Penn Medicine

Division of Pulmonary, Allergy, and Critical Care

Treatment of COVID-19: Antivirals

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April 02, 2020

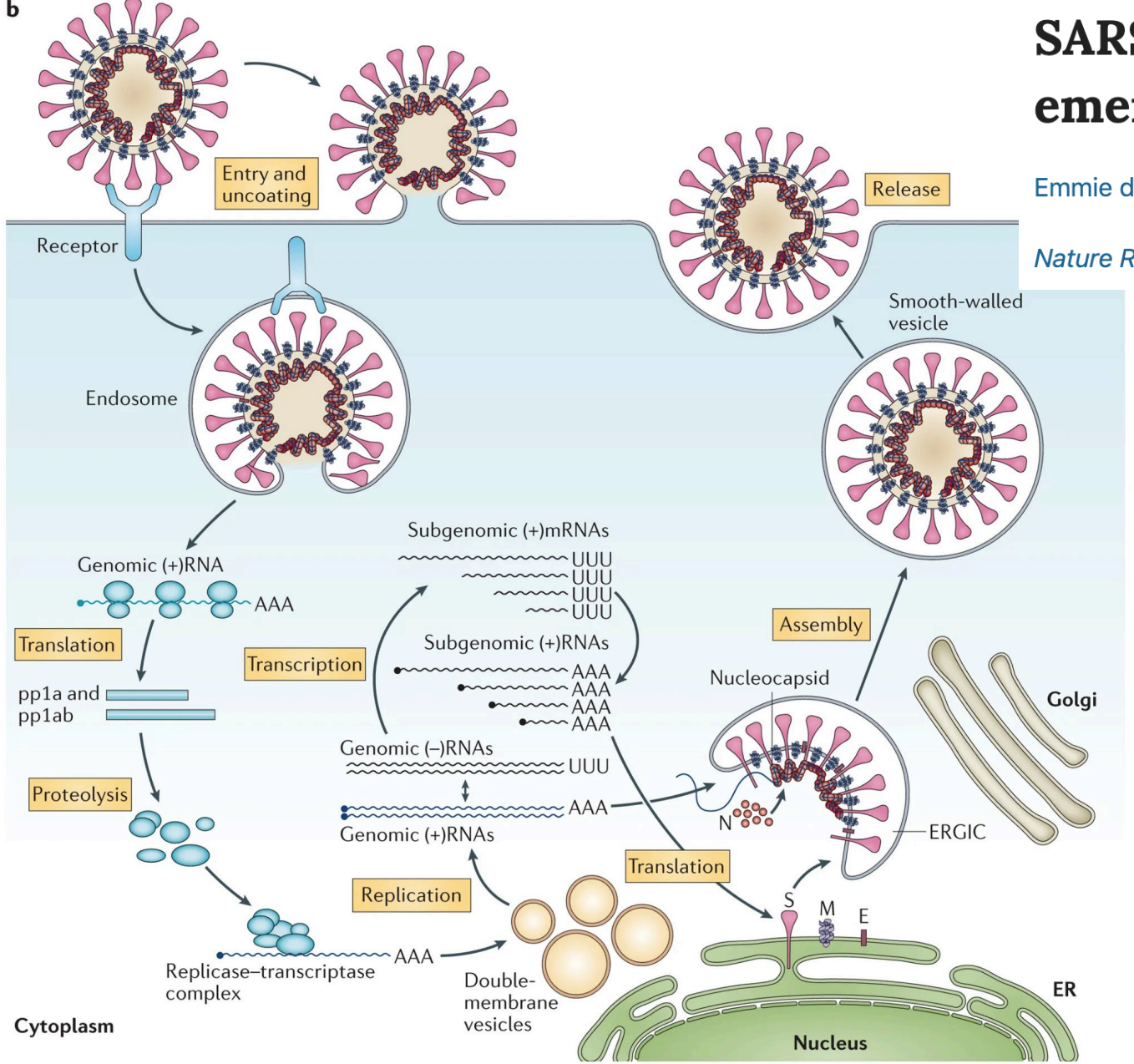
Outline

- Brief virology background, *in vitro* data
- Specific anti-viral agents
  - Hydroxychloroquine
  - Remdesivir
  - Favipiravir
  - Lopinavir/Ritonavir
- Additional therapies
- Current Penn guidance (4-2-2020)

SARS and MERS: recent insights into emerging coronaviruses

Emmie de Wit, Neeltje van Doremalen, Darryl Falzarano & Vincent J. Munster

Nature Reviews Microbiology **14**, 523–534(2016) | Cite this article



- Replication schematic from 2016 based on Sars-CoV-1 and MERS
- Sars-CoV-2 receptor: ACE2
- Note potential therapeutic targets
  - Entry
  - Endosomal acidification/release
  - Replication
  - Assembly
  - Release
- Investigational drugs:
  - Chloroquine/Hydroxychloroquine
  - Lopinavir/Ritonavir
  - Favipiravir
  - Remdesivir
  - Interferon

Wit et al., Nature Reviews Microbiology, 2016

Coronaviruses — drug discovery and therapeutic options

Alimuddin Zumla, Jasper F. W. Chan, Esam I. Azhar, David S. C. Hui & Kwok-Yung Yuen ✉

Nature Reviews Drug Discovery **15**, 327–347(2016) | Cite this article

Table 1 | **Therapeutic interventions used in patients with SARS and MERS**

Type of intervention	Therapeutic intervention	Treatment effects	Refs
Treatments used for SARS patients			
Antivirals	Ribavirin	No significant effect on clinical outcome	10,21
	Ribavirin, lopinavir–ritonavir + corticosteroids	Patients who received ribavirin, lopinavir–ritonavir and a corticosteroid had lower 21-day ARDS and death rates than those who received ribavirin and a corticosteroid	76,77
Interferon combination	Interferon alfa-1 + corticosteroid	Associated with improved oxygen saturation and more rapid resolution of radiographic lung opacities than systemic corticosteroid alone (uncontrolled study)	78
Corticosteroids	Pulsed methylprednisolone	Associated with an increased 30-day mortality rate (adjusted OR = 26.0, 95% CI = 4.4–154.8). Disseminated fungal infection and avascular osteonecrosis occurred following prolonged systemic corticosteroid therapy	79–81
		A randomized, placebo-controlled study showed that plasma SARS-CoV RNA levels in weeks 2–3 of the illness were higher in patients given hydrocortisone ($n = 10$) than those given normal saline ($n = 7$) in the early phase of the illness, suggesting that early use of pulsed methylprednisolone might prolong viraemia	82
Convalescent-phase plasma	Convalescent-phase plasma therapy	Has been used for severe respiratory tract infections including SARS and influenza. A systematic review and exploratory meta-analysis of patients with SARS or influenza treated with convalescent-phase plasma showed a reduction in mortality, but the treatment success was determined by its availability and timely administration	85,272, 273
		Among 80 non-randomized SARS patients who were given convalescent-phase plasma, the discharge rate at day 22 was 58.3% for patients ($n = 48$) treated within 14 days of illness onset versus 15.6% for those ($n = 32$) treated beyond 14 days	83,84

- Many other drug targets mentioned in this paper- great additional reading for those interested
- Targeted viral components:
  - Envelope, spike glycoprotein, enzymes, nucleic acids
- Targeted host factors:
  - Innate immune response (interferon), signaling pathways in viral replication, receptors for viral entry, proteases, and endocytosis pathways

Zumla et al., Nature Reviews Drug Discovery, 2016

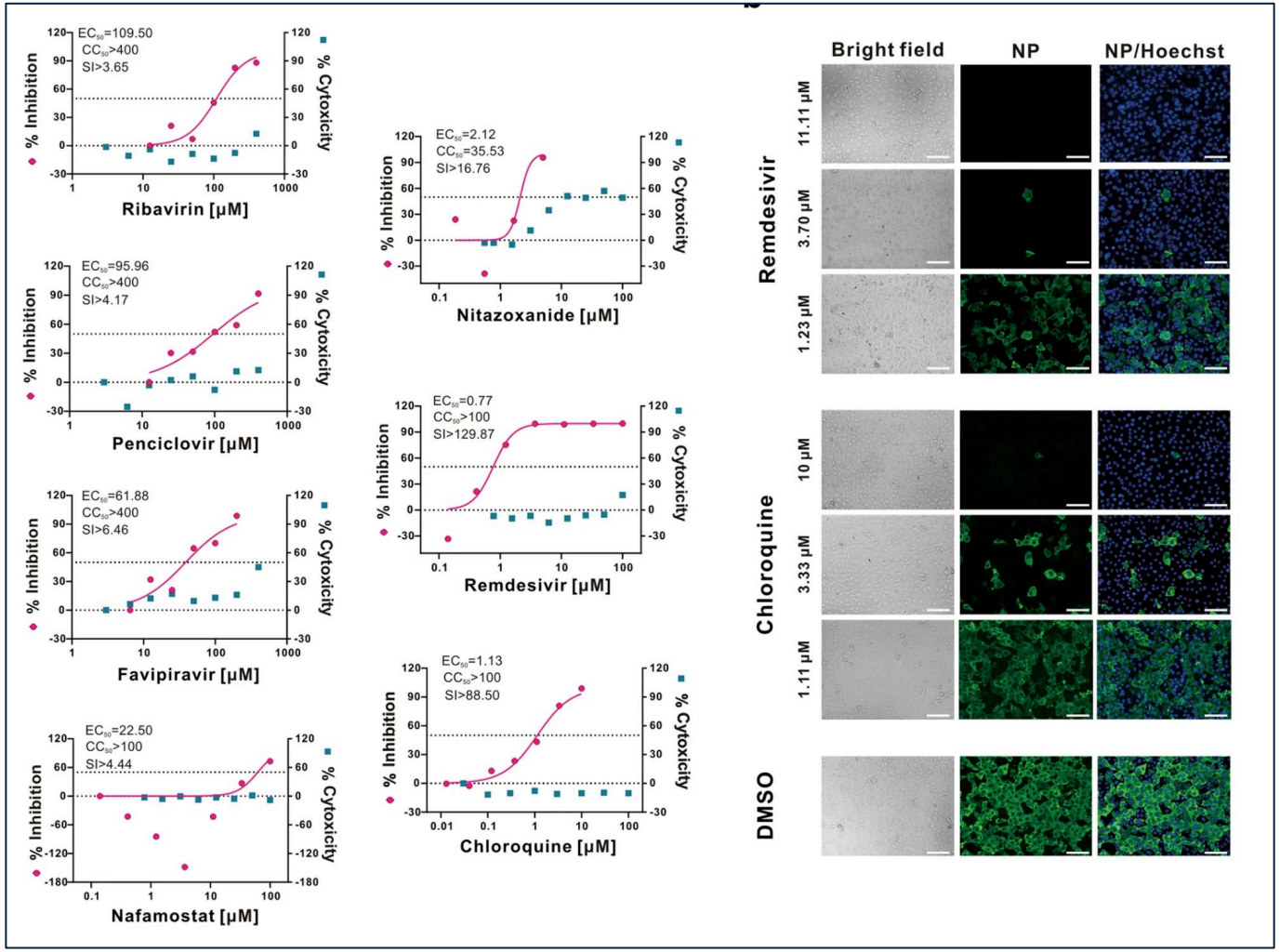
Letter to the Editor | Open Access | Published: 04 February 2020

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

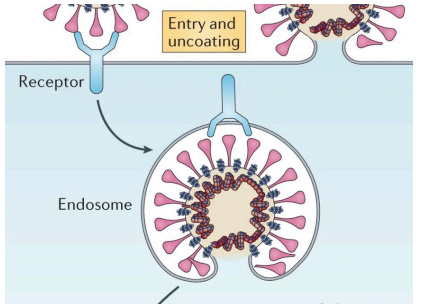
Manli Wang, Ruiyuan Cao, Leike Zhang, Xinglou Yang, Jia Liu, Mingyue Xu, Zhengli Shi, Zhihong Hu ✉, Wu Zhong ✉ & Gengfu Xiao ✉

Cell Research **30**, 269–271(2020) | Cite this article

- In vitro data using Vero E6 cell line
- Cytotoxicity to cells,
- Viral copy number (RT-PCR), immunofluorescence of viral protein
  - Remdesivir, Chloroquine, Ribavirin, Nitaxanide, Penciclovir, Favipivir, Nafamostat
  - Two had high selectivity index and low cytotoxicity

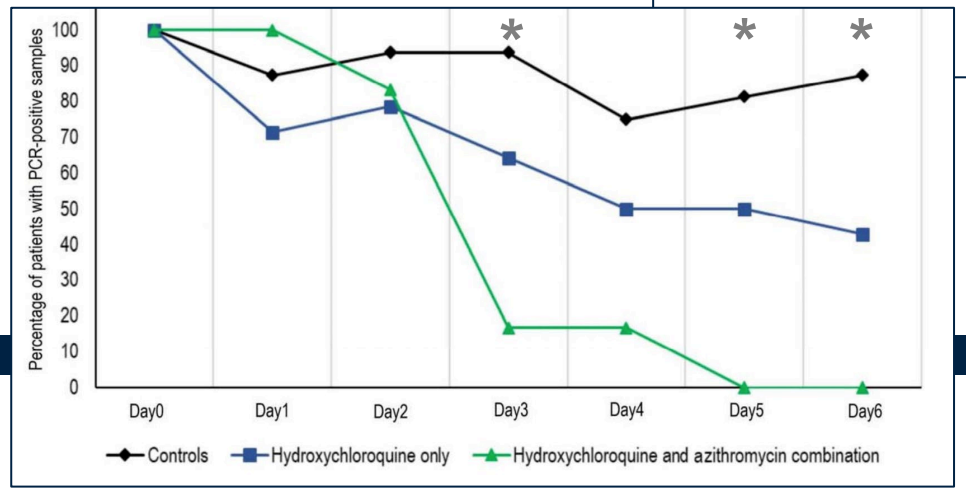


Hydroxychloroquine (Chloroquine)

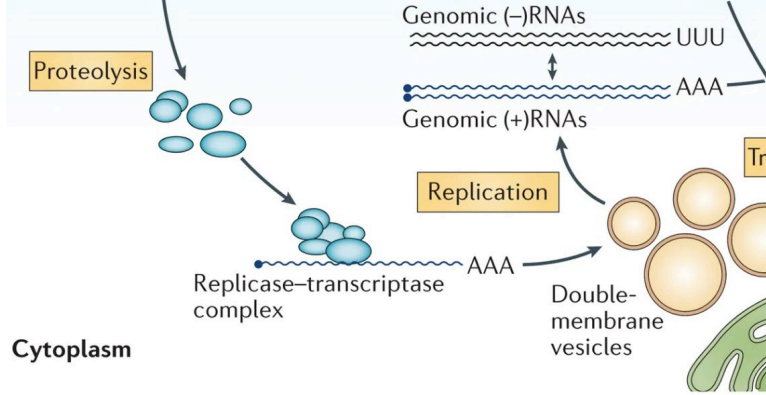


- Raises pH of endosome, preventing viral membrane from merging with endosome
- In vitro data (Wang, et al and Liu, et al)
- Small RCT from China (Chen et al., MedRxiv preprint)
  - N=62, all mild
  - Standard : O2, “antivirals”, “antibacterials”, IVIG +/- steroids
  - Intervention: standard + HCQ 200mg BID from days 1-5
  - CT day 1 to 5, fever, cough, progression, “adverse effects” →
  - HCQ patients sicker?, small numbers, unclear timing
- Non-randomized study from France (Gautret et al)
  - N=14 for HCQ, 6 for HCQ+Azithro
  - N=16 controls from outside institution
  - Looked at % pts with (+) PCR →
- Expert concensus in China:
  - HCQ for all patients

Characteristics	All	Control	HCQ	P value
Cases, n	62	31	31	
Age, mean (SD)	44.7 (15.3)	45.2 (14.7)	44.1 (16.1)	0.8809
Sex, n (%)				0.7991
Male	29 (46.8%)	15 (48.3%)	14 (45.2%)	
Female	33 (53.2%)	16 (51.7%)	17 (54.9%)	
Fever, day (SD)[a]	2.6 (1.0)	3.2 (1.3)	2.2 (0.4)	0.0008
Cough, day (SD)[b]	2.4 (1.1)	3.1 (1.5)	2.0 (0.2)	0.0016
Progressed to severe illness	4 (6.5 %)	4 (12.9 %)	0	
	2 (3.2 %)	0	2 (6.4 %)	

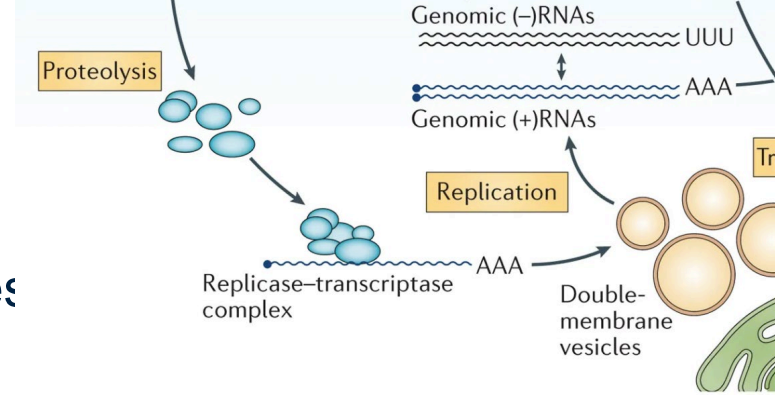


Remdesivir



- Adenosine analogue: incorporated into viral RNA
  - prevents synthesis, halts viral replication
  - Intravenous
- Activity *in vitro* against Ebola, SARS, MERS
  - *In vitro* activity against Sars-cov-2 (Wang et al)
  - Failed *in vivo* studies for Ebola
- First US case in Washington – compassionate use, recovered
- Now compassionate use is limited due to demand
- RCT's underway and actively recruiting:
  - ACTT trial(NIAID): Remdesivir (5 days) v placebo, n=440, outcome: reported severity on 8-point scale
  - Severe COVID-19 (Gilead): inpatients with sat <94% but not vented
    - standard care v 5 D v 10 D, composite outcome fever + O2 sat
  - Severe COVID-19 (Beijing, recruiting)
  - Mild/Mod COVID-19 (WuHan, recruiting)

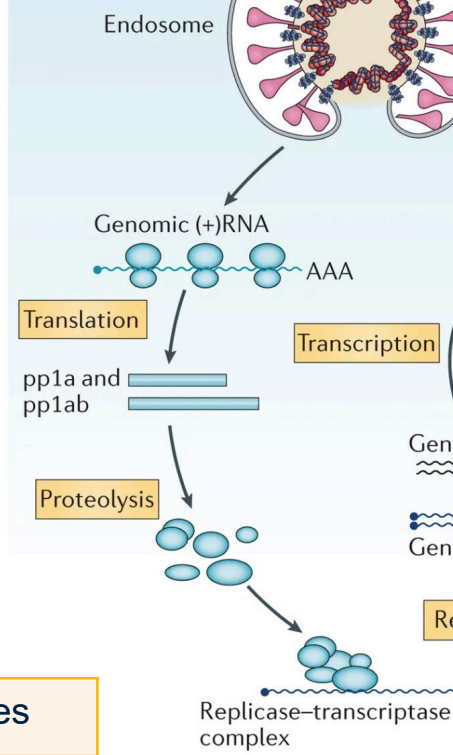
Favipiravir



- RNA polymerase inhibitor; activity *in vitro* against myriad RNA viruses
  - *In vitro* activity against Sars-cov-2 (Wang et al)
- WITHDRAWN: Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study (Cai et al, Engineering, 2020)
  - Open label non-randomized in China, n=35 versus 45 historical controls
  - Intervention: Favipiravir + inhl IFNa; Control: Lopinavir/Ritonavir + inhl IFNa
  - Primary outcome – median time to viral clearance was 5 days faster
- Favipiravir v Arbidol (Chen et al, medRx preprint)
  - Randomized, open label, superiority trial (?details)
  - N=240 (120 per group), unclear patient severity
  - Outcome: clinical recovery at day 7 (cough, fever, O2 needs): 71% v 56% recovered (cough, fever)
- RCTs underway
  - Favipiravir + Tocilizumab (China) and Favipiravir + HCQ (China)
  - Protease inhibitors/ Ostamivir/ Favipiravir/ HCQ (Thailand)

Lopinavir/Ritonavir (Kaletra)

- Lopinavir: HIV protease inhibitor, boosted by Ritonavir cyp450 interaction
- Cao et al, NEJM, 2020
  - RCT, open label
  - PNA on imaging, sat<94% or p:f<300, enrolled ~ day 13 after sympt onset
  - Given 14 days of treatment (400/100 BID) vs no treatment (no placebo pill)
- Primary outcome: clinical improvement
  - discharge or 2 point improvement in 7-point scale
- Randomization stratified by O2 need and by NEWS2 score
  - Cutoff of 5
- Randomization stratified by time from onset of symptoms
  - 12 Days



1	Outpatient, normal activities
2	Outpatient, some impairment
3	Inpatient, RA
4	Inpatient, on O2
5	Inpatient, NIV or HFNC
6	Inpatient, mech vent or ECMO
7	Death

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

Bin Cao, M.D., Yeming Wang, M.D., Danning Wen, M.D., Wen Liu, M.S., Jingli Wang, M.D., Guohui Fan, M.S., Lianguo Ruan, M.D., Bin Song, M.D., Yanping Cai, M.D., Ming Wei, M.D., Xingwang Li, M.D., Jiaan Xia, M.D., et al.

Original sample size calculated to be 160

Modified intention to treat analysis excluded the 3 patients in treatment group who died before treatment

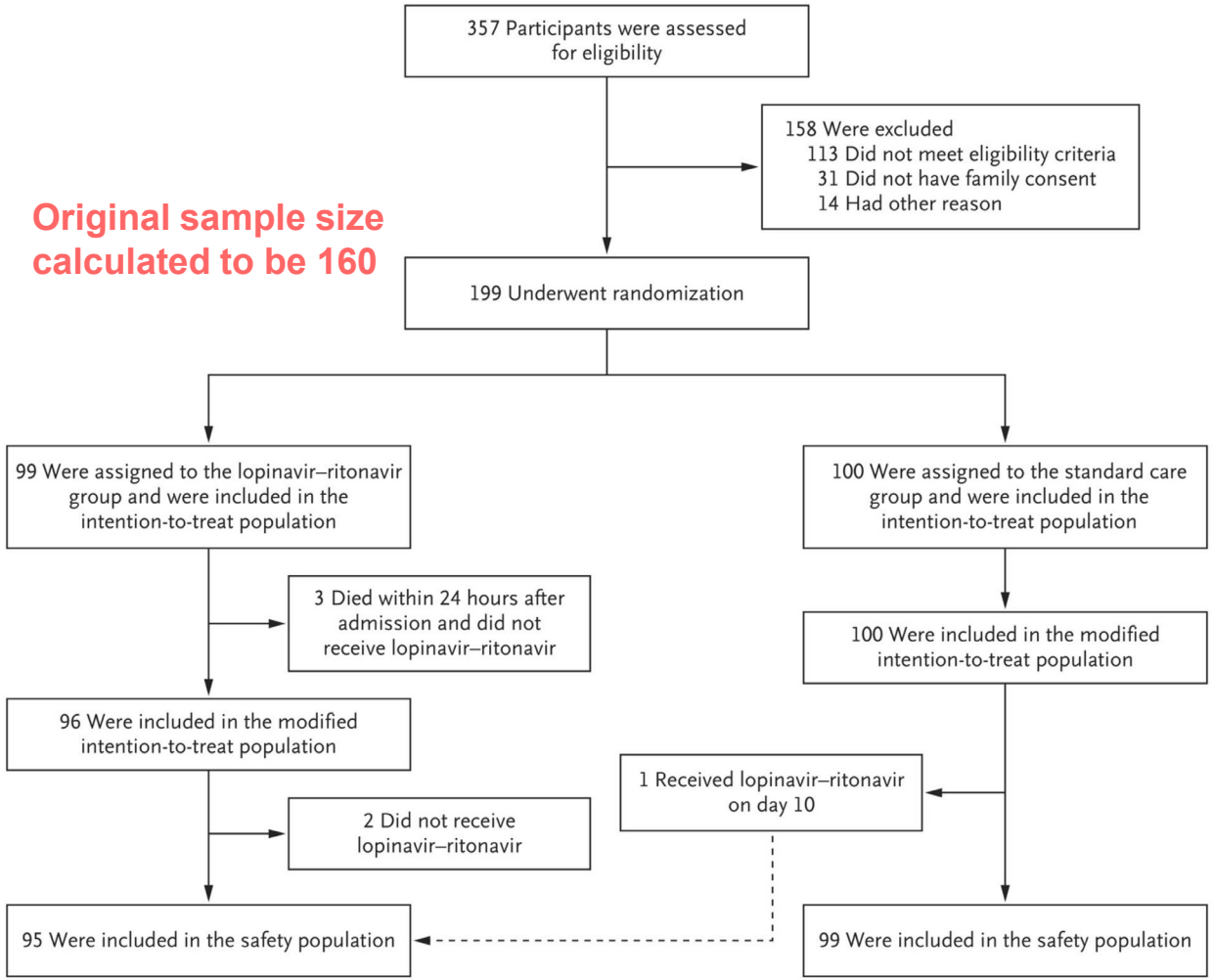


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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)
Age, median (IQR) — yr	58.0 (49.0–68.0)	58.0 (50.0–68.0)	58.0 (48.0–68.0)
Male sex — no. (%)	120 (60.3)	61 (61.6)	59 (59.0)
Coexisting conditions — no. (%)			
Diabetes	23 (11.6)	10 (10.1)	13 (13.0)
Cerebrovascular disease	13 (6.5)	5 (5.1)	8 (8.0)
Cancer	6 (3.0)	5 (5.1)	1 (1.0)
Body temperature, median (IQR) — °C	36.5 (36.4–36.8)	36.5 (36.4–37.0)	36.5 (36.5–36.8)
Fever — no. (%)	182 (91.5)	89 (89.9)	93 (93.0)
Respiratory rate >24/min — no. (%)	37 (18.8)	21 (21.6)	16 (16.0)
Systolic blood pressure <90 mm Hg — no. (%)	2 (1.0)	2 (2.0)	0
White-cell count ($\times 10^{-9}$/liter) — median (IQR)	7.0 (5.1–9.4)	7.3 (5.3–9.6)	6.9 (4.9–9.1)
4–10 $\times 10^{-9}$/liter — no. (%)	137 (70.3)	64 (67.4)	73 (73.0)
<4 $\times 10^{-9}$/liter — no. (%)	20 (10.3)	12 (12.6)	8 (8.0)
>10 $\times 10^{-9}$/liter — no. (%)	38 (19.5)	19 (20.0)	19 (19.0)
Lymphocyte count ($\times 10^{-9}$/liter) — median (IQR)	0.9 (0.6–1.2)	0.8 (0.6–1.4)	0.9 (0.5–1.2)
≥1.0 $\times 10^{-9}$/liter — no. (%)	73 (37.4)	37 (38.9)	36 (36.0)
<1.0 $\times 10^{-9}$/liter — no. (%)	122 (62.6)	58 (61.1)	64 (64.0)
Platelet count ($\times 10^{-9}$/liter) — median (IQR)	207.0 (158.0–284.0)	201.0 (155.0–287.0)	210.0 (163.0–269.5)
≥100 $\times 10^{-9}$/liter — no. (%)	186 (95.4)	91 (95.8)	95 (95.0)
<100 $\times 10^{-9}$/liter — no. (%)	9 (4.6)	4 (4.2)	5 (5.0)
Serum creatinine (μmol/liter) — median (IQR)	69.5 (57.2–82.5)	70.7 (56.4–82.7)	67.4 (58.4–82.5)
≤133 μmol/liter — no. (%)	189 (96.9)	93 (96.9)	96 (97.0)
>133 μmol/liter — no. (%)	6 (3.1)	3 (3.1)	3 (3.0)
Aspartate aminotransferase (U/liter) — median (IQR)	34.0 (26.0–45.0)	33.0 (25.0–42.0)	34.0 (27.0–45.0)
≤40 U/liter — no. (%)	155 (79.5)	78 (81.3)	77 (77.8)
>40 U/liter — no. (%)	40 (20.5)	18 (18.8)	22 (22.2)
Alanine aminotransferase (U/liter) — median (IQR)	33.0 (22.0–55.0)	33.0 (22.0–53.5)	34.0 (22.0–59.0)
≤50 U/liter — no. (%)	115 (59.0)	61 (63.5)	54 (54.5)
>50 U/liter — no. (%)	80 (41.0)	35 (36.5)	45 (45.5)
Lactate dehydrogenase (U/liter) — median (IQR)	325.0 (245.0–433.0)	322.0 (243.0–409.0)	327.0 (245.0–470.0)
≤245 U/liter — no. (%)	50 (25.8)	24 (25.3)	26 (26.3)
>245 U/liter — no. (%)	144 (74.2)	71 (74.7)	73 (73.7)
Creatine kinase (U/liter) — median (IQR)	69.0 (44.0–115.0)	57.0 (42.0–126.0)	72.0 (45.0–110.0)
≤185 U/liter — no. (%)	168 (86.6)	81 (85.3)	87 (87.9)
> 185 U/liter — no. (%)	26 (13.4)	14 (14.7)	12 (12.1)

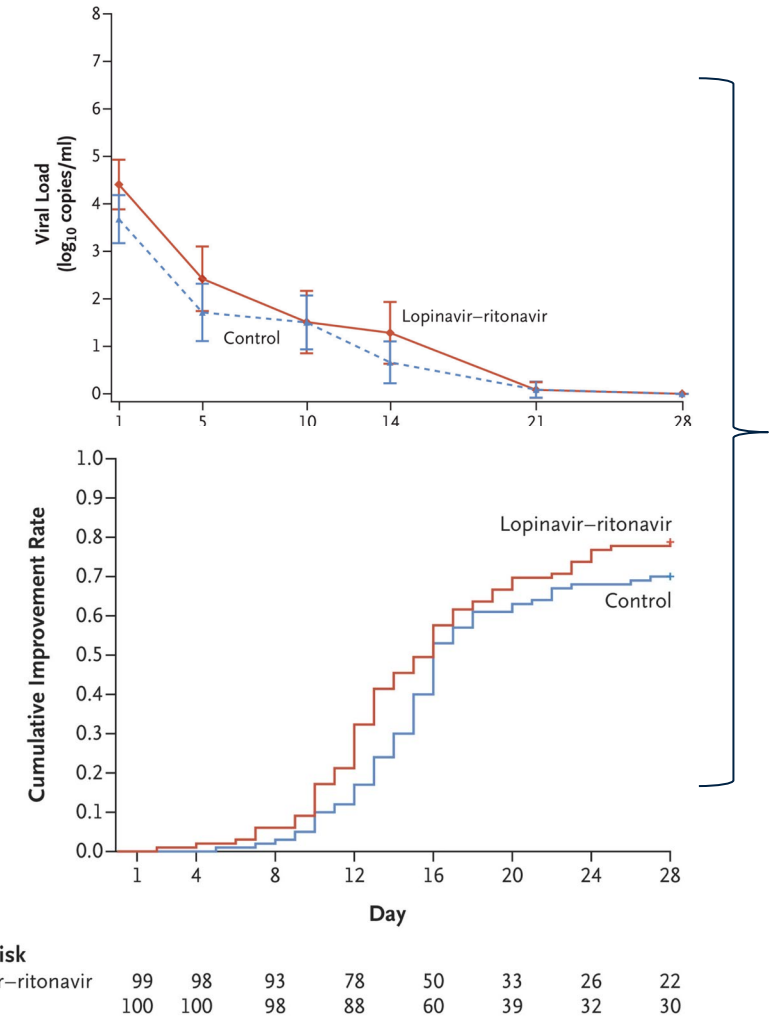
Table 2. Patients' Status and Treatments Received at or after Enrollment.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)
NEWS2 score at day 1 — median (IQR)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–7.0)
Seven-category scale at day 1			
3: Hospitalization, not requiring supplemental oxygen — no. (%)	28 (14.1)	11 (11.1)	17 (17.0)
4: Hospitalization, requiring supplemental oxygen — no. (%)	139 (69.8)	72 (72.7)	67 (67.0)
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation — no. (%)	31 (15.6)	15 (15.2)	16 (16.0)
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both — no. (%)	1 (0.5)	1 (1.0)	0
Days from illness onset to randomization — median (IQR)	13 (11–16)	13 (11–17)	13 (10–16)
Earlier (≤12 days of symptom onset) — no. (%)	90 (45.2)	42 (42.4)	48 (48.0)
Later (>12 days of symptom onset) — no. (%)	109 (54.8)	57 (57.6)	52 (52.0)
Mean viral load — $\log_{10}$ copies per ml at day 1	4.0±2.1	4.4±2.0	3.7±2.1
Using interferon at enrollment — no. (%)	22 (11.1)	9 (9.1)	13 (13.0)
Treatments during study period — no. (%)			
Vasopressors	44 (22.1)	17 (17.2)	27 (27.0)
Renal-replacement therapy	9 (4.5)	3 (3.0)	6 (6.0)
Noninvasive mechanical ventilation	29 (14.6)	10 (10.1)	19 (19.0)
Invasive mechanical ventilation	32 (16.1)	14 (14.1)	18 (18.0)
ECMO	4 (2.0)	2 (2.0)	2 (2.0)
Antibiotic agent	189 (95.0)	94 (94.9)	95 (95.0)
Glucocorticoid therapy	67 (33.7)	32 (32.3)	35 (35.0)
Days from illness onset to glucocorticoid therapy — median (IQR)	13 (11–17)	13 (12–19)	13 (9–17)
Days of glucocorticoid therapy — median (IQR)	6 (3–11)	7 (3–11)	6 (2–12)

1	Outpatient, normal activities
2	Outpatient, some impairment
3	Inpatient, RA
4	Inpatient, on O2
5	Inpatient, NIV or HFNC
6	Inpatient, mech vent or ECMO
7	Death

Table 3. Outcomes in the Intention-to-Treat Population.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)	Difference†
Time to clinical improvement — median no. of days (IQR)	16.0 (15.0 to 17.0)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)‡
Day 28 mortality — no. (%)	44 (22.1)	19 (19.2)§	25 (25.0)	−5.8 (−17.3 to 5.7)
Earlier (≤12 days after onset of symptoms)	21 (23.3)	8 (19.0)	13 (27.1)	−8.0 (−25.3 to 9.3)
Later (>12 days after onset of symptoms)	23 (21.1)	11 (19.3)	12 (23.1)	−3.8 (−19.1 to 11.6)
Clinical improvement — no. (%)				
Day 7	8 (4.0)	6 (6.1)	2 (2.0)	4.1 (−1.4 to 9.5)
Day 14	75 (37.7)	45 (45.5)	30 (30.0)	15.5 (2.2 to 28.8)
Day 28	148 (74.4)	78 (78.8)	70 (70.0)	8.8 (−3.3 to 20.9)
ICU length of stay — median no. of days (IQR)	10 (5 to 14)	6 (2 to 11)	11 (7 to 17)	−5 (−9 to 0)
Of survivors	10 (8 to 17)	9 (5 to 44)	11 (9 to 14)	−1 (−16 to 38)
Of nonsurvivors	10 (4 to 14)	6 (2 to 11)	12 (7 to 17)	−6 (−11 to 0)
Duration of invasive mechanical ventilation — median no. of days (IQR)	5 (3 to 9)	4 (3 to 7)	5 (3 to 9)	−1 (−4 to 2)
Oxygen support — days (IQR)	13 (8 to 16)	12 (9 to 16)	13 (6 to 16)	0 (−2 to 2)
Hospital stay — median no. of days (IQR)	15 (12 to 17)	14 (12 to 17)	16 (13 to 18)	1 (0 to 2)
Time from randomization to discharge — median no. of days (IQR)	13 (10 to 16)	12 (10 to 16)	14 (11 to 16)	1 (0 to 3)
Time from randomization to death — median no. of days (IQR)	10 (6 to 15)	9 (6 to 13)	12 (6 to 15)	−3 (−6 to 2)
Score on seven-category scale at day 7 — no. of patients (%)				
2: Not hospitalized, but unable to resume normal activities	4 (2.0)	4 (4.0)	0	
3: Hospitalization, not requiring supplemental oxygen	29 (14.6)	12 (12.1)	17 (17.0)	
4: Hospitalization, requiring supplemental oxygen	109 (54.8)	58 (58.6)	51 (51.0)	
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	35 (17.6)	14 (14.1)	21 (21.0)	
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	10 (5.0)	6 (6.1)	4 (4.0)	
7: Death	12 (6.0)	5 (5.1)	7 (7.0)	
Seven-category scale at day 14 — no. of patients (%)				
2: Not hospitalized, but unable to resume normal activities	71 (35.7)	43 (43.4)	28 (28.0)	
3: Hospitalization, not requiring supplemental oxygen	32 (16.1)	8 (8.1)	24 (24.0)	
4: Hospitalization, requiring supplemental oxygen	45 (22.6)	25 (25.3)	20 (20.0)	
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	11 (5.5)	5 (5.1)	6 (6.0)	
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	8 (4.0)	3 (3.0)	5 (5.0)	
7: Death	32 (16.1)	15 (15.2)	17 (17.0)	



No significant differences

However:

- Trend toward lower mortality
- Reduced ICU length of stay
- In the Modified intention to treat group (leaving out 3 initial deaths), there was a significant 1 day reduction in median time to improvement (15D versus 16D)

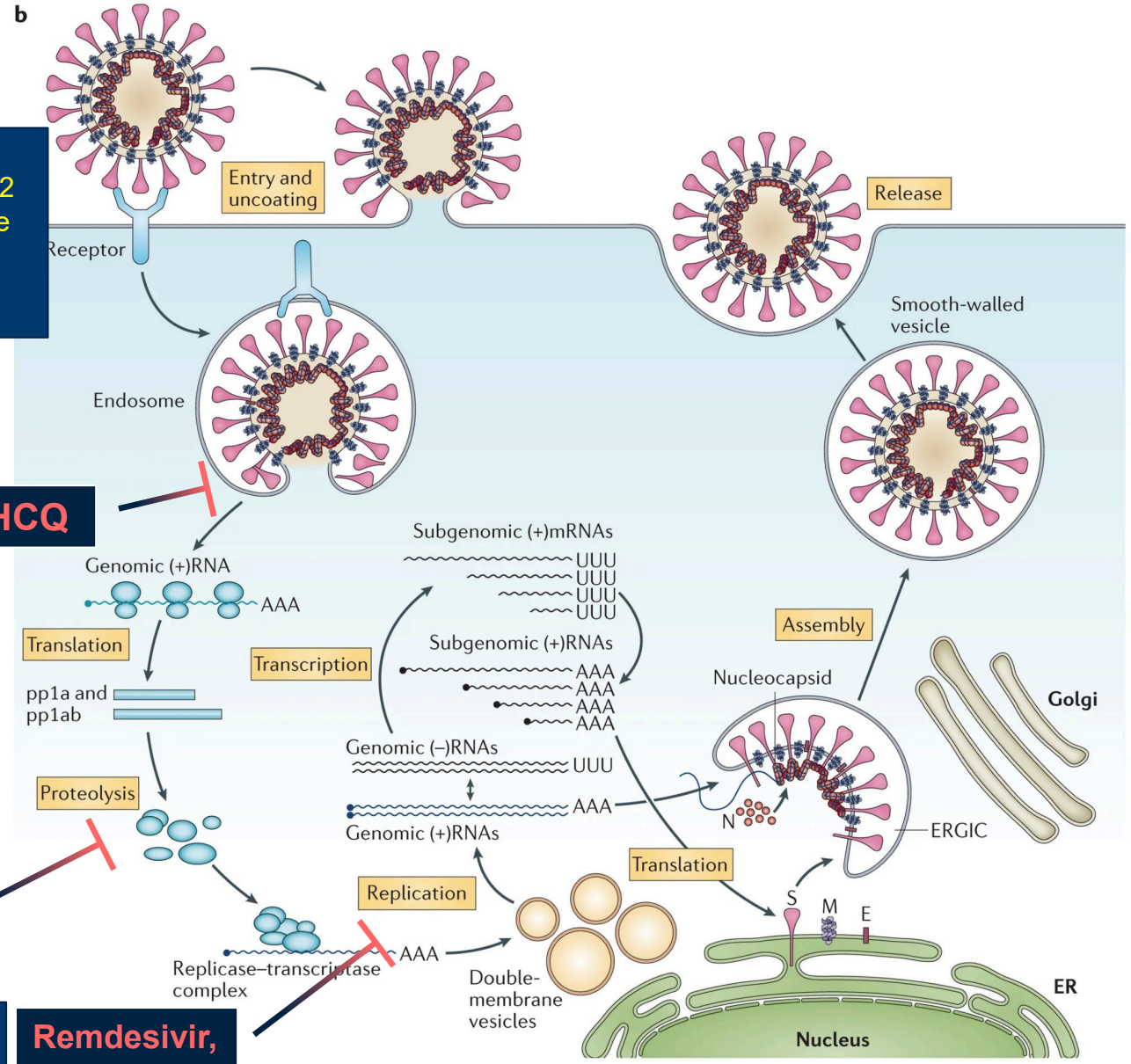
Table 4. Summary of Adverse Events in the Safety Population.*

Event	Lopinavir–Ritonavir (N=95)		Standard Care (N=99)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Any adverse event	46 (48.4)	20 (21.1)	49 (49.5)	11 (11.1)
Lymphopenia	16 (16.8)	12 (12.6)	12 (12.1)	5 (5.1)
Nausea	9 (9.5)	1 (1.1)	0	0
Thrombocytopenia	6 (6.3)	1 (1.1)	10 (10.1)	2 (2.0)
Leukopenia	7 (7.4)	1 (1.1)	13 (13.1)	0
Vomiting	6 (6.3)	0	0	0
Increased aspartate aminotransferase	2 (2.1)	2 (2.1)	5 (5.1)	4 (4.0)
Abdominal discomfort	4 (4.2)	0	2 (2.1)	0
Diarrhea	4 (4.2)	0	0	0
Stomach ache	4 (4.2)	1 (1.1)	1 (1.0)	0
Neutropenia	4 (4.2)	1 (1.1)	8 (7.6)	0
Increased total bilirubin	3 (3.2)	3 (3.2)	3 (3.0)	2 (2.0)
Increased creatinine	2 (2.1)	2 (2.1)	7 (7.1)	6 (6.1)
Anemia	2 (2.1)	2 (2.1)	5 (5.0)	4 (4.0)
Rash	2 (2.1)	0	0	0
Hypoalbuminemia	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased alanine aminotransferase	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased creatine kinase	0	0	1 (1.0)	0
Decreased appetite	2 (2.1)	0	0	0
Prolonged QT interval	1 (1.1)	0	0	0
Sleep disorders and disturbances	1 (1.1)	0	0	0
Facial flushing	1 (1.1)	0	0	0
Serious adverse event	19 (20.0)	17 (17.9)	32 (32.3)	31 (31.3)
Respiratory failure or ARDS	12 (12.6)	12 (12.6)	27 (27.3)	27 (27.3)
Acute kidney injury	3 (3.2)	2 (2.1)	6 (6.1)	5 (5.1)
Secondary infection	1 (1.1)	1 (1.1)	6 (6.1)	6 (6.1)
Shock	2 (2.1)	2 (2.1)	2 (2.0)	2 (2.0)
Severe anemia	3 (3.2)	3 (3.2)	0	0
Acute gastritis	2 (2.1)	0	0	0
Hemorrhage of lower digestive tract	2 (2.1)	1 (1.1)	0	0
Pneumothorax	0	0	2 (2.0)	2 (2.0)
Unconsciousness	1 (1.1)	0	0	0
Disseminated intravascular coagulation	1 (1.1)	0	1 (1.0)	1 (1.0)
Sepsis	0	0	1 (1.0)	1 (1.0)
Acute heart failure	0	0	1 (1.0)	1 (1.0)

- Other points:
  - Open label
  - Late enrollment
  - Likely underpowered (large confidence intervals)
  - Sub group started treatment before day 12 → trend toward faster improvement
  - Fewer ICU days (6 v 11)
  - Mortality trend
  - Perhaps “serious adverse events” of respiratory failure/ ARDS are actually the better outcomes to look at in subsequent trial
  - GI side effects

- “negative trial” but wouldn’t rule out additional investigation of Lopinavir/Ritonavir

- **Meplazumab**
- Recombinant ACE2
- Camostat mesylate
- **Baricitinib**
- Griffithsin



- Arbidol

HCQ

Lopinavir

- Ribavirin
- Galidesivir

Remdesivir, Favipiravir

Anti-virals discussed in detail

Additional "anti-viral" treatments in progress:

- **Baricitinib** – JAK inhibitor, inhibitis ACE2-mediated endocytosis
- **Meplazumab** – anti-CD147 mAb that competes with S protein – MedRxiv preprint

Additional experimental treatments not covered here:

- **Azithromycin**
- **IL6 inhibitors**
- **Convalescent Plasma**

Penn Guidance (3-26-2020)

- http://www.uphs.upenn.edu/antibiotics/COVID19.html
- An Infectious Diseases consultation is recommended for patients admitted to the hospital with SARS-CoV-2 (COVID-19) infection. **All therapies below require approval by an Infectious Diseases physician, but a one-time STAT dose may be given in situations pending infectious diseases evaluation.**
- The dose of **hydroxychloroquine** should be 400 mg Q12H for 1 day followed by 400 mg daily for 4 more days for a total duration of 5 days
- **Remdesivir** can now be considered for treatment of SARS-CoV-2 in pregnancy [the only current compassionate use indication]
- Despite reports of efficacy of azithromycin plus hydroxychloroquine to treat SARS-CoV-2, azithromycin should not be added to hydroxychloroquine only to treat SARS-CoV-2

Clinical Trials at Penn:

- **Remdesevir**:
- NIH: drug v placebo trial ongoing
  - BillShort, Pablow Tebas
  - 14 participants thus far
- Gilead: two trials ongoing
  - Kathleen Degnan, Ian Frank
- **Hydroxychloroquine**:
- Two trials still in planning stages
  - Ravi Amaravadi
  - high v low dose
  - drug v placebo for patients at home

- Wit et al., Nature Reviews Microbiology, 2016 (SARS, MERS)
- Zumla et al., Nature Reviews Drug Discovery, 2016 (SARS, MERS)
- Yang and Wang, Nature Cellular & Molecular Immunology, 2020 (COVID-19)
- Liu et al., Nature Cell Discovery, 2020 (Chloroquine vs Hydroxychloroquine in vitro)
- Wang et al., Nature Cell Research, 2020 (Chloroquine and Remdesivir in vitro)
- McChesney, The American J of Medicine, 1983 (Hydroxychloroquine v Chloroquine)
- Chen et al., MedRxiv preprint, 2020 (Hydroxychloroquine n=62 RCT from China)
- Gautret et al., Int J Antimicrobial Agents, in press, 2020 (HCQ, Azithro from France)
- Cai et al, Engineering, 2020 (WITHDRAWN; Favipiravir)
- Chen et al, medRxiv preprint, 2020 (Favipiravir v Aribdol)
- Cao et al, NEJM, 2020 (RCT Lopinavir/Ritonavir)

Penn Medicine

ARDS Management with COVID-19

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April 2, 2020

Objectives

- Review clinical features of ARDS with COVID-19
- Discuss ventilator management strategies
- Discuss adjunctive therapies for ARDS management
- Introduce helmet ventilation (Maurizio Cereda)
- Highlight UPHS strategies to support best practices

- I am NOT going to review
  - Algorithm to escalate respiratory support
  - Best practices for intubation

Disclaimers and acknowledgements

- This talk is meant to be a pragmatic guide
  - But there are a lot of unknowns….

- Recommendations formulated with input from many local experts
  - Nuala Meyer
  - Nilam Mangalmurti
  - John Reilly
  - Barry Fuchs
  - Maurizio Cereda

Clinical features of ARDS with COVID-19

- Severe hypoxia
- Diffuse ground-glass opacities
- Initial high lung compliance?
- Prolonged course of respiratory failure

- Early Seattle experience (n=18)
  - Median duration of MV 10 days (11 days among survivors)
  - Median ICU stay 14 days

Characteristics of mechanical ventilation	
Moderate or thick and purulent secretions — no./total no. (%)†	14/18 (77)
Day 1 median values	
Plateau pressure (IQR) — cm of water‡	25 (20–28)
Driving pressure (IQR) — cm of water‡	13 (11–17)
Highest F_{IO_2} — median (IQR)	0.9 (0.7–1.0)
Compliance (IQR) — ml/cm of water§	29 (25–36)
Day 2 median values	
Plateau pressure (IQR) — cm of water‡	24 (21–29)
Driving pressure (IQR) — cm of water‡	13 (12–17)
Highest F_{IO_2} — median (IQR)	0.7 (0.5–0.8)
Compliance (IQR) — ml/cm of water¶	26 (20–35)
Day 3 median values	
Plateau pressure (IQR) — cm of water‡	22 (19–28)
Driving pressure (IQR) — cm of water‡	12 (10–14)
Highest F_{IO_2} (IQR) — median (IQR)	0.6 (0.5–0.7)
Compliance (IQR) — ml/cm of water¶	37 (25–42)

Bhatraju PK et al. 2020 NEJM

An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome

Eddy Fan, Lorenzo Del Sorbo, Ewan C. Goligher, Carol L. Hodgson, Laveena Munshi, Allan J. Walkey, Neill K. J. Adhikari, Marcelo B. P. Amato, Richard Branson, Roy G. Brower, Niall D. Ferguson, Ognjen Gajic, Luciano Gattinoni, Dean Hess, Jordi Mancebo, Maureen O. Meade, Daniel F. McAuley, Antonio Pesenti, V. Marco Ranieri, Gordon D. Rubenfeld, Eileen Rubin, Maureen Seckel, Arthur S. Slutsky, Daniel Talmor, B. Taylor Thompson, Hannah Wunsch, Elizabeth Uleryk, Jan Brozek, and Laurent J. Brochard; on behalf of the American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS), EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE (ESICM), AND SOCIETY OF CRITICAL CARE MEDICINE (SCCM) WAS APPROVED BY THE ATS, ESICM, AND SCCM, MARCH 2017

AJRCCM. 2017;195(9):1253-63

- Strongly recommended:
  - Low tidal volumes
  - Limit inspiratory pressures
  - Prone positioning for severe ARDS
  - Do not use HFOV
- Conditionally recommend
  - Higher PEEP in moderate or severe ARDS
  - Recruitment maneuvers in moderate or severe ARDS
- No recommendation re: ECLS

Fan E et al. AJRCCM 2017

COVID-19 ARDS: Recommend adherence to ARMA protocol

- Ventilator mode: AC/VC
- Target tidal volume: 6 cc/kilogram predicted body weight
- Target P_{plat}: 30
- Permissive hypercapnia: pH $\geq$7.20 if needed to maintain above settings

ARDSNet. NEJM 2000

Caveat: Optimal PEEP is unclear

- Rationale for use of PEEP in ARDS
  - Alveolar recruitment (usually in setting of low compliance)
  - Prevent atelectrauma
  - Reduce lung stress and strain
  - Facilitates weaning of FiO_2
- Potential risks of PEEP
  - Overdistension causing lung injury
  - Increased intrapulmonary shunt
  - Increased dead space
  - Higher pulmonary vascular resistance

ARDSnet tables for PEEP titration

- PEEP table used in ARMA trial

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

- ARDSnet High PEEP table

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

http://www.ardsnet.org/tools.shtml

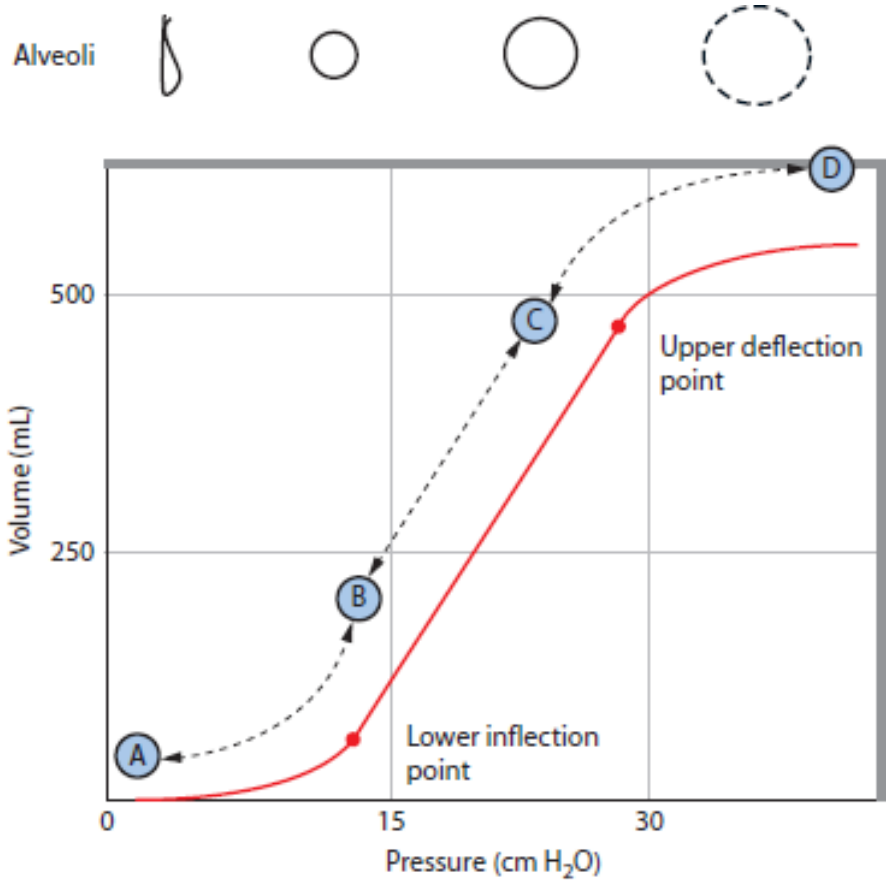
Early experience at Penn

- Many patients have improved hypoxia with higher PEEP
- Improved oxygenation may reflect vascular redistribution
- Monitor both oxygenation and driving pressure closely with PEEP titration

Pressures

Driving pressure: ΔP = Pplat - PEEP

Consider selecting PEEP based on optimal driving pressure



Source: Jesse B. Hall, Gregory A. Schmidt, John P. Kress: *Principles of Critical Care*, 4th Edition: www.accessmedicine.com

- Compliance = slope of the curve

$$C_{stat} = \Delta V / \Delta P$$

- Low compliance (high driving pressure) with atelectasis and overdistension
- **SUGGEST: Start PEEP around 10, titrate to optimize driving pressure**

Amato MBP. NEJM 2015 – vent changes resulting in lower ΔP associated with lower mortality

Monitor for potential consequences of ventilation strategy

- Barotrauma with higher PEEP

- Acidemia with low tidal volumes
  - Increase respiratory rate to compensate for low tidal volumes
  - Tolerate pH as low as 7.20

- Breath stacking with high rates to achieve required minute ventilation
  - Reduce rate if able, allowing for permissive hypercapnia
  - Reduce inspiratory time (or increase flow) to extend expiratory time – this will increase peak pressure but NOT plateau pressure

Adjunctive therapies

- Sedation and neuromuscular blockade
- Inhaled vasodilators
- Prone positioning
- Extracorporeal life support

Sedation and Neuromuscular Blockade

- Consider deep sedation early if FiO2 > 50%
  - Goal RASS -4 to -5, synchrony with ventilator, using fentanyl plus sedative

- Consider neuromuscular blockade if P:F ratio <100 on FiO2 ≥70% or higher
  - Consider bolus dosing rather than continuous infusion
  - Not mandatory even with prone positioning
  - However – if P:F ratio improves with NMB, may consider deferring proning

- *Concerns about medication shortages - sedation and NMB protocol forthcoming*

Inhaled vasodilators

- Inhaled nitric oxide (iNO) preferred over inhaled prostacyclin
  - iNO is not aerosol generating
  - Flolan can cause clogging of filters in ventilator circuit

- Consider if P:F ratio < 100 despite PEEP > 15, FiO2 > 85% and on NMB
  - Modest increase in risk for AKI
  - Some have postulated antiviral effect – unproven
  - If benefit not observed, recommend titrating off

Prone Positioning

- PROSEVA trial: Mortality benefit with daily proning for ~16h per day among patients with ARDS with P:F ratio < 150
  - HUP MICU guidelines for ARDS in general are to prone if P:F<150 despite FiO2 60% and optimized PEEP

- Limitations/consideration
  - Resource/staff intensive → PPE intensive

- Consider lengthening initial prone to > 24 hours if:
  - FiO2 > 70% despite prone
  - P:F ratio < 120 on 60% or higher (~PaO2 73)

Consider deferring prone positioning if:

- High suspicion cardiomyopathy
  - Troponin rising significantly
  - Adding epinephrine or other inotrope
  - Planning formal echo that day
- Escalating pressor requirements: norepi > 15 plus vasopressin
- Super Obesity with BMI > 50 or habitus: unable to stabilize chest with large belly
- Concern for intra-abdominal pathology
  - Colitis, tense abdomen, bladder pressure > 22 cm and low UOP

ECLS

- Criteria for consideration of VV ECMO for respiratory failure:
  - PaO2 < 80 on FIO2 100% despite proning, hemodynamic instability X 12 hours
  - Age < 65
  - BMI < 45
  - Smoking hx < 30 ppy
- Call CT surgery early
- Current plan at HUP is to administer ECMO in patient's home unit, rather than transfer to CT-SICU

Titrating Off Therapy: iNO, NMB, Sedation, Prone

- Suggest order of de-escalation
  1. iNO – titrate off when FiO2 60-70%
  2. NMB – consider interrupting while proned
  3. Sedation – consider liberalizing to RASS -2
  4. Prone positioning – may find that patients meet PROSEVA criteria for proning for longer than usual (several days?) – consider risks/costs of proning daily

Extubation considerations

- High rates of failed extubations
  - Consider more challenging SBTs?
    - PS 5 with PEEP 3 at 40% for at least 1 hour?
- Hypoxia seems to drive reintubation
- Consider extubation to helmet ventilation

Tracheostomy for patients with COVID-19

- UPHS guidelines created by multidisciplinary team (I-Pulm, surgery, ENT, anesthesia)

- Key points:
  - Consider at **21 days** of mechanical ventilation
    - Among patients without other significant co-morbidities
    - Consider earlier for pulmonary toilet or high sedation needs
  - Open surgical approach, bedside in negative pressure room
  - **Multidisciplinary decision**: primary team, surgical team, palliative care, and family
  - Direct consults to Dr. Benjamin Braslow at HUP, Dr. James Kearney at PAH, and Dr. Sean Harbison at PPMC

Helmet ventilation

- Non-invasive ventilation administered by helmet compared to face mask resulted in lower risk of intubation for patients with ARDS
  - Transparent helmet with rubber seal at the neck
  - Being used with success in Italy

- Advantages of helmet ventilation
  - Non-invasive positive-pressure ventilation
  - Less aerosolization
  - May eliminate need for intubation among some patients

Patel B et al 2016 JAMA

HEPA Filters

Fresh Gas

PEEP Valve

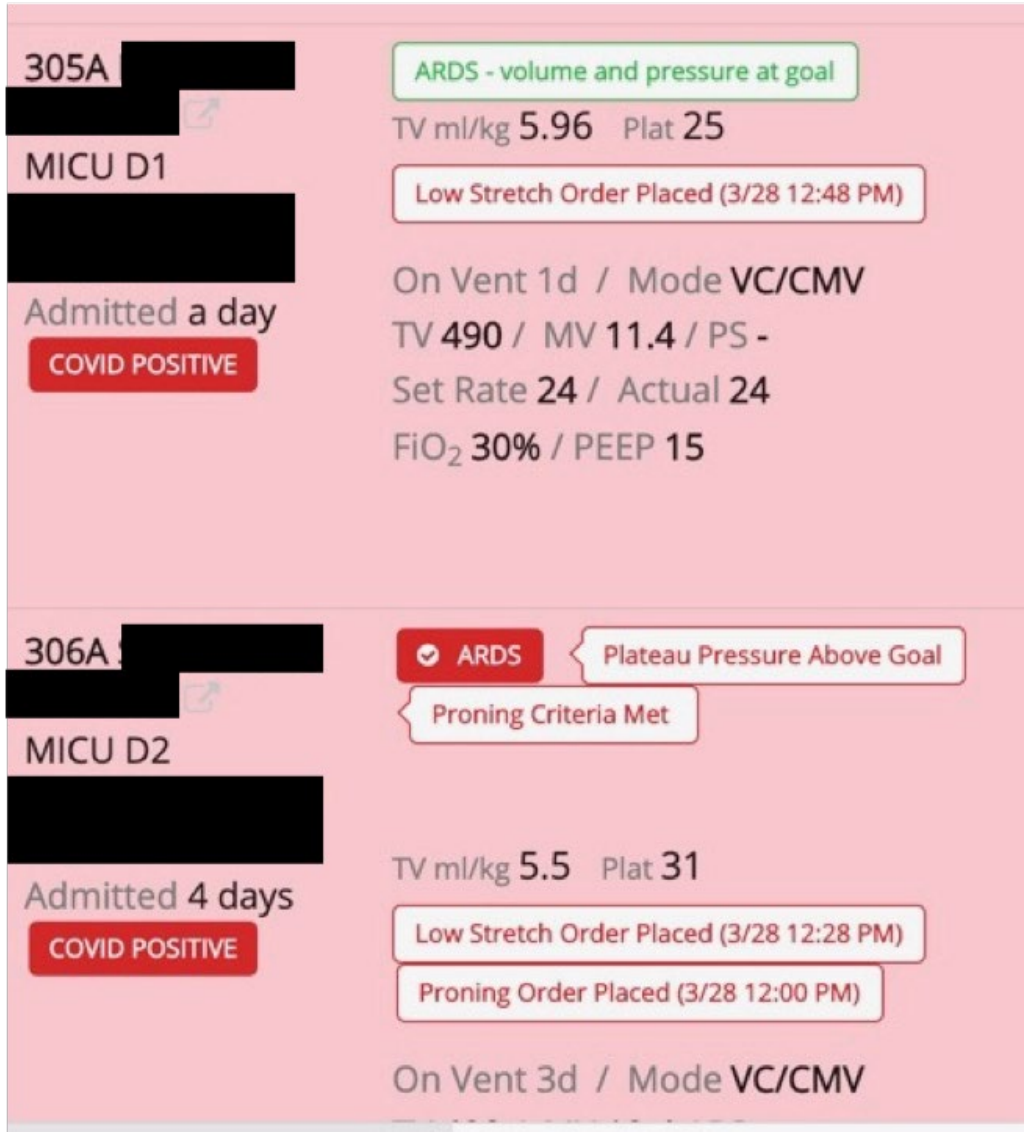
UPHS educational video
(log into VPN first; also found on UPHS COVID-19 site)

UPHS and PennChart support for ARDS management

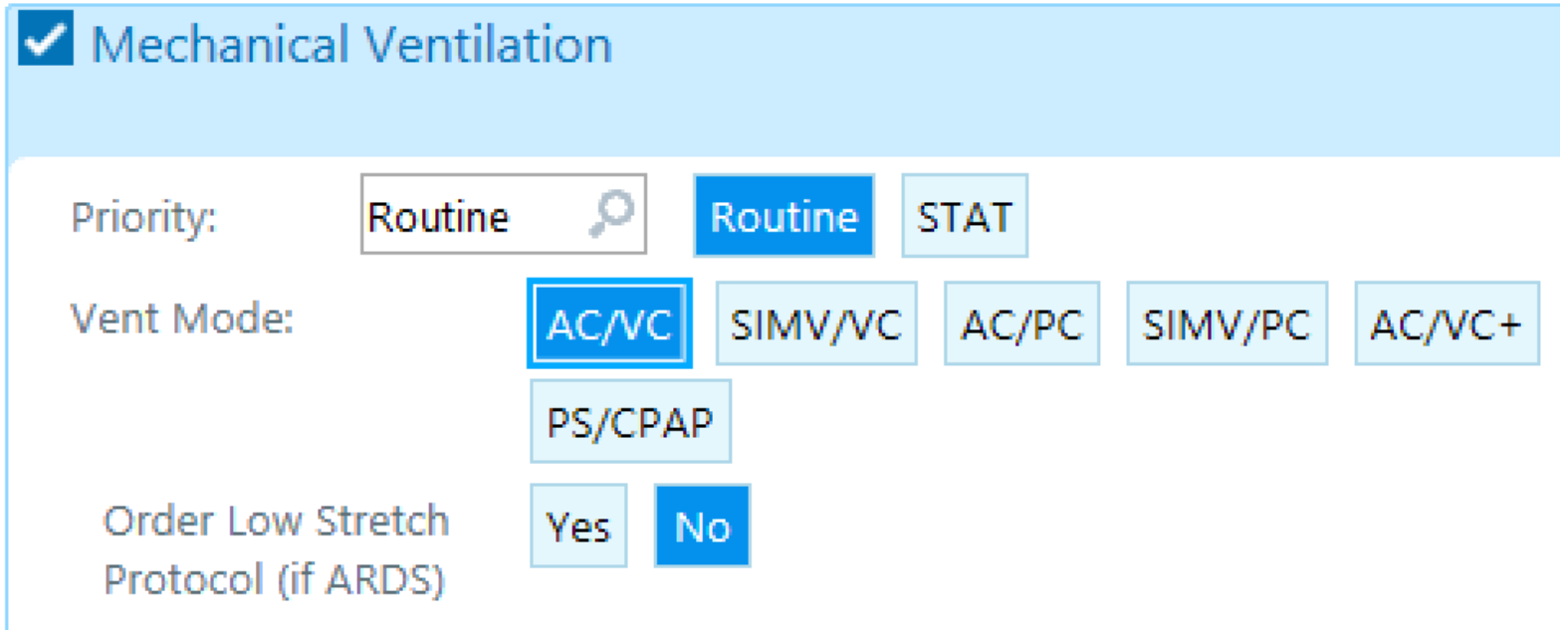
- Penn Elert
- COVID-19 Consult Team (HUP)
- ICU board with ARDS alerts
- Low stretch protocol embedded within MV order
- Proning order and flowsheet

ICU Board

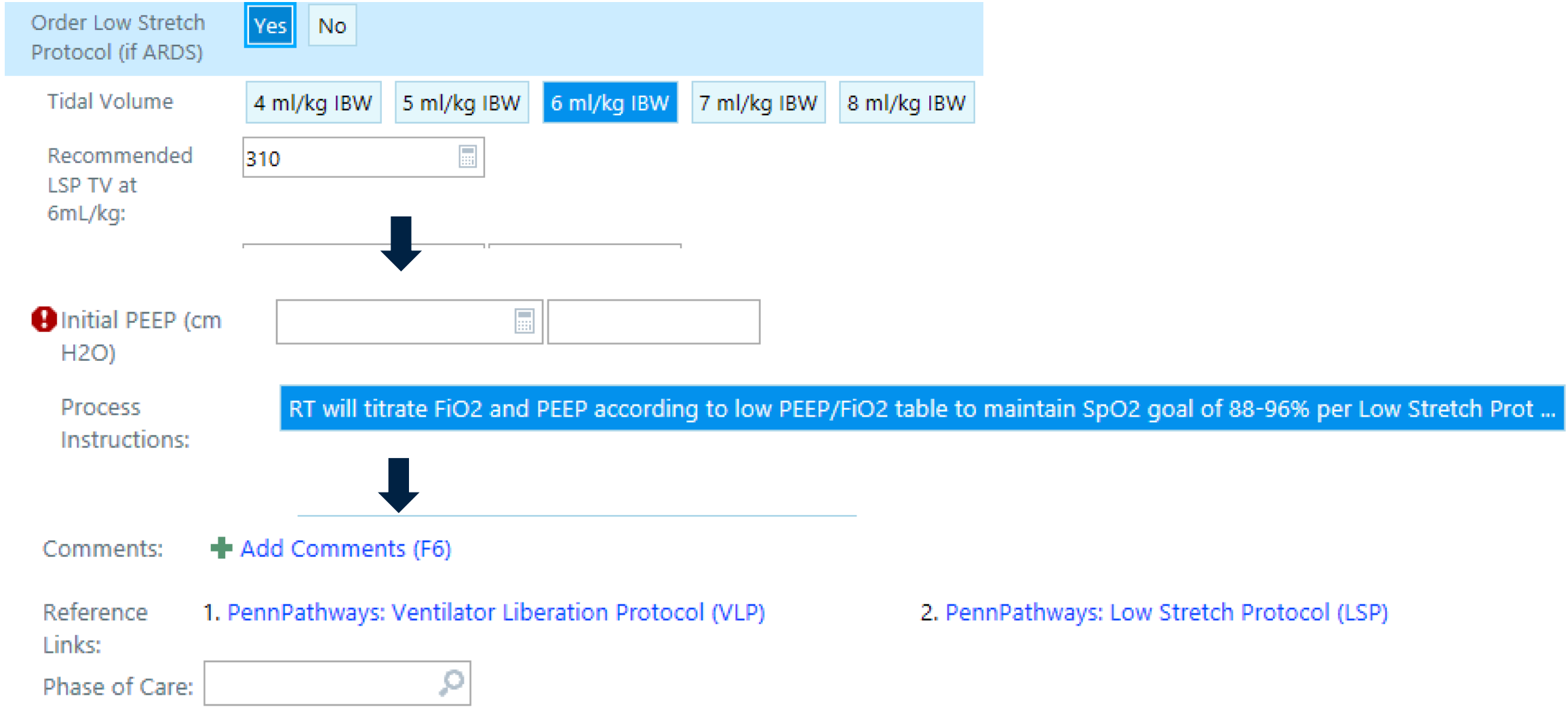
- Accessible for all ICUs via UPHS Intranet



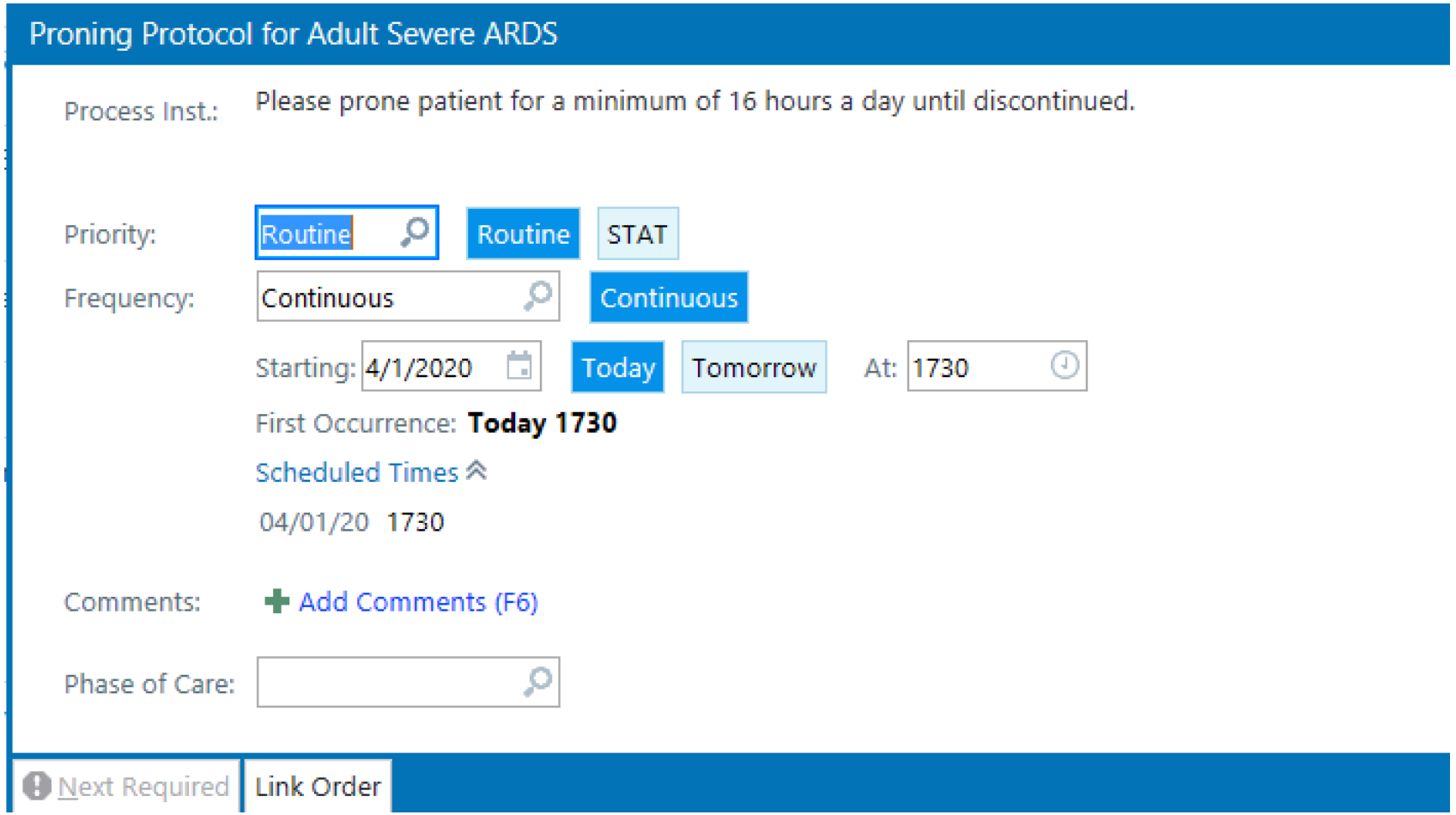
Low stretch protocol



Low stretch protocol



Proning protocol order



A few more references

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  - Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Critical Care Medicine* 2020 (e-pub).
- **Retrospective cohort of critically ill COVID 19 patients**
  - Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*. 2020 (e-pub).

Thank you!

- Questions?

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