MAYO CLINIC

Going Viral

The Role of Remdesivir in COVID-19

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Pharmacy Grand Rounds
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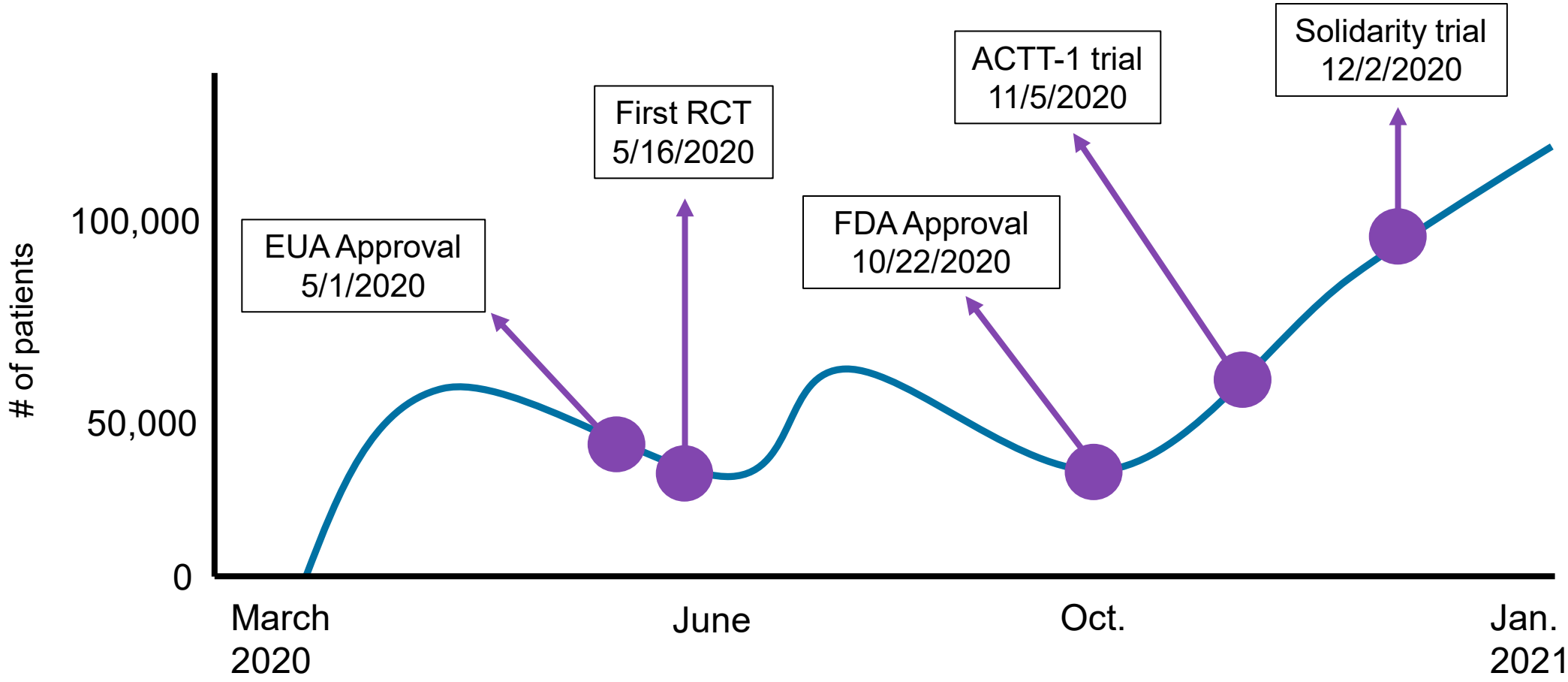
Learning Objectives

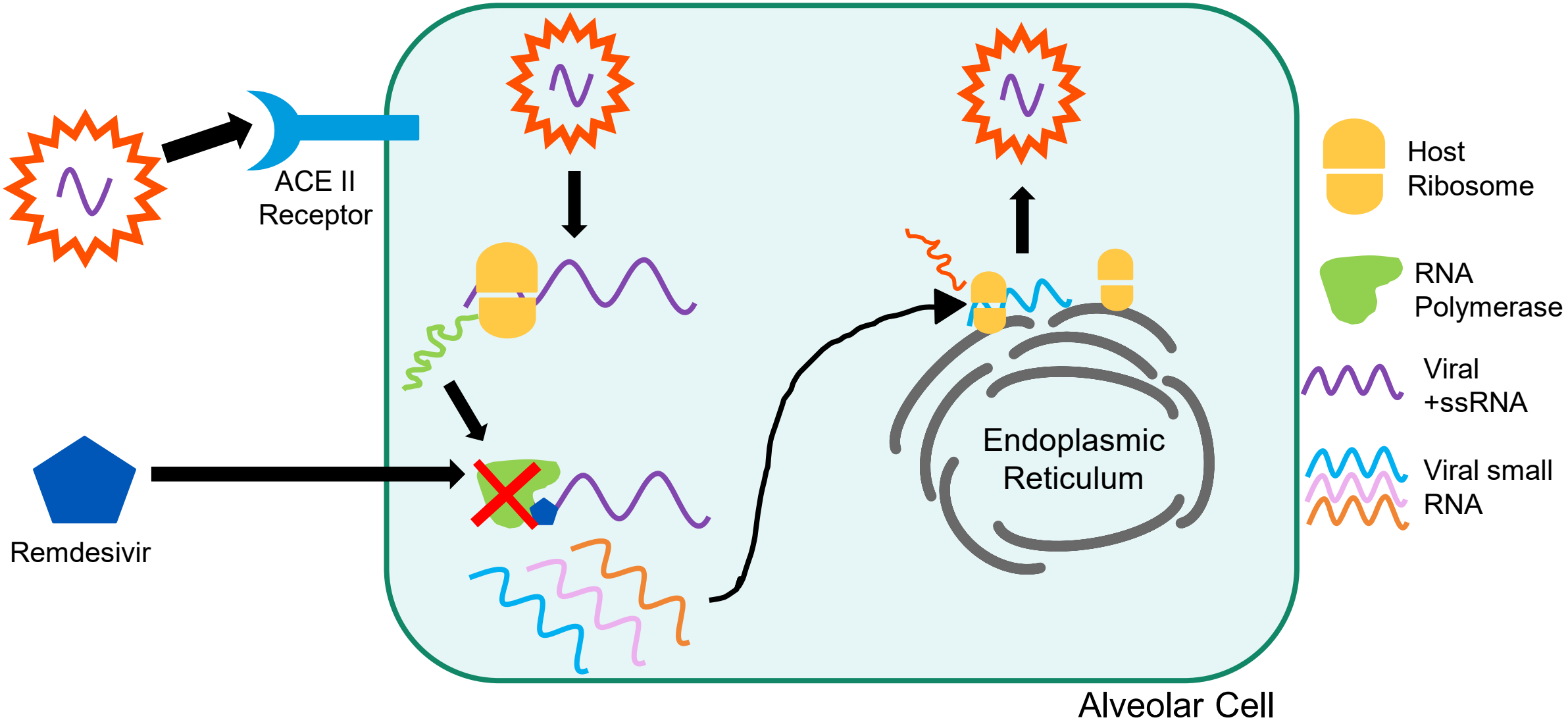
- Describe remdesivir's mechanism of action against SARS-CoV-2
- Identify optimal adult patient populations for remdesivir
- Outline future directions for remdesivir in COVID-19 treatment

Hospitalized COVID-19 Patients – United States

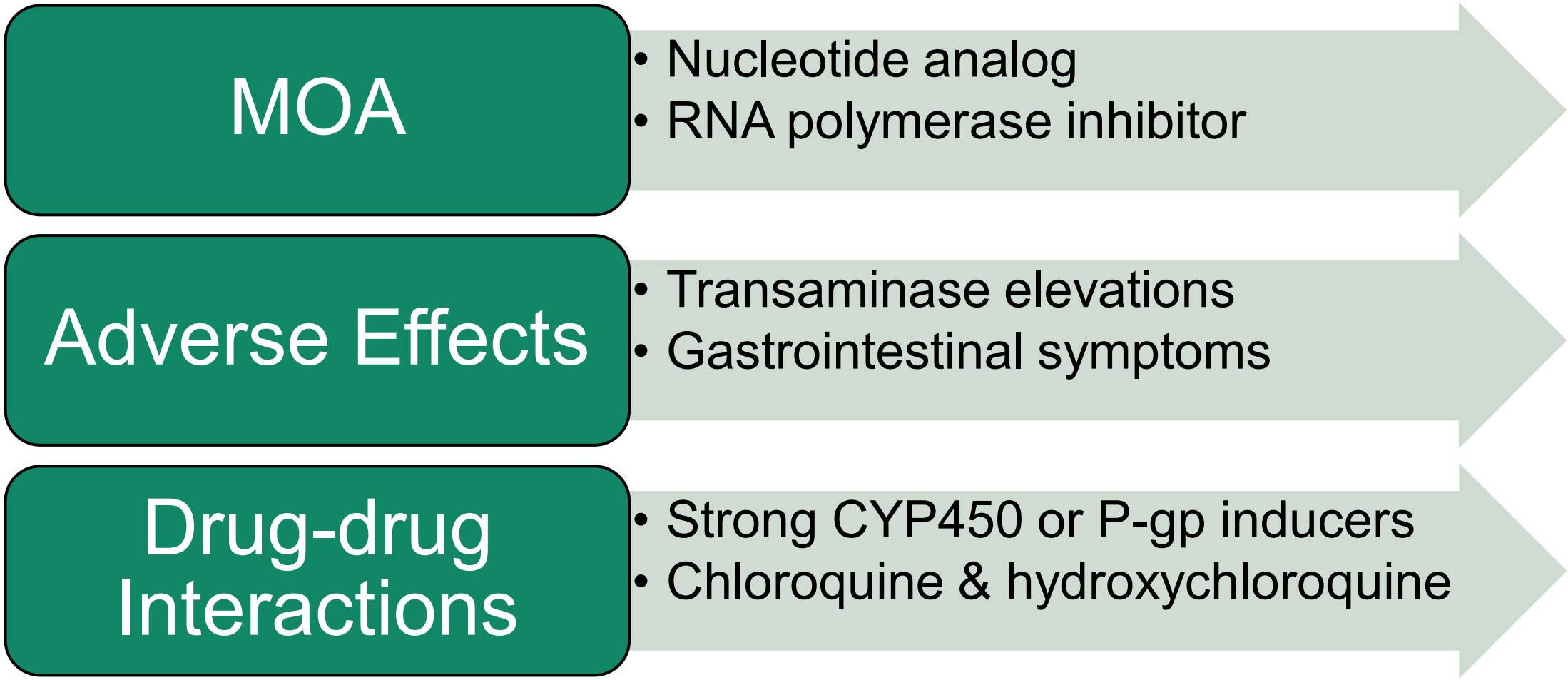


Accessed January 2021: https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html

Pharmacology



Drug Information



MOA: mechanism of action
CYP450: cytochrome P450
P-gp: P-glycoprotein

Clin Transl Sci. 2020 Sep;13(5):842-844.
Veklury [package insert]. Foster City, CA. Gilead Sciences Inc. 2020.

Assessment Question #1

- Which of the following viral replication processes does remdesivir inhibit?
  - RNA transcription
  - RNA translation
  - Protein transcription
  - Protein translation

Clinical Efficacy

1

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Wang et al. May 2020.

1

Methods

Inclusion Criteria

- Pneumonia
- SpO2 ≤ 94% on room air
- Within 12 days of symptom onset

Intervention

- Randomized 2:1
- Received 200 mg IV x 1 dose, followed by 100 mg IV days 2-10
- Matching placebo

Primary Outcome

- Time to clinical improvement within 28 days
- Defined on an ordinal scale, or discharge from the hospital

Lancet. 2020 May 16;395(10236):1569-1578.

1

Severity Score

Clinical Improvement = 2-point reduction

1	• Discharge criteria
2	• Hospital admission
3	• Low-flow oxygen
4	• High-flow oxygen
5	• ECMO or mechanical ventilation
6	• Death

ECMO: extracorporeal membrane oxygenation

Lancet. 2020 May 16;395(10236):1569-1578.

1

Baseline Characteristics

	RDV (n=158)	Placebo (n=78)
Age (yr)	66	64
Male (%)	56	65
Any comorbidity (%)	71	71
Serum creatinine (mg/dL)	0.77	0.81
Low-Flow O2 (%)	82	83
High-Flow O2 (%)	18	12
≤ 10 days from symptom onset (%)	46	60

RDV: remdesivir

Lancet. 2020 May 16;395(10236):1569-1578.

1

Results

	RDV (n=158)	Placebo (n=78)	Difference (95% CI)
Primary Outcome:			
Clinical improvement on day 28 (%)	65	58	7.5 (-5.7 to 20.7)
Secondary Outcomes:			
Time to clinical improvement (d)	21	23	1.23 (0.87 to 1.75)*
Mortality at day 28 (%)	14	13	1.1 (-8.1 to 10.3)
Duration of hospitalization (d)	25	24	0 (-4.0 to 4.0)
Any adverse event (%)	66	64	----
Increased AST (%)	5	12	----
Any serious adverse event (%)	18	26	----
Respiratory failure (%)	10	8	----

* Hazard ratio

RDV: remdesivir
AST: aspartate transaminase

Lancet. 2020 May 16;395(10236):1569-1578.

Conclusion

Strengths

- First RCT evaluating RDV in COVID-19
- Use of an ordinal scale for symptom assessment

Limitations

- Underpowered
- RDV initiated late in disease progression

Well-tolerated, but lack of significant clinical effects

RCT: randomized controlled trial
RDV: remdesivir

2 Remdesivir for the Treatment of Covid-19 – Final Report (ACTT-1)

Beigel et al. November 2020.

2

Methods

Inclusion Criteria

- Hospitalized adults
- PCR positive
- Infiltrates on imaging or oxygen requirement
- eGFR ≥ 30 mL/min

Intervention

- Randomized 1:1
- Received 200 mg IV x 1 dose, followed by 100 mg IV days 2-10
- Matching placebo

Primary Outcome

- Time to recovery
- Recovery defined as a score of 1, 2, or 3 on a severity ordinal scale

PCR: polymerase chain reaction
eGFR: estimated glomerular filtration rate

N Engl J Med 2020; 383:1813-1826.

2

Severity Score

1	• Not hospitalized and no limitations of activities
2	• Not hospitalized with limitations of activities
3	• Hospitalized, no longer requiring ongoing care
4	• Requiring ongoing medical care, but no O2 supplement
5	• Requiring any supplemental oxygen
6	• Requiring high-flow oxygen devices
7	• Invasive mechanical ventilation or ECMO
8	• Death

ECMO: extracorporeal membrane oxygenation

N Engl J Med 2020; 383:1813-1826.

2

Baseline Characteristics

	RDV (n=541)	Placebo (n=521)
Age (yr)	58.6	59.2
Male (%)	65.1	63.7
White (%)	51.6	55.1
Time from symptom onset (days, IQR)	9, 6-12	9, 7-13
Any coexisting condition (%)	81.7	81.2
Medical care, no oxygen (%)	3.9	12.1
Supplemental oxygen (%)	42.9	39
High-flow oxygen (%)	17.6	18.8
Mech vent or ECMO (%)	24.2	29.6

RDV: remdesivir
ECMO: extracorporeal membrane oxygenation

N Engl J Med 2020; 383:1813-1826.

2

Results

	RDV (n=541)	Placebo (n=521)	RR (95% CI)
Primary Outcome:			
Time to recovery – all groups (d)	10	15	**1.29 (1.12 to 1.49)**
Secondary Outcomes:			
Time to recovery			
Medical care, no oxygen (d)	5	6	1.29 (0.91 to 1.83)
Supplemental oxygen (d)	7	9	**1.45 (1.18 to 1.79)**
High-flow oxygen (d)	15	20	1.09 (0.76 to 1.57)
Mech vent or ECMO (d)	29	28	0.98 (0.7 to 1.36)

RDV: remdesivir
ECMO: extracorporeal membrane oxygenation

N Engl J Med 2020; 383:1813-1826.

2

Results

	RDV (n=541)	Placebo (n=521)	RR (95% CI)
Secondary Outcomes:			
Mortality – all groups (n)	59	77	0.73 (0.52 to 1.03) *
Supplemental oxygen (n)	9	25	**0.3 (0.14 to 0.64) ***
Improvement of 1 category (d)	7	9	**1.23 (1.08 to 1.41)**
Improvement of 2 categories (d)	11	14	**1.29 (1.12 to 1.48)**
Duration of hospitalization (d)	12	17	**-5 (-7.7 to -2.3)**
Duration of O2 supplementation (d)	13	21	**-8 (-11.8 to -4.2)**

* Hazard ratio

RDV: remdesivir

N Engl J Med 2020; 383:1813-1826.

Conclusion

Strengths

- Generalizable patient population
- Patients stratified by disease severity

Limitations

- Overall results driven by score 5 patients
- Other experimental drug use prior to enrollment was allowed

RDV is superior to placebo in reducing time to recovery of COVID-19

RDV: remdesivir

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

Pan et al. December 2020.

3

Methods

Inclusion Criteria

- Hospitalized adult patients
- Diagnosis of Covid-19
- No previous receipt of trial medication

Intervention

- Randomized 1:1
- Received 200 mg IV x 1 dose, followed by 100 mg IV days 2-10
- Compared with standard of care

Primary Outcome

- In-hospital mortality

N Engl J Med. DOI: 10.1056/NEJMoa2023184.

3

Study arms

Adaptive study design

1 Remdesivir

2 Hydroxychloroquine

3 Lopinavir/ritonavir

4 Interferon beta-1a

5 Standard of care

N Engl J Med. DOI: 10.1056/NEJMoa2023184.

Baseline Characteristics

	RDV (n=2743)	Standard of care (n=2708)
Age 50-69 (%)	46.7	47.5
Male (%)	62.2	63.7
Low-flow or hi-flow O2 (%)	66.6	66.9
Bilateral lung lesions (%)	79.3	79.5
Corticosteroid use (%)	47.8	47.6
European/Canadian (%)	26.1	25.8

RDV: remdesivir

N Engl J Med. DOI: 10.1056/NEJMoa2023184.

3

Results

	RDV (n=2743)	Standard of care (n=2708)	RR (95% CI)
Primary Outcome:			
In-hospital mortality (%)	12.5	12.7	0.95 (0.81 to 1.11)
Secondary Outcomes:			
Mortality – no mech ventilation (%)	9.4	10.6	0.86 (0.67 to 1.11)
Mortality – mech ventilation (%)	43	37.8	1.2 (0.8 to 1.8)
Initiation of ventilation (%)	11.9	11.5	----
Composite mortality and ventilation (%)	18.5	18.9	0.97 (0.85 to 1.10)

RDV: remdesivir

N Engl J Med. DOI: 10.1056/NEJMoa2023184..

Conclusion

Strengths

- Mortality as primary outcome
- Largest sample size

Limitations

- Open label study design
- Heterogeneity of standard of care

RDV did not reduce mortality, initiation of ventilation, or hospital duration

RDV: remdesivir

ACTT-1

n = 1062

Primary endpoint:
Time to recovery

Faster time to recovery

Solidarity

n = 5451

Primary endpoint:
Mortality

No mortality benefit

N Engl J Med 2020; 383:1813-1826.
N Engl J Med. DOI: 10.1056/NEJMoa2023184.

Recommendations

WHO	IDSA	NIH
• Recommend against the use of remdesivir	• Hospitalized patients with severe COVID-19 • Severe = SpO2 < 94% on RA, or requiring supplemental oxygen, ECMO, mechanical ventilation	• Hospitalized patients who require supplemental oxygen • Not patients who require mechanical ventilation

https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients
https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v3.6.0.pdf

Assessment Question #2

- Which of the following can be concluded from the clinical studies evaluating remdesivir use?
  - The greatest benefit has been shown in patients requiring no oxygen at baseline
  - No mortality benefit has been shown in any patient populations
  - Time to clinical recovery may be shorter with the use of remdesivir
  - The greatest benefit has been shown in patients mechanically ventilated at baseline

Remdesivir Use*

Patient Population

- Hospitalized adults with pulmonary disease

- Respiratory rate > 30 breaths/min
- SpO2 < 93% on RA
- Pneumonia by chest X-ray

Dosing

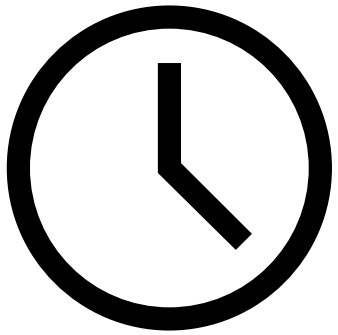
- 200 mg IV x 1 dose, followed by 100 mg IV daily

Duration

?

RA: room air

* AskMayoExpert Rochester site recommendations as of 1/25/21



Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Goldman et al. November 2020.

Methods

Inclusion Criteria

- Patients ≥ 12 y.o. with PCR confirmed disease
- Radiographic evidence
- SpO2 < 94% or receiving supplemental O2

Intervention

- Randomized 1:1
- Both groups received 200 mg IV x 1 dose
- Followed by 4 or 9 days of 100 mg IV daily

Primary Outcome

- Clinical status assessed on day 14
- Assessed on a 7-point ordinal scale

PCR: polymerase chain reaction

N Engl J Med 2020; 383:1827-1837

Severity Score

1	• Death
2	• Receiving invasive mech vent or ECMO
3	• Requiring high-flow oxygen devices
4	• Requiring low-flow supplemental O2
5	• Requiring ongoing medical care, but no O2 supplement
6	• Hospitalized, no longer requiring ongoing care
7	• Not hospitalized

ECMO: extracorporeal membrane oxygenation

N Engl J Med 2020; 383:1813-1826.

Baseline Characteristics

	5-Day (n=200)	10-Day (n=197)
Age (yr)	61	62
Male (%)	60	68
Clinical Status*		
Mech vent or ECMO (%)	2	5
High-flow oxygen (%)	24	30
Low-flow oxygen (%)	56	54
No supplemental O2 (%)	17	11

* p = 0.02

ECMO: extracorporeal membrane oxygenation

N Engl J Med 2020; 383:1827-1837

Results

	5-Day (n=200)	10-Day (n=197)	Baseline-Adjusted Difference (95% CI)
Primary Outcome: Clinical status at day 14*			
Death (%)	8	11	---
Mech vent or ECMO (%)	8	17	---
High-flow oxygen (%)	4	5	---
Low-flow oxygen (%)	10	7	---
Medical care, no oxygen (%)	6	7	---
Hospitalized (%)	4	2	---
Discharged (%)	60	52	---
Secondary Outcomes:			
Time to clinical improvement (d)	10	11	0.79 (0.61 to 1.01)
Time to recovery (d)	10	11	0.81 (0.64 to 1.04)

* p = 0.14

ECMO: extracorporeal membrane oxygenation

N Engl J Med 2020; 383:1827-1837

Conclusion

Strengths

- Targeted patient population to receive shorter course
- Use of an ordinal scale for disease severity

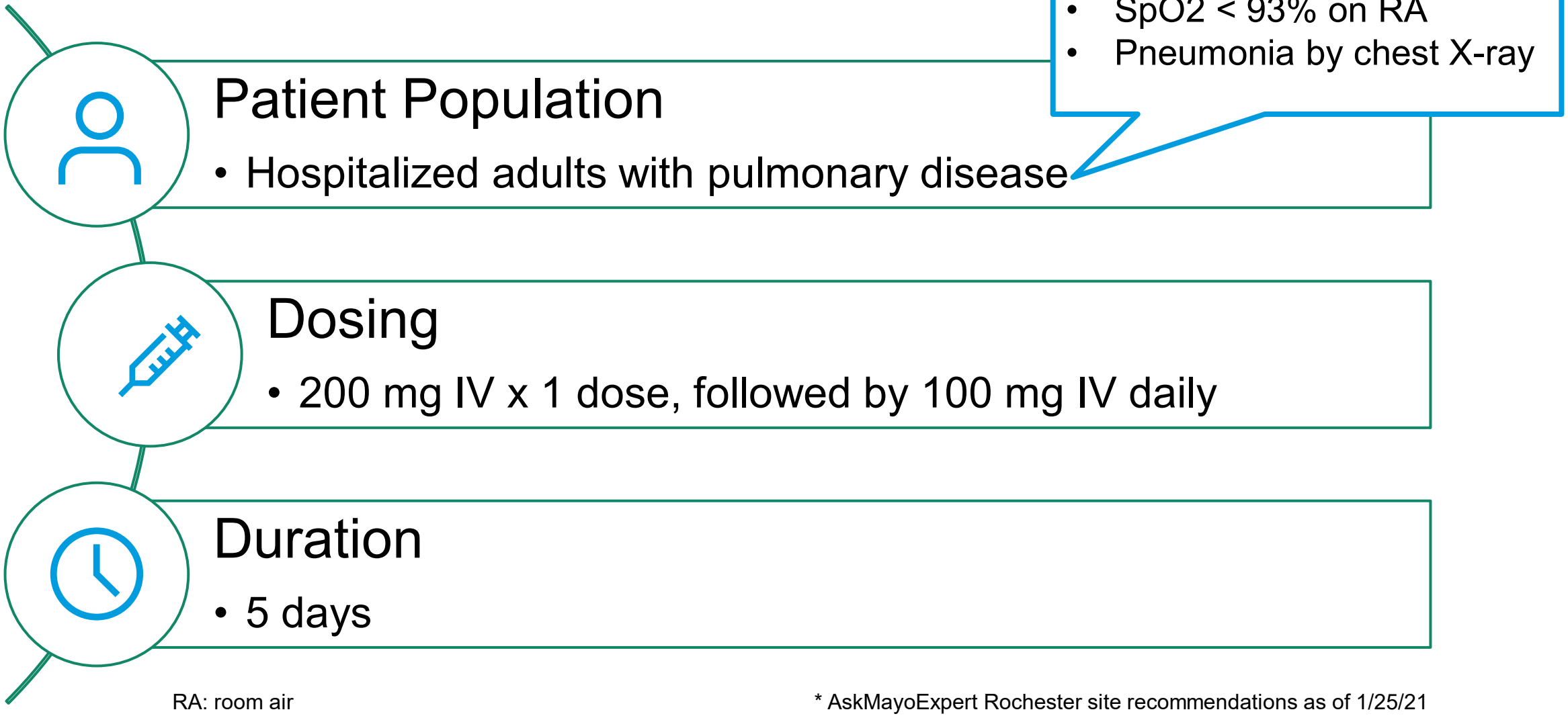
Limitations

- Imbalance in disease severity at baseline
- Underpowered

No significant difference in efficacy between 5- & 10-day courses of RDV

RDV: remdesivir

Remdesivir Use*

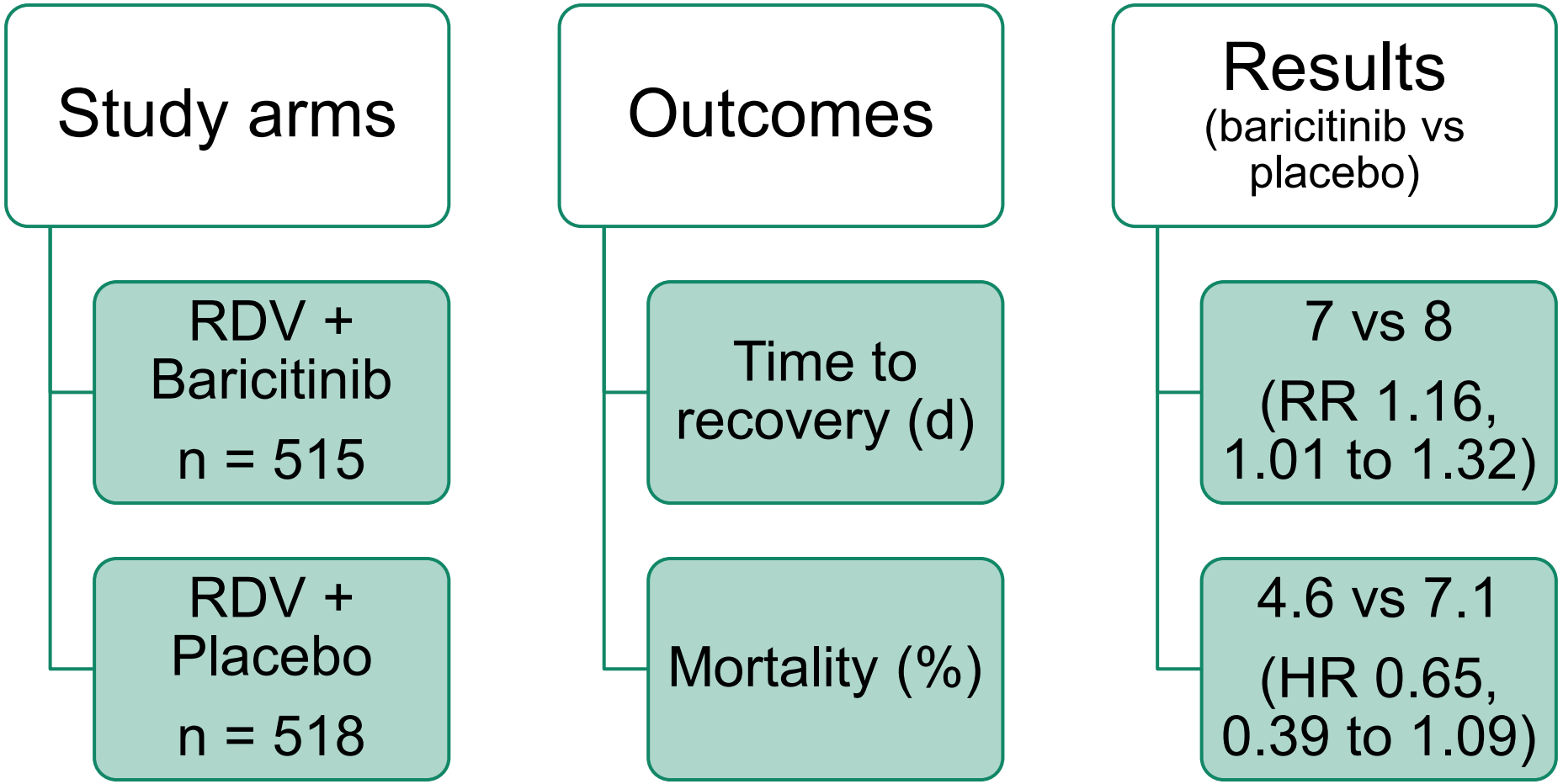


RA: room air

* AskMayoExpert Rochester site recommendations as of 1/25/21

Future Directions

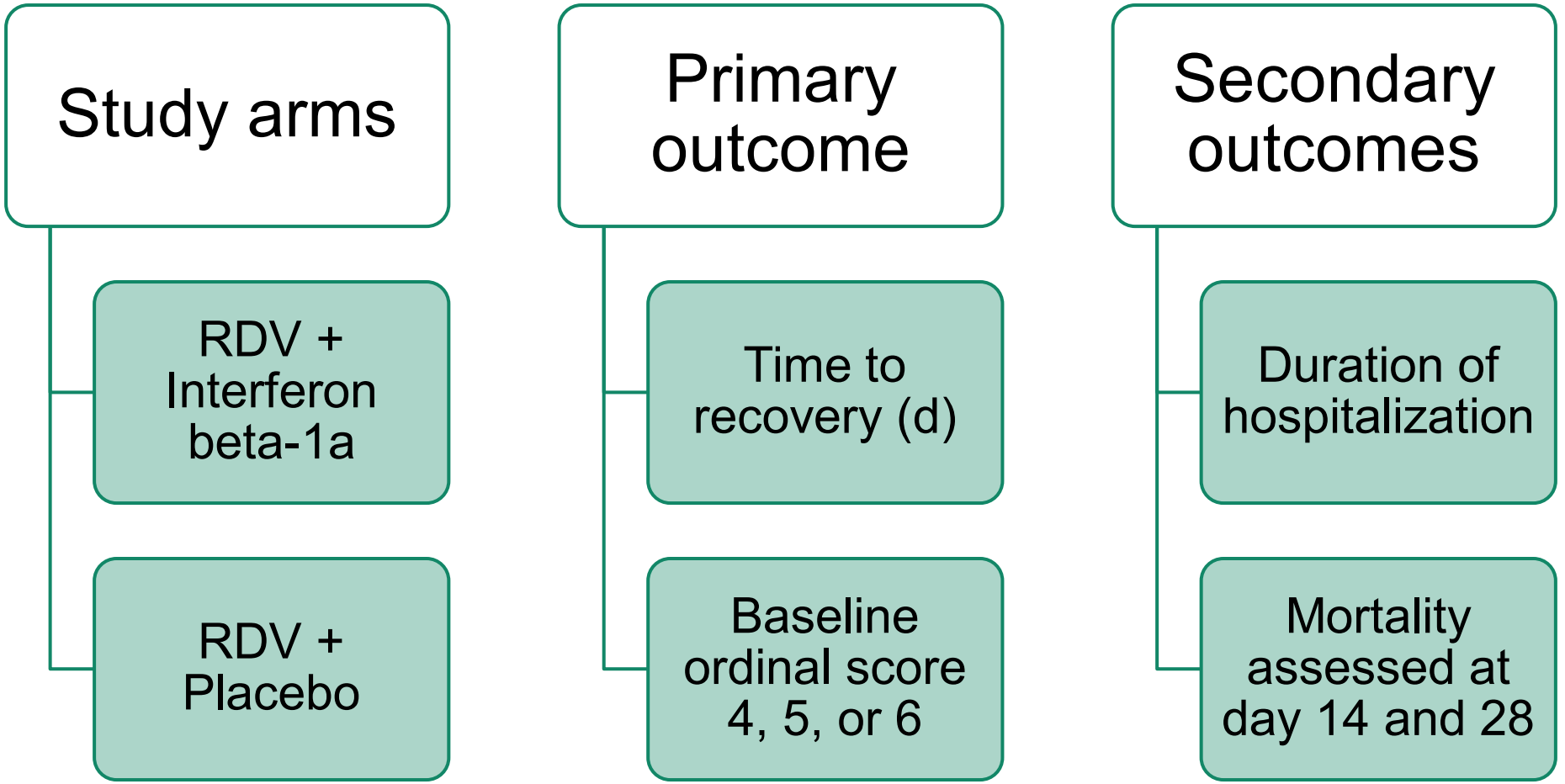
RDV + Baricitinib – ACTT-2



RDV: remdesivir

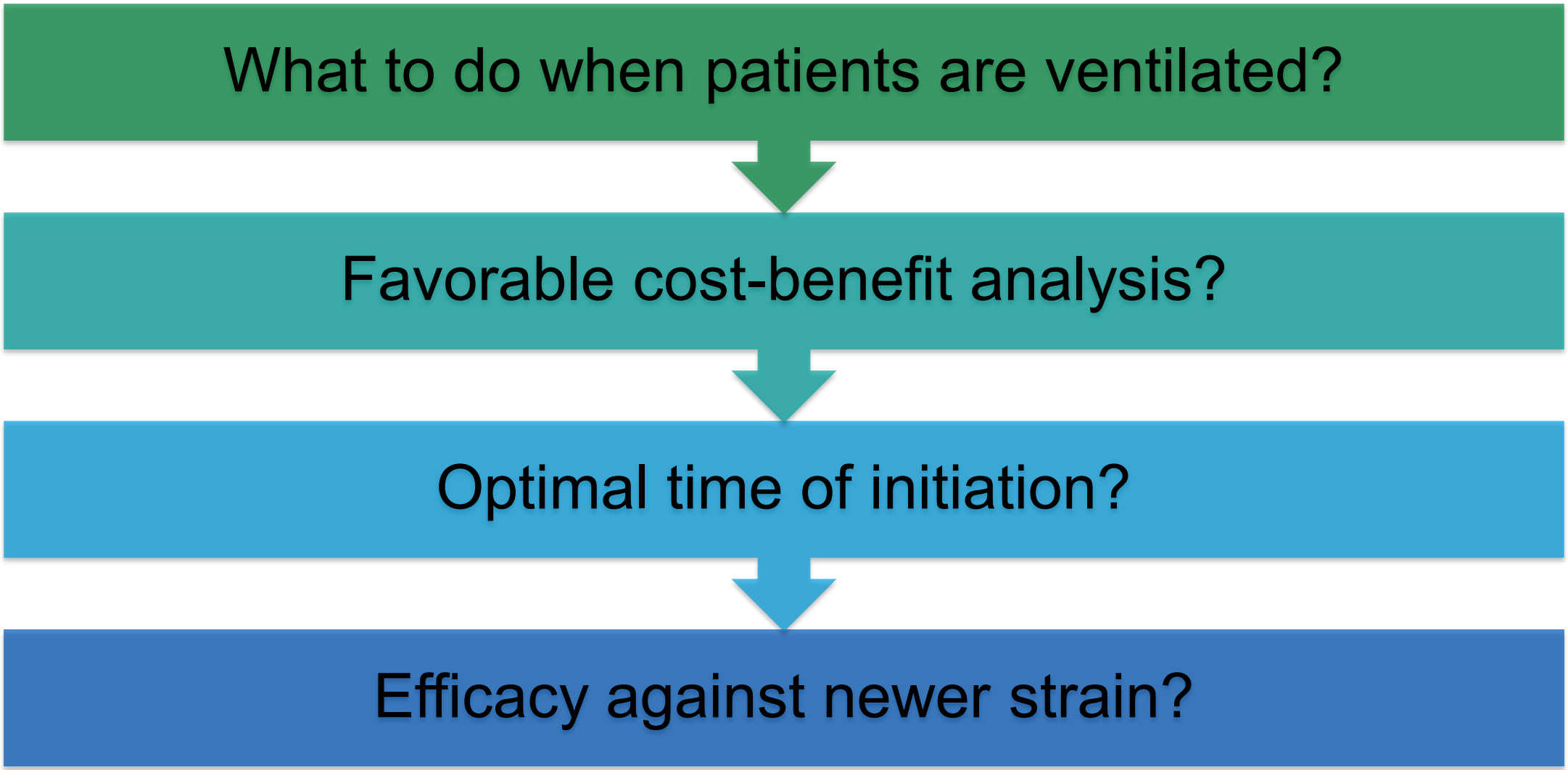
N Engl J Med 2020; 383:1827-1837

RDV + Interferon beta-1a – ACTT-3



RDV: remdesivir

Unanswered Questions



Assessment Question #3

- Which patient would be the **best** candidate for remdesivir based on ACTT-1 criteria?
  - Allogeneic bone marrow transplant recipients
  - Asymptomatic, outpatient
  - Requiring oxygen via nasal cannula, SpO2 95%
  - Increased shortness of breath, SpO2 95%

Conclusions

- Remdesivir prevents viral replication via inhibition of RNA-dependent RNA polymerase
- Remdesivir has shown to improve time to clinical recovery in patients requiring low-flow oxygen
- Many unanswered questions to be explored

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