MAYO CLINIC

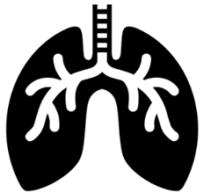
The Next Dex Thing? Corticosteroids in ARDS

Nicholas Vollmer, PharmD
PGY-2 Critical Care Pharmacy Resident

Objectives

- Describe the mechanism of benefit for corticosteroids in Acute Respiratory Distress Syndrome
- Compare and contrast key historic literature evaluating the use of corticosteroids in ARDS
- Identify how recent landmark trials on corticosteroids in ARDS impacts management

Acute Respiratory Distress Syndrome (ARDS) is an intense inflammatory process of the lungs in response to acute pulmonary and systemic insults



Villar et al. *Lancet Respir Med*. 2020;8:267-76.

ARDS Definitions

Characteristics	1994 AECC Definition	2012 Berlin Definition
Onset	Acute	≤ 7 days since onset of clinical condition
Imaging	Bilateral opacities	Bilateral opacities not attributed to pleural effusion, atelectasis, or nodules
Non-cardiogenic pulmonary edema	No evidence of increased pressure in L atrium or pulmonary wedge	RF not attributed to HF or volume overload
Oxygenation	ALI: $PaO_2/FiO_2 \leq 300$ mmHg ARDS: $PaO_2/FiO_2 \leq 200$ mmHg	PaO_2/FiO_2 with ≥ 5 cm H_2O of PEEP: Mild ARDS: 201-300 mmHg Moderate ARDS: 101-200 mmHg Severe ARDS: <100 mmHg

Bernard et al. *American Journal of Respiratory and Critical Care Medicine*. 1994;149:3
Ferguson et al. *Intensive Care Med*. 2012;38:1573-1582.

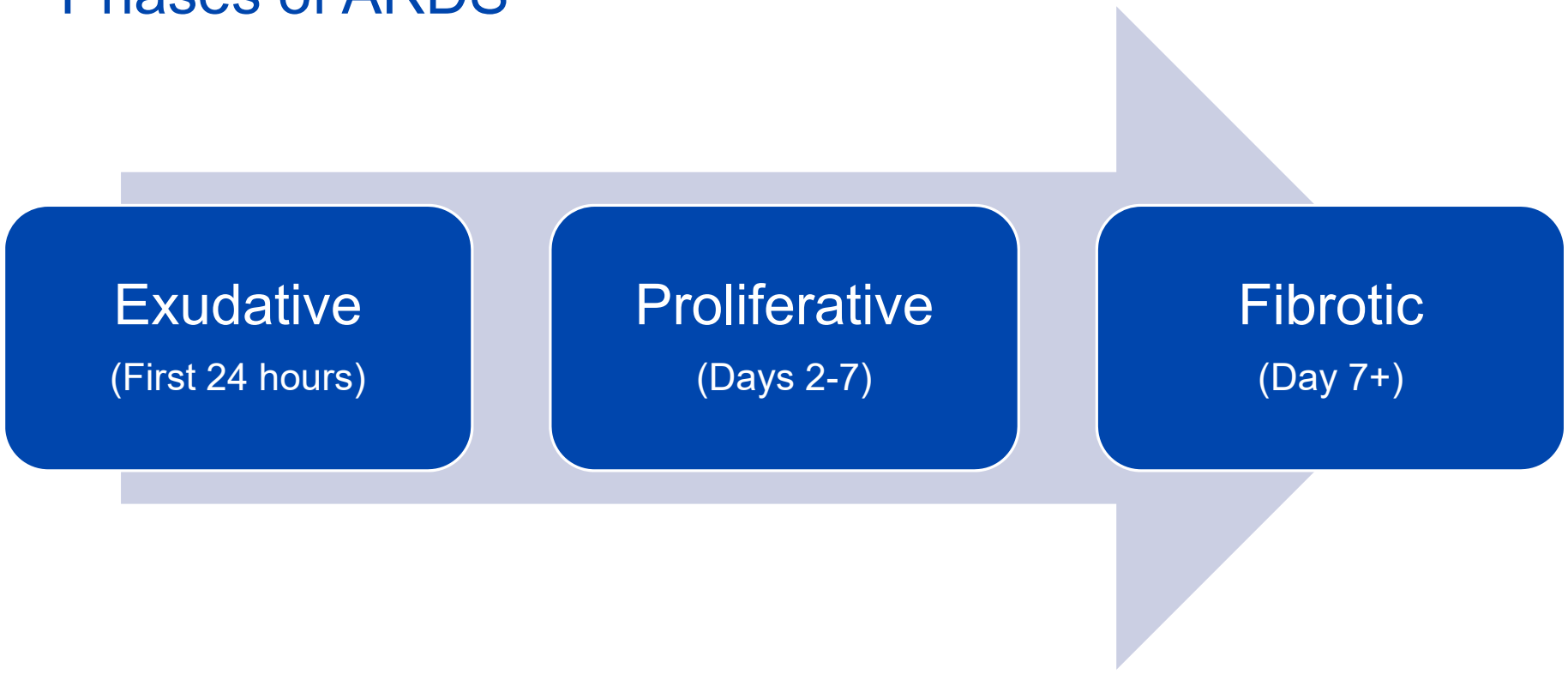
AECC: American European Consensus Conference
ALI: Acute Lung Injury
RF: Respiratory Failure
HF: Heart Failure
PaO_2: Partial Pressure of Oxygen
FiO_2: Fraction of Inspired Oxygen

ARDS Phenotypes

Direct vs indirect lung injury	Hypoxia severity	Precipitating factor	Timing of onset
Radiographic	Genetic defined	Biomarker defined	Hyperinflammatory versus uninflamed

Reilly et al. *Sim Respir Crit Care Med.* 2019;40:19-30.
Kitsios et al. *Critical Care Med.* 2019;47:12.

Phases of ARDS



Matthay and Zemans. *Annu Rev Pathol.* 2011;6:147-163.
Thompson et al. *New Engl J Med.* 2017;377:562-72.

ARDS Management Strategies

Beneficial

- Low tidal volume
- Prone positioning
- Recruitment maneuvers
- Conservative fluid management

Not beneficial

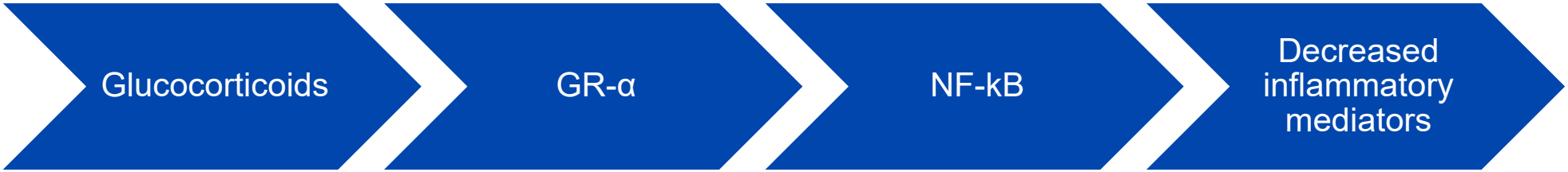
- Inhaled nitric oxide
- Active protein c
- Ketoconazole
- Short-acting beta$_2$ agonists
- Statins

Controversial

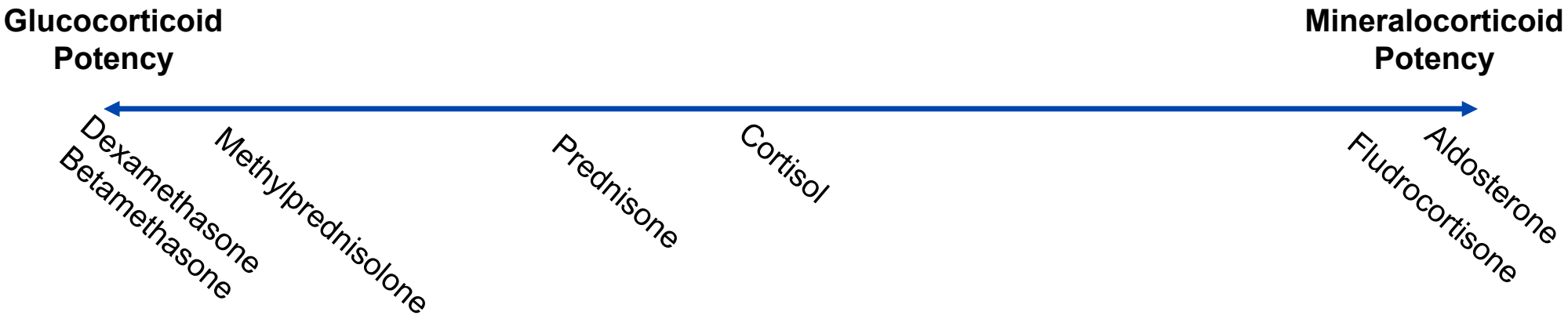
- Inhaled prostaglandins
- Neuromuscular blockers

Brower et al. *N Engl J Med*. 2000;342(18):1301.
Geurin et al. *N Eng J Med*. 2013;368(23):2159.
Fan et al. *Am J Respir Crit Care Med*. 2017;195(9):1253.
Silversides et al. *Crit Care Med*. 2018;46(10):1600.
Pipeling and Fan. *JAMA*. 2010;304(22):2521.
Adhikari et al. *Crit Care Med*. 2014;42(2):404-12.
Fuller et al. *CHEST*. 2015;147(6):1510-1522.
Liu et al. *Am J Respir Crit Care Med*. 2008;178(6):618
ARDSNetwork. *JAMA*. 2000;283(15):1995.
Perkins et al. *Am J Respir Crit Care Med*. 2014;189(6):674
Truwit et al. *N Eng J Med*. 2014;370(23):2191.
McAuley et al. *N Eng J Med*. 2014;371(18):1695
Papzian et al. *N Eng J Med*. 2010;363(12):1107.
Moss et al. *N Engl J Med*. 2019;380(21):1997.

Why Corticosteroids?



Choosing a Steroid



Anti-inflammatory Effects
Hyperglycemia

Hypernatremia
Fluid Retention

Liu et al. *Allergy Asthma Clin Immunol.* 2013;9:30.

Which of the following is true regarding corticosteroids role in ARDS?

- Increase inflammation preventing leaky alveolar membranes reducing fluid influx
- Prevent fibrosis by suppressing developing autoantibodies
- Decrease inflammatory mediators reducing pulmonary and systemic inflammation
- Increase NF-kB presence limiting fibrous tissue formation

Which of the following is true regarding corticosteroids role in ARDS?

- Increase inflammation preventing leaky alveolar membranes reducing fluid influx
- Prevent fibrosis by suppressing developing autoantibodies
- **Decrease inflammatory mediators reducing pulmonary and systemic inflammation**
- Increase NF-kB presence limiting fibrous tissue formation

History of Steroids in ARDS

1998
Meduri
JAMA

History of Steroids in ARDS

1998
Meduri
JAMA

- Meduri MP protocol vs control
- ARDS defined by 1994 AECC criteria
- Key inclusion: At least 7 days of MV with a LIS ≥ 2.5 and less than 1 point reduction from day 1 of ARDS

Meduri et al. *JAMA*. 1998;280:159-165.

MP: Methylprednisolone
AECC: American European Consensus Conference
LIS: Lung Injury Score

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	MP Dose (mg/kg)
Loading dose	2
Day 1-14	2
Day 15-21	1
Day 22-28	0.5
Day 29-30	0.25
Day 31-32	0.125

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Day 1-14	2
Day 15-21	1
Day 22-28	0.5
Day 29-30	0.25
Day 31-32	0.125

	MP (n=16)	Placebo (n=8)
Survivors of ICU admission, %	100	37
Survivors of hospital admission, %	87	37
MODS-free at day 28, days (SEM)	16 (2)	6 (2)
MV duration, median days	11.5	23

All results were statistically significant

Meduri et al. *JAMA*. 1998;280:159-165.

MP: Methylprednisolone
AECC: American European Consensus Conference
LIS: Lung Injury Score
ICU: Intensive Care Unit
MODS: Modified Organ Dysfunction Score
MV: Mechanical Ventilation
SEM: Standard of Error Mean

History of Steroids in ARDS

1998
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JAMA

2006
ARDSNet
NEJM

Meduri et al. *JAMA*. 1998;280:159-165.
ARDS Clinical Trials Network. *N Engl J Med*. 2006;354:1671-84.

History of Steroids in ARDS

1998
Meduri
JAMA

2006
ARDSNet
NEJM

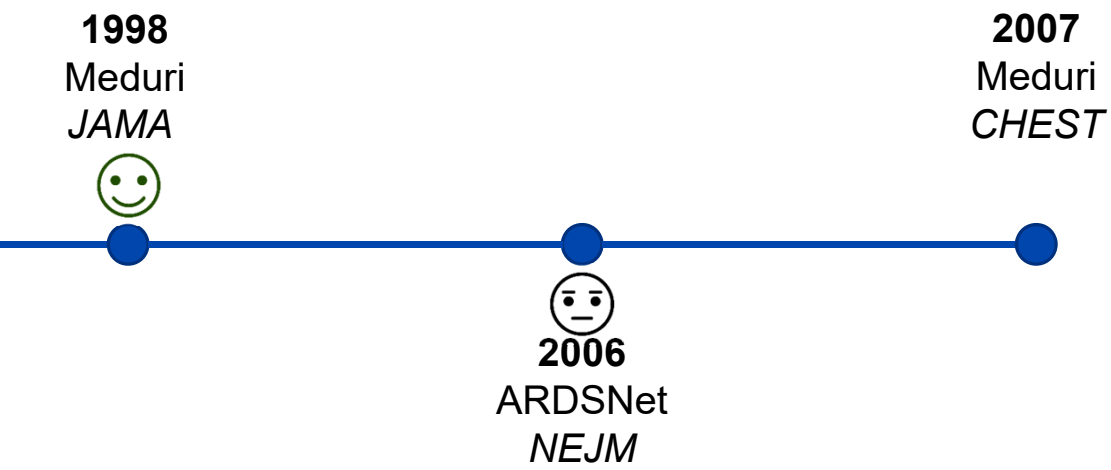
- Modified Meduri MP protocol vs control
- ARDS defined by 1994 AECC criteria
- Key inclusion: 7-28 days after onset of ARDS

	MP (n=89)	Placebo (n=91)	P-Value
60-day mortality, %	29.2	28.6	1
60-day mortality in ARDS onset ≥14 days, %	35	9	0.02
Return to MV, %	22.5	7	0.008
ICU-free days at day 28, days (SD)	8.9 (8.2)	6.2 (7.8)	0.02
MV-free days at day 28, days (SD)	11.2 (9.4)	6.8 (8.5)	<0.001

Meduri et al. *JAMA*. 1998;280:159-165.
ARDS Clinical Trials Network. *N Engl J Med*. 2006;354:1671-84.

MP: Methylprednisolone
BAL: Bronchoalveolar Lavage
ICU: Intensive Care Unit

History of Steroids in ARDS



Meduri et al. *JAMA*. 1998;280:159-165.
ARDS Clinical Trials Network. *N Engl J Med*. 2006;354:1671-84.
Meduri et al. *CHEST*. 2007;131:954-963.

History of Steroids in ARDS

1998
Meduri
JAMA

2006
ARDSNet
NEJM

2007
Meduri
CHEST

- Modified Meduri MP protocol vs placebo
- Key inclusion: ARDS defined by AECC classification within 72hr

	MP (n=63)	Placebo (n=28)
Extubation or ≥ 1-point reduction in LIS, %	69.8	35.7
PaO_2/FiO_2 ratio in ventilated patients, mean (SE)	256 (19)	179 (21)
MODS score, mean (SD)	0.9 (1.1)	1.9 (1.4)
Duration of MV, median days (IQR)	5 (3-8)	9.5 (6-19.5)
Length of ICU stay, median days (IQR)	7 (6-12)	14.5 (6-20.5)

All results were statistically significant

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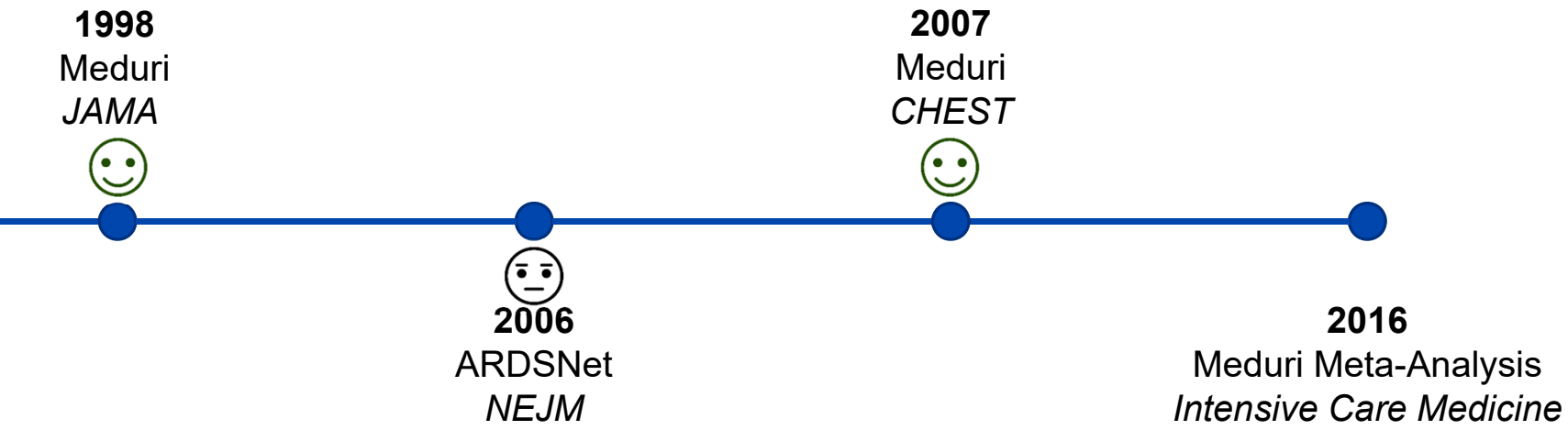

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Meduri et al. *CHEST*. 2007;131:954-963.
Meduri et al. *Intensive Care Medicine*. 2016;42:829-840.

History of Steroids in ARDS

Updated meta-analysis of 4 RCTs

	MP (n=186)	Placebo (n=136)
Hospital mortality, %	20	33
Hospital mortality randomized before day 14, %	20	39
Infection rate, %	32	41
Achieved unassisted breathing by day 28, %	80	50

All results were statistically significant

2016
Meduri Meta-Analysis
Intensive Care Medicine

Meduri et al. *JAMA*. 1998;280:159-165.
ARDS Clinical Trials Network. *N Engl J Med*. 2006;354:1671-84.
Meduri et al. *CHEST*. 2007;131:954-963.
Meduri et al. *Intensive Care Medicine*. 2016;42:829-840.

RCTs: Randomized controlled trial
MV: Mechanical Ventilation
ICU: Intensive Care Unit

2017 SCCM/ ESCIM CIRCI Guidelines

Consistently found significant reductions in:

- Systemic inflammatory markers
- Duration of MV
- Hospital mortality

Principles of use:

- Early ARDS (<72h)
- Only associated with hyperglycemia
- Methylprednisolone is drug of choice
  - Greater lung tissue penetration
  - Longer residence time
  - Slow wean

Annane et al. *Intensive Care Med*. 2017;43:1751–1763

CIRCI: Critical Illness-Related Corticosteroid Inusfficiency
MV: Mechanical Ventilation

2017 SCCM/ ESCIM CIRCI Guidelines

Consistently found significant reductions in:

- Systemic inflammation markers

Should corticosteroids be the standard of care in ARDS?

- Only associated with hyperglycemia
- Methylprednisolone is drug of choice
  - Greater lung tissue penetration
  - Longer residence time
  - Slow wean

Annane et al. *Intensive Care Med*. 2017;43:1751–1763

CIRCI: Critical Illness-Related Corticosteroid Inusfficiency
MV: Mechanical Ventilation

DEXA-ARDS

Multicenter, RCT of 17 ICUs across Spain from 2013 through 2018

Dexamethasone IV 20mg once daily on days 1-5
10mg once daily on days 6-10
n=139

Placebo
n=138

Inclusion	Exclusion
ARDS by AECC or Berlin criteria	Receiving corticosteroid or immunosuppressant agents
Established moderate-to-severe ARDS at 24 hours	Severe COPD
	CHF
	DNR

Villar et al. *Lancet Respir Med*. 2020;8:267-76.

RCT: Randomized controlled trial
ICU: Intensive Care Unit
IV: Intravenous
AECC: American European Consensus Conference
COPD: Chronic Obstructive Pulmonary Disease
CHF: Congestive Heart Failure
DNR: Do-not-Resuscitate

DEXA-ARDS

Multicenter, RCT of 17 ICUs across Spain from 2013 through 2018

Outcomes

Primary: Number of ventilator free days at day 28

Secondary: All-cause mortality at day 60

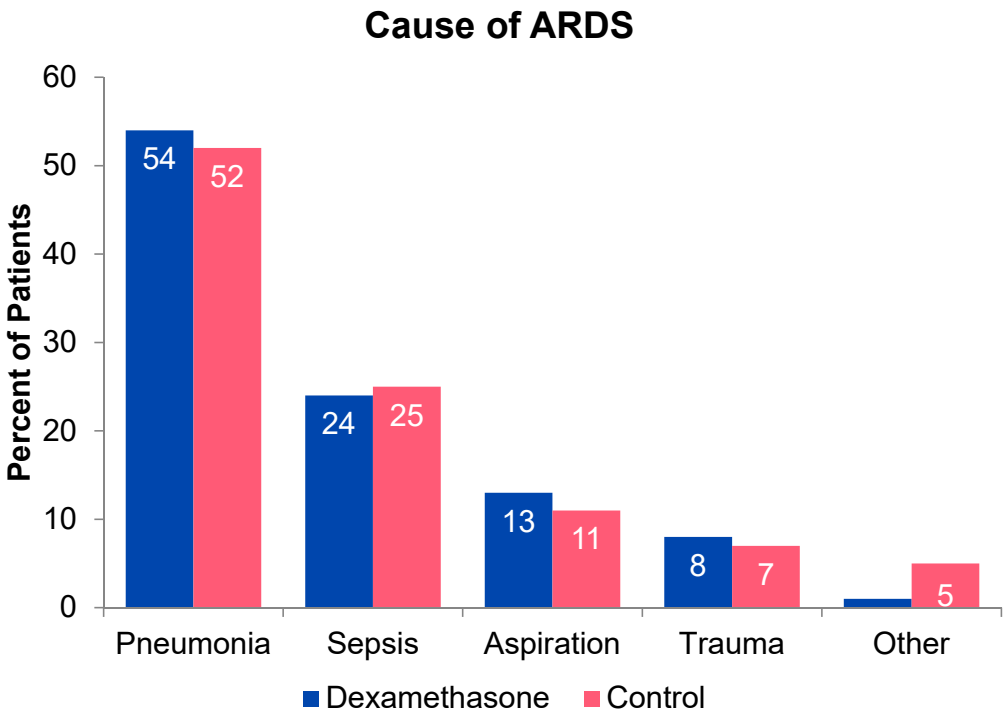
ARDS by AECC or Berlin criteria	immunosuppressant agents
Established moderate-to-severe ARDS at 24 hours	Severe COPD
	CHF
	DNR

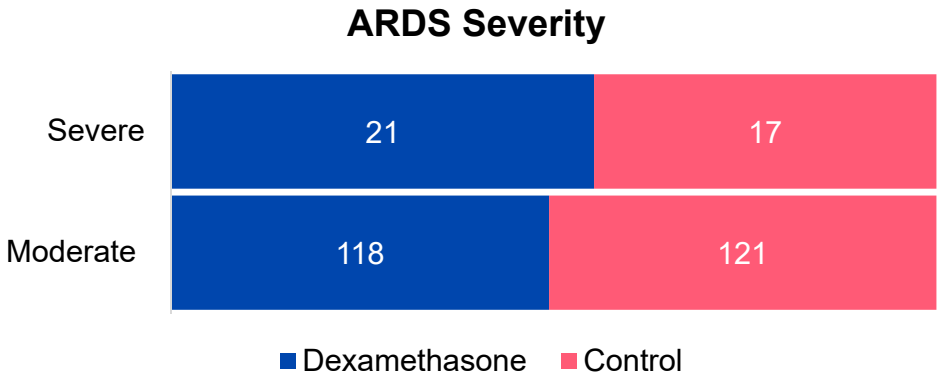
Villar et al. *Lancet Respir Med*. 2020;8:267-76.

RCT: Randomized controlled trial
ICU: Intensive Care Unit
IV: Intravenous
AECC: American European Consensus Conference

COPD: Chronic Obstructive Pulmonary Disease
CHF: Congestive Heart Failure
DNR: Do-not-Resuscitate

DEXA-ARDS: Baseline Characteristics

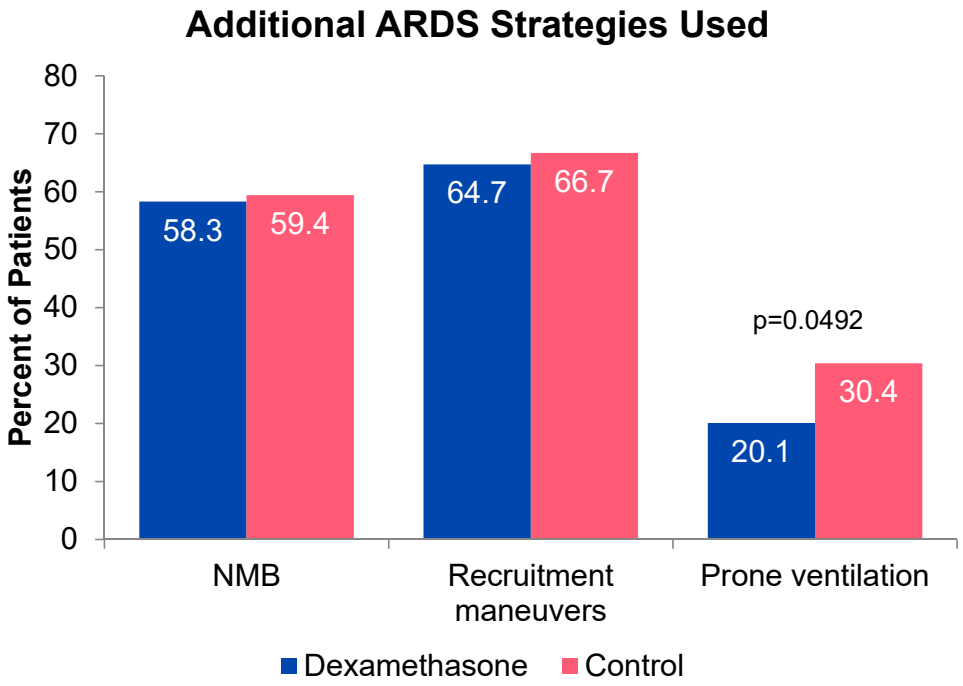




No statistically significant differences

Villar et al. *Lancet Respir Med*. 2020;8:267-76.

DEXA-ARDS: Baseline Characteristics

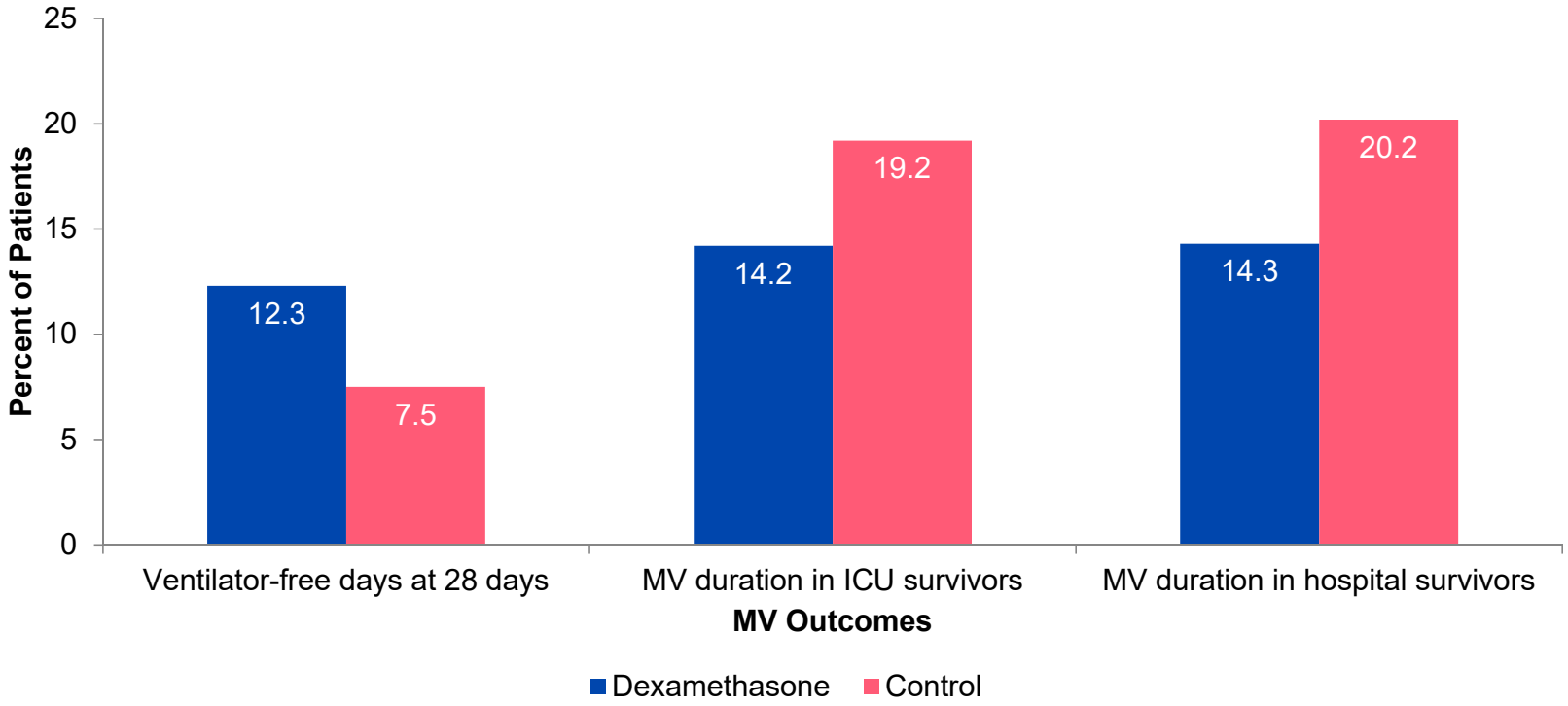


- Balanced baseline groups
- Impact of prone ventilation?

Villar et al. *Lancet Respir Med*. 2020;8:267-76.

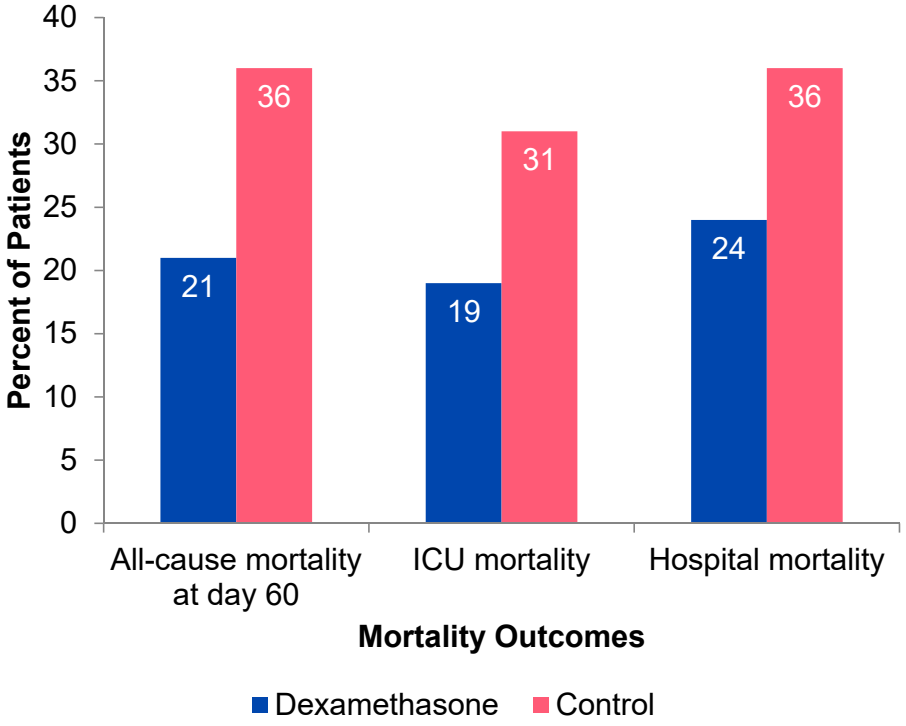
NMB: Neuromuscular Blocker

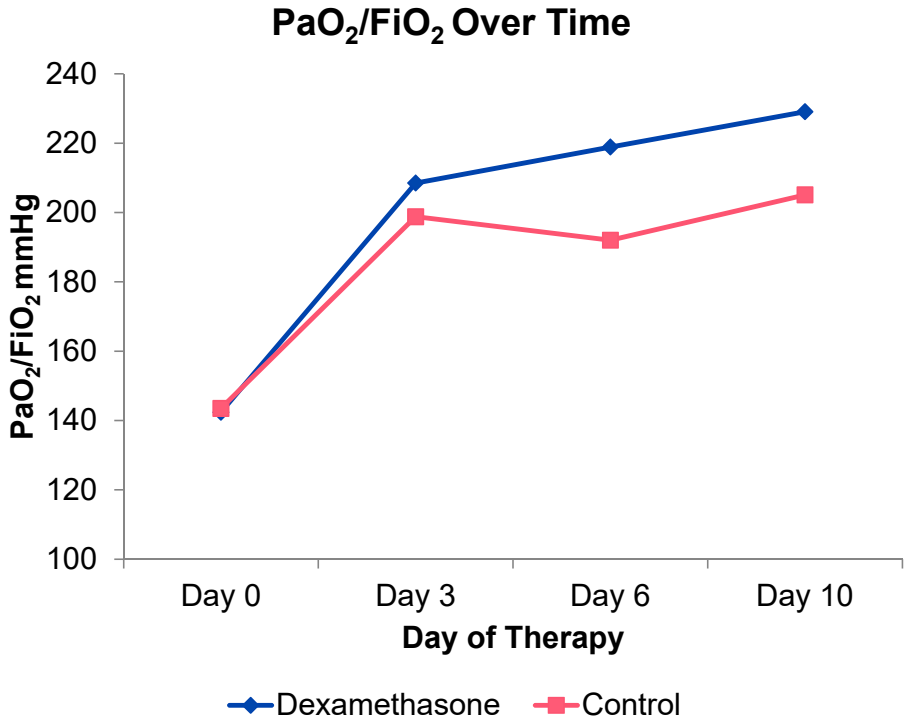
DEXA-ARDS: Results



All outcomes were statistically significant

DEXA-ARDS: Results





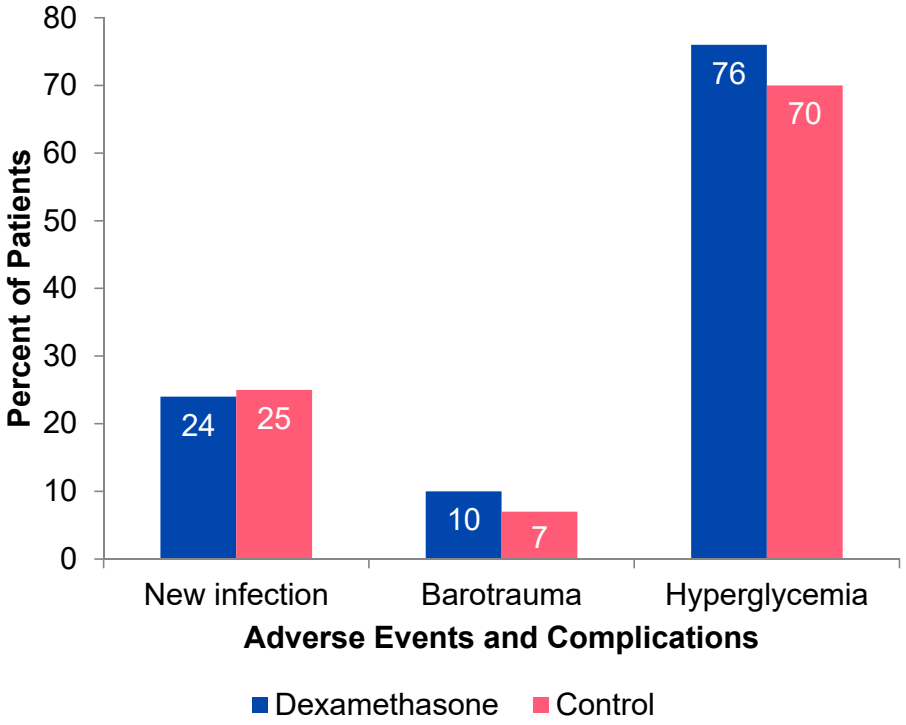
All outcomes were statistically significant

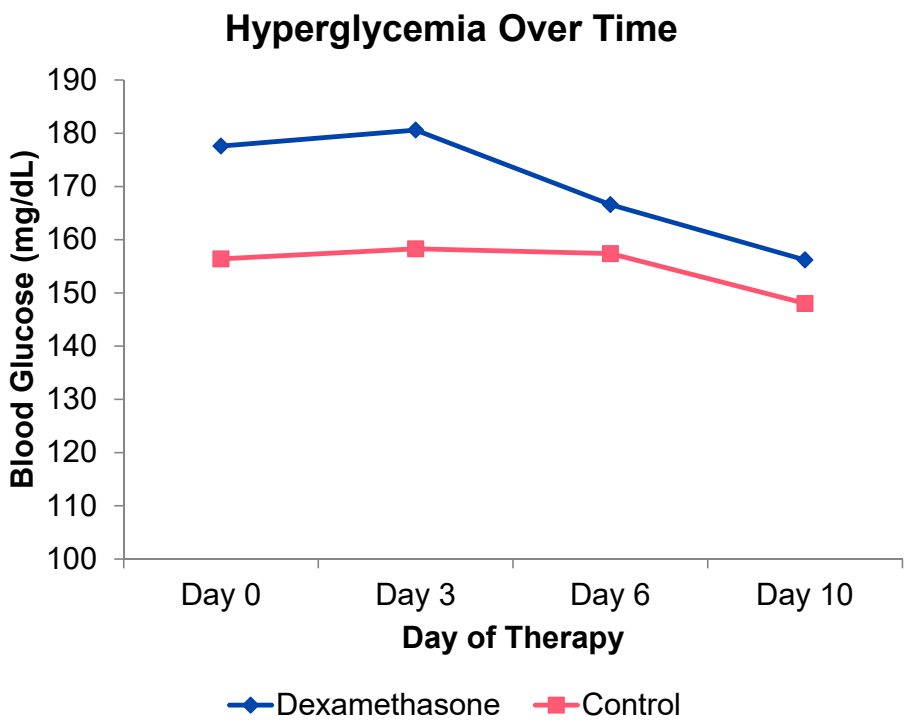
Villar et al. *Lancet Respir Med*. 2020;8:267-76.

MV: Mechanical Ventilation
ICU: Intesive Care Unit
PaO_2 : Partial Pressure of Oxygen

FiO_2 : Fraction of Inspired Oxygen

DEXA-ARDS: Adverse Events and Complications





No statistically significant differences

Villar et al. *Lancet Respir Med*. 2020;8:267-76.

DEXA-ARDS: Strengths & Weaknesses

Strengths

- Used lung-protective strategies
- Utilized dexamethasone as steroid
- Different dose, duration, and administration regimen
- Consistent, standardized approach to evaluating patients

Weaknesses

- Early trial stop
- Dexamethasone was NOT masked
- How dexamethasone dose was chosen
- Supportive cares were not controlled
- Strict inclusion and exclusion

Villar et al. *Lancet Respir Med*. 2020;8:267-76.

Which of the following differed with the DEXA-ARDS study compared to the previous studies?

- Classified ARDS by Berlin definition
- Longer total duration of steroids
- Standardized assessment of PaO_2/FiO_2 among patients
- Controlled what other ARDS strategies were allowed to be used

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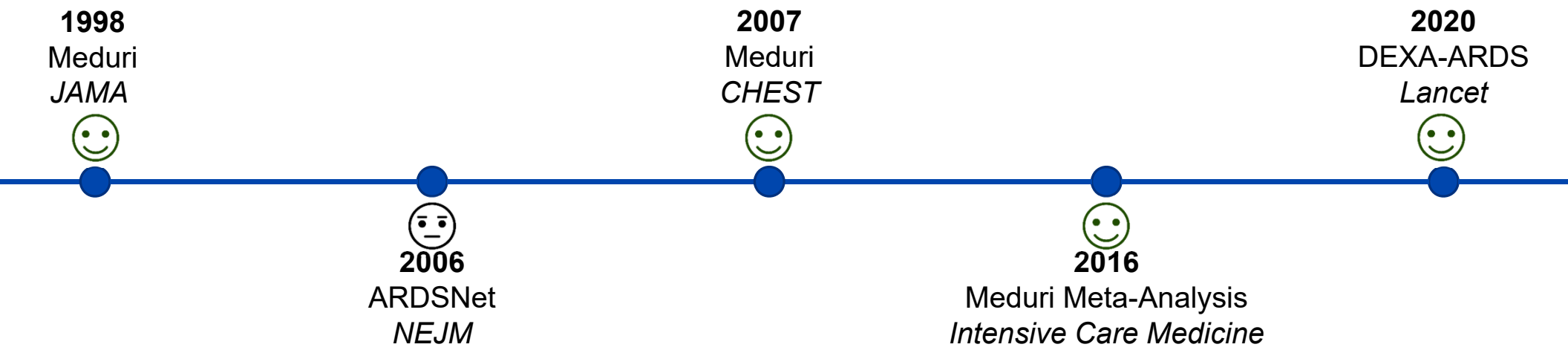
History of Steroids in ARDS



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History of Steroids in ARDS

1998
Meduri
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NEJM

2020
DEXA-ARDS
t
Meduri Meta-Analysis
Intensive Care Medicine

Is there a benefit of corticosteroids in viral ARDS?

Meduri et al. *JAMA*. 1998;280:159-165.
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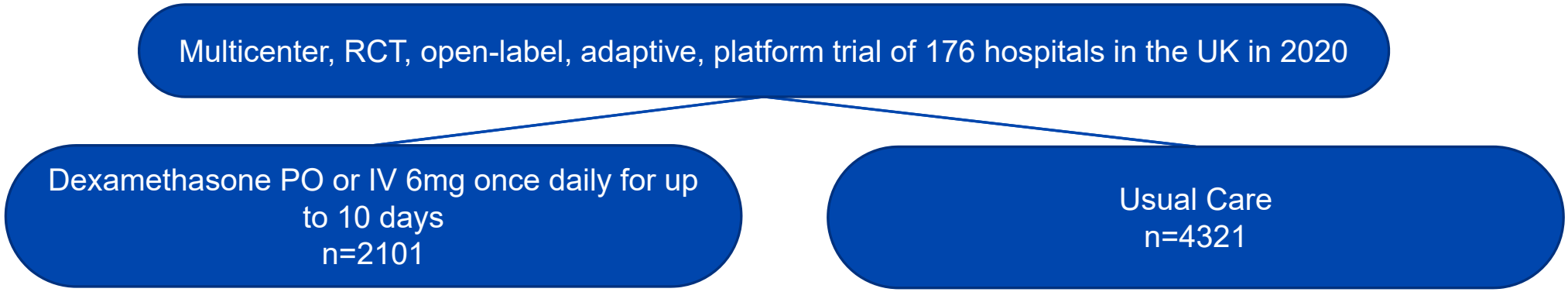
RECOVERY Trial



Inclusion	Exclusion
Clinically suspected or lab confirmed COVID-19	Dexamethasone unavailable at time of recruitment for either arm
No medical history that would put patient at risk for participation	

RECOVERY Collaborative Group. *New Eng J Med.* 2020.

UK: United Kingdom
PO: Oral
IV: Intravenous

RECOVERY Trial

Multicenter, RCT, open-label, adaptive, platform trial of 176 hospitals in the UK in 2020

Outcomes

Primary: All-cause mortality within 28 days

Secondary:
- -Time to hospital discharge
- -Death
- -Receipt and duration of MV
- -Receipt of renal HD or hemofiltration
- -Receipt of MV/ ECMO
- -Cause-specific mortality
- -Major cardiac arrhythmia

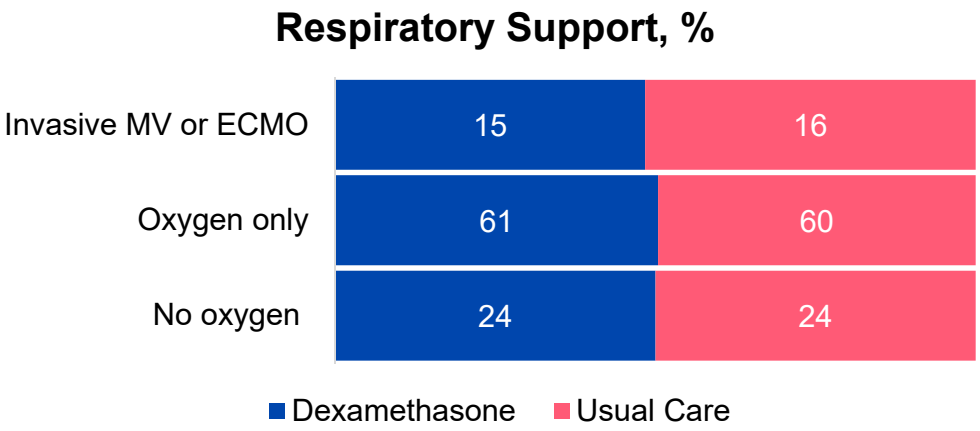
COVID-19	of recruitment for either arm
No medical history that would put patient at risk for participation	

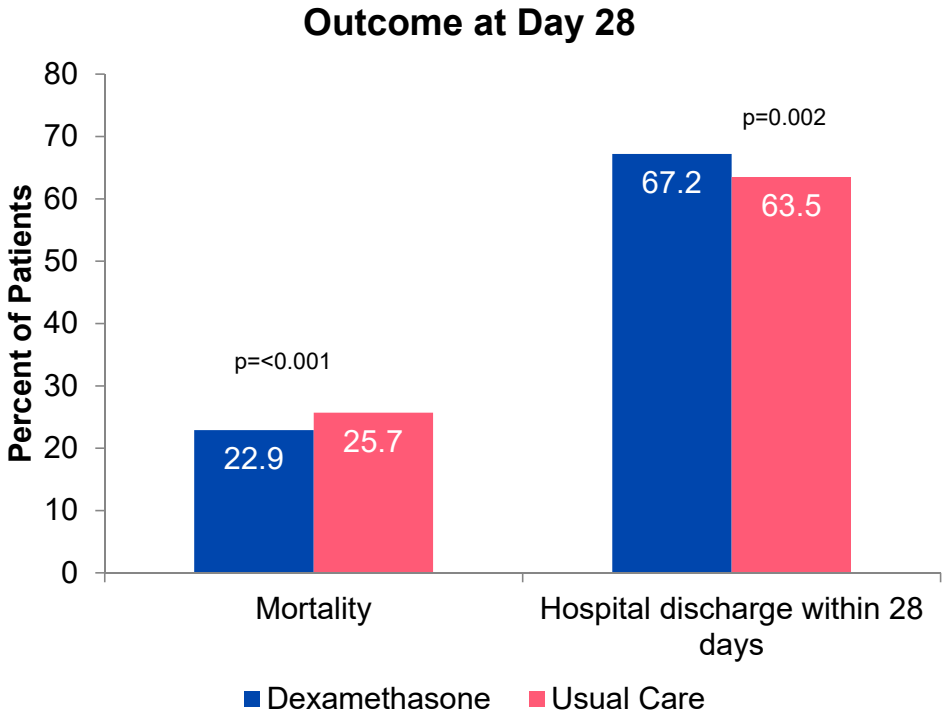
RECOVERY Collaborative Group. *New Eng J Med.* 2020.

UK: United Kingdom
PO: Oral
IV: Intravenous
HD: Hemodiialysis

MV: Mechanical Ventilation
ECMO: Extracorporeal Membrane Oxygenation

RECOVERY: Baseline Characteristics

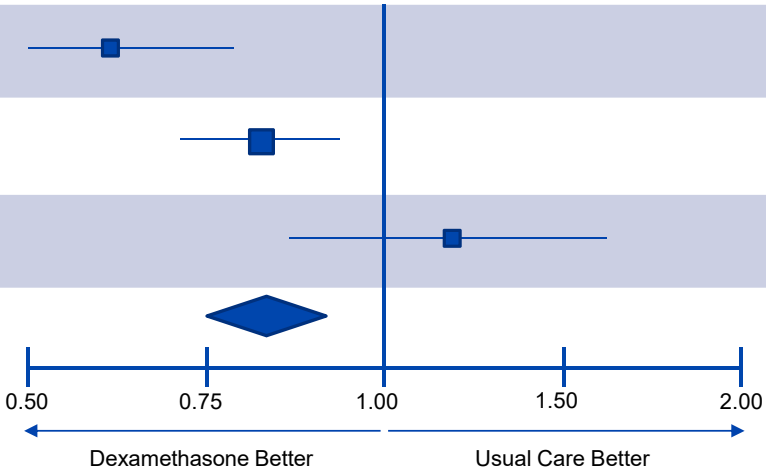




RECOVERY Collaborative Group. *New Eng J Med.* 2020.

MV: Mechanical Ventilation
ECMO: Extracorporeal Membrane Oxygenation

Respiratory support at randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	No. of events / total no. (%)		
Invasive MV	95 / 324 (29.3)	283 / 683 (41.4)	0.64 (0.51 - 0.81)
Oxygen only	298 / 1279 (23.3)	682 / 2604 (26.2)	0.82 (0.72 - 0.94)
No oxygen received	89 / 501 (17.8)	145 / 1034 (14.0)	1.19 (0.91 - 1.55)
All patients	**482 / 2104 (22.9)**	**1110 / 4321 (25.7)**	**0.83 (0.75 - 0.93)**
			P < 0.001



Dexamethasone reduced death by:

1/3 in those receiving MV
1/5 in those receiving oxygen only

RECOVERY Collaborative Group. *New Eng J Med.* 2020.

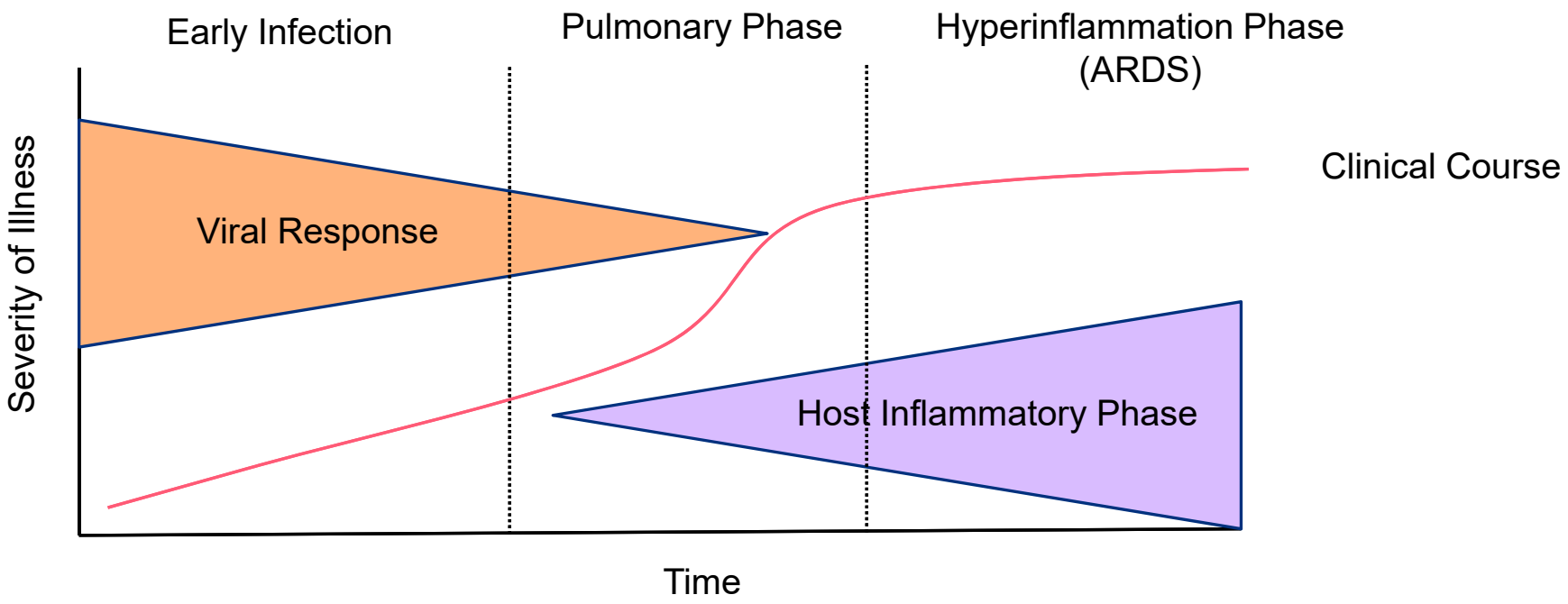
MV: Mechanical Ventilation

RECOVERY: Concerns

- Unavailable dexamethasone exclusion criteria
- Open-label
- Sample size estimation
- Poor statistical descriptions
- Prespecified analysis of respiratory support a potential type I error
- Certain outcomes never analyzed
- Applicability of secondary outcomes

RECOVERY Collaborative Group. *New Eng J Med.* 2020.
Morris et al. *Zendoo*. 2020.

Window of Steroid Use?



Yuki et al. *Clinical Immunology*. 2020;108:427.

I would recommend using a steroid to treat ____.

- ARDS (not from COVID-19)
- COVID-19 ARDS
- Both
- Neither

I would recommend using a steroid to treat ____.

- ARDS (not from COVID-19)
- COVID-19 ARDS

Open ended

- Both
- Neither

Overall Thoughts

Heterogeneity in ARDS

Heterogeneity in steroids

Need for subsequent studies and analyses

Personal Recommendations

ARDS

- Pneumonia and sepsis are reasonable indications
- DEXA-ARDS dexamethasone regimen

COVID

- Consider if patient is requiring oxygen
- Overall promising results, but need further studies

Summary

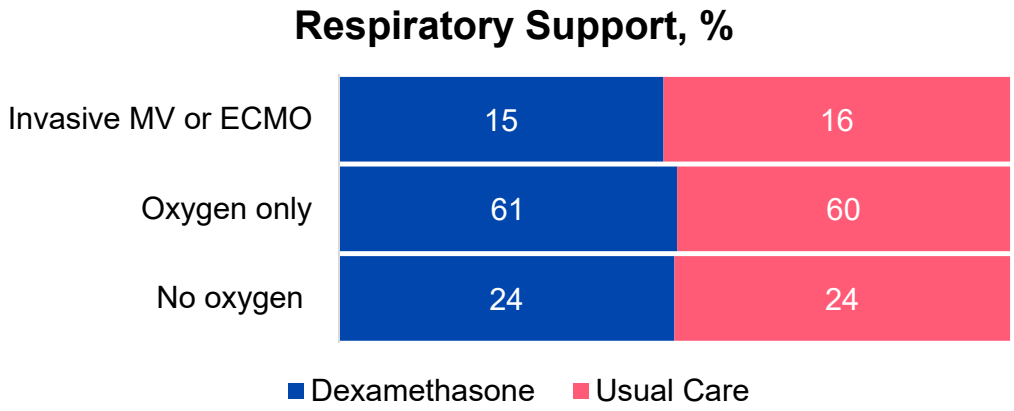
- Corticosteroids in ARDS have been area of practice controversy for decades
- The recent results from the DEXA-ARDS and RECOVERY trials highlight the benefit of dexamethasone in early ARDS
- Further research is needed to identify appropriate patient populations that benefit most from steroid use

MAYO CLINIC

Questions & Comments

Nicholas Vollmer, PharmD
PGY-2 Critical Care Pharmacy Resident

RECOVERY: Baseline Characteristics



	Dexamethasone	Usual Care
Age, mean	66.9	65.8
Diabetes, %	25	24
Heart disease, %	28	27
Chronic lung disease, %	20	22
Positive COVID test, %	88	89

	Dexamethasone	Usual Care	Invasive MV or ECMO	Oxygen only	No oxygen
Days since symptom onset, median (IQR)	8 (5-13)	9 (5-13)	13 (8-18)	9 (5-12)	6 (3-10)

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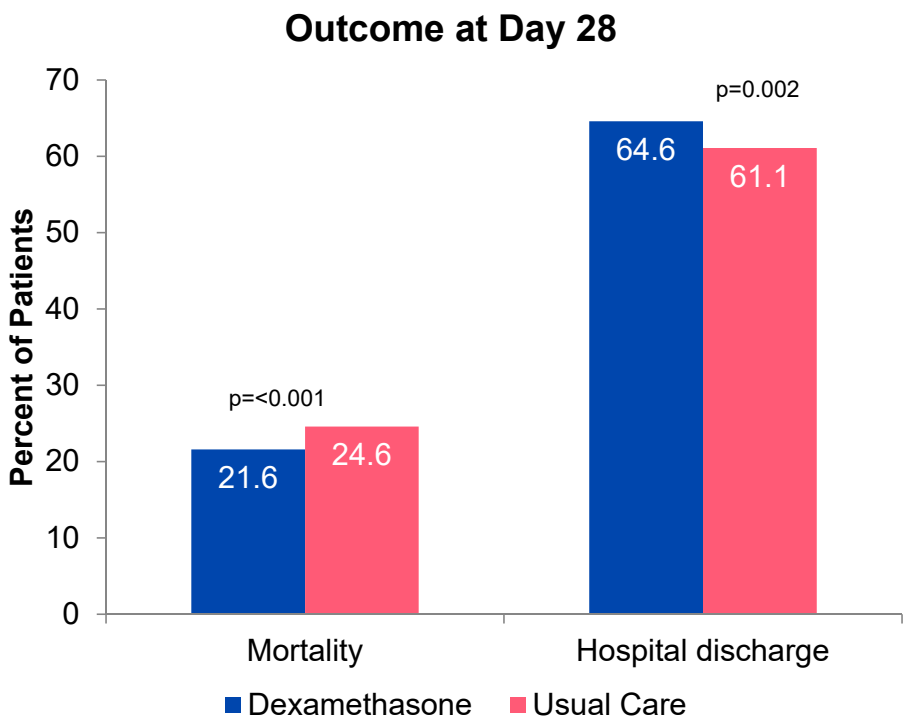
MV: Mechanical Ventilation
ECMO: Extracorporeal Membrane Oxygenation

RECOVERY: Results



Mortality at Day 28 (p<0.001)		
Days since symptom onset	RR	95% CI
≤ 7	1.01	0.87 – 1.17
> 7	0.69	0.59 – 0.80

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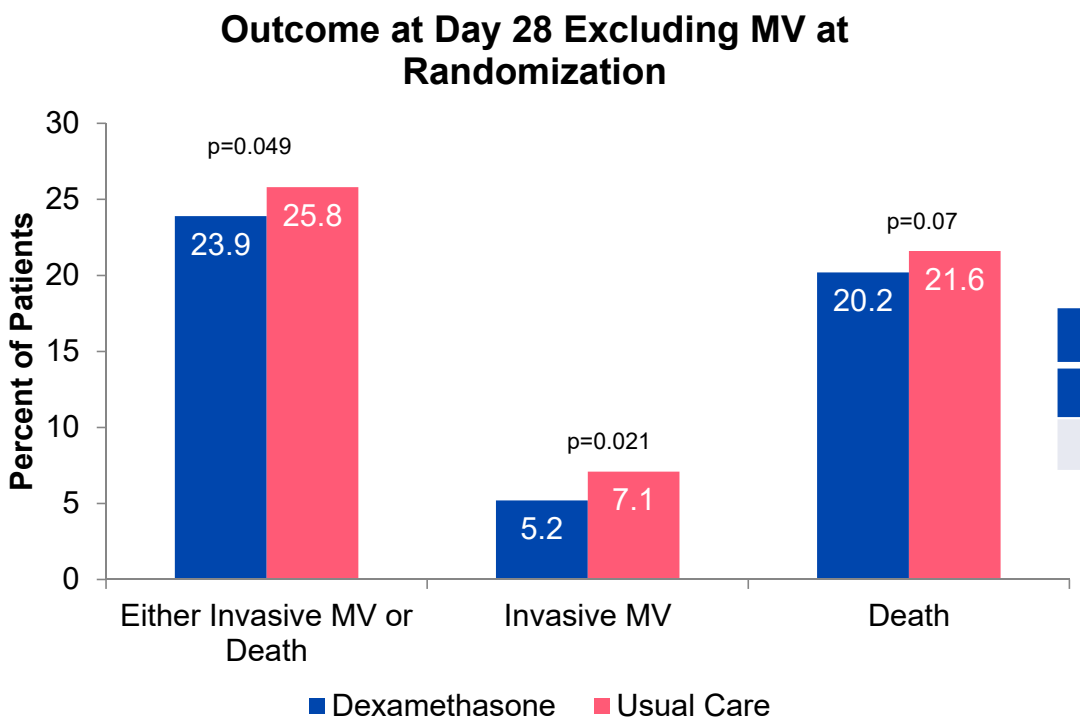
RR: Relative Risk
CI: Confidence Interval

RECOVERY: Results



Discharged from Hospital within 28 Days		
	RR	95% CI
Dexamethasone vs Usual Care	1.1	1.03 – 1.17

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RR: Relative Risk
CI: Confidence Interval