

Guidance on the use of Oral Ribavirin in the Treatment of Respiratory Viruses

Purpose of Guideline:

To provide guidance on the use of ribavirin for treatment of respiratory syncytial virus (RSV) in oncology patients and lung transplant recipients.

Section I: Immunocompromised Oncology Patients

Background:

Respiratory Syncytial Virus (RSV) is a paramyxovirus. It causes upper and lower respiratory tract infections. It predominantly affects children, elderly, and those with severe immunodeficiency.¹ Treatment of RSV infections in those with severe immunodeficiency in the oncology population, especially HSCT recipients, can consist of supportive care, ribavirin, immunomodulators (palivizumab, IVIG), and steroids.² The treatment regimen is not standardized amongst institutions due to a lack of literature which clearly delineates the optimal treatment regimen.^{3,30} Therefore, various formulations and dosing regimens of ribavirin, either alone or in combination with an immunomodulator, have been used for the treatment of RSV infections.⁴

Patients to be considered for therapy of RSV

Table 1: High Risk^{11,12}

- Receipt of allogeneic or autologous hematopoietic stem cell transplant (HSCT) within the past 30 days
- Receipt of allogeneic or autologous HSCT AND absolute lymphocyte count less than 300 cells/mm³
- Receipt of allogeneic HSCT with active graft versus host disease (GVHD) on immunosuppressants*
- Leukemia or HSCT patients with absolute neutrophil count less than 500 cells/mm³

*corticosteroids included

Clinical assessment and testing for possible RSV infection:

Clinical assessment:

Symptoms of upper and lower respiratory tract infections are described below.

Symptoms of upper respiratory tract infections:⁴

- Influenza-like symptoms such as runny nose, fever, sore throat, cough
- No infiltrate on chest x-ray

Lower respiratory tract infection symptoms:⁵

- Cough, increased oxygen requirement, wheezing
- New infiltrate on chest x-ray

Testing:

- Testing for RSV should be completed by BioFire PCR using either nasal wash (*preferred*) or BAL specimens.
- Testing by RIA (rapid antigen) is discouraged in this patient population.

Treatment:

Empiric use of ribavirin is not recommended; only patients who meet all three of the following criteria should be considered for ribavirin therapy:

- Symptoms of upper or lower respiratory tract infection (as described above)
- Positive molecular test for RSV
- High risk for RSV disease progression (meets at least one of the criteria listed in Table 1)

Additional treatment considerations:

The immunomodulators, palivizumab and intravenous immune globulin, have also been used in conjunction with ribavirin for the treatment of RSV infections. It has been suggested to consider combination therapy in those HSCT patients with multiple risk factors.⁴ Specifically, European guidelines suggest that allogeneic HSCT patients that have LRTID or are at high risk for progression to LRTID be treated with combination therapy (IVIG + ribavirin).⁹

- IVIG for use in combination with ribavirin should be dosed at 500mg/kg IV every other day x 3-5 doses.¹⁸⁻²²
- Palivizumab is not recommended for use in the adult immunocompromised oncology patients at Nebraska Medicine.

Ribavirin use:

Table 2: Summary of Oral Ribavirin Use*

Oral dose	15-20mg/kg/day divided into TID administration for 7-10 days
Dose adjustments	Follow the European Guideline recommendations for dose adjustments in renal dysfunction as outlined in table 3. <i>Note: Specific renal dose adjustments for oral ribavirin when used for the treatment of RSV are not available from the literature. Considerations should be made on the risk/benefit to the specific patients.</i>
Administration	Take with food
Monitor	CBC, serum creatinine, sign/symptoms of adverse effects

*See further detailed information in the sections below; refer to Table A1 for a literature review summary on the use of oral ribavirin.

Dosing:

- Oral ribavirin is the only formulation of ribavirin available for the treatment of RSV at Nebraska Medicine. The preferred dosing regimen is 15-20mg/kg/day divided into TID administration.⁷ When using tablets or capsules, the dose should be rounded to the nearest 200mg.
- Dose adjustments for renal insufficiency are not well-defined when ribavirin is used for treatment of RSV infections especially considering there are multiple different initial dosing regimens used.⁹ Ribavirin does accumulate in patients with decreased renal function and patients should be carefully monitored for toxicity such as hemolytic anemia.^{6,13}
 - Experience with intravenous ribavirin has shown that even patients with severe renal dysfunction (CrCl <30ml/min) tolerate a 7 day course of therapy for Hemorrhagic Fever with Renal Syndrome (HFRS), however, extreme caution should be taken and monitoring for toxicity should occur.¹³⁻¹⁵
 - Many studies on oral ribavirin do not report on specific renal dose adjustments made nor if any were made.^{7,8, 23,24}

Table 3: Renal dose adjustments

European Guidelines ⁹	Original maximum dosing regimen (IV/PO): 10mg/kg/dose Q8h Dose adjustments: CrCl 30-50ml/min – 200mg Q8h CrCl 10-30m/min – 200mg daily
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Administration:

- Oral ribavirin should be taken with food.⁶

Mechanism of action:

- Ribavirin inhibits replication of RNA and DNA viruses. It inhibits RNA polymerase activity and inhibits the initiation and elongation of RNA fragments which prevents viral protein synthesis.⁶

Pharmacokinetics:^{6, 16, 17}

- Ribavirin’s absolute bioavailability is reduced due to first-pass metabolism. Administering ribavirin with a high fat meal increases the AUC and the peak concentrations by 70%. Ribavirin is “*metabolized via a reversible phosphorylation pathway in nucleated cells and a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite.*”¹⁶ The metabolites, triazole carboxamide and triazole carboxylic acid, and unchanged ribavirin are excreted renally.
- In patients with renal dysfunction, AUC_{0-t} values (*time zero to last measured concentration*) after a single oral dose are increased 2 fold when CrCl is 30-60ml/min and increased 3 fold when CrCl is 10-30ml/min. The increase in AUC_{0-t} values in renal insufficiency were thought to be due to alteration of both renal and non-renal clearance of ribavirin.

Table 4: Pharmacokinetics

Absorption/bioavailability	64%
Distribution	2825L Prolonged in erythrocyte, Does not bind to plasma proteins
Metabolism	Hepatic, intracellular

Half-life of elimination	24h (single dose), 298h (multiple doses, BID)
Time to peak serum concentration	Capsule: 3h Tablet: 2h
Excretion	Urine 61%, Feces 12% (in 336h); unchanged ribavirin 17% of administered dose; ribavirin and triazole metabolites excreted renally

Contraindications to oral ribavirin formulations: ⁶

- Hypersensitivity to the ribavirin product, pregnant women or women who may become pregnant, males with pregnant female partners, patients with hemoglobinopathies, patients with autoimmune hepatitis, concomitant use with didanosine, and some specific products have contraindications for use in patients with CrCl<50ml/min

Warnings/precautions: ⁶

- A boxed warning exists for hemolytic anemia which may occur with oral therapy. Patients with significant or unstable cardiac disease should avoid use of ribavirin due to the potential for the hemolytic anemia leading to a myocardial infarction. Elderly patients may be more prone to adverse events such as anemia. Experience with the use of ribavirin for treatment of hepatitis C indicates that anemia usually occurs within 1-2 weeks after initiation of oral ribavirin therapy.
- For those patients that have renal impairment, dose adjustments or discontinuation of therapy may be needed.
- A boxed warning also exists regarding the teratogenic effects of ribavirin observed in animal studies. Pregnancy should be avoided during and for 6 months after treatment in both female patients and the female partners of male patients treated with ribavirin.
- This is a hazardous agent and special handling and disposal is required.

Adverse reactions (oral therapy):^{2, 7,8}

- Hemolytic anemia, nephrotoxicity, drug rash, lactic acidosis, altered mental status

Monitoring:⁶

- CBC (baseline, twice weekly while on therapy)²³
- In patients with new onset anemia, a blood smear should be evaluated for schistocytes.
- Renal function (e.g., serum creatinine)

Section II: Lung Transplant Recipients

Background: In lung transplant recipients respiratory syncytial virus (RSV) can produce severe lower respiratory tract infections, such as bronchiolitis, pneumonia and respiratory failure.²⁷ RSV infections have also been associated with the development of bronchiolitis obliterans syndrome in lung allograft recipients. Bronchiolitis obliterans is an inflammatory obstruction of the bronchioles resulting in progressive narrowing of bronchiolar lumens and airflow obstruction.²⁷ Once bronchiolitis obliterans syndrome develops, progressive decline in pulmonary function is typical. The limited literature available includes case series and observational studies which have shown an association with improved outcomes.^{26,33}

Patients to be considered for therapy of RSV

Table 1: High Risk

- All lung transplant recipients

Refer to Section I for clinical assessment and testing for RSV infection, treatment, and dosing of ribavirin.

Section III: Guideline Development

Background on the development of these guidelines:

These guidelines were established by consensus based on information derived from case-control studies, single-center cohort studies, a systematic review, national/international guidelines, and clinician opinion. Where applicable, specific recommendations were selected and categorized according to level of evidence support.

Table 5: Guideline Recommendations and Levels of Evidence

Recommendation	Evidence Level ^o
Oral ribavirin should be a treatment consideration only in patients who meet the following criteria: symptoms of upper or lower respiratory tract infection, a positive molecular test for RSV, and are at high risk of disease progression.	BIII
The recommended dose of oral ribavirin is 15-20mg/kg/day divided and given TID for 7-10 days.	BIII
Palivizumab is not recommended for addition to ribavirin for the treatment of RSV in immunocompromised oncology patients.	CIII
The addition of IVIG (500mg/kg IV QOD x 3-5 doses) to ribavirin therapy should be reserved for allogeneic HSCT patients with LRTID or who are at high risk for progression to LRTID.	CIII

^o Recommendations categorized per the Infectious Disease Society of America - United States Public Health Service grading system for ranking recommendations (see table 6 below).

Table 6: Description of Quality of Evidence/Strength of Recommendation

Quality of evidence	Strength of recommendation
I Evidence from ≥ 1 properly randomized, controlled trial	A Good evidence to support a recommendation for use
II Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments	B Moderate evidence to support a recommendation for use
III Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	C Poor evidence to support a recommendation

Table A1

Immunocompromised Oncology Patients			
First author, Year	Title	Study	Results
Gorcea CM, 2017	Effective use of oral ribavirin for respiratory syncytial viral infections in allogeneic haematopoietic stem cell transplant recipients	Retrospective single center review in the UK	-23 HSCT RSV+ patients treated with ribavirin -PO ribavirin: 15 mg/kg/day in three divided doses for 10 days; no subsequent dose escalation, aerosolized ribavirin used patients who progressed to LRTI -At diagnosis: 7 patients = LRTI, 16 patients = URTI -Ribavirin AE: nausea, hemolytic anemia (not proven to be ribavirin related) -One RSV-related death
Chu HY, 2016	Clinical outcomes in outpatient respiratory syncytial virus infection in immunocompromised children	Retrospective cohort review of children with RSV+ infection diagnosed as outpatients	-7/54 patients received ribavirin (no dose listed) -15/54 admitted to hospital, 1 admitted to ICU -No patients died due to RSV
Marcelin R, 2014	Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients	Retrospective chart review of RSV PCR+ patients (mod-severely immunocompromised)	-34/38 received oral ribavirin ($\geq 75\text{kg} = 800\text{mg}$ twice daily, $< 75\text{g} = 600\text{mg}$ twice daily) for 5-10 days Dose adjustment for mild renal insufficiency (CrCl not defined): 400mg twice daily <i>*Treatment decision in patients with renal insufficiency based on risk/benefit for each patient</i> -24 dev pneumonia -3/38 died, none due to RSV infection
Lehners N, 2013	Risk factors and containment of respiratory syncytial virus outbreak in a hematology and transplant unit	Retrospective chart review of RSV infected patients during outbreak	-Recommended dose of oral ribavirin therapy during outbreak ($< 65\text{kg}$: 800mg daily; 65-80kg: 1000mg daily; $> 80\text{kg}$: 1200mg daily - all given as two separate doses). -16/56: asymptomatic or minor URTID, 40/56 developed LRTID (13 progressed from URTID, 27 presented at that stage during diagnosis) -36 patients received ribavirin; generally well tolerated -Multivariate analysis: treatment with ribavirin protective against fatal outcome
Gueller A, 2013	Successful systemic high-dose ribavirin treatment of respiratory syncytial virus-induced infections occurring pre-engraftment in allogeneic hematopoietic stem cell transplant recipients	[abstract only] case series	10 patients with RSV infection after allo-HSCT; 5 w/LRTID received IV RBV, 5 w/URTID received oral ribavirin (none progressed to LRTID). One death d/t septic shock occurred.
Park SY, 2013	Efficacy of oral ribavirin in hematologic disease patients with paramyxovirus infection: analytic strategy using propensity scores	Propensity-matched case control study	-Oral ribavirin dosed at 15-20mg/kg/day divided TID (treatment group) -145 were positive (66 PIV, 60 RSV, 21 hMPV) -114/145 received oral ribavirin -More cases of severe underlying disease in the non-ribavirin group -7 cases developed AE during therapy: 4 (hemolytic anemia), 2 (nephrotoxicity), 1 (drug rash) -30 day mortality was not different between the two groups (treatment vs supportive care)
Casey J, 2013	Oral ribavirin for treatment of respiratory syncytial virus and parainfluenza 3 virus infections post allogeneic haematopoietic stem cell transplantation	Retrospective review	Oral ribavirin started at 10mg/kg/day given in 4 divided doses and increased by 10mg/kg/day to a max of 60mg/kg/day. 15 patients received RBV for RSV (n=13) or PIV3 (n=2). Outcome: 11 patients lived, 4 died (n=3 respiratory failure, n=1 HHV-6 encephalitis) <i>Authors recommend starting dose at 20mg/kg/day with dose escalation up to max of 60mg/kg/day.</i>
Shah JN, 2011	Management of RSV infections in adult recipients of hematopoietic stem cell transplantation	Review	6 studies on the use of oral or IV ribavirin with or w/o an immunomodulator were combined for a total study population of 210 patients -progression to LRI (46%) -among those who progressed to LRI, pts treated with AR + immunomodulator (24%) had lower mortality than those treated with AR alone (50%) or with IV/PO ribavirin +/- immunomodulatory (54%)
Anak S, 2010	Respiratory syncytial virus infection outbreak among pediatric patients with	[abstract only]	Notes that 6/30 patients were positive for RSV antigen in RSV outbreak. Treatment for 5/6 consisted of IVIG and oral ribavirin (20-25mg/kg/day divided TID). Five patients recovered fully.

	oncologic diseases and/or BMT.		Authors conclude that mortality may be low “when diagnosed and treated early enough.”
Chakrabarti S, 2001	Pre-emptive oral ribavirin therapy of paramyxovirus infections after hematopoietic stem cell transplantation: a pilot study	Pilot study	<ul style="list-style-type: none"> -Patients with PIV 3 and RSV were initiated on oral ribavirin, those with severe symptoms were treated with aerosolized ribavirin, those not responding to oral or aerosolized ribavirin were treated with IV ribavirin -Oral dose escalating schedule (15-60mg/kg/day) -Results: <ul style="list-style-type: none"> -10 episodes of paramyxovirus infection (n=7) treated with oral ribavirin (9/10 symptomatic) <ul style="list-style-type: none"> -5 RSV, 5 PIV <ul style="list-style-type: none"> -RSV: improved with oral ribavirin, none → LRI -PIV: 2 improved with oral ribavirin, 2 needed IV ribavirin d/t probable LRI (1 retreated with oral post IV), 1 died despite IV therapy -AE of oral ribavirin: reversible anemia
Sparrelid E, 1997	Ribavirin therapy in bone marrow transplant recipients with viral respiratory tract infections		<ul style="list-style-type: none"> -10/13 received systemic therapy (IV, PO); of those 6 also received inhaled/aerosolized -3/13 received only aerosolized therapy -Overall, 3/13 died (1 AR only, 1 both, 1 systemic only); of those that died – all had pneumonia
Lung Transplantation			
Burrows F, 2015	Oral ribavirin for respiratory syncytial virus infection after lung transplantation: Efficacy and cost-efficiency		<ul style="list-style-type: none"> - Day 1: IV loading dose (n=52) oral loading dose (n=2) at 33mg/kg; Day 2: Oral ribavirin (20 mg/kg/day) in 53 episodes. Mean duration of therapy 8 days (range 6-31 days) - Mean forced expiratory volume in 1 sec: Decreased from 2.38 + 0.78 liters to 2.07 + 0.85 liters(p < 0.001) at presentation; Recovered to 2.26 + 0.82 liters at cessation of ribavirin; Maintained at 2.31 + 0.81 liters within 3 months
Fuehner T, 2011	Single-center experience with oral ribavirin in lung transplant recipients with paramyxovirus infections		<ul style="list-style-type: none"> - PV-infected recipients treated with oral ribavirin x 14 days (n=38) compared to pts unable to receive ribavirin (n=29) due to contraindications, instead standard dose of corticosteroid increased. - All patients with proven PV were planned to receive oral ribavirin for 14 days in a dosage of 15-20 mg/kg/day in two divided doses. - Measured: Recovery of graft function (FEV₁, home spirometry), time to recovery (home spirometry 50%, 75% and 90%) and new development of BOS: Median FEV₁ dropped 20% from baseline in the ribavirin group versus 18% in the non-ribavirin group during infection; Graft function recovered within 30 days: 84% of patients treated with ribavirin and 59% of the non-ribavirin group (P=0.02); New onset of BOS within 6 months: 5% of the ribavirin group versus 24% of the non-ribavirin group (P=0.02).
Pelaez A, 2009	Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection		<ul style="list-style-type: none"> - 5 patients (3 bilateral, 2 single lung) with dx RSV and documented fall in FEV₁ of > 10% - Oral ribavirin (15 to 20 mg/kg in 3 divided doses for total of 10 days), and IV corticosteroids (10 to 15 mg/kg/day intravenously) for 3 days and then resumed the previous prednisone maintenance dose. - After clearance of RSV infection, there was resolution of FEV₁ to baseline after 3 to 10 months, which was maintained at follow-up of 565 days

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