UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

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Breathing HazARDS: A Comprehensive Review of Acute Respiratory Distress Syndrome

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Disclosure

- Financial Conflicts of Interest
  - The presenter, Colton P. Radford, PharmD, has no financial conflicts of interest to disclose
  - The project mentor, Brianne Wolfe, PharmD, BCPS, BCCCP, has no financial conflicts of interest to disclose
- Off-Label Uses of Medications
  - There will be no off-label uses of medications discussed

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Pharmacist Learning Objectives

At the conclusion of this activity, *pharmacists* should be able to successfully:

- Discuss basic acute respiratory distress syndrome (ARDS) pathophysiology
- Recognize underlying risk factors of ARDS development
- Identify non-pharmacological therapies for ARDS management
- Evaluate the risks and benefits of pharmacological treatment strategies (sedation, paralysis, glucocorticoids, etc.) for ARDS
- Develop a patient-specific pharmacological regimen for the management of a patient with ARDS

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Technician Learning Objectives

At the conclusion of this activity, *technicians* should be able to successfully:

- Define ARDS
- Identify risk factors for developing ARDS
- Distinguish medications which may be utilized in the treatment of ARDS

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Abbreviations

- AC/VC – Assist control/volume control
- AECC – American-European Consensus Conference
- ARDS – Acute respiratory distress syndrome
- BMI – Body mass index
- CPAP – Continuous positive airway pressure
- CVP – Central venous pressure
- CXR – Chest x-ray
- ESICM – European Society of Intensive Care Medicine
- FiO_2 – Fraction of inspired oxygen
- HFNC – High-flow nasal cannula
- IBW – Ideal body weight
- ICU – Intensive care unit
- ICUAW – ICU-associated weakness
- IVP – Intravenous push
- LIS – Lung injury score

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Abbreviations

- MICU – Medical intensive care unit
- NC – Nasal cannula
- NMBAs – Neuromuscular blocking agents
- PaO_2 – Partial pressure of arterial oxygen
- PEEP – Positive end expiratory pressure
- PIP – Peak inspiratory pressure
- Pplateau – Pressure plateau
- PTSD – Post-traumatic stress disorder
- QOL – Quality of life
- SCCM - Society of Critical Care Medicine
- SpO_2 – Oxygen saturation
- SSC – Surviving Sepsis Campaign
- TOF – Train of four
- TV – Tidal volume

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History and Background

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History

- The term ARDS was first coined in 1967
- Case series of 12 ICU patients
  - Syndrome that manifested with acute onset of:
    - Tachypnea, hypoxemia, loss of pulmonary compliance
  - Based upon five key clinical features:

1. Severe dyspnea
2. Tachypnea
3. Refractory cyanosis
4. Reduced lung compliance
5. CXR with diffuse infiltrates

Ashbaugh et al. *The Lancet*. 1967 Aug 12; 290(7511): P319-323.
Imagine available at: https://commons.wikimedia.org/wiki/File:ARDSSevere.png

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History

- In 1988, the LIS was developed to expand upon the definition of ARDS
  - Based upon four key clinical features:

1. Pulmonary consolidations seen on CXR
2. Lung compliance
3. $PaO_2:FiO_2$ ratio
4. PEEP

LIS (0-16)
- 0 = no injury
- 1-2.5 = mild to moderate injury
- >2.5 = severe injury

Murray et al. *Am Rev Respir Dis*. 1988; 138(3):720-723.

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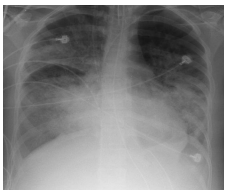
History

- The first globally accepted definition was declared by the AECC in 1994



1. Acute onset of respiratory failure
2. CXR with bilateral pulmonary infiltrates
3. Hypoxemia ($PaO_2:FiO_2$ ratio $\leq$ 200 mmHg)
4. No evidence of cardiogenic edema

Bernard et al. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824.
Image available at: Image: https://commons.wikimedia.org/wiki/File:ARDS_X-Ray.jpg

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Berlin Definition

Timing
- Onset within 1 week of known clinical insult or new/worsening respiratory symptoms

Chest Imaging
- Bilateral pulmonary opacities

Origin of Edema
- Not fully explained by cardiac failure or fluid overload

Oxygenation
- Mild: $PaO_2:FiO_2$ ratio 200 to ≤ 300 mmHg with PEEP or CPAP ≥ 5 cm H_2O
- Moderate: $PaO_2:FiO_2$ ratio <100 to ≤ 200 mmHg with PEEP ≥ 5 cm H_2O
- Severe: $PaO_2:FiO_2$ ratio ≤ 100 mmHg with PEEP ≥ 5 cm H_2O

Ranieri et al. JAMA. 2012;307(23):2526-2533.

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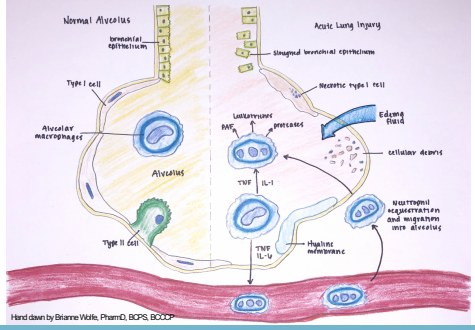

Hand drawn by Brianne Wolfe, PharmD, BCPS, BCCCP

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Pharmacist Question 1

(True or False) ARDS pathophysiology can be described as “capillary damage resulting in alveolar space fluid collection, pro-inflammatory cytokine release, and neutrophil attraction that impairs oxygenation”.

1. True
2. False

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Technician Question 1

(True or False) ARDS can be easily described as “the rapid accumulation of fluid in the lungs that can occur from many causes”.

1. True
2. False

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ARDS Etiology

- Pulmonary ARDS
  - Direct lung insult due to local inflammation
- Extrapulmonary ARDS
  - Indirect lung injury due to systemic inflammation

Pulmonary ARDS	Extrapulmonary ARDS
• Aspiration	• Sepsis
• Pneumonia	• Shock
• Toxin inhalation	• Pancreatitis
• Drowning	• Trauma
• Lung contusion/trauma	• Blood transfusions
• Fat embolism	• Drug-induced
• Pulmonary vasculitis	• Burns

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Rezoagli et al. *Ann Transl Med.* 2017;5(14):282.
Bellani et al. *JAMA.* 2016;315(8):788-800.

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COVID-19

- Coronavirus, SARS-CoV-2 (COVID-19) was first identified in Wuhan, China in December 2019

Worldwide (as of 10/22/2020)
- More than 41.4 million cases and 1.1 million deaths have been reported worldwide

United States (as of 10/22/2020)
- Over 8.3 million reported cases in the United States and roughly 221,000 deaths

Utah (as of 10/22/2020)
- Confirmed cases: 98,006
- Total hospitalizations: 4,807
- Total deaths: 557

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CDC – CDC COVID Data Tracker. Accessed October 22, 2020.

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COVID-19 ARDS

Comorbidities and Risk of COVID-19 Hospitalization

1.5x	3x	4x	4.5x	5x
•Asthma	•Hypertension •BMI ≥ 30 •Diabetes	•Chronic kidney disease	•BMI ≥ 40 •2 conditions	•≥3 conditions

Risk of COVID-19 Hospitalization and Death by Age

Age 18-29	Age 40-49	Age 50-64	Age 65-74	Age 85+
Comparison Group	•Hospitalization: 3x •Death: 10x	•Hospitalization: 4x •Death: 30x	•Hospitalization: 5x •Death: 90x	•Hospitalization: 13x •Death: 630x

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CDC – COVID-19 Associated Hospitalization Related to Underlying Medical Conditions. Accessed September 9, 2020.
CDC – COVID-19 Associated Hospitalization and Death by Age. Assessed September 9, 2020.

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Pharmacist Question 2

A 46 year old female presents to the emergency department with respiratory distress. Which of the following disease states would contribute to her development of ARDS? (select all that apply)

1. Pneumonia
2. SARS-CoV2
3. Gout
4. Pancreatitis
5. Cellulitis

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Technician Question 2

In 2020, which of the following risk factors has resulted in a significant increase in ARDS cases worldwide?

1. H1N1
2. SARS-CoV1
3. H5N1
4. SARS-CoV2

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ARDS Epidemiology

- ARDS is an underestimated syndrome
  - Many studies have attempted to determine the incidence of ARDS
  - Huge variability in reported incidence
    - United States: 38.9 to 82.4 cases per 100,000 people
- LUNG-SAFE Trial (2016)
  - 459 ICUs (50 countries, 5 continents) over a 4 consecutive week period in winter 2014
  - 2012 Berlin Definition
  - Incidence: 10.4% of ICU admissions per year (5.5 cases per ICU bed per year)

ARDS Reported Incidence by Continent	
South America	10.1 cases*
Europe	17.9 cases*
Australia	34 cases*
North America	78.9 cases*

*per 100,000 people

Incidence of COVID-19 ARDS
14.8%

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Rezoagli et al. *Ann Transl Med.* 2017;5(14):282.
Bellani et al. *JAMA.* 2016;315(8):788-800.
Sun et al. *J Med Vent.* 2020;92(6):612-617.

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ARDS Morbidity

- Despite improving mortality, long-term ARDS survivors have been shown to suffer from significant long-term complications and reduced QOL
  - Physical (ICUAW)
    - Muscle weakness, wasting, and nerve injury/damage starts within the first few days of critical illness
  - Neuropsychological (PTSD)
- Hodgson et al.
  - Mechanically ventilated for >24 hours
  - Found that 52% of ICU survivors have had ICUAW
  - ICUAW development was associated with higher 90-day mortality

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Hodgson et al. *Crit Care.* 2015;19(1):81.

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ARDS Morbidity

Herridge et al 2003	Herridge et al 2011
Mortality • 1-year = 11% (12/109)	**Mortality** • 2-years = 12.8% (14/109) • 3-years = 14.7% (16/109) • 4-years = 16.5% (18/109) • 5-years = 19.3% (21/109)
Returned to Work • 3-months = 15.7% (13/83) • 6-months = 31.7% (26/82) • 12-months = 48.2% (40/82)	**Returned to Work** • 2-years = 48.2% (40/82) • 3-years = 70.4% (50/71) • 4-years = 73% (46/63) • 5-years = 76.6% (49/64)
Global Assessment • 82% of baseline body weight	**Global Assessment** • No patient had demonstrable weakness on exam, but all commented on a perceived level of weakness
Median Distance Walked in 6 Minutes • 3-months = 281 m (49% predicted) • 6-months = 396 m (64% predicted) • 12-months = 422 m (66% predicted)	**Median Distance Walked in 6 Minutes** • 2-years = 416 m (68% predicted) • 3-years = 418 m (67% predicted) • 4-years = 406 m (71% predicted) • 5-years = 463 m (76% predicted)

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Herridge et al. *N Engl J Med.* 2003;348(8):683-693.
Herridge et al. *N Engl J Med.* 2011;364(14):1293-1304.

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ARDS Mortality

- Hospital mortality has been associated with ARDS severity

Mild: 35% → Moderate: 40% → Severe: 46%

- **COVID-19 ARDS** mortality appears to be worse than typical ARDS

ICU Admission: 26-62% → Mechanically Ventilated: 66-94%

University of Utah Health (as of 9/19/2020)
- ICU admissions: 150 patients
- Ventilated mortality: 40%
- Overall ICU mortality: 20%
- Total deaths: 39 patients

Bellani et al. JAMA. 2016;315(8):788-800.
Gibson et al. Med J Aust. 2020;213(2):54.e1.

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Pharmacist Question 3

While ARDS treatment regimens have been associated with a reduction in mortality, ARDS morbidity can have significant negative effects on a patient for years following hospital discharge. Which of the following ARDS morbidities is appropriately paired with a precipitating treatment. (select all that apply)

1. Alveolar damage and diuresis
2. Reduced 6-minute walking distance and vasoactive agents
3. ICU-associated weakness and paralysis
4. PTSD and inadequate sedation

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Patient Case and Literature Review

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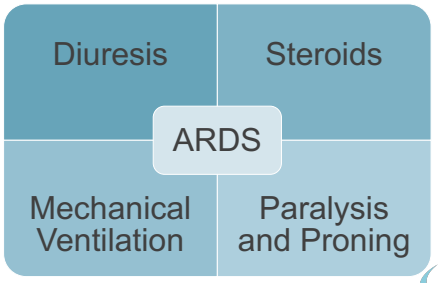

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Patient Case

- A 46-year-old female with a past medical history significant for asthma, type 2 diabetes mellitus, and hypothyroidism presented to the emergency department with a 6-day history of worsening cough and shortness of breath
- Denies recent travel; however, her son-in-law recently tested positive for COVD-19

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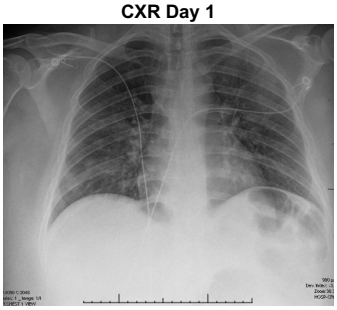
CXR Day 1



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Patient Case

- She was found to be COVID-19 positive and subsequently admitted to the COVID-19 internal medicine floor on 5L NC
  - Dexamethasone was initiated on hospital day 2 (day 8 of illness)

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Steroids in ARDS

SCCM/ESICM Guidelines

- **Early ARDS**
  - Methylprednisolone 1 mg/kg/day for 14 days then 14 days taper
- **Persistent ARDS**
  - Methylprednisolone 2 mg/kg/day for 14 days then 14 days taper

SSC COVID-19

- **COVID-19 and refractory shock**
  - Low-dose corticosteroids (IV hydrocortisone 200 mg/day)
- **Mechanically ventilated patients with COVID-19 ARDS**
  - Low-dose corticosteroids (IV hydrocortisone 200 mg/day)

Annane et al. Crit Care Med. 2017;45:1922-1978-2488.
Alhazzani et al. Intensive Care Med. 2020;46(5):854-877.

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Steroids in ARDS

Meduri et al (1998)

Intervention	Methylprednisolone (n = 16)	Placebo (n = 8)	
Dosing Regimen	Loading Dose: 2 mg/kg • Day 1-14: 2 mg/kg/day • Day 15-21: 1 mg/kg/day • Day 22-28: 0.5 mg/kg/day • Day 29-30: 0.25 mg/kg/day • Day 31-32: 0.125 mg/kg/day	Placebo loading dose • Placebo day 1-32	
ICU Mortality	0 (0%)	5 (62%)	p=0.002; NNT=2
Hospital Mortality	2 (12%)	5 (62%)	p=0.03; NNT=2

Meduri et al. JAMA. 1998;280(2):159-165.

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Steroids in ARDS

Meduri et al (2007)

Intervention	Methylprednisolone (n = 63)	Placebo (n = 28)	
Dosing Regimen	Loading Dose: 1 mg/kg • Day 1-14: 1 mg/kg/day • Day 15-21: 0.5 mg/kg/day • Day 22-25: 0.25 mg/kg/day • Day 26-28: 0.125 mg/kg/day	Placebo loading dose • Placebo day 1-28	
ICU Mortality	13 (20.6%)	12 (42.9%)	RR 1.39; p=0.03; NNT=5
Hospital Mortality	15 (23.8%)	12 (42.9%)	RR 1.33; p=0.07

Meduri et al. Chest. 2007;131(4):954-963.

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Steroids in ARDS

Villar et al (2020) – DEXA-ARDS Trial

Intervention	Dexamethasone (n = 139)	Standard of Care (n = 138)	
Dosing Regimen	• Day 1-5: 20 mg/day • Day 6-10: 10 mg/day	Physicians had the option to add steroids at their discretion if the patient had non-resolving ARDS	
Ventilator-free Days	12.3 days	7.5 days	ARR 4.8; p<0.0001
ICU Mortality	26 (19%)	43 (31%)	p=0.0166; NNT=8
Hospital Mortality	33 (24%)	50 (36%)	p=0.0235; NNT=8

Villar et al. Lancet Respir Med. 2020;8(3):267-276.

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Steroids in COVID-19 ARDS

Horby et al (2020) – RECOVERY Trial

Intervention	Dexamethasone (n = 2104)	Standard of Care (n = 4321)	
Dosing Regimen	Day 1-10: 6 mg IV/PO daily	-	
28 Day Mortality	454 (21.6%)	1065 (24.6%)	RR 0.83; p<0.001; NNT=33
• No Oxygen (n/N)	85/501 (17%)	137/1034 (13.2%)	RR 1.22 (0.93-1.61)
• Oxygen Only (n/N)	275/1279 (21.5%)	650/2604 (25%)	RR 0.8 (0.7-0.92); NNT=29
• Invasive Ventilation (n/N)	94/324 (29%)	278/683 (40.7%)	RR 0.65 (0.51-0.82); NNT=9
28 Day Discharge	1360 (64.6%)	2639 (61.1%)	RR 1.11; p=0.002

Horby et al. N Engl J Med. 2020;NEJMoa2021436.

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Patient Case

- On hospital day 5 (day 11 of illness), the patient's respiratory status worsened, requiring 60% HFNC and transfer to the MICU
  - Diuresis was initiated with a goal of net negative 1-2 L per day
  - Dexamethasone continued

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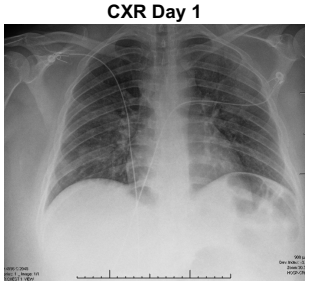
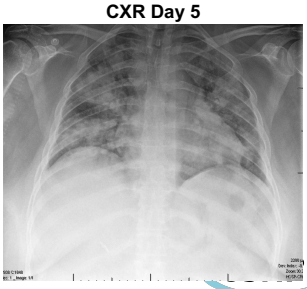
CXR Day 1



CXR Day 5



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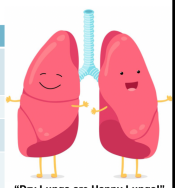
Diuresis in ARDS

Wiedemann et al (1998) – FACTT Trial			
Intervention	**Conservative "CVP <4 mmHg" (n=503)**	**Liberal "CVP >4 mmHg" (n=497)**	
60 Day Mortality (n; %)	128 (25.5%)	141 (28.4%)	p=0.3
Ventilator-free Days			
• Days 1-28	14.6 ± 0.5	12.1 ± 0.5	p<0.001
ICU-free Days			
• Days 1-7	0.9 ± 0.1	0.6 ± 0.1	p<0.001
• Days 1-28	13.4 ± 0.4	11.2 ± 0.4	p<0.001



"Dry Lungs are Happy Lungs!"
-every pulmonologist ever

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Wiedemann et al. *N Engl J Med.* 2006;354(24):2564-2575.
Image available at: Image: https://www.dreamstime.com/cute-cartoon-funny-lungs-character-strong-smiling-lung-human-respiratory-system-happy-internal-organ-mascot-healthy-medical-image159971393

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Patient Case

- On hospital day 6 (day 12 of illness), the patient's respiratory status continues to worsen and she is subsequently intubated for worsening hypoxemia secondary to COVID-19 ARDS
  - Ventilator mode
    - AC/VC
  - Ventilator settings
    - TV: 6 mL/kg
    - PEEP: 14
    - FiO_2: 75%

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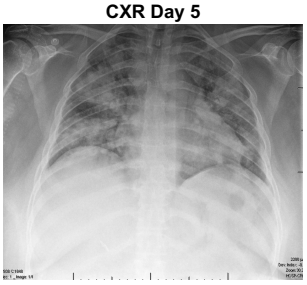
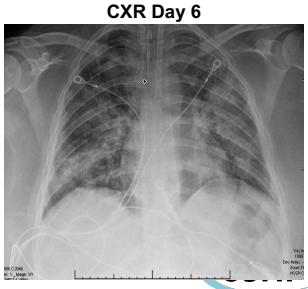
CXR Day 5



CXR Day 6



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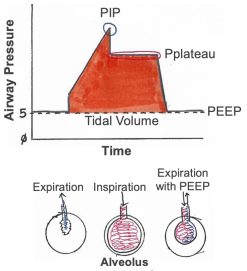
Mechanical Ventilation

- TV:
  - Measure of the amount of air a person inhales during a normal breath
    - Roughly 500 mL per inspiration or 7 mL/kg of IBW
- PEEP:
  - Pressure in the lungs above atmospheric pressure that exists at the end of expiration which aids in oxygenation
- PIP
  - Highest level of pressure applied to the lungs during inhalation
- Pplateau
  - Pressure applied to small airways and alveoli during positive-pressure mechanical ventilation and measured during the inspiratory pause



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Cawley. Pharmacotherapy. 2007;27(2):250-266.

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Mechanical Ventilation in ARDS

Annals of Intensive Care

- TV: 6 mL/kg of IBW
- Pplateau: <30 cm H_2O
- PEEP: >5 cm H_2O

SSC COVID-19

- TV: 4-8 mL/kg of IBW
- Pplateau: <30 cm H_2O
- PEEP: >10 cm H_2O

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Rhodes et al. *Crit Care Med.* 2017;45:3486-592.
Papazian et al. *Ann Intensive Care.* 2019;9(1):69.
Albuzzani et al. *Intensive Care Med.* 2020;46(5):854-877.

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Sedation in ARDS

Analago-sedation (opioid based) and non-benzodiazepine sedatives (propofol, dexmedetomidine) are preferred for ICU sedation

COVID-19 patients have been requiring deeper sedation to maintain ventilator synchrony and adequate oxygenation

Sedation in paralysis

- Adequate sedation must be obtained prior to paralysis initiation and repeatedly assessed throughout the paralytic course in order to prevent conscious paralysis and PTSD
- ICU-associated PTSD has been associated with significant morbidity

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Devlin et al. *Crit Care Med.* 2018;46(9):e825-e873.

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Sedation Monitoring

RIKER Sedation-Agitation Scale		
Score	State	Behavior
7	Dangerous agitation	Aggressive behavior, trying to remove catheters, thrashing
6	Very agitated	Requiring restrains
5	Agitated	Anxious or physically agitated
4	Calm cooperative	Calm and follows commands
3	Sedated	Arouse to verbal stimuli and follows simple commands
2	Very sedated	Arouse to physical stimuli but does not follow
1	Unarousable	Minimal to no response

Riker R et al. *Crit Care Med.* 1999 Jul;27(7):1325-9.

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Sedation Monitoring

Richmond Agitation-Sedation Scale		
Score	State	Behavior
+4	Combative	Violent, immediate danger to staff
+3	Very Agitated	Pulling at or removing tubes, aggressive
+2+	Agitated	Frequent non-purposeful movements, fights ventilator
1	Restless	Anxious, apprehensive but not aggressive
0	Alert and Calm	
-1	Drowsy	Sustained awakening to voice (>10 seconds)
-2	Light Sedation	Briefly awake to voice (<10 seconds)
-3	Moderate Sedation	Movement or eye-opening to voice (no eye contact)
-4	Deep Sedation	No response to voice, responsive to physical stimulation
-5	Un-rousable	No response to voice or physical stimulation

Sessler C et al. *Am J Respir Crit Care Med.* 2002 Nov 15;166(10):1338-44.

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Sedation in ARDS

Sedation for PARALYZED Patients			
Preferred Agents	**propofol infusion** 0-75 mcg/kg/min **AND**	**fentanyl infusion** 25-200 mcg/hour **+/-** **oral oxycodone** 5-10 mg every 4-6 hours	**OR** **IVP lorazepam** 1-4 mg every 4-6 hours as needed **midazolam infusion** 2-10 mg/hour
Adjunctive Agents	**oral quetiapine**	**ketamine infusion**	**IV phenobarbital**
Sedation for NON-PARALYZED Patients			
Preferred Agents	**propofol infusion** 0-75 mcg/kg/min **AND**	**IVP fentanyl** 25-50 mcg every 2 hours as needed	
Alternative Agents	**dexmedetomidine infusion** 0.2-1.5 mcg/kg/hour	**IVP lorazepam** 1-4 mg every 4-6 hours as needed	**midazolam infusion** 2-10 mg/hour
Adjunctive Agents	**oral quetiapine** 25-50 mg every 6-12 hours	**ketamine infusion** 0.1-0.4 mg/kg/hour	**IV phenobarbital** 1 mg/kg/dose every 8 hours

Devlin et al. *Crit Care Med.* 2018;46(9):e825-e873.

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Patient Case

- On hospital day 7 (13 of illness), her PaO_2:FiO_2 ratio was 58 and the decision was made to paralyze and prone the patient
  - Cisatracurium
    - Bolus: 0.2 mg/kg
    - Infusion: 5 mcg/kg/min titrated based upon TOF goal 1-2
    - Re-bolus: 0.1 mg/kg
  - Prone ventilation for 16 hours then supine for 8 hours

Example PaO_2:FiO_2 ratio calculation
- PaO_2: 49 mmHg
- FiO_2: 85% (0.85)
- PaO_2:FiO_2 ratio = 49/0.85 = 58

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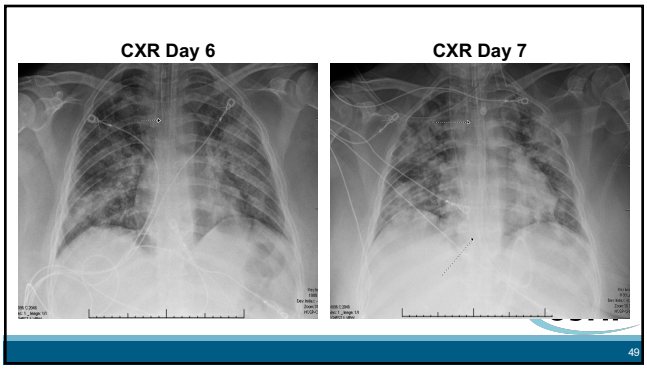

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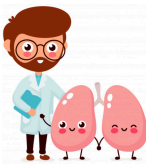
Paralysis in ARDS

Annals of Intensive Care

- NMBAs should be considered for mechanically ventilated patients with a PaO_2:FiO_2 ratio < 150 mmHg
- NMBAs should be administered within 48 hours of ARDS development and for no longer than 48 hours

SSC COVID-19

- NMBAs should be considered for mechanically ventilated patients with moderate to severe ARDS for up to 48 hours
  - Moderate: PaO_2:FiO_2 ratio <100 to ≤ 200 mmHg
  - Severe: PaO_2:FiO_2 ratio ≤ 100 mmHg



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Papazian et al. *Ann Intensive Care.* 2019;9(1):69.
Alhazzani et al. *Intensive Care Med.* 2020;46(5):854-877.
Murray et al. *Crit Care Med.* 2016;44(11):2079-2103.

Image available at: https://www.dreamstime.com/cute-funny-smiling-doctor-healthy-happy-lungs-cute-funny-smiling-doctor-pulmonologist-healthy-happy-lungs-healthcare-image157232724

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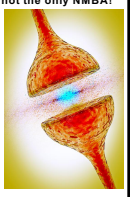
Paralysis in ARDS

Cisatracurium is not the only NMBA!

Cisatracurium	
Mechanism	Non-depolarizing neuromuscular blocking agent
Pharmacokinetics	• Onset: 2-3 min • Peak effect: 3-5 min • Metabolism: Hofmann elimination • Rapid, non-enzymatic degradation to laudanosine and inactive metabolites • Half-life: 22-29 min • Excretion: 95% urine; 4% feces
Titratable-Dosing Strategy	**Bolus:** 0.2 mg/kg **Infusion:** 5 mcg/kg/min titrated based upon TOF goal 1-2 **Re-bolus:** 0.1 mg/kg
Fixed-Dosing Strategy	**Loading dose:** 15 mg **Maintenance dose:** 37.5 mg/hour **Bolus doses:** 20 mg



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Nimbex (cisatracurium besylate) [prescribing information]. North Chicago, IL: AbbVie Inc; October 2018.
Murray et al. *Crit Care Med.* 2016;44(11):2079-2103.

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TOF Monitoring

- Battery-powered simulator delivers an electrical current to a superficial nerves (ulnar, facial, or posterior tibial) in a series of four consecutive impulses
- Muscle movement (twitches) following impulse delivery are observed and can estimate the degree of NMBA

Train of Four Responses	
Response	**Approximate Blockage**
Four twitches	0-75%
Three twitches	75%
Two twitches	80%
One twitch	90%
Absent twitches	100%

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Other Considerations with Paralysis

Ophthalmologic Considerations

- **Ocular lubricant**
  - Applied to both eyes every 4 hours or as needed for dry eyes

Gastrointestinal Considerations

- **Bowel regimen**
  - Docusate 100 mg per feeding tube twice daily
  - Sennosides 17.6 mg per feeding tube twice daily
  - Polyethylene glycol 17 grams per feeding tube twice daily
- **Enteral feeding**
  - Early enteral nutrition (≤2 days after NMBA initiation) may be associated with:
    - Reduced in-hospital mortality [RR 0.75 (0.59-0.96); NNT 15]
    - Reduced length of hospital stay [RR 0.8 (0.69-0.96)]

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Chiba et al. *Crit Care Med.* 2019 Aug;47(8):1072-1080.

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Paralysis in ARDS

Papazian et al (2010) – ACURASYS Trial

Intervention	Cisatracurium (n = 178)	Placebo (n = 162)	
Dosing Regimen	Loading dose: 15 mg • 37.5 mg/hour continuous infusion for 48 hours	Placebo for 48 hours	
90 Day Mortality	56 (31.6%)	66 (40.7%)	HR 0.68 (0.48-0.98); NNT=11
28 Day Mortality	42 (23.7%)	54 (33.3%)	RR 0.71 (0.51-1.00)
Ventilator-free Days • Days 1-28 • Days 1-90	 10.9 ± 9.7 53.1 ± 35.8	 8.5 ± 9.4 44.6 ± 37.5	 p=0.04 p=0.03

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Papazian et al. *N Engl J Med.* 2010;363(12):1107-1116.

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Paralysis in ARDS

Moss et al (2019) – Rose Trial

Intervention	Deep Sedation with Cisatracurium (n = 178)	Light Sedation without Cisatracurium (n = 162)	
Dosing Regimen	Deep Sedation • RASS -4 to -5 • Riker 1-2 Loading dose: 15 mg • 37.5 mg/hour continuous infusion for 48 hours	Light Sedation • RASS 0 to -1 • Riker 3-4	
90 Day Mortality	213 (42.5%)	216 (42.8%)	Difference -0.3; p=0.93
28 Day Mortality	184 (36.7%)	187 (37%)	Difference -0.3 (-6.3 to 5.7)
Ventilator-free Days	9.6 ± 10.4	9.9 ± 10.9	Difference -0.3 (-1.7 to 1)
ICUAW • Day 1-7 • Day 1-28	 41% 46.8%	 31.3% 25.7%	 Difference -9.7 (-21.5 to 2.1) Difference -19.4 (-38.2 to -0.6)

Moss et al. *N Engl J Med.* 2019;380(21):1997-2008.

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Pharmacist Question 4

A 52 year old, 84 kg male with a past medical history of ADHD, HTN, and type 2 DM is transferred to your MICU from an outside hospital for the management of COVID-19 ARDS. The patient is intubated (PEEP 10; PaO_2/FiO_2 195), sedated, and tolerating the ventilator on arrival. The medical resident has never worked with a COVID-19 patient before and asks for your opinion on initiating therapies. Which of the following interventions may be clinically efficacious and safe in this patient based upon available literature. (select all that apply)

1. Dexamethasone 6 mg daily
2. Cisatracurium 0.1 mg/kg bolus followed by a 5 mcg/kg/min infusion (titrate to a TOF 1-2)
3. Furosemide 40 mg every 8 hours (goal net negative 1-2 L)
4. Albuterol 20 mg/hour continuous inhalation

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Prone Position in ARDS

Annals of Intensive Care

- Prone position ventilation is recommended over supine ventilation in adults with ARDS from sepsis and a PaO_2:FiO_2 ratio <150
  - Recommended for at least 16 consecutive hours

SSC COVID-19

- Prone position ventilation is recommended for adults with COVID-19 and moderate to severe ARDS
  - Recommended for 12-16 hours

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Papazian et al. *Ann Intensive Care.* 2019;9(1):69.
Alhazzani et al. *Intensive Care Med.* 2020;46(5):854-877.
Rhodes et al. *Crit Care Med.* 2017;45(3):486-552.

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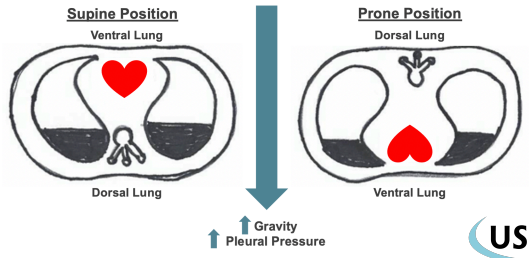
Prone Lungs



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Prone Position in ARDS

Guérin et al (2013) – PROSEVA Trial

Intervention	Prone Position (n = 237)	Supine Position (n = 299)	
Position Time	Prone: 16 hours Supine: 8 hours	Prone: 0 hours Supine: 24 hours	
28 Day Mortality	38 (16%)	75 (32.8%)	HR 0.39; p<0.001; NNT=6
90 Day Mortality	56 (23.6%)	94 (41%)	HR 0.44; p<0.001; NNT=6
Ventilator-free Days			
• Days 1-28	14 ± 9	10 ± 10	P<0.001
• Days 1-90	57 ± 34	43 ± 38	P<0.001

For how many days do you prone patients?

- For ≥ 28 days (if necessary)
- Stop prone ventilation when the PaO_2:FiO_2 ratio ≥ 150 mmHg with a PEEP ≤ 10 mm H_2O and an FiO_2 ≤ 60% for 4 hours after the last prone session

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Guérin et al. *N Engl J Med.* 2013;368(23):2159-2168.

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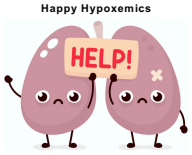
"Awake" Self-Proning in COVID-19 ARDS

- Caputo et al.
  - Self-proning/positional change
    - Median patient age: 59 years (IQR 50-68)
    - Median SpO_2 without supplemental oxygen: 75% (IQR 62-82)
    - Median SpO_2 with supplemental oxygen: 82% (IQR 72-85)
  - Outcomes
    - Change in SpO_2: 14% (p = 0.001)
      - Mean of 80% at triage to a mean of 94% after 5 minutes of proning



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Caputo et al. *Acad Emerg Med.* 2020;27(5):375-378.
Image available at: https://www.dreamstime.com/cute-lungs-set-healthy-unhealthy-human-organ-vector-modern-style-cartoon-character-illustration-icon-design-bad-habits-image150469596

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"Awake" Self-Proning in COVID-19 ARDS

- Thompson et al.
  - Self-proning for as long as tolerable (up to 24 hours/day)
  - Outcomes
    - Change in SpO_2: range 1% to 34%
    - SpO_2 > 95% within 1 hour of proning: 19 patients (65.5%)
- Weatherald et al.
  - Large, rapid review of 35 studies with 414 patients
  - Awake prone positioning is a promising therapy for patients with COVID-19; however, lack key clinical details necessary to guide physician decision making

Thompson et al. *JAMA Intern Med.* 2020;e203030.
Weatherald et al. *J Crit Care.* 2020.

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Pharmacist Question 5

Which of the following non-pharmacological interventions have shown to have a mortality benefit in ARDS? (select all that apply)

1. Prone ventilation
2. Lights out
3. Low tidal volume ventilation
4. Supine ventilation

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Technician Question 3

You are preparing to deliver medications to the floor when a pharmacist calls down and asks you to restock the COVID unit medication cabinet with ARDS medications. Which medications should you restock? (select all that apply)

1. Furosemide vials (diuretic)
2. Dexamethasone vials (steroid)
3. Voriconazole (antifungal)
4. Fentanyl vials (opioid)
5. Ondansetron (anti-emetic)

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Patient Case

- On hospital day 10 (16 of illness), paralysis was stopped after ~72 hours
- Her PaO_2:FiO_2 ratio was 103 and improving
  - Ventilator mode
    - AC/VC
  - Ventilator settings
    - TV: 6 mL/kg
    - PEEP: 12
    - FiO2: 65%

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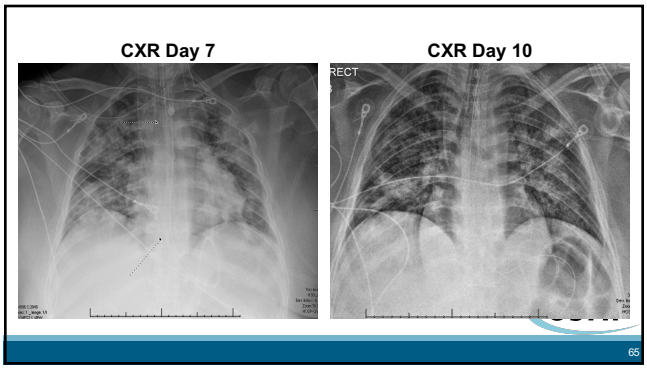

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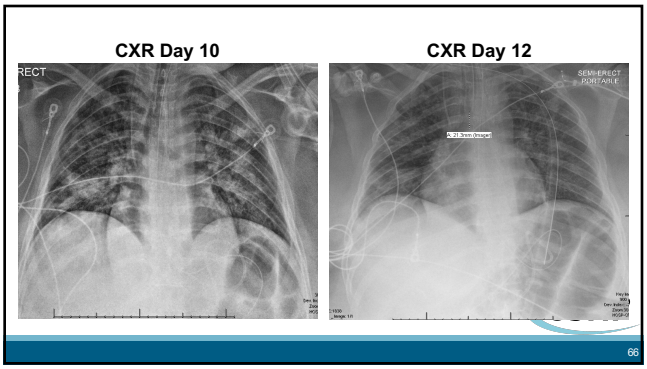

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Patient Case

- On hospital day 14 (20 of illness), the patient was extubated to HFNC and her PaO_2:FiO_2 ratio was 136
  - Intubated for 8 days
- On hospital day 16 (22 of illness), the patient was transferred out of the MICU to the COVID-19 internal medicine service
- The patient spent 3 days on the COVID-19 internal medicine service and was discharge home after a 25 day hospitalization

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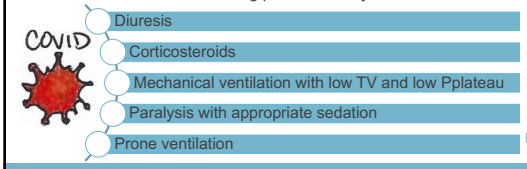
In Summary

- ARDS is a severe and life-threatening syndrome associated with significant morbidity and mortality
- COVID-19 ARDS management coincides with traditional ARDS management; however, new data is being published daily



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68

68

Thank You

- Dr. Brianne Wolfe
- Dr. Laura Steffens

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References

- Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46(5):854-887.
- Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2017;45(12):2078-2088.
- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute Respiratory Distress in Adults. *The Lancet*. 1967 Aug 12; 290(7511): P319-323.
- Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*. 2016;315(8):788-800.
- Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824.

70

70

References

- Caputo ND, Strayer RJ, Levitan R. Early Self-Proning in Awake, Non-intubated Patients in the Emergency Department: A Single ED's Experience During the COVID-19 Pandemic. *Acad Emerg Med*. 2020;27(5):375-378.
- Cawley MJ. Mechanical ventilation: a tutorial for pharmacists. *Pharmacotherapy*. 2007;27(2):250-266.
- CDC – CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#cases_totalcases, September 29, 2020.
- CDC – COVID-19 Associated Hospitalization Related to Underlying Medical Conditions. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-underlying-medical-conditions.html, September 9, 2020.
- CDC – COVID-19 Hospitalization and Death by Age. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html, September 9, 2020.
- Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873.

71

71

References

- Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Med J Aust*. 2020;213(2):54-56.e1.
- Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168.
- Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
- Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.
- Hodgson C, Bellomo R, Berney S, et al. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. *Crit Care*. 2015;19(1):81.
- Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. *N Engl J Med*. 2020;NEJMoa2021436.

72

72

Reference

- Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131(4):954-963.
- Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;280(2):159-165.
- Moss M, Huang DT, Brower RG, et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2019;380(21):1997-2008.
- Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome [published correction appears in Am Rev Respir Dis 1989 Apr;139(4):1065]. *Am Rev Respir Dis*. 1988;138(3):720-723.
- Murray MJ, DeBlock H, Erstad B, et al. Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. *Crit Care Med*. 2016;44(11):2079-2103.
- Nimbex (cisatracurium besylate) [prescribing information]. North Chicago, IL: AbbVie Inc; October 2019.

73

Reference

- Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Early Enteral Nutrition in Patients Undergoing Sustained Neuromuscular Blockade: A Propensity-Matched Analysis Using a Nationwide Inpatient Database. *Crit Care Med*. 2019 Aug;47(8):1072-1080.
- Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.
- Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann Intensive Care*. 2019;9(1):69.
- Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.
- Rezoagli E, Fumagalli R, Bellani G. Definition and epidemiology of acute respiratory distress syndrome. *Ann Transl Med*. 2017;5(14):282.
- Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. 2017;45(3):486-552.

74

References

- Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med*. 1999 Jul;27(7):1325-9.
- Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J *Respir Crit Care Med*. 2002 Nov 15;166(10):1338-44.
- Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. *J Med Virol*. 2020;92(6):612-617.
- Thompson AE, Ranard BL, Wei Y, Jelic S. Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure [published online ahead of print, 2020 Jun 17]. *JAMA Intern Med*. 2020;e203030.
- Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276.
- Weatherald J, Solverson K, Zuege DJ, Loroff N, Fiest KM, Parhar KKS. Awake prone positioning for COVID-19 hypoxemic respiratory failure: A rapid review [published online ahead of print, 2020 Aug 27]. *J Crit Care*. 2020.
- Wiedemann HP, Wheeler AP, Bernard GR. et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.

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Breathing HazARDS: A Comprehensive Review of Acute Respiratory Distress Syndrome

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