

Diagnosis and Management of Viral Respiratory Tract Infections in High Risk Allogeneic or Autologous Blood and Marrow Transplant Recipients or Leukaemia patients *

Scope

This document provides guidance on the diagnosis and management of viral respiratory tract infections (RTI) in high risk patient groups*.

*High risk patient groups (HRPG) include:

- Receipt of allogeneic or autologous BMT within past 100 days and those >100 days with continued immunosuppression
- Receipt of allogeneic or autologous BMT and absolute lymphocyte count of less than $0.3 \times 10^9/L$
- Receipt of allogeneic BMT with active GvHD on immunosuppression including corticosteroids
- Leukaemia patients with an absolute neutrophil count less than $0.5 \times 10^9/L$

Introduction

Viral RTI are common in the high risk patient groups (HRPG) and include:

- Respiratory Syncytial Virus (RSV)
- Parainfluenza viruses
- Influenza A & B
- Adenovirus/Metapneumovirus/Rhinovirus
- Coronaviruses including SARS-CoV-2

Although the majority of these viruses tend to show a seasonal variation in the general population this is not necessarily the case for immunocompromised individuals. Patients within the HRPG who develop viral upper respiratory tract infection should be considered for antiviral therapy to reduce the risk of pneumonia and death.

Diagnosis

All HRPG (<100 days and those >100 days with continued immunosuppression/cGVHD or with other high risk features increasing risk of progression from URTI to LRTI e.g. receiving chemotherapy, neutropenia, lymphopenia etc.) should have a throat swab taken ideally at the onset of respiratory symptoms.

Samples:

- A 'flocked' swab in virus transport medium should be used; the swab needs to be swept deeply in the throat, almost causing the patient to gag. Swab and medium are available on the Haematology Ward and in the Out Patient Department.

Investigations:

- Swabs should be sent to the Microbiology Department at the John Radcliffe Hospital and the clinical details should clearly indicate that this is a BMT/Leukaemia patient.

On a correct EPR encounter, request **Respiratory PCR (community acquired)**. The respiratory panel (Biofire) includes adenovirus, coronaviruses 229E, HKU1, NL63, OC43, SARS-CoV-2 and MERS-CoV, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A H1, influenza A H1-2009, influenza A H3, influenza B, parainfluenza viruses 1-4, respiratory syncytial virus, Bordetella pertussis and parapertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae.

- Results of the Respiratory panel should be available on same day, please contact lab if results not in EPR.
- NB for the non-HRPG seen in clinic with respiratory symptoms, the EPR request should be for **Influenza/RSV PCR** (performed daily), unless being admitted to the ward.
- Current national/local guidance for SARS-CoV-2 testing should be followed.

Minimising spread

- Inpatients with suspected or confirmed viral RTI should be nursed on the Haematology Ward in a negative or neutral pressure side room with the door closed.
- Strict isolation is required in both cases. The patient should be confined to their room to avoid social contact with other immunocompromised patients. These infections are spread by close contact with infected secretions, by large particle aerosols and by fomites.
- Standard barrier nursing precautions plus vigilant hand washing or alcohol hand rub is essential.
- Health care workers should be aware of their ability to be a vector in this setting, and wear and dispose of PPE appropriately
 - Respiratory protective equipment (RPE) (FFP3 masks) are recommended when caring for patients with suspected and confirmed seasonal respiratory viruses including SARS-CoV-2 when carrying out aerosol generating procedures (AGPs)
 - RPE (FFP3 masks) are recommended when caring for patients with a suspected or confirmed infection spread predominantly by the airborne route (during the infectious period).
 - PPE (including fluid resistant surgical masks (FRSM)) are indicated when caring for patients with suspected and confirmed seasonal respiratory viruses including SARS-CoV-2
- Health care workers should be immunised with the seasonal influenza vaccine and with SARS-CoV-2 vaccine according to national schedules.
- Ensure patients practice good respiratory hygiene by covering the mouth if coughing or sneezing, and by safe disposal of oral and nasal secretions. If tolerated, patients should wear a FRSM.
- All equipment removed from the room (e.g. infusion pumps) should be cleaned with a detergent and water solution, ensuring that this is not against the manufacturer's guidelines. It is imperative that the equipment is then dried thoroughly.
- All surfaces in the room should be thoroughly cleaned daily.
- Full terminal clean of the room following patient discharge.
- Multiple, confirmed cases could be cohort nursed, in a 2-bedded bay with the door closed.
- Follow guidelines as per protective isolation protocol (B.6.0)

- All staff working in the clinical area should be fit tested for FFP3 mask (if possible).
- All staff working on the Haematology unit must report respiratory symptoms to the nurse in charge. They should be excluded from clinical duties if they have a sore throat, uncontrolled coughing/sneezing, or a runny nose requiring frequent wiping.
- Staff with probable/suspected 'flu or 'SARS-CoV-2 like symptoms (fever of >38°C or history of fever **plus** two or more symptoms of cough or other respiratory symptoms, chills, sore throat, headache, muscle aches) must stay away from work and contact GoodShape and their manager.
- In all areas, staff working with a common cold should follow the advice below to further reduce risk of spread:
 - Cough or blow nose away from patients/clinical areas
 - Dispose of tissues immediately after use, preferably into a lidded waste bin
 - Clean hands after sneezing/coughing/handling used tissues and after all contact with the face

Visitors/relatives should be advised to be vigilant about hand washing or alcohol hand rub and avoid contact with all other patients on the ward. Visitors/relatives must not visit the ward if they have respiratory symptoms, including symptoms consistent with the common cold. During an epidemic influenza or other respiratory virus season, consideration should be given to restricting visitors/relatives. This decision should be made in collaboration with the infection, prevention and control team.

Outpatients

In cases of proven infection, provision should be made for the patient to be directed straight to a consultation room to avoid prolonged contact with other immunocompromised patients in waiting/treatment areas. Staff should apply the above precautions.

Management

1. Respiratory Syncytial Virus (RSV)

- 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. The treatment regimen is not standardized amongst institutions due to a lack of literature which clearly delineates the optimal treatment regimen. 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.

Investigations: Respiratory virus screen PCR or Influenza/RSV PCR according to risk group and season, CXR, Serum Ig's and electrophoresis and consider CT chest if chest CXR and clinical examination not confirmatory of LRTI.

Treatment:

Empiric use of ribavirin is not recommended; only patients who have a positive molecular test for RSV and meet one of the two criteria below should be considered for ribavirin therapy:

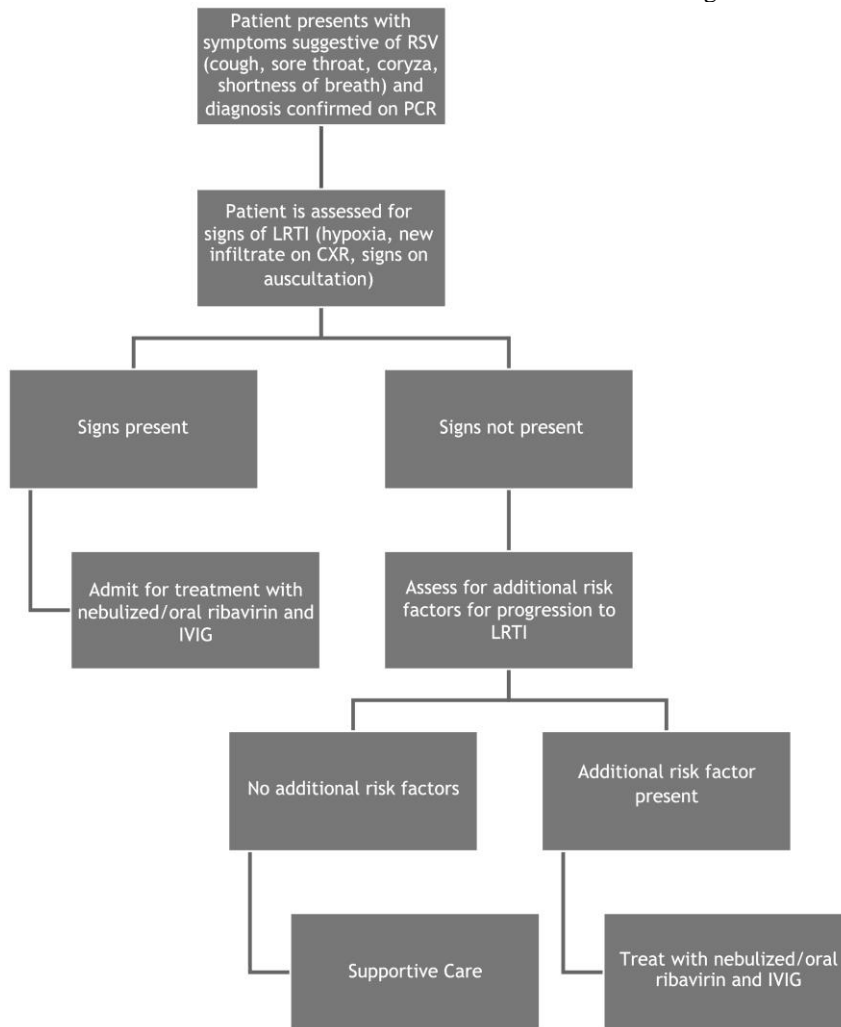
- Symptoms and signs of lower respiratory tract infection (clinical, imaging).
- Treatment may be considered occasionally in patients with upper respiratory tract infection. The following are associated with high risk for progression from URTI to LRTI: pre-engraftment, lymphopenia $<0.3 \times 10^9/l$, > 60 years, GVHD, mismatched, haploidentical related or umbilical cord blood donor transplant, neutropenia $<0.5 \times 10^9/l$.

It is generally only patients on immunosuppression or within 12 months of transplant who will require therapy.

Immunoglobulin:

- Consider commencement of IV Immunoglobulin (in combination with ribavirin) at a total treatment dose of 2g/kg administered over 2-4 days. All cases should be discussed with Dr Siraj Misbah (Consultant Immunologist) or if Dr Misbah is unavailable, Dr John Reynolds (contactable via email).

Department of Clinical Haematology
Oxford BMT Programme



Ribavirin

Ribavirin is unlicensed for the treatment of RSV. Various dosing schedules and regimes have been used in different publications from retrospective and prospective studies. The dosing regimen of ribavirin is therefore not standardized amongst institutions/guidelines due to a lack of literature which clearly delineates the optimal treatment regimen. A recent study from the Oxford unit during 2015-2017 has been published on 49 RSV episodes (47% URTI and 53% LRTI) treated with short courses of oral ribavirin combined with intravenous immunoglobulin. All patients with URTI recovered without pharmacological intervention. Progression from URTI to LRTI occurred in 15%. Treatment with oral ribavirin was given until significant symptomatic improvement (median 7 days [3-12]). RSV-attributable mortality was low (2%) (Balassa K, J. Infection 2019).

- Oral Ribavirin (available in tablet or liquid formulation) should be used whenever possible.
- IV Ribavirin should be used where oral route is not appropriate (e.g. malabsorption) or unavailable.

Dosing in normal renal function (CrCl > 50ml/min):

<p>Oral dose (Rory Sallach,2014)</p>	<p>15-20 mg/kg/day divided into TDS administration for 7-10 days Dose should be rounded to the nearest 200 mg To be taken with food</p>
<p>Intravenous dose (EUCIL4, 2013)</p>	<p>Day 1: 600 mg loading dose, then 200 mg TDS Day 2: 400 mg TDS Day 3: Increase the dose to a maximum of 10 mg/kg TDS</p>

Dosing in impaired renal function (CrCl < 50ml/min):

Ribavirin accumulates in patients with decreased renal function; substantial increases in ribavirin plasma concentrations are seen in patients with creatinine clearance < 50 ml/min. Considerations should be made on the risk/benefit to the specific patients with close monitoring of side effects particularly haemolytic anaemia. The European Guideline (EUCIL4, 2013) for ribavirin dose adjustments in renal dysfunction make the following recommendation:

Renal Dose adjustments (for both oral and intravenous routes):

CrCl 30-50 ml/min – Maximum 200 mg TDS
 CrCl 10-30 m/min – 200 mg once daily with close clinical and laboratory monitoring.

Ribavirin monitoring

FBC (baseline then twice weekly while on therapy) if Hb is falling add a reticulocyte count, U&E, serum creatinine, LFTs, sign/symptoms of adverse effects. Pregnancy test in appropriate groups prior to commencement(see below)

Haemolytic anaemia: Ribavirin does accumulate in patients with decreased renal function and patients should be carefully monitored for toxicity such as haemolytic anaemia.

Patients should have a FBC, Reticulocyte count, LDH, Bilirubin twice weekly one week after commencing Ribavirin and then weekly for a period of 3 weeks. Should Hb begin to drop, consideration should be given to arrange a blood transfusion. This can be arranged at patient’s local hospital.

FBC monitoring and blood transfusions can be arranged by the BMT specialist nurses. In a recent series of Oxford patients (Balassa K, J. Infection 2019) 4/24 BMT patients (16.7%) were admitted with haemolytic anaemia following Ribavirin.

Warnings/precautions:

A warning exists for haemolytic anaemia which may occur. Patients with significant or unstable cardiac disease should avoid use of ribavirin due to the potential for the haemolytic anaemia leading to a myocardial infarction. Elderly patients may be more prone to adverse events such as anaemia.

Experience with the use of ribavirin for treatment of hepatitis C indicates that anaemia 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.

Pregnancy: A warning also exists regarding the teratogenic effects of ribavirin observed in animal studies. Exclude pregnancy before treatment; effective contraception essential during treatment and for 4 months after treatment in women and for 7 months after treatment in men and the female partners of male patients treated with ribavirin.

Hazardous agent: This is a hazardous agent and special handling and disposal is required. The drug should be handled as per cytotoxic handling requirements. The tablets should not be broken or crushed.

2. Influenza A & B

Testing as per above

On positive result commence Oseltamivir as per UKHSA guidelines. Oseltamivir is also indicated for patients with complicated Influenza A or B infection after 48 hours of symptoms (consider discussion with Churchill ID Consult team bleep 5039). Five days is the minimum duration for treatment, and in the immunocompromised population may be continued for longer, depending on response.

The selection of first line antivirals in severely immunosuppressed individuals should take account of the subtype of influenza causing infection, or if not yet known, the dominant strain of influenza that is circulating during the current influenza season.

Inhaled zanamivir (Diskhaler) should be used first line when the dominant circulating strain has a high risk of oseltamivir resistance. If Zanamivir is not immediately available, commence Oseltamivir. Intravenous Zanamivir may be available for patients unable to tolerate the respiratory or oral route on a case by case basis.

The current UKHSA recommendations on post-exposure prophylaxis for influenza infection should be followed.

3. Parainfluenza (HPIV)

Treatment of HPIV is generally supportive together with respiratory isolation. Reduction of steroid dosage where feasible and appropriate may be a valid approach. No proven anti-viral agent exists although some agents are in early phase clinical trials, including multivirus specific T-cell therapies. Ribavirin may be considered in selected high-risk patients with LRTI, based on anecdotal reports. Discuss with Consultant Microbiologist/ Churchill Infection consult team (bleep 5039). Consider IVIG therapy in this patient group.

4. Adenovirus

Adenovirus infection post BMT may be asymptomatic or present as an URTI, enteritis or cystitis. Adenovirus is now recognised as a significant pathogen in children following BMT with reported mortality rates as high as 60% in disseminated infection. Adenovirus can be detected in blood, stool, urine, throat swab or NPA/NPW. Confirmed cases should be discussed with Consultant Microbiologist / Churchill Infection consult team (bleep 5039). Antiviral therapy may be advised. Cidofovir is currently very difficult to obtain, and ribavirin may be considered in selected high-risk patients with LRTI, based on anecdotal reports.

5. SARS-CoV-2

Consult Churchill Infectious consult team (bleep 5039) if advice required.

References:

- Khawaja F, Chemaly RF. Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies. *Haematologica*. 2019 Jul;104(7):1322-1331. doi: 10.3324/haematol.2018.215152. Epub 2019 Jun 20. PMID: 31221784; PMCID: PMC6601091.
- Baldwin et al. Outcome and clinical course of 100 patients with adenovirus infection following bone marrow transplantation. Bone Marrow Transplant Unit, Bristol, UK. *Bone Marrow Transplant*. (2000) Dec: 26(12): 1333-8.
- Walls T, Shankar AG, Shingadia D. Adenovirus: an increasingly important pathogen in paediatric bone marrow transplant patients. *Lancet Infectious Diseases* (2003) Feb: 3(2): 79-86. Review.
- Marcelin JR, Wilson JW, Razonable RR; The Mayo Clinic Hematology/Oncology and Transplant Infectious Diseases Services. Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients. *Transpl Infect Dis*. 2014 Mar 13.
- Park SY, Baek S, Lee SO, et al. Efficacy of oral ribavirin in hematologic disease patients with paramyxovirus infection: analytic strategy using propensity scores. *Antimicrob Agents Chemother*. 2013 Feb;57(2):983-9.
- Lehners N, Schnitzler P, Geis S, et al. Risk factors and containment of respiratory syncytial virus outbreak in a hematology and transplant unit. *Bone Marrow Transplant*. 2013 Nov;48(12):1548-53.
- Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. *Clin Microbiol Rev*. 2014 Jul;27(3):441-62. Review.
- Hirsch et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus. *CID* 2013;56: 258-266
- Dignan FL et al. BCSH/BSBMT/UK clinical virology network guideline: diagnosis and management of common respiratory viral infections in patients undergoing treatment for haematological malignancies or stem cell transplantation. *Br J Haematol*. 2016 173(3):380-93.
- Rory Sallach, Emily Kreikemeier, Alison Freifeld MD. Unpublished Individual institution guideline 2014. "Guidelines on the use of Oral Ribavirin in the Treatment of Respiratory Syncytial Virus in Immunocompromised Oncology Patients".
- Balassa K, Salisbury R, Watson E, Lubowiecki M, Tseu B, Maouche N, Jeffery K, Misbah SA, Benamore R, Rowley L, Barton D, Pawson R, Danby R, Rocha V, Peniket A. Treatment stratification of respiratory syncytial virus infection in allogeneic stem cell transplantation. *J Infect*. 2019 Jun;78(6):461-467.
- <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control/covid-19-guidance-for-maintaining-services-within-health-and-care-settings-infection-prevention-and-control-recommendations>
- <https://www.nice.org.uk/guidance/ng164/resources/covid19-rapid-guideline-haematopoietic-stem-cell-transplantation-pdf-66141900749509>

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1058443/ukhsa-guidance-antivirals-influenza-11v4.pdf

Authors

Tim Littlewood, BMT Programme Director, Version 1, 2004
 Claire Humphries, Cancer Pharmacist, Version 1, 2004
 Denise Wareham, BMT Co-ordinator, Version 2, 2008, Version 3, 2013
 Katie Jeffery, Consultant Virologist, Version 2, 2008, Version 3, 2013

Audit

These processes are subject to the OxBMT/IEC audit programme

Circulation

NSSG Haematology Website

Review

Name	Revision	Date	Version	Review date
Dr Katie Jeffrey, Consultant Virologist Denise Wareham, BMT Coordinator	Compliance with Jacie standards, review of process, insertion of Jacie standards into document Compliance with Trust guidelines	Jan 2013	3.0	Jan 2015
Dr Katie Jeffrey. Consultant Virologist Sandy Hayes, Quality Manager Nadjoua Maouche, Senior Haematology Pharmacist.	Inclusion of oral and IV Ribavirin, removal of nebulised form. Update if risk factors and references. Removal of Jacie standard.	Dec 2015	4.0	Dec 2017
Sandy Hayes, Quality Manager. Dr Robert Danby, Consultant Haematologist	Reduction in duration of oral ribavirin administration to 7 days. Changes to patient follow up guidance	Jan 2016	4.1	Dec 2017
Sandy Hayes, Quality Manager	Removal of line regarding assay sensitivity	Mar 2016	4.2	Dec 2017
Cheukie-Kie Cheung, Specialist Cancer Pharmacist Dr Katie Jeffery, Consultant Virologist	Minor amendment Minor amendments	Feb 2017	4.3	2017 when lab changes in place
Lara Rowley BMT NP Dr Katalin Balassa, BMT Fellow	Additions and amendments: HRPG, BCSH guidelines Ribavirin dosing, IVIG Generic changes	Apr 2018	4.4	Apr 2020

Department of Clinical Haematology
 Oxford BMT Programme

Dr Katie Jeffery, Consultant Virologist				
Dr Katie Jeffery, Consultant Virologist	Minor amendments Addition of guidance for staff with respiratory infection	June 2019	4.5	June 2020
Prof Katie Jeffery, Consultant Virologist	Addition of SARS-CoV_2	April 2023	4.6	April 2025