Ribavirin

A Review of Pertinent Drug Information for SARS-CoV-2

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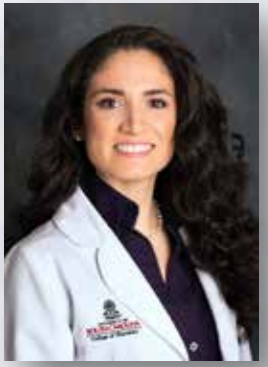

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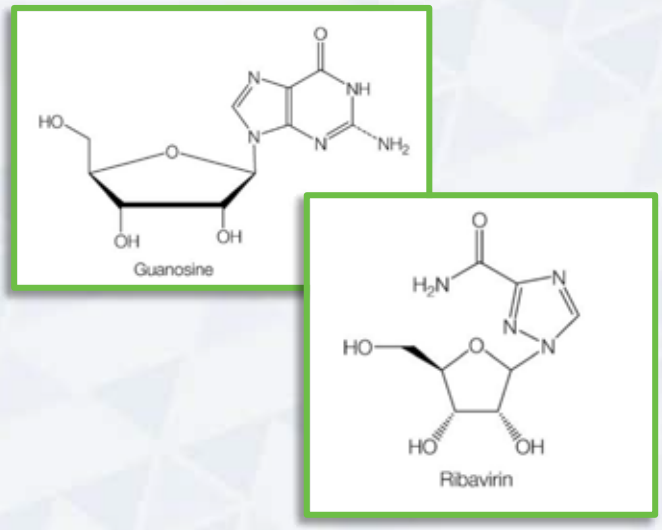
Data as of March 22, 2020

Mechanism of Action



- **Guanosine analogue**
  - Phosphorylated intracellularly by adenosine kinase
  - Metabolites: Ribavirin mono-, di-, and triphosphate
- Direct
  - Inhibition of RNA polymerase → chain termination
  - Inhibition of RNA capping activity
  - Lethal mutagenesis of RNA genome
- Indirect
  - Inhibition of inosine monophosphate dehydrogenase (IMPDH) → guanosine triphosphate (GTP) depletion
  - Enhancement of T-cell-mediated immunity favoring T-helper type 1 cytokine profile

→ **Broad-spectrum** antiviral activity

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Grayson ML, et al. Kucers': The use of antibiotics. 6th ed. London: Hodder Arnold, 2010. 252 Ribavirin and Viramidine. 2923-2958.
Loustaud-Ratti V, et al. World J Hepatol. 2016 Jan 18;8(2):123–130.
Coren G, et al. CMAJ. 2003 May 13;168(10):1289–1292.

Dosing

200 mg
Oral Tablet
Copegus®
Moderiba®
Ribasphere®

200 mg
Oral Capsule
Rebetol®
Ribasphere ®

40 mg/mL
Oral Solution
Rebetol®

6000 mg
Inhaled Solution
Virazole®

Chronic Hepatitis C Virus (HCV)[1]
as combination therapy

Weight	Adult Daily Dose	Dosing Regimen
< 75kg	**1000 mg PO**	400 mg PO QAM, 600 mg PO QPM
≥75kg	**1200 mg PO**	600 mg PO BID

Respiratory Syncytial Virus (RSV)[2,3]

Dosage Form	Adult Daily Dose	Dosing Regimen
Oral	**1200 mg - 2400 mg PO**	(a) 600-800 mg PO BID-TID (b) 10-30 mg/kg/d in 3 div. doses
Inhaled	**6000 mg INH**	(a) 2000 mg INH over 2-3 h TID (b) 6000 mg INH over 18 h daily

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1. AASLD-IDSA. 2019 Nov 6. Accessed on 2020 Mar 18 at http://www.hcvguidelines.org
2. Foolad F, et al. Clin Infect Dis. 2019 May 2;68(10):1641-1649.
3. Hirsch HH, et al. Clin Infect Dis. 2013 Jan;56(2):258-266.

Dosing

Severe Acute Respiratory Syndrome (SARS)[1-3]
+ combination corticosteroids

Therapy	Adult Daily Dose	Dosing Regimen
Very High Dose	**4000 mg IV (≅ 8000 mg PO)**	2000 mg IV load, 1000 mg IV Q6h x 4 d, 500 mg IV Q8h x 3 d
High Dose	**3600 mg PO**	(a) 2400-4000 mg PO load, 1200 mg PO TID x 14 d OR (b) 8 mg/kg IV Q8h x 14 d

Middle East Respiratory Syndrome (MERS)[4,5]
± interferon or lopinavir/ritonavir

Adult Daily Dose	Dosing Regimen
1800-3600 mg PO	2000 mg PO load, 1200 mg PO TID x 4d, 600 mg PO TID x 4-8 d

Much higher dosing for coronaviruses

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1. Booth CM, et al. JAMA.2003 Jun;289(21):280—2809.
2. Chu CM, et al. Thorax. 2004;59:252–256. doi: 10.1136/thorax.2003.012658.
3. Chan KS, et al. Hong Kong Med J. 2003;9:399-406.
4. Arabi YM, et al. Clin Infect Dis. 2019 Jun 25. doi: 10.1093/cid/ciz544 [Epub ahead of print]
5. Park SY, et al. J Hosp Infect. 2019 Jan;101(1):42-46.

Dosing

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
+ interferon-α or lopinavir/ritonavir

Adult Daily Dose	Dosing Regimen
1000-1500 mg IV (≅ 2000-3000 mg PO)	500 mg IV Q8h-Q12h up to 10 d

Clinical Data?

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National Health Commission (NHC) of the People's Republic of China. The diagnosis and treatment guide of COVID-19 pneumonia caused by new coronavirus infection 7th Edition. 2020 Mar 3. Translated to English. Accessed on 2020 Mar 12 on http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm

In Vitro Data

- SARS coronavirus 1 (SARS-CoV-1)
  - Inhibited by ribavirin at **50 µg/mL**[1] or **500–5000 µg/mL**[2]
  - Cytotoxic effects: 200–1000 µg/mL[2]
- MERS coronavirus (MERS-CoV)
  - Ribavirin half-maximal inhibitory concentration (IC_{50}): **41.5 µg/mL**[3]
  - Potency improved in combination with interferon-α2b

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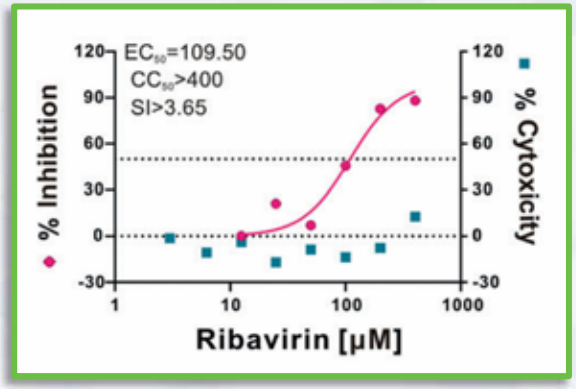
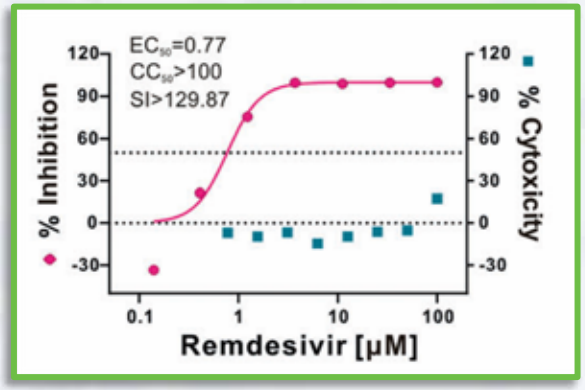
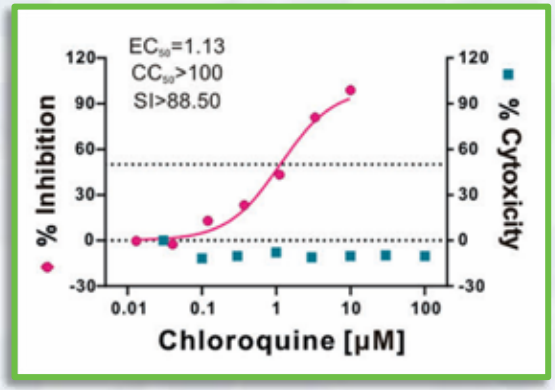
1. Chu CM, et al. Thorax. 2004;59:252–256. doi: 10.1136/thorax.2003.012658.
2. Tan EL, et al. Emerging Infect Dis. 2004;10(4):581-6.
3. Falzarano D, et al. Sci Rep. 2013;3:1686. doi: 10.1038/srep01686.

In Vitro Data







- SARS-CoV-2
  - Ribavirin half-maximal effective concentration (EC_{50}): **109.5 µM** (vs. 0.77-1.13 µM)
  - Half-cytotoxic concentration (CC_{50}): > 400 µM
  - Selectivity index (SI) = CC_{50}/EC_{50} → > 3.65

100-fold *less* potent than remdesivir or chloroquine

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Wang M, et al. Cell Res. 2020;30(3):269–271. doi.org/10.1038/s41422-020-0282-0.

Animal Data

Addition of ribavirin **may contribute to pathogenesis** of SARS-CoV-1 lung infection in mice

- Ribavirin in SARS-CoV-1 replication models in mice
  - ↑ virus lung titers
  - ↑ time virus detected lungs
  - ↑ proinflammatory cytokines

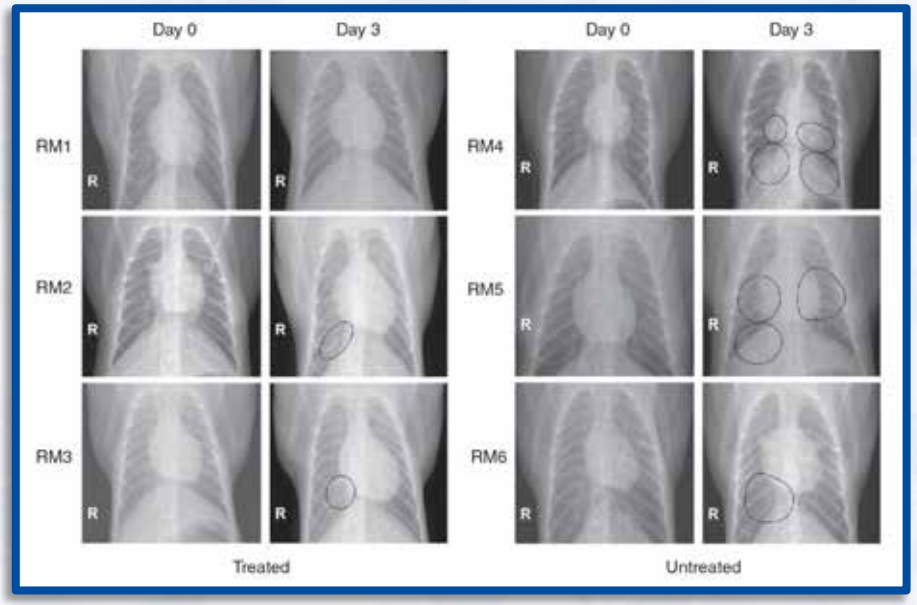
Intraperitoneal administration			
Treatment (mg/kg)	Day of sacrifice	Virus titer (log_{10} $CCID_{50}$/g)[b]	Percent body weight change
Virus-infected mice			
75[c]	Day 3	4.3 ± 0.5*	−13*
	Day 7	5.3 ± 0.01*	+2
Placebo	Day 3	3.8 ± 0.4	+12
	Day 7	0	+15
Uninfected mice			
75[c]	Day 3	0	−14*
	Day 7	0	+3
Placebo	Day 3	0	+6
	Day 7	0	+21

Barnard DL, et al. Antiviral Res. 2006 Aug;71(1):53-63.

Animal Data

Ribavirin with interferon-α2b **improved outcomes** rhesus macaque model of MERS infection

- Ribavirin combination in rhesus macaques with MERS
  - ↓ breathing abnormalities
  - ↓ pulmonary radiographic abnormalities
  - ↓ proinflammatory markers



Falzarano D, et al. Nat Med. 2013 Oct;19(10):1313-1317. doi: 10.1038/nm.3362.

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Select *In Vivo* Data

Study	Virus	Design	Outcomes
Chan et al 2003	**SARS-CoV-1**	Retrospective, matched cohort study Initial or rescue LPV/r + RBV + steroids (n=75) vs. RBV + steroids (n=977)	Poor outcomes with RBV + steroids alone: • **14-15.6% mortality** vs. 2.3-12.9% with LPV/r • **11-18.1% intubation** vs. 0-9.7% with LPV/r
Chu et al 2004	**SARS-CoV-1**	Prospective cohort study LPV/r + RBV + steroids (n=41) vs. RBV + steroids (n=111)	Poor outcomes with RBV + steroids alone: • **28.8% ARDS or death** vs. 2.4% with LPV/r (p<0.001)
Chiou et al 2005	**SARS-CoV-1**	Retrospective observational cohort study RBV + steroids if no improvement (n=44) vs. Steroids if no improvement (n=7)	**Persistent or progressive symptoms** at 2 days with RBV: • **93%** vs. 43% without RBV Significant adverse drug events with RBV: • **73% anemia** vs. 14% without RBV • **39% hypoxemia** vs. 14% without RBV

LPV/r = lopinavir/ritonavir; RBV = ribavirin; ARDS = acute respiratory distress syndrome

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1. Chan KS, et al. Hong Kong Med J. 2003;9:399-406.
2. Chu CM, et al. Thorax. 2004;59:252–256. doi: 10.1136/thorax.2003.012658.
3. Chiou H, et al. Chest. 2005;128:263-272.

Select *In Vivo* Data

SARS-CoV-1

- Ribavirin mostly in combination with lopinavir/ritonavir (LPV/r) or interferon
- 2006 Systematic Review[1]: **Ribavirin data inconclusive or suggest possible harm**

Treatment	Inconclusive[a]	Possible Harm[a]	Total Studies with Evidence (English and Chinese)[b]
Ribavirin	26	4	30
Corticosteroid	25	4	29
LPV/r	2	0	2
IFN-α	3	0	3
Convalescent plasma or Immunoglobulin	7	0	7

Hemolytic Anemia: 36% - 61%

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Stockman LJ, Bellamy R, Garner P. PLoS Med. 2006 Sep;3(9):e343.

Select *In Vivo* Data

Study	Virus	Design	Outcomes
Arabi et al 2019	**MERS-CoV**	Retrospective, observational cohort study RBV + IFN (n=144) vs. No RBV or IFN (n=205)	**No decrease** in 90-day mortality • aOR 1.03, 95% CI 0.73-1.44 **No faster viral clearance** of MERS-CoV • aHR 0.65, 95% CI 0.30-1.44
Park et al 2018	**MERS-CoV**	Retrospective, observational cohort study of healthcare workers with high-risk exposure to MERS-CoV RBV + LPV/r as PEP (n=22) vs. No PEP (n=21)	**Lower MERS-CoV infection rate** in PEP group: • **0%** vs. 28.6% in no PEP group (OR 0.41, 95% CI 0.27-0.60) • 45% anemia, 40% leukopenia in PEP group

RBV = ribavirin; IFN = interferon; LPV/r = lopinavir/ritonavir; PEP = post-exposure prophylaxis; aOR = adjusted odds ratio; CI = confidence interval; aHR = adjusted hazard ratio

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1. Arabi YM, et al. Clin Infect Dis. 2019 Jun 25. doi: 10.1093/cid/ciz544 [Epub ahead of print]
2. Park SY, et al. J Hosp Infect. 2019 Jan;101(1):42-46.

Safety

Black Box Warnings:

… The **hemolytic anemia** associated with [ribavirin] therapy may result in worsening of cardiac disease that **has lead to fatal and nonfatal myocardial infarctions**. Patients with a history of significant or unstable cardiac disease should not be treated with [ribavirin]…

…**Significant teratogenic and embryocidal effects** have been demonstrated in all animal species exposed to ribavirin. Therefore, [ribavirin] therapy is **contraindicated in women who are pregnant and in the male partners** of women who are pregnant…

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Product Information: REBETOL(R) oral capsules, oral solution, ribavirin oral capsules, oral solution. 2013.
Product Information: COPEGUS(R) oral tablets, ribavirin oral tablets. 2011.

Adverse Drug Events

- Anemia (50-73%)
  - Hemolytic anemia (36-82%)
  - ↓ Hemoglobin > 2 g/dL (50%)
- Hypocalcemia (55-58%)
- Hypomagnesemia (46-50%)
- Bradycardia (34%)
- Transaminitis (22%)

Hemolysis

- Inhibition of intracellular energy metabolism and oxidative membrane damage
- Accelerated extravascular hemolysis

Bone Marrow Suppression

- Occurs at high doses via inhibition of IMPDH

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1. Chiou H, et al. Chest. 2005;128:263-272.
2. Muller MP, et al. Pharmacotherapy. 2007;27(4):494-503.
3. Knowles SR, et al. Clin Infect Dis. 2003 Oct 15;37(8):1139-42.

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Chiou et al 2005

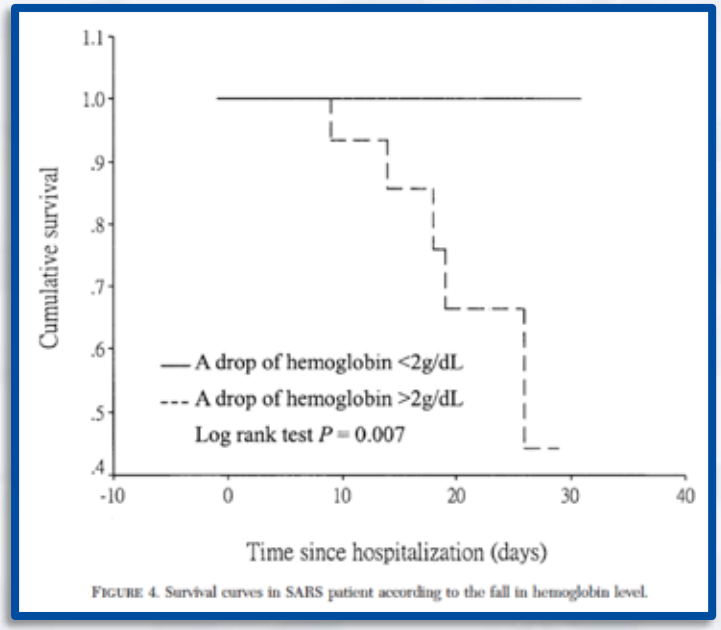

FIGURE 4. Survival curves in SARS patient according to the fall in hemoglobin level.

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1. Chiou H, et al. Chest. 2005;128:263-272.
2. Muller MP, et al. Pharmacotherapy. 2007;27(4):494-503.
3. Knowles SR, et al. Clin Infect Dis. 2003 Oct 15;37(8):1139-42.

Drug-Drug Interactions

- Contraindicated with **didanosine**: ↑ didanosine exposure & mitochondrial toxicity
- Major Drug Interactions:

Drug	Interaction
Azathioprine	Increased azathioprine-induced myelotoxicity
Zidovudine	Decreased zidovudine efficacy, hepatic and hematologic toxicity
Abacavir	Lactic acidosis
Stavudine	Decreased stavudine efficacy, lactic acidosis
Warfarin	Fluctuations in INR

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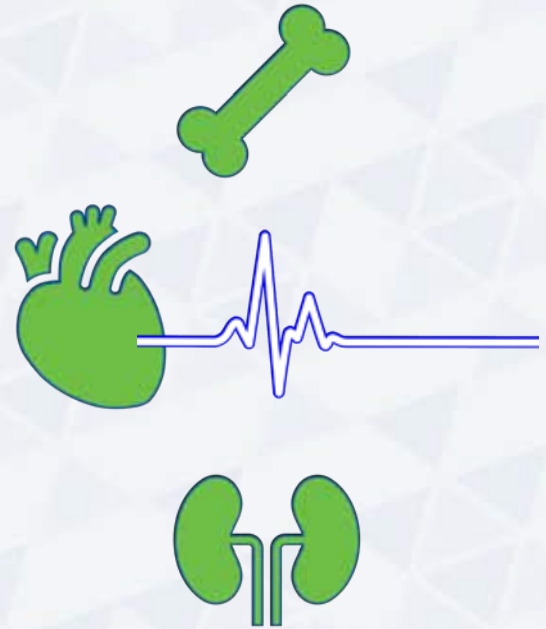
Clinical Pearls

- Generally, provide total daily dose in 2 divided doses (3, if high dose)
- Hematologic effects are dose-dependent & reversible
  - ✓ Baseline & daily CBC
  - Consider ribavirin dose reduction, if needed
- Consider ✓ baseline electrocardiogram (ECG) for patients with cardiac instability
  - ± Continuous cardiac monitoring
- ✓ Electrolytes & renal function (for dosing) daily



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Relevant Clinical Trials

Trial Number	Study Title	Location
ChiCTR2000029387	Comparative effectiveness and safety of ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate novel coronavirus pneumonia	China
NCT04276688	Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	China

- Ribavirin notably **absent** from WHO's global SOLIDARITY trial of the four most promising treatments for COVID-19[2]

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1. ClinicalTrials.gov. Accessed on 2020 Mar 21 at https://clinicaltrials.gov/
2. Kupferschmidt K, Cohen J. ScienceMag. 2020 Mar 22. Accessed on 2020 Mar 22 at https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments

Summary

- Dosing
  - Unclear, high dosing being attempted/investigated internationally for SARS-CoV-2
- *In vitro*
  - Ribavirin **less potent** than other potential agents for SARS-CoV-2
  - Likely has **narrow** therapeutic range for coronaviruses
- *In vivo*
  - Minimal/no efficacy data to suggest benefit with prior coronaviruses
- Safety
  - Anemia: Dose-dependent, common, associated with poor outcomes
  - Electrolyte and cardiac abnormalities described
  - Requires close laboratory & cardiac monitoring

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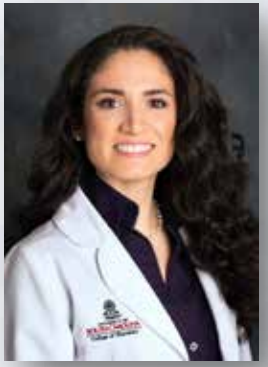

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