Poster #P-2021

How have COVID-19 treatment guidelines and the scientific evidence evolved throughout the pandemic and endemic eras?

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Conclusions

- To assure that providers in the hospital setting are aware of and deploy evidence-based optimal care for patients with COVID-19, recommendations should rely on current evidence, including real-world data
- Our comprehensive evaluation of scientific literature indicates that evidence of remdesivir impact on mortality in hospitalized COVID-19 patients continues to accumulate throughout the pandemic and endemic eras and covered the full range of disease severity
- A significant survival benefit across disease severity levels among hospitalized patients treated with remdesivir was found in appropriately powered studies
- Guideline recommendations have not evolved in parallel with the evolving evidence, which may explain recommendations against the use of remdesivir in certain population subgroups (e.g. IMV/ECMO) based on earlier studies that were underpowered to detect a significant impact
- Up to date clinical treatment guidelines are essential to inform today's clinical practitioners who are managing patients hospitalized for COVID-19

Background

- The rapid pace of the COVID-19 pandemic created a pressing need for guidance in clinical decision-making in an era when scientific evidence was lacking.[1]
- With progressive understanding of the natural history of COVID-19 and accumulation of knowledge on clinical management, guidelines recommended several treatment options including remdesivir (RDV), a broad-spectrum antiviral.
- Four years after the start of the pandemic, clinical practice guidelines have not evolved to incorporate the totality of the accumulating evidence and most have not updated remdesivir recommendations for hospitalized patients in the general population since 2022.[2-4]
  - Given the evolving nature of COVID-19, it is critical to systematically extract, summarize, and synthesize the totality of scientific evidence to inform clinical decision making

Objectives

- To summarize the accumulating evidence for remdesivir in the management of COVID-19 among hospitalized adults throughout COVID-19 eras through a comprehensive systematic literature review and to contrast with the evidence informing current treatment recommendations in clinical guidelines.

Methods

Search strategy

- Databases searched:
  - MEDLINE (including MEDLINE In-Process, MEDLINE In-Data-Review, and MEDLINE Epub Ahead of Print).
  - Embase database
  - The Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)
  - Other sources: Gray literature searches of conference proceedings and clinical trial registries
  - Period: From January 2019 to December 2023

Inclusion criteria

- Observational, real-world (RW) studies and interventional, randomized clinical trials (RCTs) reporting efficacy of remdesivir in hospitalized COVID-19 patients

Data screening and extraction

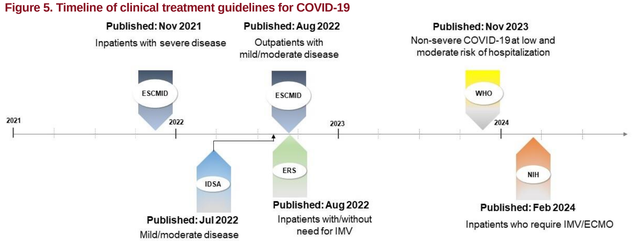
- A dual-reviewer approach was used for abstract screening, full-text review, and data extraction. Discrepancies were discussed between reviewers until a consensus was reached. Over 80 variables regarding study and patient characteristics, treatments, efficacy and safety outcomes were extracted

Risk of bias assessment

The quality of included publications was appraised using:

- the University of York CRD guidelines for interventional studies[5]
  - The guidelines assess the risk of bias in included studies caused by inadequacies in study design, conduct or analysis that may have led to the treatment effect being over or underestimated
- the Downs and Black checklist for non-interventional studies[6]
  - The checklist assesses the quality of reporting (9 items), external validity (3 items), internal validity (bias and confounding [7 items]), and power (1 item)

Figure 5. Timeline of clinical treatment guidelines for COVID-19



Guideline literature review methodology: Systematic review (IDSA, NIH, WHO); ADOLOPMENT criteria (ESCMID).
Guideline appraisal of publications: GRADE (ESCMID, IDSA, WHO); not mentioned (NIH).
Abbreviations: ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; IMV, invasive mechanical ventilation; NIH, National Institutes of Health; WHO, World Health Organization.

Results

Literature search results

- 8,022 relevant references were identified (3,777 in MEDLINE, 12,761 in Embase, 14 in CDSR, and 1,470 in CENTRAL)
- 2,241 additional references were identified through gray literature searches and the bibliography of identified SLRs
- A total of 192 publications including peer-reviewed articles, conference abstracts and posters stemming from 122 unique studies (21 RCTs and 101 RW studies) were retained
  - Across all unique studies, there were 25,174 participants enrolled in RCTs and 1,279,859 in RW studies

Remdesivir impact on mortality in patients hospitalized for COVID-19

- Of the 122 unique studies, 108 reported number of deaths, mortality rate, or risk of mortality
- 21 studies (5 RCTs and 16 RW studies) comparatively assessed the risk of mortality at 28-30 days between remdesivir and no remdesivir groups overall or by oxygen support at admission **(Table 1)**
  - RCTs and small sample size RW studies did not universally demonstrate a significant difference in mortality in all severity groups of RDV-treated patients **(Figures 1-4)**
  - RW studies powered for mortality endpoint, with appropriate sample sizes, showed a significant survival benefit across disease severity levels defined by **oxygen support requirement at admission, regardless of COVID-19 era (Figures 1-4)**

Review of guideline recommendations for use of remdesivir in hospitalized patients impact

- The timeline of most recent guideline recommendations for remdesivir use is summarized in Figure 5
- Guideline recommendations for COVID-19 treatment are based on RCTs conducted in the early pandemic era (Table 2)
  - The IDSA, ESCMID and ERS guidelines have not been updated since 2022[2-4, 7]
  - The WHO guidelines were updated recently (November 2023), but still relied on the RCTs conducted in the pre-Omicron period for remdesivir recommendations[8]
  - The 2024 NIH recommendations for immunocompetent COVID-19 patients were based exclusively on RCTs; RW effectiveness was considered only for recommendations applicable to patients with immunocompromising conditions, for whom the RCT data provided little insight[9]
    - The NIH announced that no further updates will follow the recommendations issued in February 2024[10]

Figure 1. Remdesivir efficacy and effectiveness on 28–30-day mortality in hospitalized adults with COVID-19 not requiring oxygen support at admission

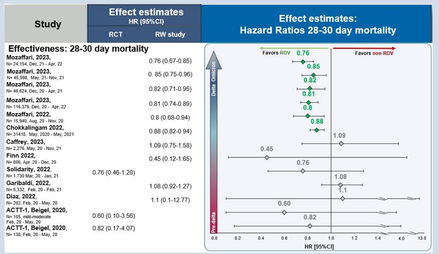


Figure 2. Remdesivir efficacy and effectiveness on 28–30-day mortality in hospitalized adults with COVID-19 requiring low flow oxygen support at admission

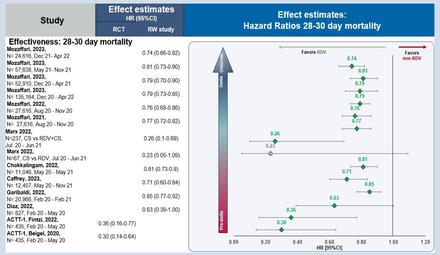


Figure 3. Remdesivir efficacy and effectiveness on 28–30-day mortality in hospitalized adults with COVID-19 requiring high flow oxygen support at admission

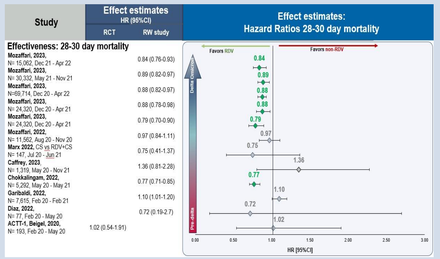
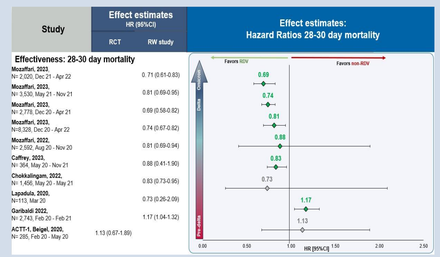


Figure 4. Remdesivir efficacy and effectiveness on 28–30-day mortality in hospitalized adults with COVID-19 requiring invasive mechanical ventilation at admission



Abbreviations: CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RW, real-world.

Table 1. Characteristics of studies reporting remdesivir efficacy and effectiveness on mortality in hospitalized adults with COVID-19

Author, Year, Study Name	Study period (Month Year)	Study design	Sample size, N	% of patients not requiring supplemental O_2 at baseline	Duration of RDV treatment	Primary efficacy outcome
Ader, 2021[11], DisCoVeRy*	Mar 20 - Jan 21	RCT	832	NR	5 /10 days[a]	Clinical status at 15 days (WHO ordinal scale)
Beigel, 2020[12], ACTT-1	Feb 20 - May 20	RCT	1,062	12% in treated 14% in untreated	up to 10 days[b]	Time to recovery
Olender, 2021[13], SIMPLE-Severe	Feb 20 - May 20	RCT	1,767	14.1% in treated 14.1% in untreated	5/10 days[c]	Clinical recovery at 14 days; Mortality at 28 days
Henao-Restrepo, 2022[14], SOLIDARITY	Mar 20 - Jan 21	RCT	14,304	NR	10 days	Mortality at 28 days
Wang, 2020[15]*	Feb 20 - Mar 20	RCT	236	0% in treated 4% in untreated	10 days	Time to clinical improvement
Bechman, 2022[16]	Mar 20 - Feb 21	RW, prospective	3,949	NR	NR	Mortality at 28 days
Benfield 2021[17]*	Feb 20 - Dec 20	RW, retrospective	2,747	NR	NR	Survival status at 30 days; mechanical ventilation
Breskin, 2023[18]*	May 20 - Dec 21	RW, retrospective	71,068	NR	NR	Mortality at 30 days; incidence of IMV/ECMO
Caffrey, 2023[19]*,	May 20 - Nov 21	RW, retrospective	18,874	17.7% in treated 15.9% in untreated	NR	Time to inpatient mortality
Chokkalingam, 2022[20]*,	May 20 - May 21	RW, retrospective	113,579	64.2%	NR	Time to inpatient mortality
De Vito, 2022[21]*	Aug 20 - Oct 21	RW, retrospective	1,080	NR	NR	Mortality at 28 days
Diaz, 2022[22]*,	Feb 20 - May 20	RW, retrospective	1,138	37.4% in treated 36.3% in untreated	5 /0 days	Overall survival
Dobrowolska 2023[23]*,	Aug 21 - Apr 22	RW, retrospective	1,822	NR	5 or 10 days	Need for O_2 therapy; Need for mechanical ventilation; Mortality at 28 days
Finn, 2022[24]	Apr 20 - Dec 20	RW, prospective	2,230	NR	NR	LOS, 30-day readmission; Post-discharge 30-day mortality
Garibaldi, 2022[25]*	Feb 20 - Feb 21	RW, retrospective	36,656	15.6% in treated 13.5% in untreated	5 days	Time to clinical improvement
Grundmann, 2023[26]	Jan 20 - Jun 21	RW, prospective	89,297	NR	NR	Risk of neurological complications
Lapadula 2020[27]	Mar 20 - Mar 20	RW, retrospective	113	0%	10 days	Time to mortality; Time to hospital discharge
Leding, 2023[28]*,	Feb 20 - Apr 21	RW, retrospective	3,826	56.2% in treated 55.4% in untreated	NR	Use of IMV; Mortality at 30 days
Marx, 2022[29]	Jul 20 - Jun 21	RW, retrospective	839	13.6% in treated 11.4% in untreated	NR	Time to clinical improvement
Mozaffari, 2022[30]*	Aug 20 - Nov 20	RW, retrospective	45,542	27.6% in treated 27.6% in untreated	NR	Inpatient mortality at 14 days and 28 days
Mozaffari, 2023[31]	Dec 20 - Apr 22	RW, retrospective	213,264	35% overall	NR	Mortality at 14 days and 28 days

ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; LOS, length of hospital stay; NR, not reported; RCT, randomized controlled trial; RW, real world. *Corticosteroids were used in both remdesivir and no remdesivir groups. **Corticosteroids were used in all patients receiving remdesivir. *Remdesivir was administered for a total duration of 10 days; cessation was allowed after 5 days if the participant was discharged from the hospital.37. [b] Patients were randomized to either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days.39, [c] Patients were randomized to remdesivir 200 mg on day 1 followed by remdesivir 100 mg/day either on days 2–5 or on days 2–10.55 Note: Studies that did not have mortality as primary endpoint are highlighted

Table 2. Summary of guideline recommendations for remdesivir use in hospitalized patients with COVID-19 in the general population and the scientific evidence base

GUIDELINE (date of last update for RDV recommendations)	Recommendation	Scientific basis for recommendations (trial name or author)	Study design	Study period
NIH,US[9] (Feb 2024)	**For the following hospitalized patient categories, RDV is recommended to be administered for 5 days (or until hospital discharge, whichever comes first):** • **LFO** – **minimal conventional oxygen** • **HFNC/NIV** – **all patients who:** ○ **are immunocompromised** ○ **have evidence of ongoing viral replication** ○ **are within 10 days of symptom onset** **There is insufficient evidence for the Panel to recommend either for or against RDV use in patients requiring IMV/ECMO**	**ACTT-1**	**RCT**	**Feb 2020 - May 2020**
		CATCO	RCT	Aug 2020 - Apr 2021
		DisCoVeRy	RCT	Mar 2020 - Jan 2021
		Goldman, et al.	RCT	Mar 2020 - Jun 2020
		Mozaffari, et al.	RWD	Dec 2020 - Apr 2022
		PINETREE	RCT	Sep 2020 - May 2021
		REMDACTA	RCT	Jun 2020 -Jan 2021
		Spinner, et al.	RCT	Mar 2020 - May 2020
		Wang, et al.	RCT	Mar 2020 - May 2020
		WHO Solidarity Trial, Final Report	RCT	Mar 2020 - Jan 2021
ESCMID[2,7](Aug 2022)	• There is a **conditional recommendation** for RDV use in patients with mild COVID-19 • There is a **conditional recommendation against** RDV use in patients with severe/critical COVID-19 requiring HFO • There is a **conditional recommendation** for RDV use in hospitalized COVID-19 patients not requiring **IMV/ECMO**	ACTT-1	RCT	Feb 2020 - May 2020
		Budi, et al.	SR based on 13 observation studies with 113 pregnant people	The search was conducted on Jul 26, 2021
		Mahajan, et al.	RCT	Jun 2020 - Dec 2020
		Mozaffari, et al.	RWD	Aug 2020 - Nov 2020
		Spinner, et al.	RCT	Mar 2020 - May 2020
		Wang, et al.	RCT	Feb 2020 - Mar 2020
IDSA,US[4](Jul 2022)	• There is a **conditional recommendation** for a 5-day RDV course (rather than 10-day) in patients **on supplemental oxygen not mechanically ventilated** • **In severe COVID-19** patients RDV treatment is **suggested over no antiviral** treatment • **There is a recommendation against routine initiation of RDV in patients on IMV/ECMO**	ACTT-1	RCT	Feb 2020 - May 2020
		Goldman, et al.	RCT	Mar 2020 - Jun 2020
		PINETREE	RCT	Sep 2020 - May 2021
		Wang, et al.	RCT	Feb 2020 - Mar 2020
		WHO Solidarity Trial, Final Report	RCT	Mar 2020 - Jan 2021
WHO[8] (Sep 2022)	• **Conditional recommendation** for RDV use in patients with **severe COVID-19** • **Conditional recommendation** against RDV use in patients with **critical COVID-19**	ACTT-1	RCT	Feb 2020 - May 2020
		CATCO	RCT	Aug 2020 - Apr 2021
		DisCoVeRy	RCT	Mar 2020 - Jan 2021
		Mahajan, et al.	RCT	Jun 2020 - Dec 2020
		PINETREE	RCT	Sep 2020 - May 2021
		Wang, et al.	RCT	Feb 2020 - Mar 2020
		WHO Solidarity Trial, Final Report	RCT	Mar 2020 - Jan 2021
European Respiratory Society[3, 32, 33] (August 2022)	• **No recommendation** for use of RDV in patients **not requiring IMV** • Recommendation **against RDV** use in patients **requiring IMV**	ACTT-1	RCT	Feb 2020 - May 2020
		Crichton, et al.	SR of CT	Search up until the end of Feb 2021
		Mahajan, et al.	RCT	Jun 2020 - Dec 2020
		PINETREE	RCT	Sep 2020 - May 2021
		Spinner, et al.	RCT	Mar 2020 - May 2020
		Wang, et al.	RCT	Feb 2020 - Mar 2020
		WHO Solidarity Trial, Final Report	RCT	Mar 2020 - Jan 2021

ECMO, extracorporeal membrane oxygenation; ESCMID, European Society of Clinical Microbiology and Infectious Diseases :HFNC, high flow nasal cannula; IDSA, Infectious Diseases Society of America ; IMV, invasive mechanical ventilation; LFO, low flow oxygen; MV, mechanical ventilation; NIH, National Institutes of Health; NIV, non-invasive mechanical ventilation; NSO, no supplemental oxygen; RCT, randomized controlled trial; RDV, remdesivir; RWD, real world data; SR, systematic review; WHO,World Health Organization ;

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