%) [95% CI]	723 (30.4 [8.6-32.3]	260 (36.4) [32.9-40.0]	336 (30.4) [29.7-35.3]	127 (22.8) [19.3-26.5]	<.001


Zone Of
Overdistention
"Safe"
Window
Zone Of
Derecruitment
And Atelectasis
Volume
Pressure

Setting PEEP

Defined range

- Low PEEP arm of ExPress (5-9 cm H_2O)

Plateau pressure limit

- High PEEP arm of ExPress (28-30 cm H_2O)

PEEP-FiO_2 Table

- **Higher vs. Lower – ARMA, LOVS, ALVEOLI**

Pressure/Volume measurements

Transpulmonary pressure limit

Decremental PEEP titration

VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

High Stretch

- V_T: 11.8
- P_{PLAT}: 32-34
- RR: 18
- V_{MIN}: 13
- PEEP: 8

Mortality 40%

Low Stretch

- V_T: 6.2 ml/kg
- P_{PLAT}: 25 cm H_2O
- RR: 29
- V_{MIN}: 13 L/min
- PEEP: 9 cm H_2O

Mortality 31%*

*p=0.005

Table 1 ARDSNet table of FiO_2 and PEEP values to keep $SpO_2 \geq 88\%$ or $PaO_2 \geq 55$ mmHg

FiO_2	30%	40%	40%	50%	50%	60%	70%	70%	70%	80%	90%	90%	90%	100%
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

JAMA. 2008;299(6):637-645

Table 2. Allowable PEEP Ranges at Specified Levels of FIO_2[a]

	Fraction of Inspired Oxygen (FIO_2)							
	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Control PEEP ranges, cm H_2O	5	5-8	8-10	10	10-14	14	14-18	18-24
Lung open ventilation PEEP ranges, cm H_2O								
After protocol change	5-10	10-18	18-20	20	20	20-22	22	22-24

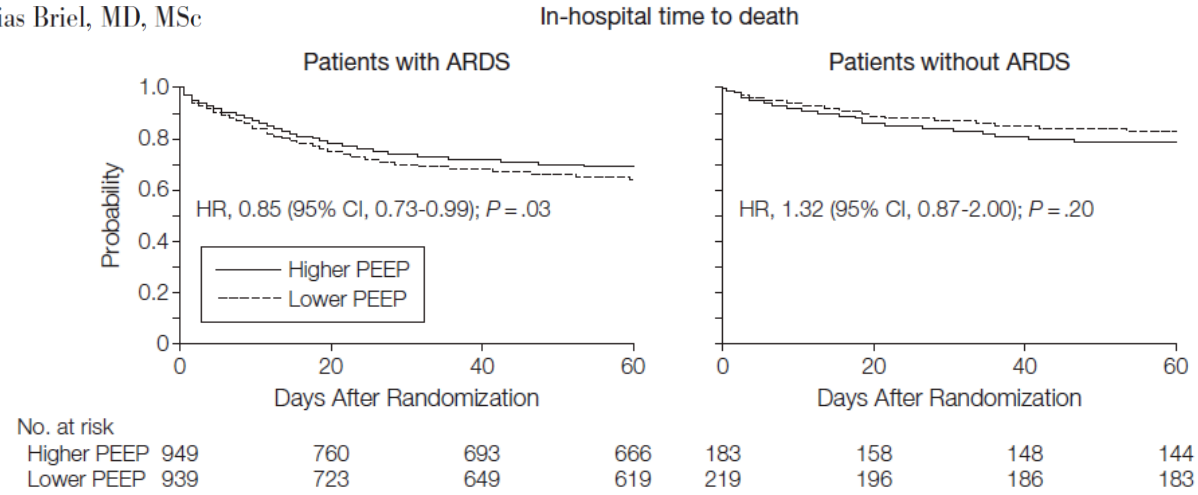
Abbreviation: PEEP, positive end-expiratory pressure.

[a] Both ventilation strategies included a protocol for reducing PEEP when plateau pressure exceeded the assigned plateau pressure limit or when mean arterial pressure decreased to less than 60 mm Hg, whether or not this occurred in the setting of an increase in PEEP.

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome

Systematic Review and Meta-analysis

Matthias Briel, MD, MSc



ICU Mortality: RR 0.85 (0.76-0.94)

Hosp Mortality: RR 0.90 (0.81-1.0)

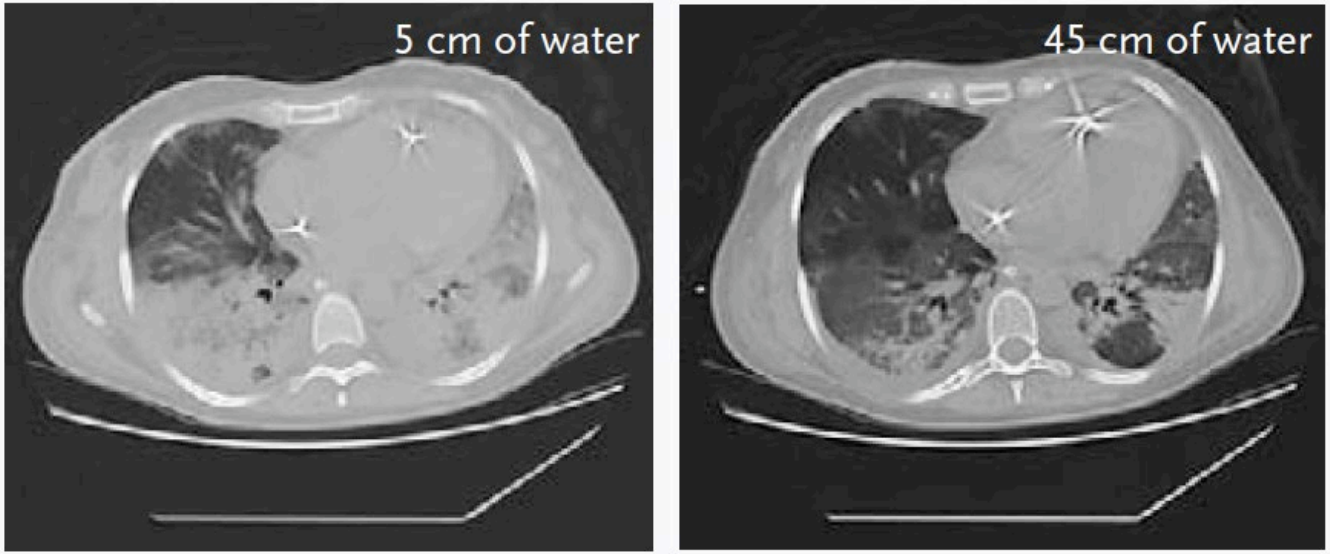
JAMA. 2010;303(9):865-873

N Engl J Med 2006;354:1775-86.

Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D., F.R.C.P., Pietro Caironi, M.D., Massimo Cressoni, M.D., Davide Chiumello, M.D., V. Marco Ranieri, M.D., Michael Quintel, M.D., Ph.D., Sebastiano Russo, M.D., Nicolò Patroniti, M.D., Rodrigo Cornejo, M.D., and Guillermo Bugedo, M.D.

Higher Percentage of Potentially Recruitable Lung

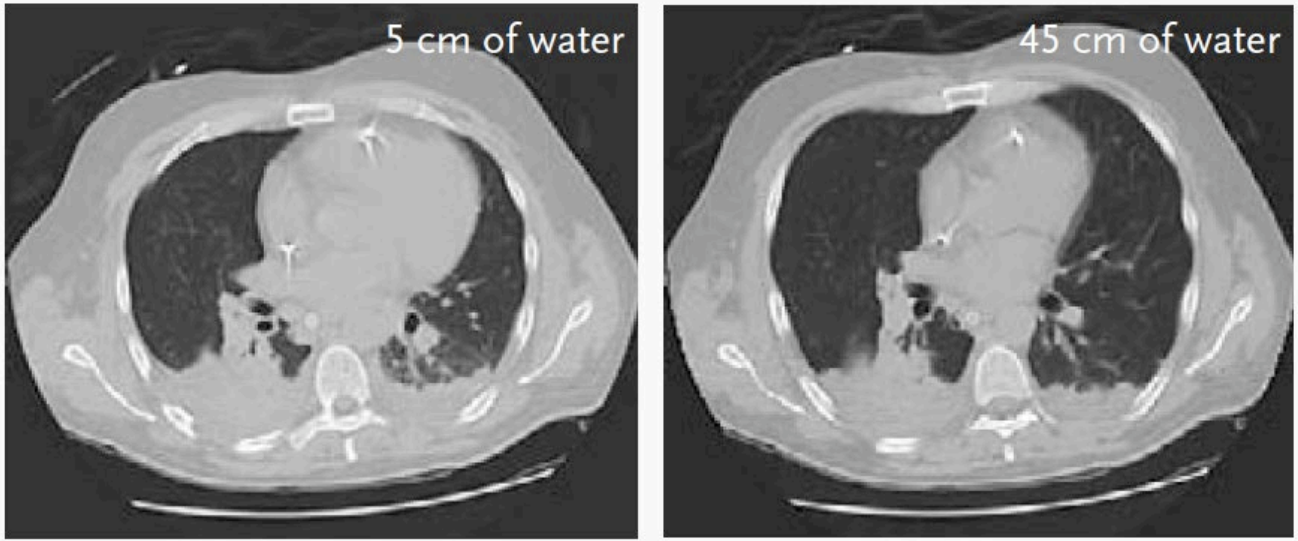


N Engl J Med 2006;354:1775-86.

Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D., F.R.C.P., Pietro Caironi, M.D., Massimo Cressoni, M.D., Davide Chiumello, M.D., V. Marco Ranieri, M.D., Michael Quintel, M.D., Ph.D., Sebastiano Russo, M.D., Nicolò Patroniti, M.D., Rodrigo Cornejo, M.D., and Guillermo Bugedo, M.D.

Lower Percentage of Potentially Recruitable Lung



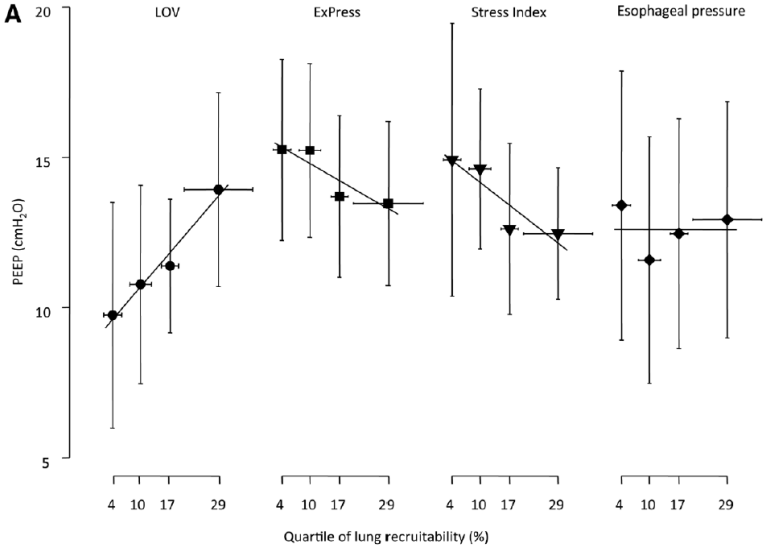
Bedside Selection of Positive End-Expiratory Pressure in Mild, Moderate, and Severe Acute Respiratory Distress Syndrome*

Crit Care Med 2014; 42:252–264

Davide Chiumello, MD[1,2]; Massimo Cressoni, MD[2]; Eleonora Carlesso, MSc[2]; Maria L. Caspani, MD[1]; Antonella Marino, MD[2]; Elisabetta Gallazzi, MD[2]; Pietro Caironi, MD[1,2]; Marco Lazzerini, MD[3]; Onnen Moerer, MD[4]; Michael Quintel, MD[4]; Luciano Gattinoni, MD, FRCP[1,2]

Only PEEP by O_2 gave

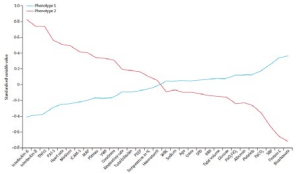
higher PEEP with increasing severity & recruitability



Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

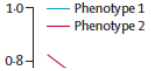
Lancet Respir Med 2014; 2: 611–20

Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network



ARMA & ALVEOLI Trials

Latent Class Modeling



	Phenotype 1 (n=404)		Phenotype 2 (n=145)		
	Low PEEP (n=202)	High PEEP (n=202)	Low PEEP (n=71)	High PEEP (n=74)	p value*
Mortality at 90 days	33 (16%)	48 (24%)	36 (51%)	31 (42%)	0·049
Ventilator-free days	20 (10–25)	21 (3–24)	2 (0–21)	4·5 (0–20)	0·018
Organ failure free-days	22 (11–26)	22 (9–26)	4 (0–18)	6·5 (0–21)	0·003

Data are n (%) or median (IQR). *p value for interaction between positive end-expiratory pressure (PEEP) assignment and phenotype.

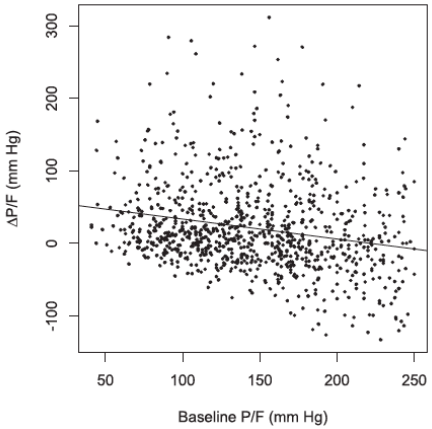
***Table 5*: Differences in response to PEEP strategy by phenotype (ALVEOLI cohort only)**

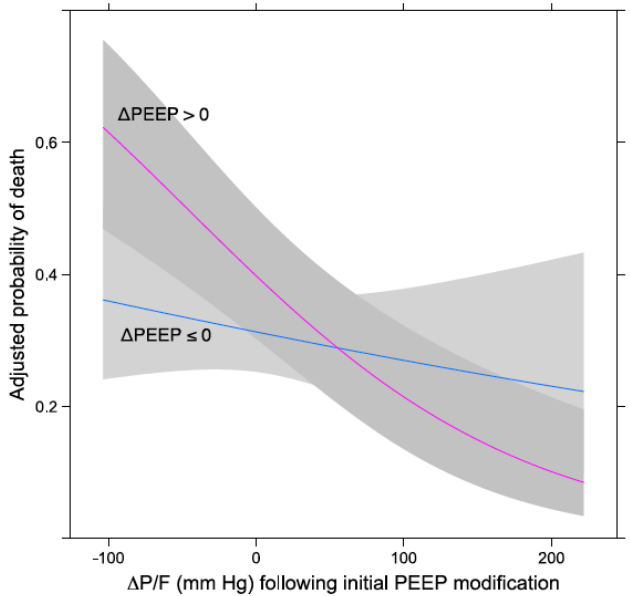
Oxygenation Response to Positive End-Expiratory Pressure Predicts Mortality in Acute Respiratory Distress Syndrome

A Secondary Analysis of the LOVS and ExPress Trials

Ewan C. Goligher[1,2,3,4], Brian P. Kavanagh[1,5,6], Gordon D. Rubenfeld[1,2,7], Neill K. J. Adhikari[1,2,7], Ruxandra Pinto[7], Eddy Fan[1,2,4], Laurent J. Brochard[1,2,8], John T. Granton[1,2,4], Alain Mercat[9], Jean-Christophe Marie Richard[10], Jean-Marie Chretien[11], Graham L. Jones[12], Deborah J. Cook[12,13], Thomas E. Stewart[1,2,4], Arthur S. Slutsky[1,2,4], Maureen O. Meade[12,13], and Niall D. Ferguson[1,2,3,4]

Am J Respir Crit Care Med Vol 190, Iss 1, pp 70–76, Jul 1, 2014



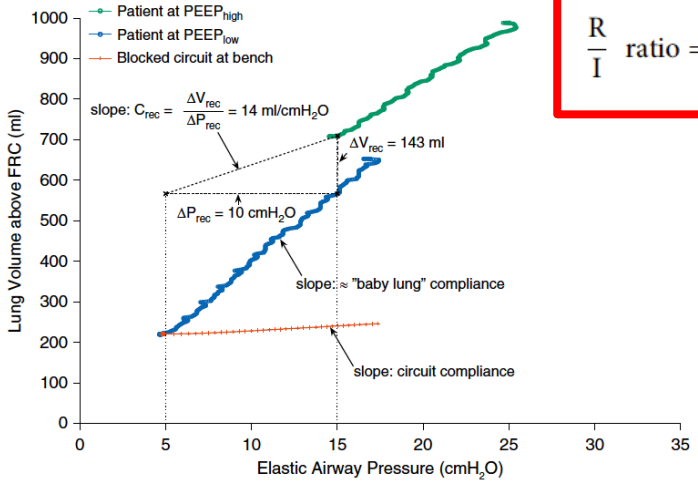


Potential for Lung Recruitment Estimated by the Recruitment-to-Inflation Ratio in Acute Respiratory Distress Syndrome

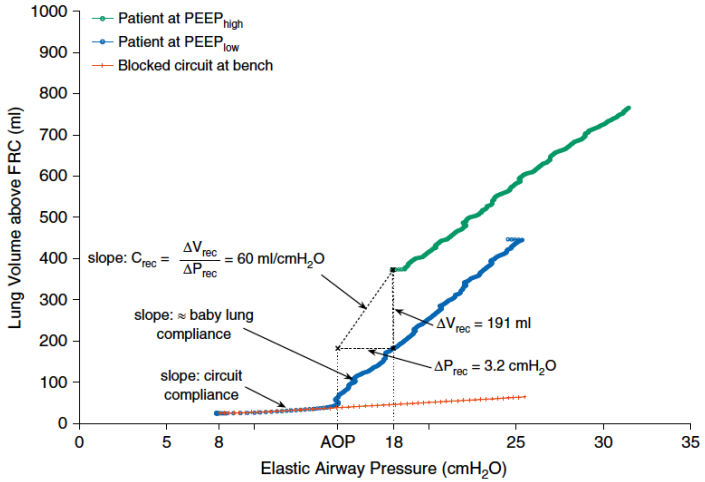
A Clinical Trial

Am J Respir Crit Care Med Vol 201, Iss 2, pp 178–187, Jan 15, 2020

Lu Chen[1,2,3], Lorenzo Del Sorbo[3,4], Domenico L. Grieco[5], Detajin Junhasavasdikul[6], Nuttapol Rittayamai[7], Ibrahim Soliman[8], Michael C. Sklar[3], Michela Rauseo[9], Niall D. Ferguson[3,4], Eddy Fan[3,4], Jean-Christophe M. Richard[10], and Laurent Brochard[1,2,3]*



$$\frac{R}{I}\ \text{ratio} = \frac{Crec}{Crs\ \text{at}\ PEEP_{low}\ \text{or above}\ AOP}.$$

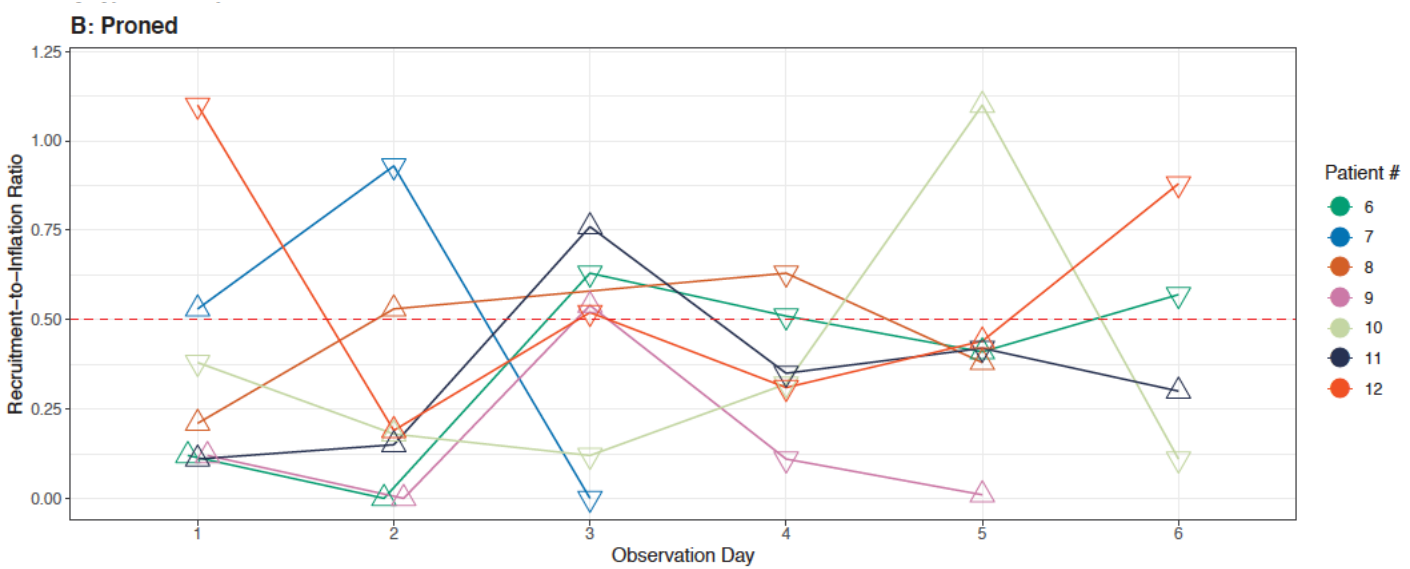


rtmaven.com

Lung Recruitability in SARS-CoV-2 Associated Acute Respiratory Distress Syndrome: A Single-center, Observational Study

Chun Pan[1,2], Lu Chen[3,4], Cong Lu[3,4], Wei Zhang[5], Jia-An Xia[2], Michael C. Sklar[3,4], Bin Du[6], Laurent Brochard[3,4,+], Haibo Qiu[1,2]

$$R/I\ ratio = \frac{V_{Te,H\rightarrow L} - V_{Te,H}}{V_{Ti}} \times \frac{P_{plat,L} - PEEP_L}{PEEP_H - PEEP_L} - 1$$



Spontaneous Breathing in ARDS

When to allow any?

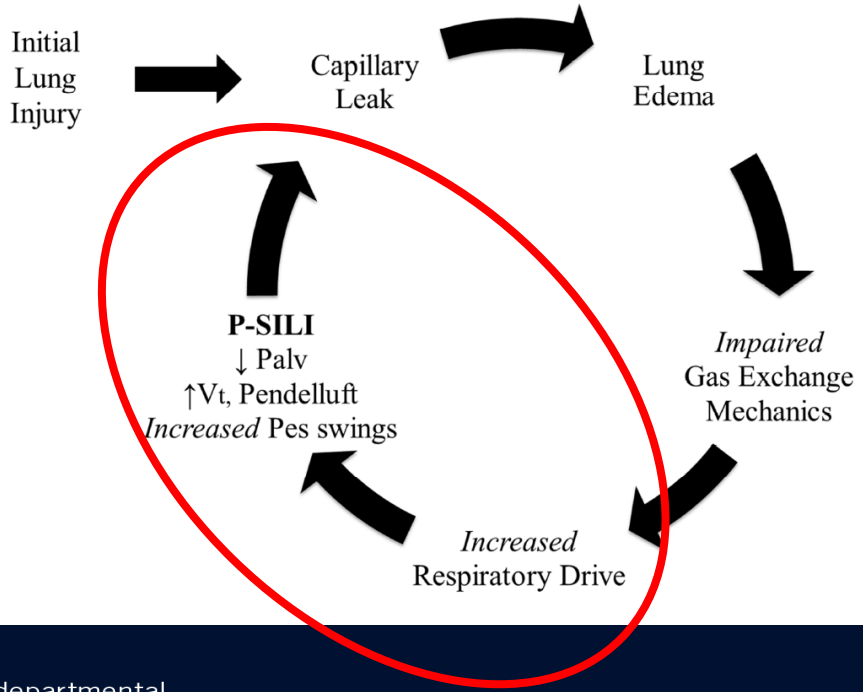
How much to allow?

Consider maintaining normal effort levels – implies measuring effort

Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure

AJRCCM Articles in Press. Published on 14-September-2016 as 10.1164/rccm.201605-1081CP

Laurent Brochard[1,2], Arthur Slutsky[1,2], Antonio Pesenti[3,4]

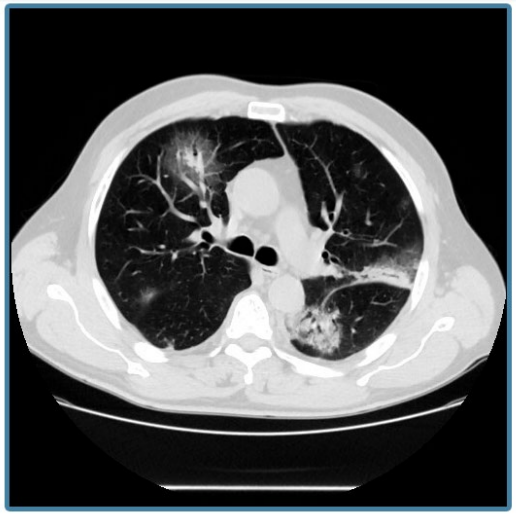


Intensive Care Medicine

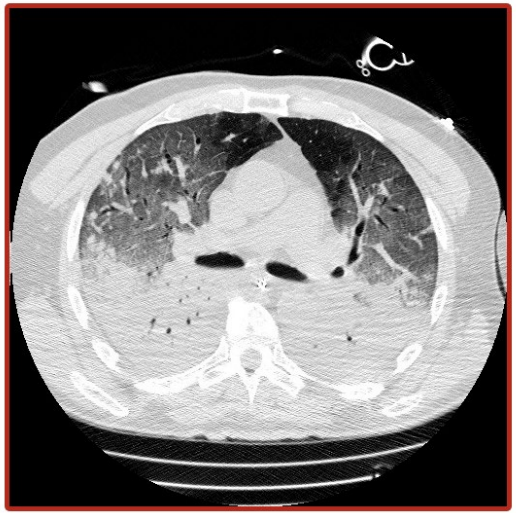
EDITORIAL Un-edited accepted proof

COVID-19 pneumonia: different respiratory treatment for different phenotypes?

L. Gattinoni[1], D. Chiumello[2], P. Caironi[3], M. Busana[1], F. Romitti[1], L. Brazzi[4], L. Camporota[5]



PaO_2/FiO_2
95 mmHg



PaO_2/FiO_2
84 mmHg

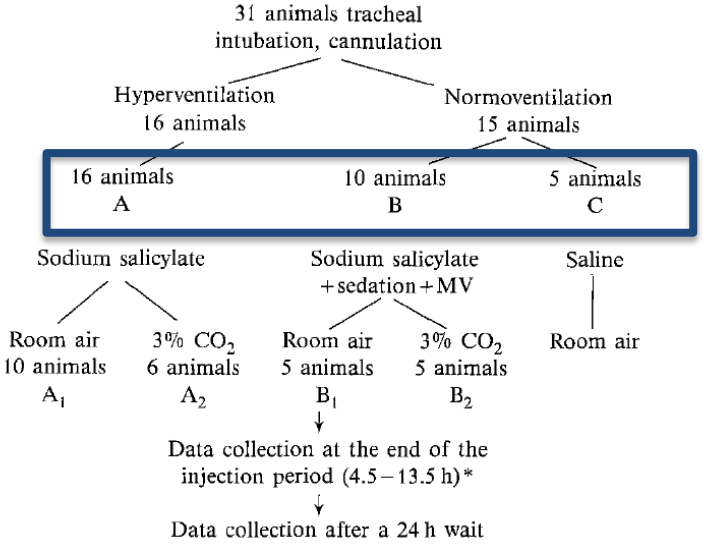
Original articles

Intensive Care Med (1988) 15:8–14

Intensive Care Medicine

Acute respiratory failure following pharmacologically induce hyperventilation: an experimental animal study

D. Mascheroni*, T. Kolobow, R. Fumagalli*, M. P. Moretti**, V. Chen and D. Buckhold



RR 25 then 70/min

V_T 7 then 9-15ml/kg

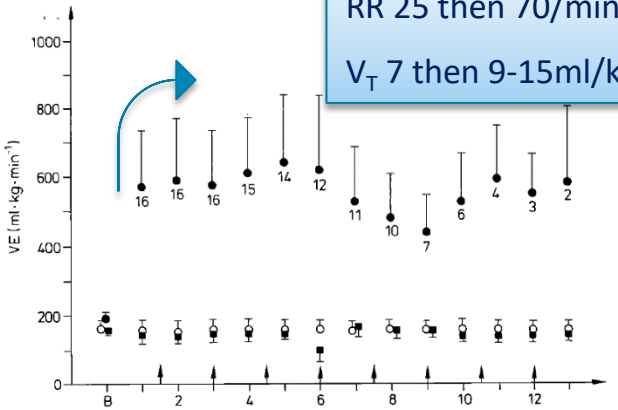


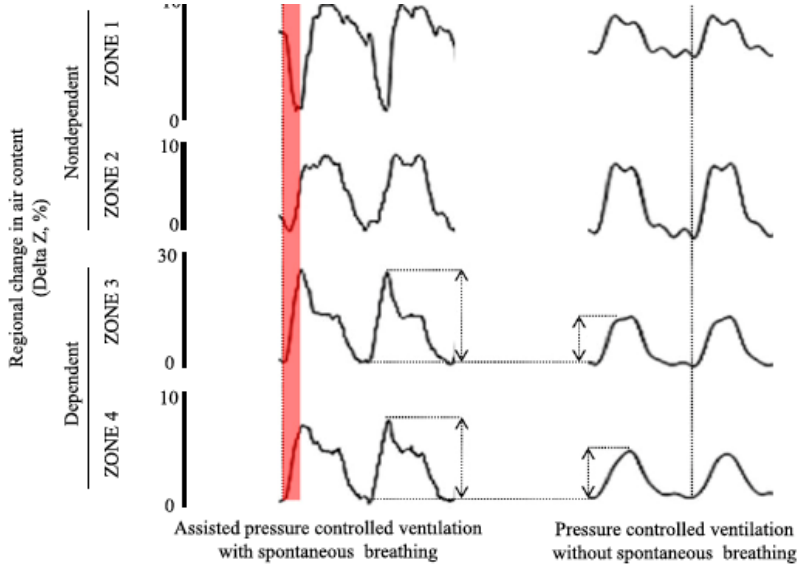
Table 1. Gross pathologic findings

Group	Normal lungs	Mild lesions	Severe lesions
A	2	5[a]	9†
B	10	0	0
C	5	0	0

Spontaneous Effort Causes Occult Pendelluft during Mechanical Ventilation

Am J Respir Crit Care Med Vol 188, Iss. 12, pp 1420–1427, Dec 15, 2013

Takeshi Yoshida[1,2], Vinicius Torsani[1], Susimeire Gomes[1], Roberta R. De Santis[1], Marcelo A. Beraldo[1], Eduardo L. V. Costa[1], Mauro R. Tucci[1], Walter A. Zin[3], Brian P. Kavanagh[4,5], and Marcelo B. P. Amato[1]

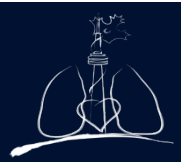


Spontaneous Breathing in ARDS

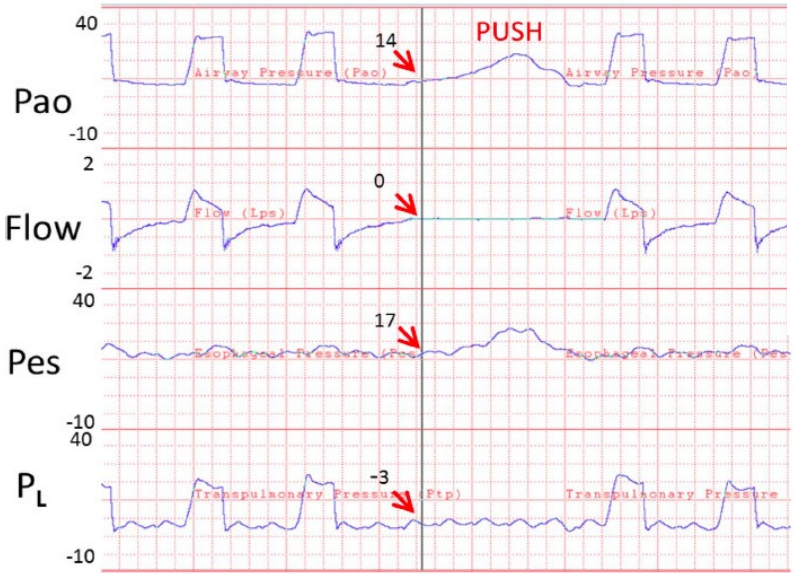
- PRO
  - Prevent diaphragm atrophy (overassist myotrauma)
  - Improved hemodynamics
  - Less sedation and associated adverse effects
  - Progress patients towards liberation
- CONs
  - Direct overdistention injury
  - Pendelluft injury
  - Increased lung perfusion
  - Dyssynchrony – double-trigger
  - Expiratory muscle activation leading to decreased EELV

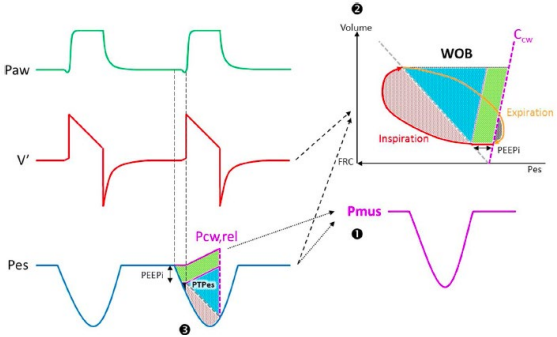
Effect Modifiers:

ARDS Severity; Smaller Baby Lung; High Drive; Injurious Settings



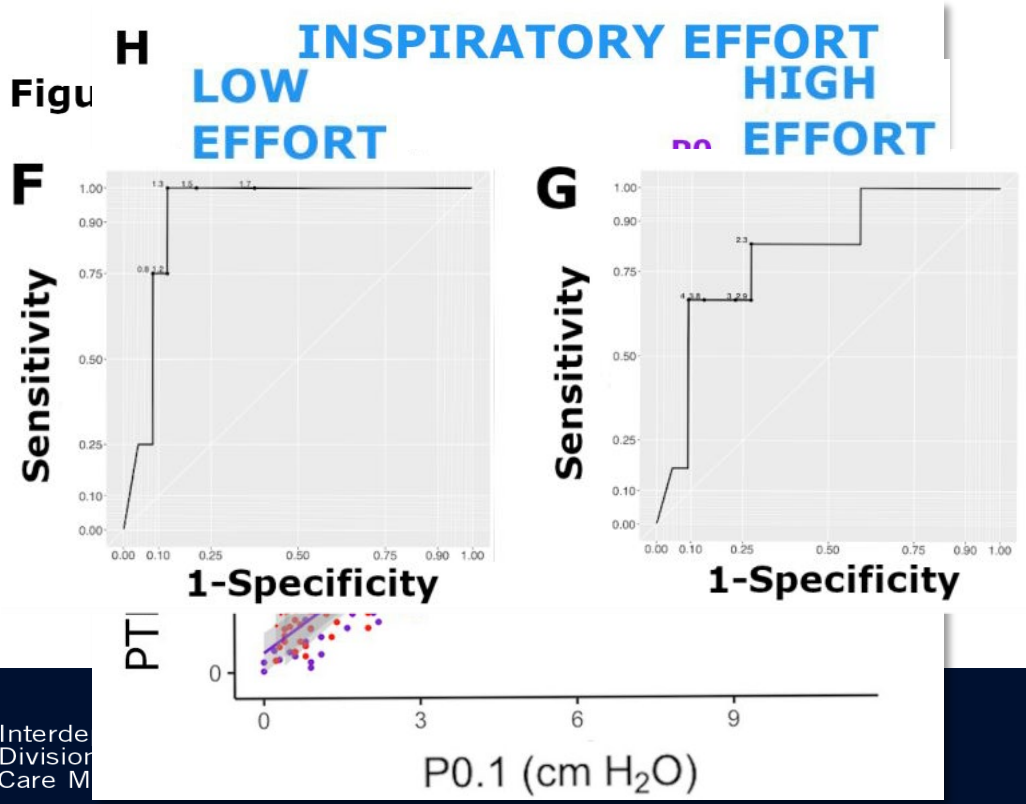
Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives



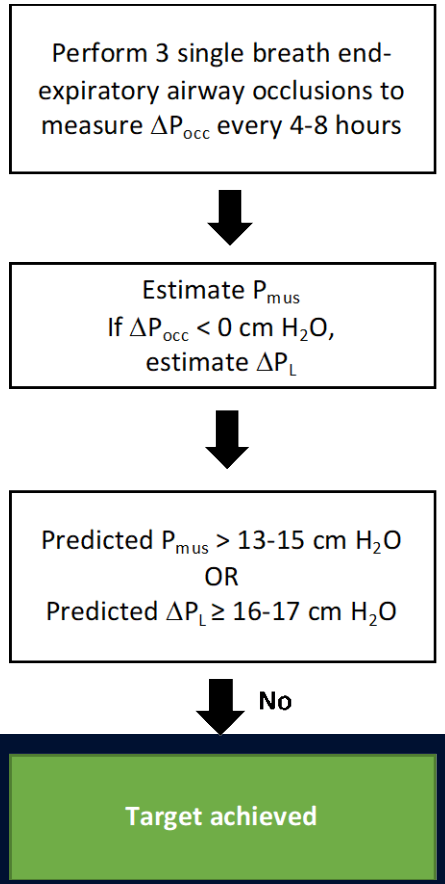


Airway Occlusion Pressure as an Estimate of Respiratory Drive and Inspiratory Effort During Assisted Ventilation

Telias I, et al. AJRCCM 2020 In Press



End-Expiratory Exclusion Manoeuvre



Predicted Pmus = $-0.7 \times \Delta P_{occ}$

Predicted ΔP_L = (Peak Paw– PEEP) – $0.6 \times \Delta P_{occ}$

Consider P_{es} monitoring to guide clinical management
or
consider modifying sedation and ventilation to achieve predicted Pmus and ΔP_L within acceptable limits

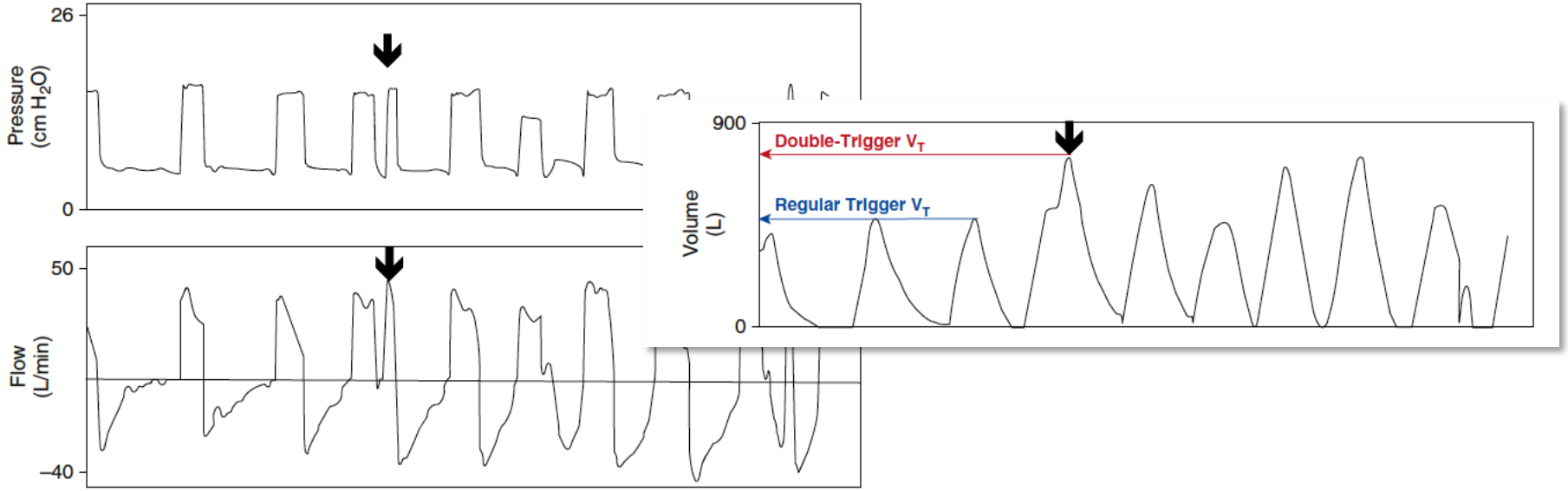
Fifty Years of Research in ARDS

Spontaneous Breathing during Mechanical Ventilation

Risks, Mechanisms, and Management

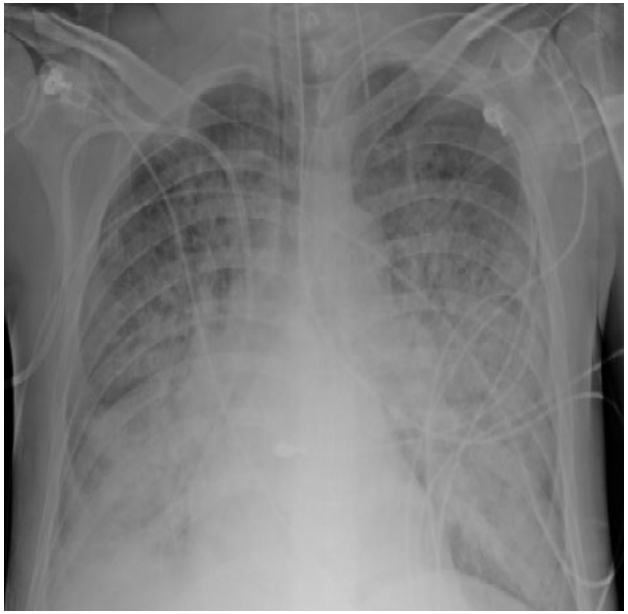
Am J Respir Crit Care Med Vol 195, Iss 8, pp 985–992, Apr 15, 2017

Takeshi Yoshida[1,2,3,4], Yuji Fujino[4], Marcelo B. P. Amato[5], and Brian P. Kavanagh[1,2,3]

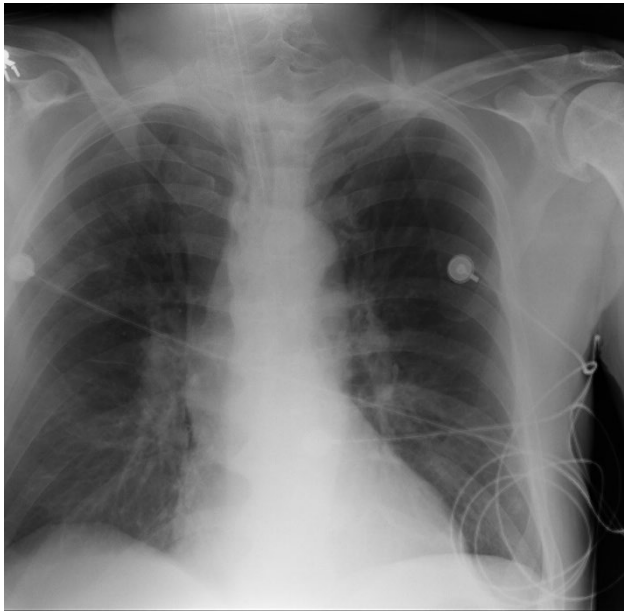


Opinion Based Medicine…

Set V_T=6 ml/kg (or lower)
Control breath size if mod-severe ARDS
Try Higher PEEP



Set V_T=6-8 ml/kg
Tolerate larger spontaneous breaths as long as effort not extreme
Try Lower PEEP



Take Home Points

- COVID-19 ARDS is like ARDS - i.e. heterogeneous
- Tailor PEEP to recruitability
- Impact of spontaneous breathing during ARDS depends on timing and severity
- Measuring patient effort is important
- When allowing spontaneous breathing – consider normalizing efforts to protect both lung and diaphragm

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Interdepartmental Division of Critical Care Medicine

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UNIVERSITY OF TORONTO
Interdepartmental Division of Critical Care Medicine

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

N Engl J Med 2010;363:1107-16

28-day Mortality:

24% - Nimbex

33% - Placebo

p=0.05


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Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

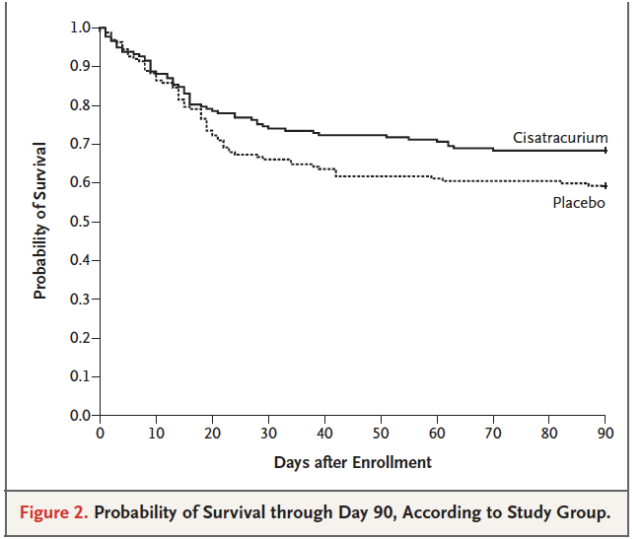


Figure 2. Probability of Survival through Day 90, According to Study Group.

Spontaneous Ventilation in ARDS

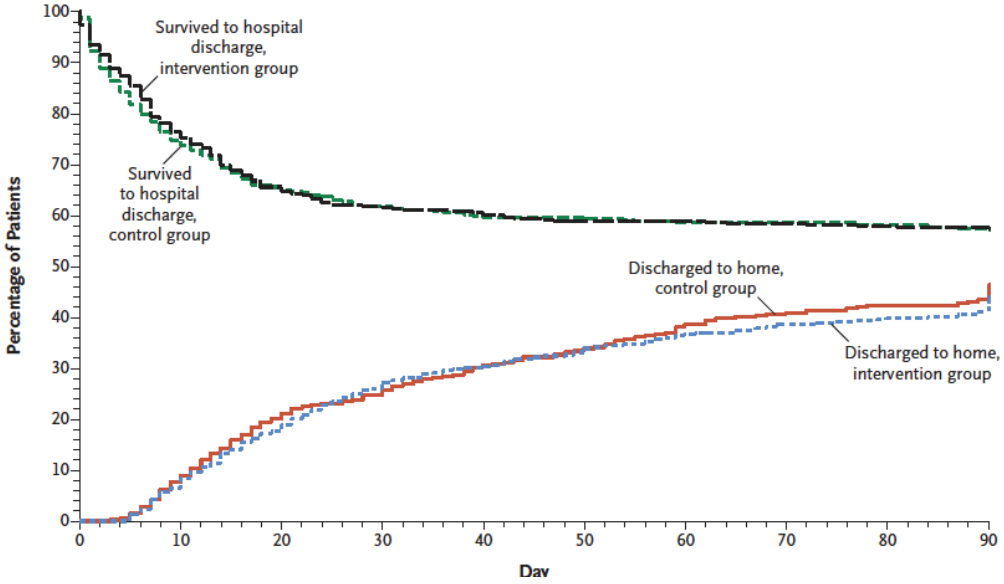
- ROSE Trial Results

Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

N ENGL J MED NEJM.ORG

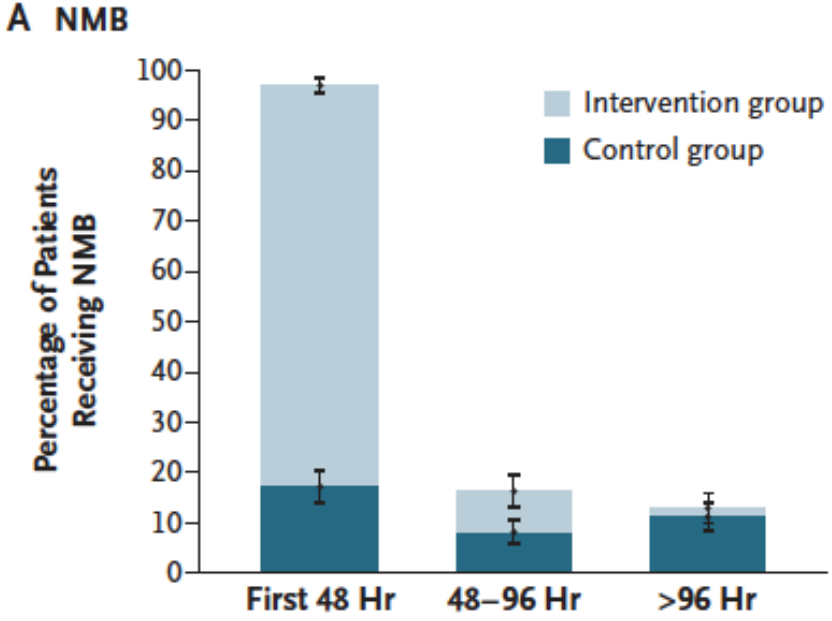
The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

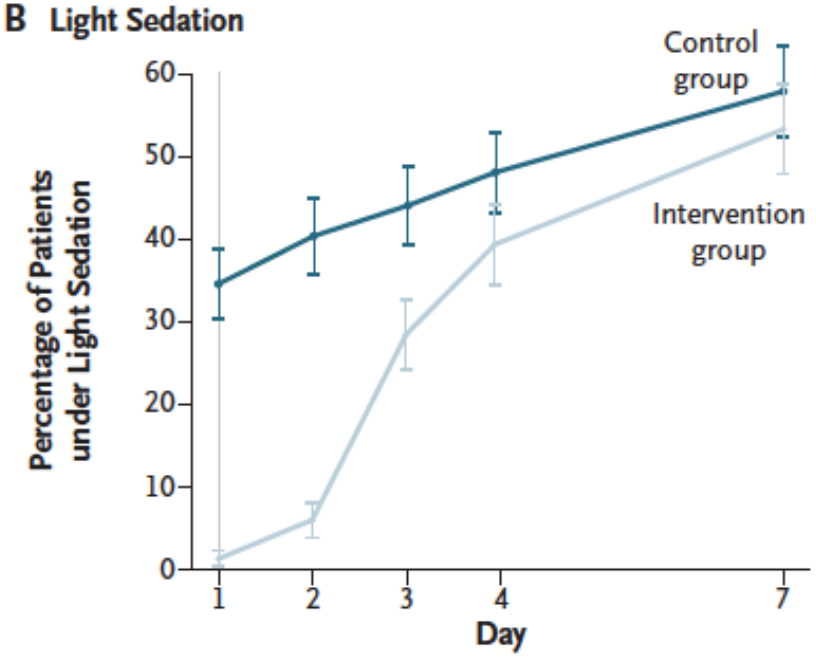
- 1006 early ARDS P/F < 150
- 48h cisatricurium & deep sedation *vs.* lighter sedation
- Higher PEEP in both groups
- 15% prone in both groups
- Primary: 90-day mortality
- Stopped for futility



Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

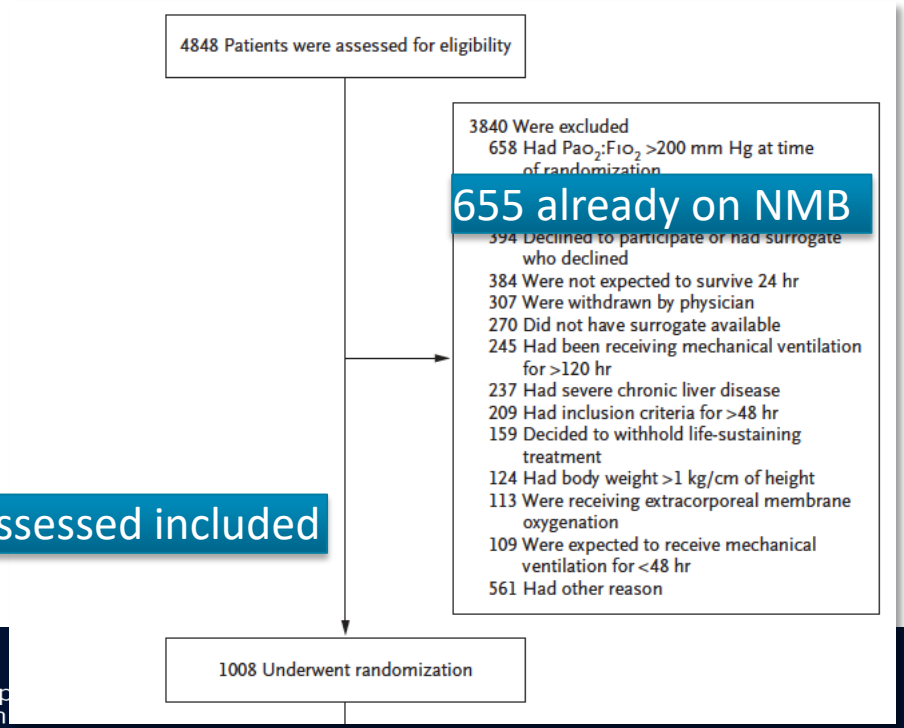
N ENGL J MED NEJM.ORG





Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

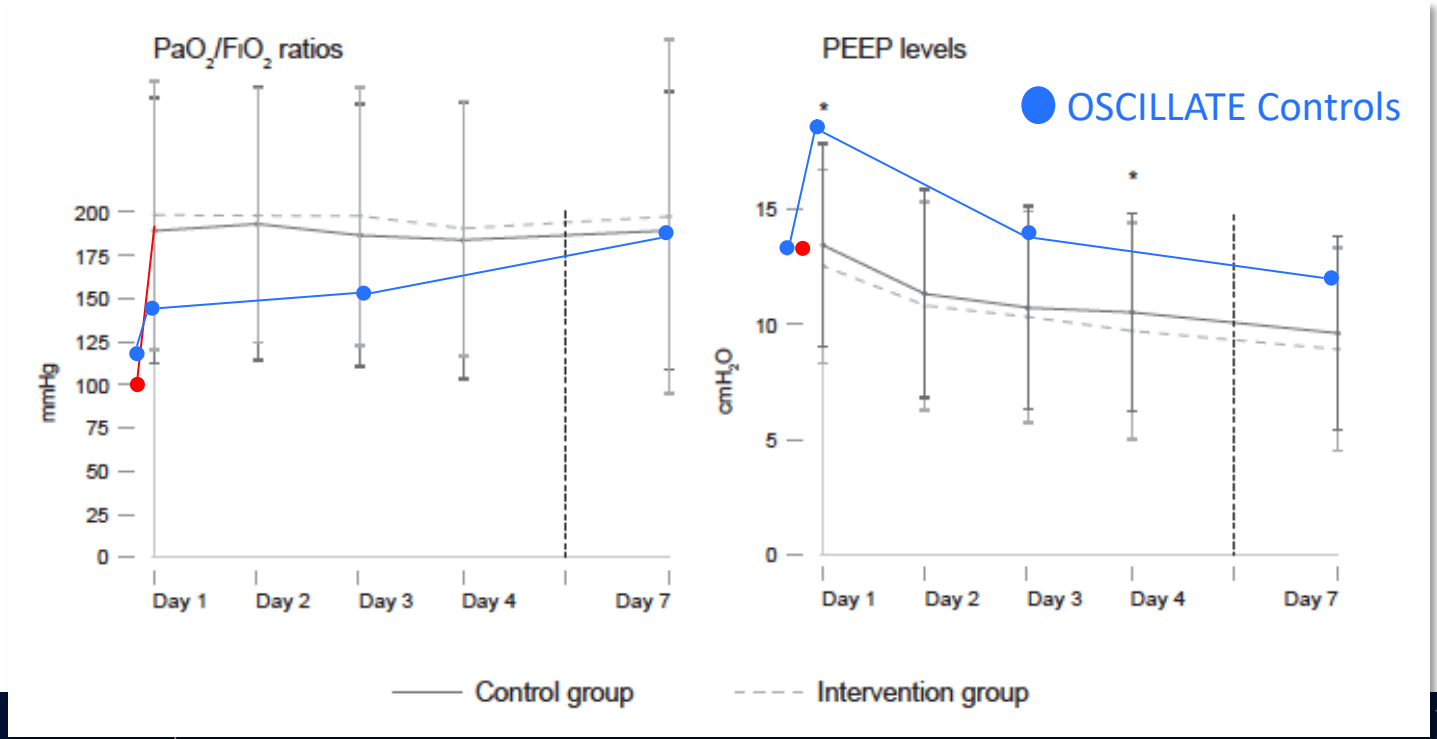


Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Intervention Group (N=501)	Control Group (N=505)
Age — yr	56.6±14.7	55.1±15.9
Female sex — no. (%)†	210 (41.9)	236 (46.7)
White race — no. (%)†	361 (72.1)	344 (68.1)
Shock at baseline — no. (%)	276 (55.1)	309 (61.2)
Median time from enrollment to randomization (IQR) — hr	8.2 (4.0–16.4)	6.8 (3.3–14.5)
Assessments and measurements		
APACHE III score‡	103.9±30.1	104.9±30.1
Total SOFA score§	8.7±3.6	8.8±3.6
Tidal volume — ml/kg of predicted body weight¶	6.3±0.9	6.3±0.9
F_{IO_2}‖	0.8±0.2	0.8±0.2
Inspiratory plateau pressure — cm of water**	25.5±6.0	25.7±6.1
PEEP — cm of water††	12.6±3.6	12.5±3.6
P_{aO_2}:F_{IO_2} — mm Hg‡‡	98.7±27.9	99.5±27.9
Imputed P_{aO_2}:F_{IO_2} — mm Hg§§	94.8±26.7	93.2±28.9

Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome



Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome

N ENGL J MED NEJM.ORG

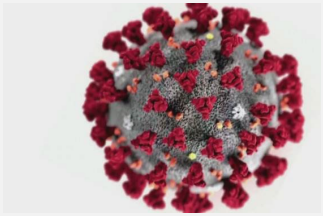
The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

Why are ROSE and ACURASYS results different?

- Higher PEEP?
- Lighter sedation comparator?
- Lower use of proning (15% vs. ~50%)
- Less sick patients

Spontaneous Ventilation in ARDS

- Rose Trial Results
- Spontaneous is not always better



Clinical Trials During COVID 19

John Granton MD FRCPC
Head,
Division of Respirology
University Health Network and Sinai Health System
Professor of Medicine,
Faculty of Medicine, University of Toronto

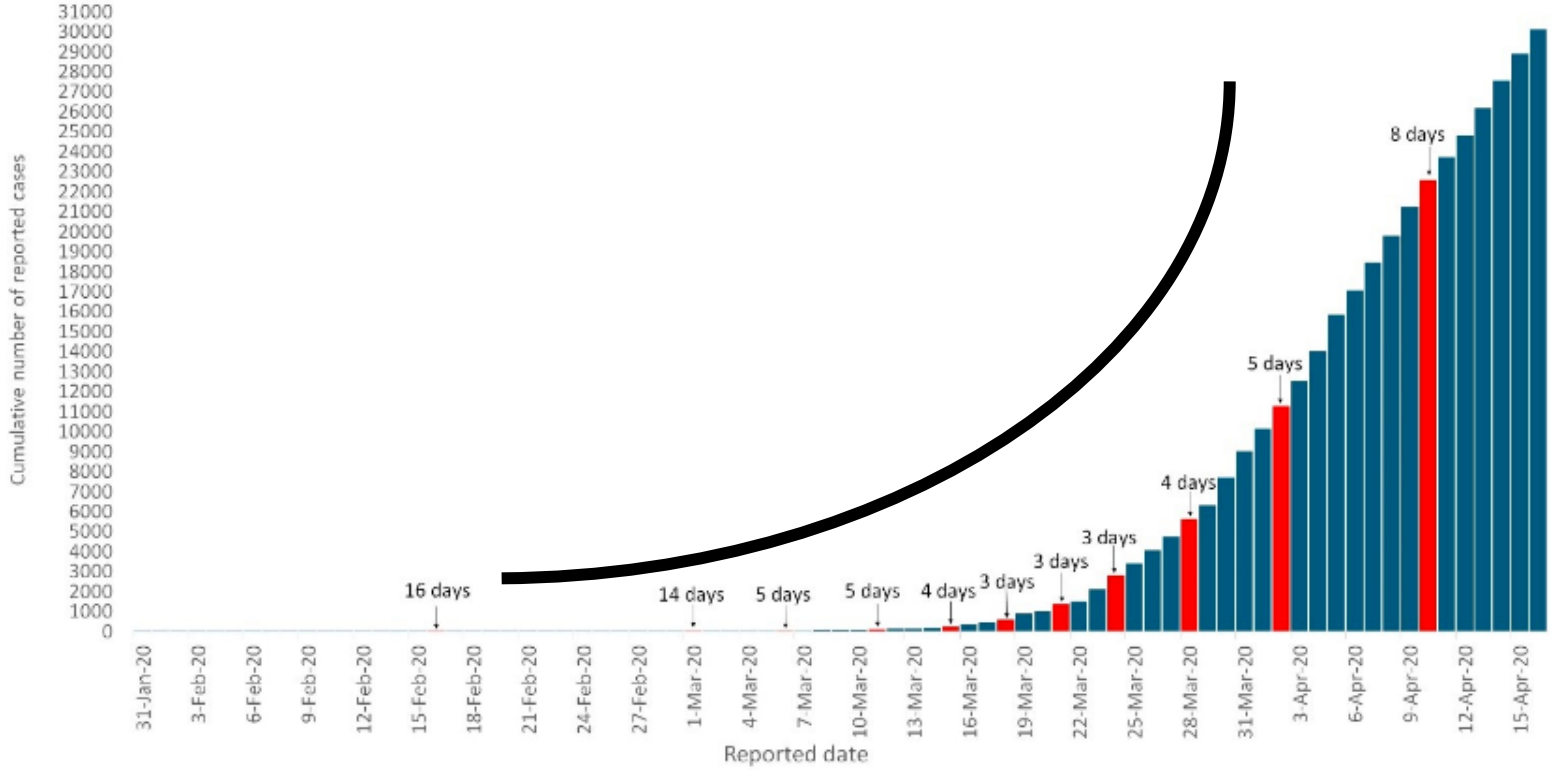
UNIVERSITY HEALTH NETWORK / MOUNT SINAI HOSPITAL
CRITICAL CARE MEDICINE
Toronto Critical Care.org
UHN ECLS PROGRAM
Sinai Health System
UHN

Objectives

- Lessons learned ?
- Challenges in conducting clinical trials during a pandemic
- Clinical trials underway
- Trial design during a pandemic

Government of Canada | Gouvernement du Canada

Doubling time of cumulative number of reported COVID 19 clinical trials



NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Filters

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Status

Recruitment :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Expanded Access :

Eligibility Criteria

Age : years OR

Age Group :

- Child (birth–17)
- Adult (18–64)
- Older Adult (65+)

Sex :

- All

Showing: 1-10 of **657** studies 10 studies per page

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Row	Saved	Status			Locations
1		Recruiting NEW	Application of Desferal to Treat **COVID-19**		• Regenerative Medicine Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran Kermanshah, Iran, Islamic Republic of
2		Active, not recruiting NEW	Clinical Study To Evaluate The Performance And Safety Of Favipiravir in **COVID-19**	• **COVID-19**	• Drug: Favipiravir • Other: Placebo • Asst Fatebenefratelli Sacco Milano, Italy
3		Not yet recruiting NEW	CORonavirus (**COVID-19**) Diagnostic Lung UltraSound Study	• **COVID-19**	• Diagnostic Test: Lung ultrasound
4		Not yet recruiting NEW	Study to Evaluate the Efficacy and Safety of Tocilizumab Versus Corticosteroids in Hospitalised **COVID-19** Patients With High Risk of Progression	• **COVID-19**	• Drug: Tocilizumab • Drug: Methylprednisolone • University Malaya Medical Centre Kuala Lumpur, Malaysia
5		Recruiting NEW	**COVID-19** Symptom Tracker	• **COVID-19**	• Other: No Intervention • Massachusetts General Hospital Boston, Massachusetts, United States • King's College London London, United Kingdom
6		Not yet recruiting NEW	The Phase 2 Study to Evaluate the Safety and Efficacy of Clevudine in Patients With Moderate **COVID-19**	• **COVID-19**	• Drug: Clevudine • Drug: Hydroxychloroquine
7		Not yet recruiting NEW	Hyperbaric Oxygen Therapy (HBOT) as a Treatment for **COVID-19** (**COVID-19**) Infection	• **COVID-19**	• Device: Hyperbaric Oxygen Therapy • Ochsner Medical Center New Orleans, Louisiana, United States
8		Not yet recruiting NEW	**COVID-19** Endoscopy Survey	• **COVID-19**	• Other: Practice details • Kings County Hospital Center, Brooklyn, NY, USA Albertson, New York, United States • Faculty of Medicine, Zagazig University Zagazig, Sharkia, Egypt • Al-Azhar Univerisity Cairo, Egypt • Ahvaz Imam hospital Ahvaz, Iran, Islamic Republic of

Showing: 1-10 of 657 studies 10 studies p

Row | Saved | Status

Recruiting NEW

Application of Desf

Approaches / Theories

Antiviral
- Vaccines
- Prophylaxis
- Early vs late infection

Anti-inflammatory

Anti-coagulants

Anti-microbial

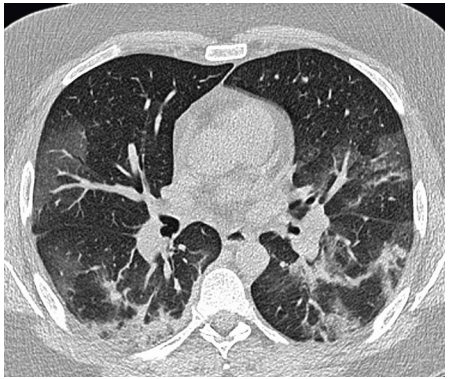
Organ specific

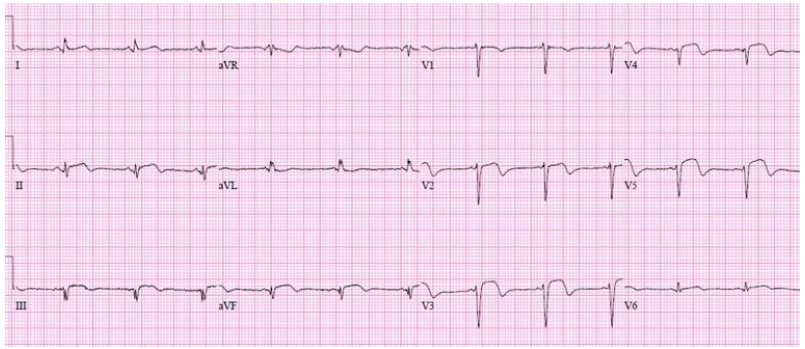
JAMA | Original Investigation

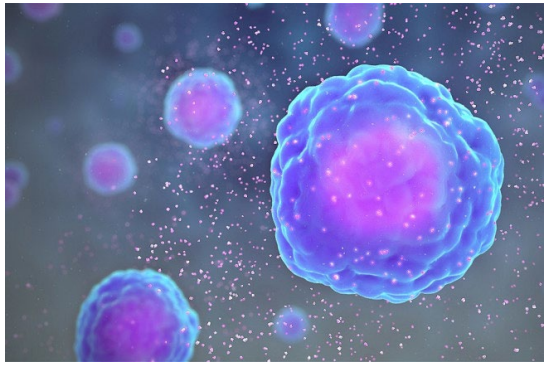
Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy

Giacomo Grasselli, MD; Alberto Zangrillo, MD; Alberto Zanella, MD; Massimo Antonelli, MD; Luca Cabrini, MD; Antonio Castelli, MD; Danilo Cereda, MD; Antonio Coluccello, MD; Giuseppe Foti, MD; Roberto Fumagalli, MD; Giorgio Iotti, MD; Nicola Latronico, MD; Luca Lorini, MD; Stefano Merler, MS; Giuseppe Natalini, MD; Alessandra Piatti, MD; Marco Vito Ranieri, MD; Anna Mara Scandroglio, MD; Enrico Storti, MD; Maurizio Cecconi, MD; Antonio Pesenti, MD; for the COVID-19 Lombardy ICU Network

April 6
JAMA. doi:10.1001/jama.2020.5394

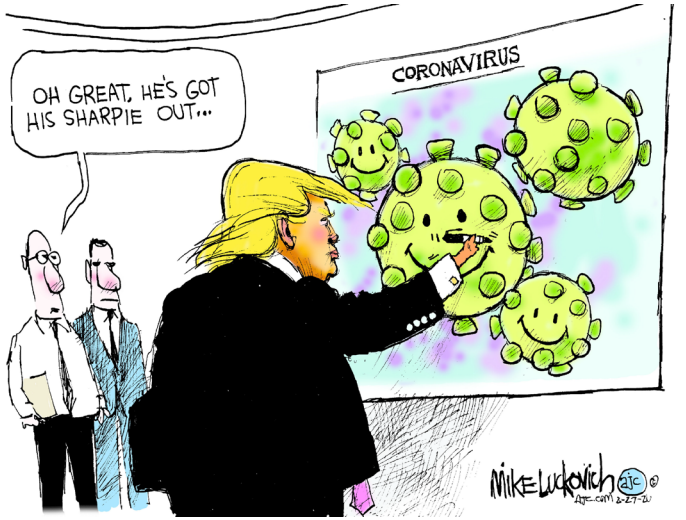






Challenges during a pandemic

- Lack of coordinated efforts
- Funding
- Trial approval and execution
- Research personnel
- Consent
- Barriers to collecting data
- Surge in clinical activity vs constrained resources



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Perspective

Drug Evaluation during the Covid-19 Pandemic

Benjamin N. Rome, M.D., and Jerry Avorn, M.D.

Pitfalls of

- Open label studies
- Off label use

April 14, 2020
DOI: 10.1056/NEJMp2009457

OPEN ACCESS Freely available online PLOS MEDICINE

SARS: Systematic Review of Treatment Effects

Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]

1 Centers for Disease Control and Prevention, Respiratory and Enteric Viruses Branch, Atlanta, Georgia, United States of America, **2** Department of Veterans' Affairs, Atlanta Research and Education Foundation, Decatur, Georgia, United States of America, **3** James Cook University Hospital, Middlesbrough, United Kingdom, **4** Liverpool School of Tropical Medicine, Liverpool, United Kingdom

September 2006; 3(9): e343

54 SARS treatment studies,
15 in vitro studies, and three ARDS trials

26 studies of ribavirin were classified as inconclusive, and 4 showed possible harm.

7 studies of convalescent plasma or IVIG, 3 of IFN type I, and 2 of lopinavir/ritonavir were inconclusive.

29 studies of steroid use, 25 were inconclusive and 4 were classified as causing possible harm.

What Did We Learn From the Emergency Use Authorization of Peramivir in 2009?

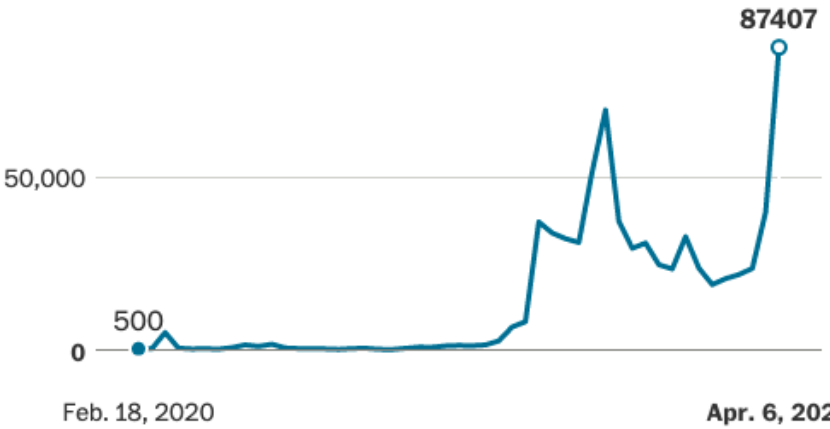
Andrew T. Pavia

Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Utah, Salt Lake City

"A crisis is a terrible thing to waste"
Paul Rohmer

Clinical Infectious Diseases
2012;55(1):16–8

Social media mentions of hydroxychloroquine



Claims about hydroxychloroquine and chloroquine as a treatment for covid-19 surged on social media in the second half of March and early April.

Source: Brandwatch, Crowdtangle

THE WASHINGTON POST

Hydroxychloroquine +/- Azithromycin

April 18th, 129 trials involving chloroquine and hydroxychloroquine, alone, or in combination, or in combination with other drugs in the prevention or treatment

Most = non-blinded trials.

5 have been “published”
1 open-label trial of hydroxychloroquine or hydroxychloroquine + azithromycin;
1 open-label randomized placebo-controlled study of hydroxychloroquine; and
1 randomized comparison of hydroxychloroquine with standard care,
1 case series,
1 observational study designed to emulate a randomized controlled trial in 181 patients

Ferner Aronson
https://www.cebm.net/covid-19/hydroxychloroquine-for-covid-19-what-do-the-clinical-trials-tell-us/

Compassionate Use of Remdesivir for Patients with Severe Covid-19

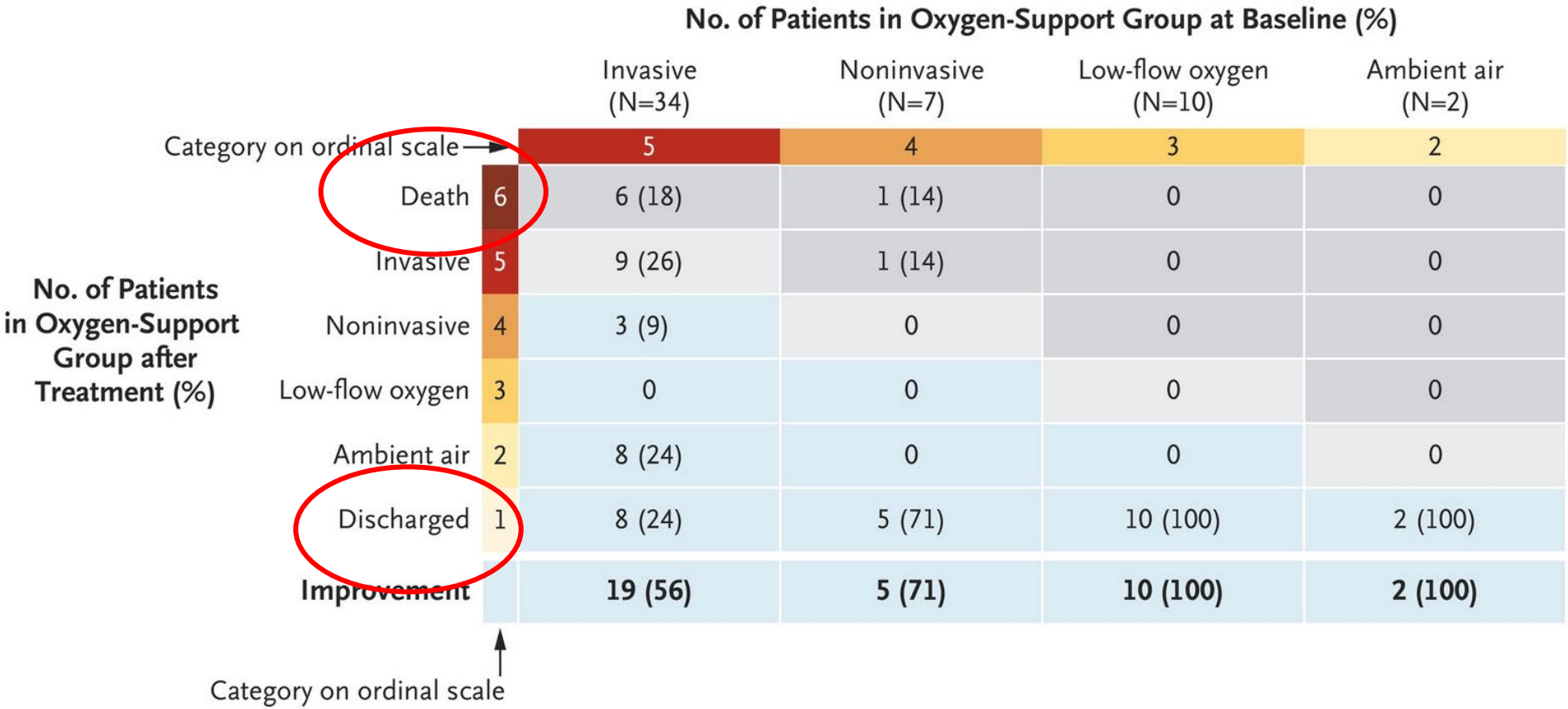
J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Rolda A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

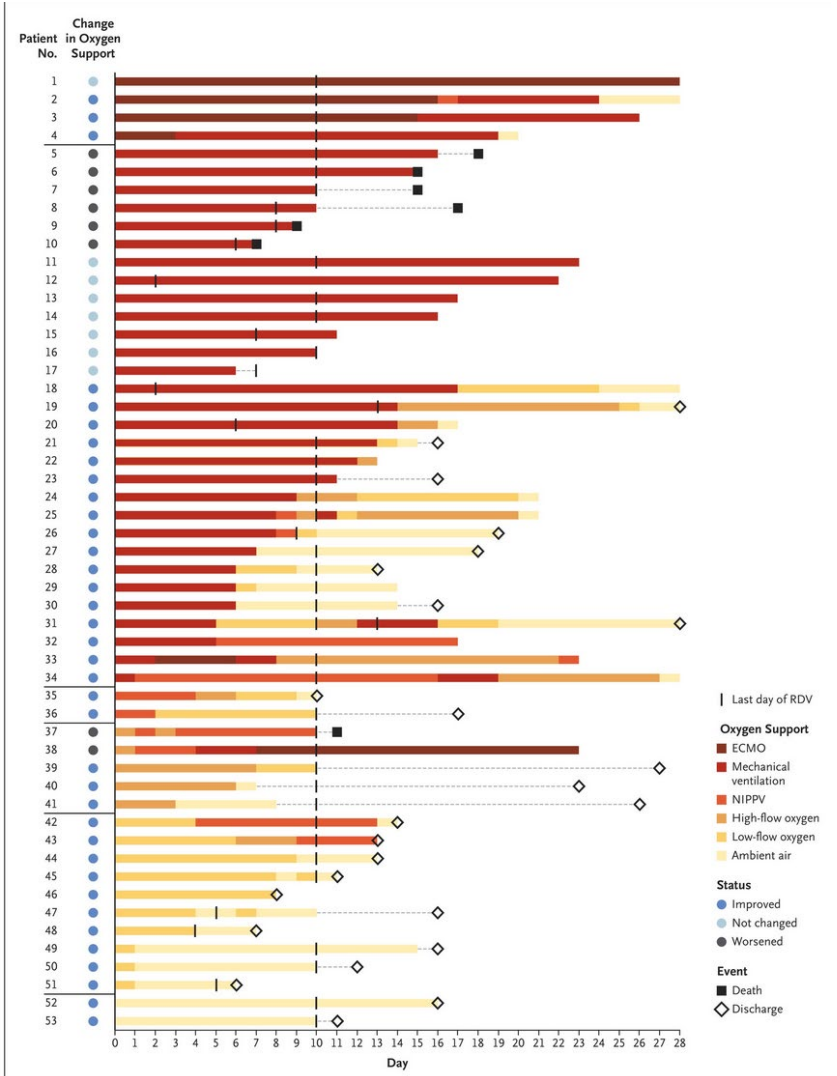
April 10
DOI: 10.1056/NEJMoa2007016

53/61 patients with oxygen saturation of 94% or less.

10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment.

Seven of the 53 patients (13%) died.
6 of 34 patients (18%) who were receiving invasive ventilation and
1 of 19 (5%) who were receiving noninvasive oxygen support


No. of Patients in Oxygen-Support Group at Baseline (%)
Invasive (N=34)
Noninvasive (N=7)
Low-flow oxygen (N=10)
Ambient air (N=2)
Category on ordinal scale
5
4
3
2
No. of Patients in Oxygen-Support Group after Treatment (%)
Death 6 6 (18) 1 (14) 0 0
Invasive 5 9 (26) 1 (14) 0 0
Noninvasive 4 3 (9) 0 0 0
Low-flow oxygen 3 0 0 0 0
Ambient air 2 8 (24) 0 0 0
Discharged 1 8 (24) 5 (71) 10 (100) 2 (100)
Improvement 19 (56) 5 (71) 10 (100) 2 (100)
Category on ordinal scale



April 10

DOI: 10.1056/NEJMoa2007016

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

199 patients with pneumonia
Oxygen saturation (Sao2) of 94% or less *or*
Pao2:Fio2 at or below 300 mg Hg

Open label
Comparator = standard of care

March 18
DOI: 10.1056/NEJMoa2001282

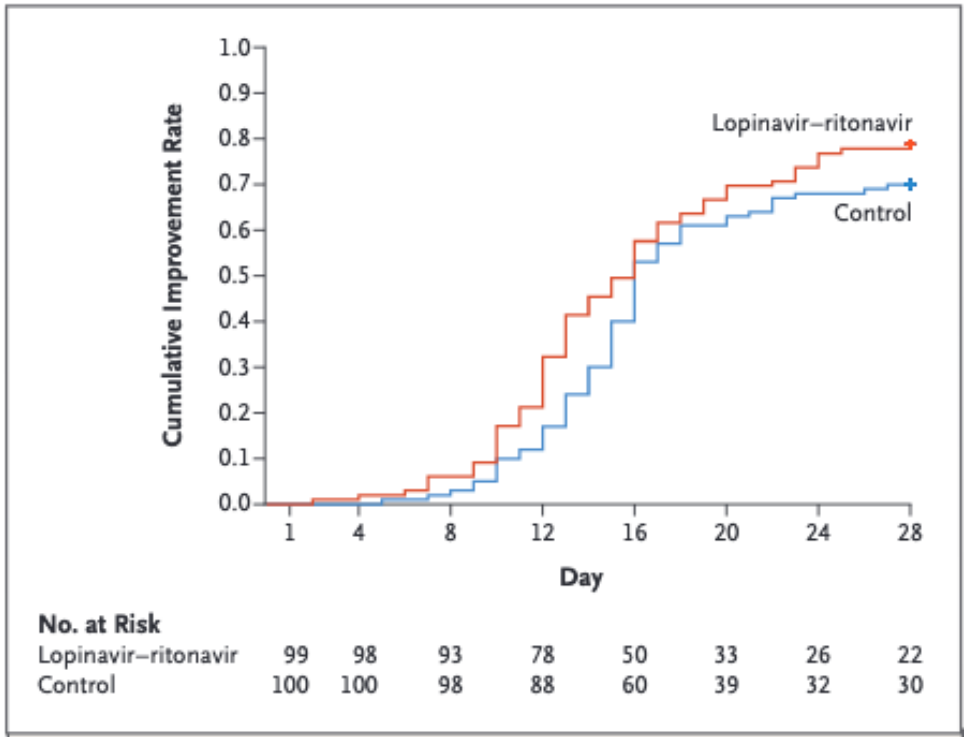
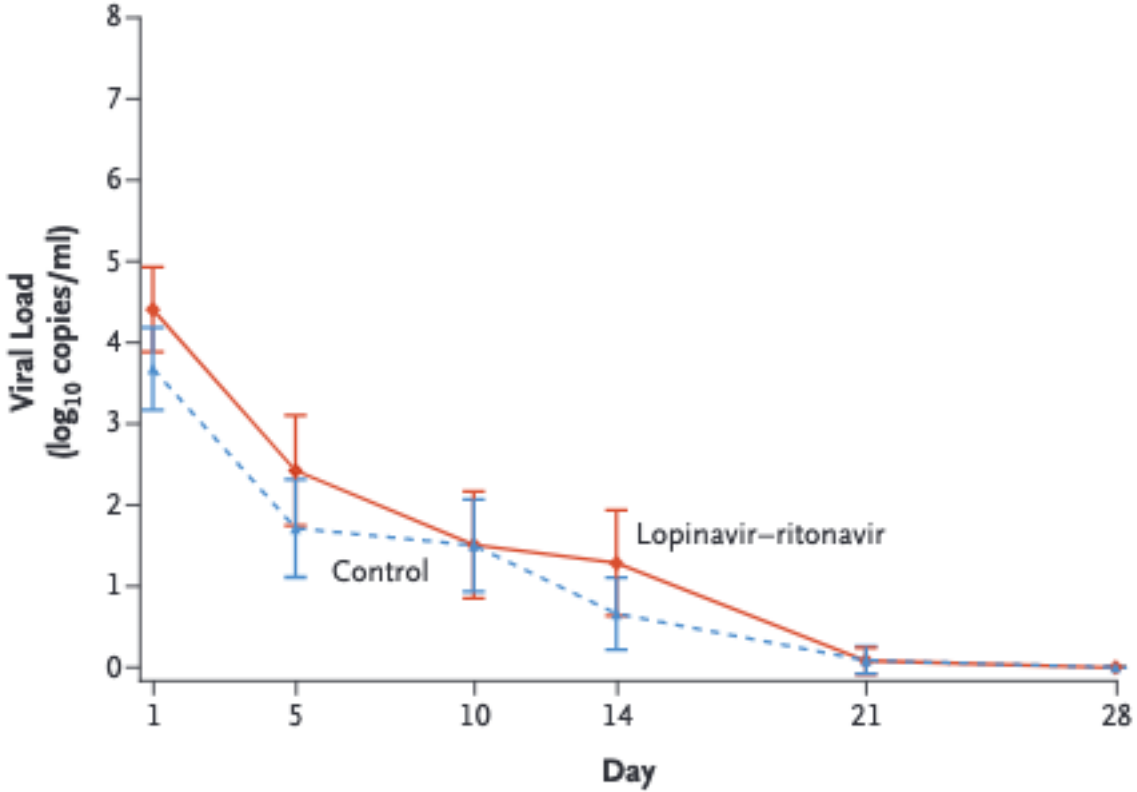


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

Median, 16 days vs. 16 days;
HR for clinical improvement, 1.31;
95% CI: 0.95 to 1.80; P = 0.09

Cao et al. March 18
DOI: 10.1056/NEJMoa2001282



Cao et al. March 18
DOI: 10.1056/NEJMoa2001282

Canadian Blood Services
BLOOD PLASMA STEM CELLS ORGANS & TISSUES

CONCOR-1

A Randomized, Open-Label Trial of **CON**valescent Plasma for Hospitalized Adults With Acute **CO**VID-19 **R**espiratory Illness

COVID-19 Convalescent plasma

1200 patients 2:1 randomization

Comparator = standard of care

Primary outcome
intubation or death at 30 days

THE LANCET

COMMENT | ONLINE FIRST

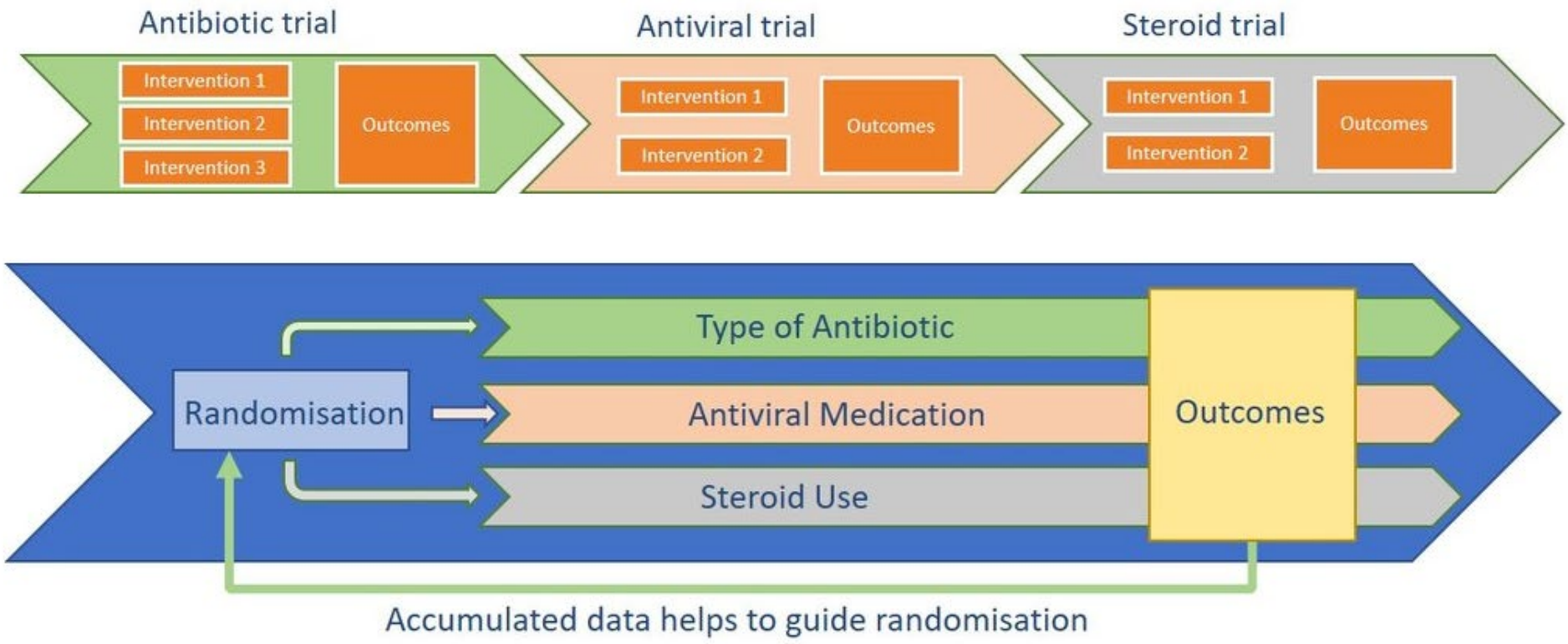
Global coalition to accelerate COVID-19 clinical research in resource-limited settings

COVID-19 Clinical Research Coalitionnick.white@covid19crc.org † • Show footnotes

Published: April 02, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30798-4 •

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

REMAP-CAP



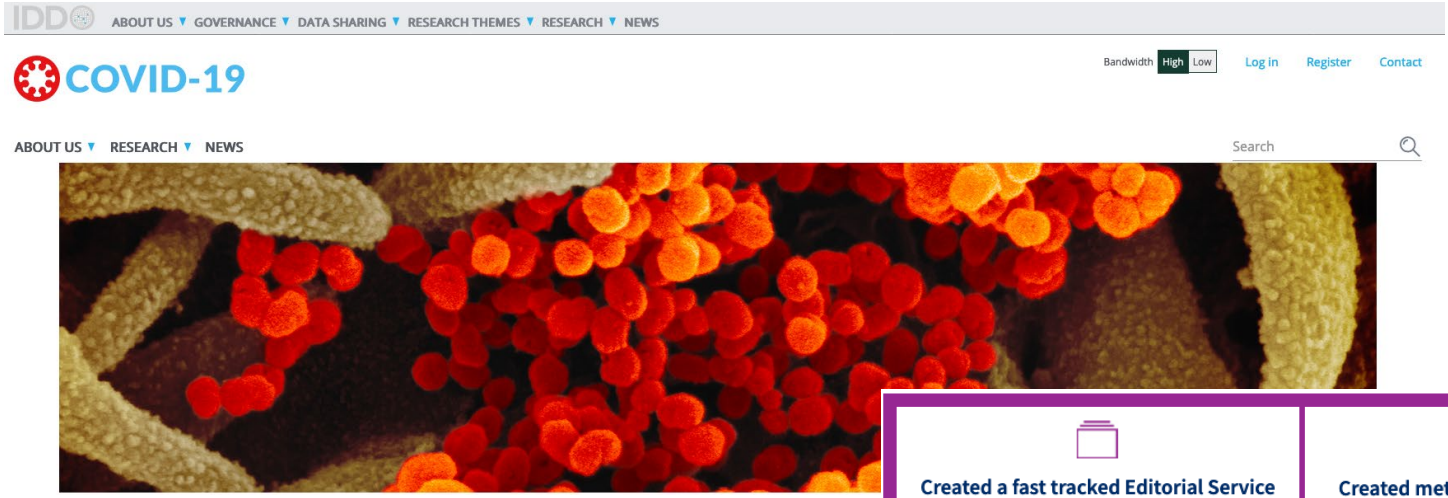
Lopinavir / Ritonavir

Remdesivir

Interferon beta – 1

OH-chloroquine

Keeping up with the literature



Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Created a fast tracked Editorial Service and documentation

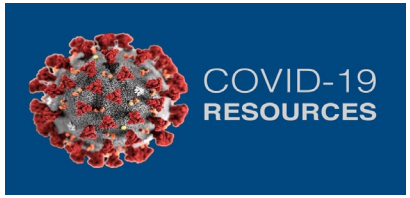
Created methods guidance for Rapid Reviews

Cochrane's work on Rapid Reviews in response to COVID-19

Prioritized questions while working closely with front-line healthcare workers & health agencies

Completed work on a Rapid Review that focuses on several quarantine questions

KEEPING UP WITH THE LITERATURE



https://www.criticalcare.utoronto.ca/covid-19-resources

COVID-19 Guidelines

The Surviving Sepsis Campaign (SSC) has released Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19).

Surviving Sepsis Campaign®

Guideline Access

- *Intensive Care Medicine*: Guideline
- *Critical Care Medicine*: Guideline I Infographic 1 I Infographic 2
- Concise Recommendations Tables: Infection Control and Testing I Hemodynamics I Ventilation I Therapy I Combined Recommendations Tables
- Webcast Recording I Webcast Slides
- Podcast

Additional Resources

ESCIM COVID-19
SCCM Emergency Response: COVID-19

Cochrane Special Collections

Coronavirus (COVID-19): evidence relevant to critical care

14 April 2020

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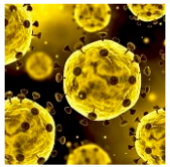

First published on 11 February 2020 and updated on an ongoing basis; last updated on 14 April 2020 (changes detailed below)

This Special Collection is one of a ***series of collections on COVID-19****. It is also available in* ***Simplified Chinese****,* ***Czech****,* ***German****,* ***Farsi****,* ***French****,* ***Japanese****,* ***Bahasa Malaysia****,* ***Polish****,* ***Portuguese****,* ***Russian****, and* ***Spanish****.*

The aim of this Special Collection is to ensure immediate access to systematic reviews most directly relevant to the management of people hospitalized with severe acute respiratory infections. It includes reviews that are relevant to the **WHO interim guidance**, and reviews identified as relevant by **Cochrane Acute and Emergency Care**, informed by Cochrane groups in affected regions.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interminable Meetings Found Ineffective for Treatment of COVID-19

W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical Treatment Expert Group for Covid-19*

ABSTRACT

BACKGROUND

Since December 2019, when coronavirus disease 2019 (Covid-19) first emerged in Wuhan city hospital administrators have attempted to fight the spread of this global pandemic with use interminable meetings, but little is known about about their anti-viral efficacy.

METHODS

We performed an adaptive design block randomized trial of Inte versus Getting Out of My Way and Letting Me Do My Job (GO were randomized to either GOMWLMDMJ or standard of care. time to actually care for patients, median stupid questions per uni furious anger.

RESULTS

Over a median of 2.8 months of follow up IM was found to be i COVID-19. No patient centered outcome was found to be impr outcome event (actual patient care) increased by of 135.5% in th and 942 of 978 (96.3%) administrators were found to have little Wasting my time was found to decrease significantly (RR 0.60; 9 [CI], 0.42 to 0.78; P=0.001).

28-day mortality was found to strongly favor a GOMWLMDMJ 95% CI, 1.83 to 1.98; P=0.02), as was hospital LOS , 6 and 12; hazard ratio, 1.42; 95% CI, 1.10 to 1.84; P=0.007, and ill-conceived mandates by people who have not seen a patient in years were decreased by 89.3% (CI, 76.5% to 111.4%; P=0.02).

Of note powerpoint slide usage decreased significantly RR 0.44 confidence interval [CI], 0.42 to 0.76; P=0.001 as did time spent listening to some blowhard jabber on about some leadership book he once read while muted while trying to accomplish an actual task (3.2 hours CI, 1.1 to 8,6; P=0.03).

CONCLUSIONS

Interminable Meetings were found uniformly ineffective to the treatment of COVID-19. As such their continued role in treatment of the widening SARS-CoV-2 global pandemic should be minimized in favor of actual medicine. (Manuscript was written while listening to some blowhard jabber on about some leadership book he once read while muted. ClinicalTrials.gov number, NCT4604216)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Zhong at the State Key Laboratory of Respiratory Disease, National Clinical

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at NEJM.org.

DOI: 10.1056/NEJMoa2002032