Diagnosis & management of viral respiratory tract infection in high risk allogeneic or autologous BMT or leukaemia patients

Version 5.1

Contents

Scope

This document provides guidance on the diagnosis and management of viral respiratory tract infections (RTI) in high-risk allogeneic or autologous bone marrow transplant (BMT) recipients or leukaemia patients.

1. Introduction

Viral RTIs are common in high-risk patients and include:

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

Although many of these viruses show seasonal variation in the general population, this is not necessarily the case within immunocompromised individuals.

High risk patients who develop viral upper respiratory tract infection should be considered for antiviral therapy to reduce the risk of pneumonia and death.

1.1. High-risk criteria

- 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 x 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 x 10^9/L

2. Diagnosis

All high-risk patients should have a throat swab taken ideally at the onset of respiratory symptoms.

2.1. 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 Outpatient Department.

2.2. 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 or leukaemia patient.

Within Oxford, 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.

Panel results should be available on same day, please contact lab if results not in EPR**.**

For patients not in the high-risk groups 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.

3. Minimising infection spread

3.1. Inpatients

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. 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.

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 fluid resistant surgical mask (FRSM).

Standard barrier nursing precautions plus vigilant hand washing, or alcohol hand rub is essential.

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)

3.2. Inpatient visitors/relatives

Visitors or 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.

3.3. 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.

3.4. Staff

Health care workers should be aware of their ability to be a vector in this setting, and wear and dispose of PPE appropriately. All staff working in the clinical area should be fit tested for FFP3 mask (if possible).

- Respiratory protective equipment (RPE) (FFP3 mask) is recommended when caring for patients with suspected or 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

Healthcare workers should be immunised with the seasonal influenza vaccine and with SARS-CoV-2 vaccine according to national schedules.

3.5. Staff illness

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

3.6. Environment or equipment

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.

Request full terminal clean of the room following patient discharge.

4. Management

4.1. 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.

4.2. 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.

4.3. Treatment criteria

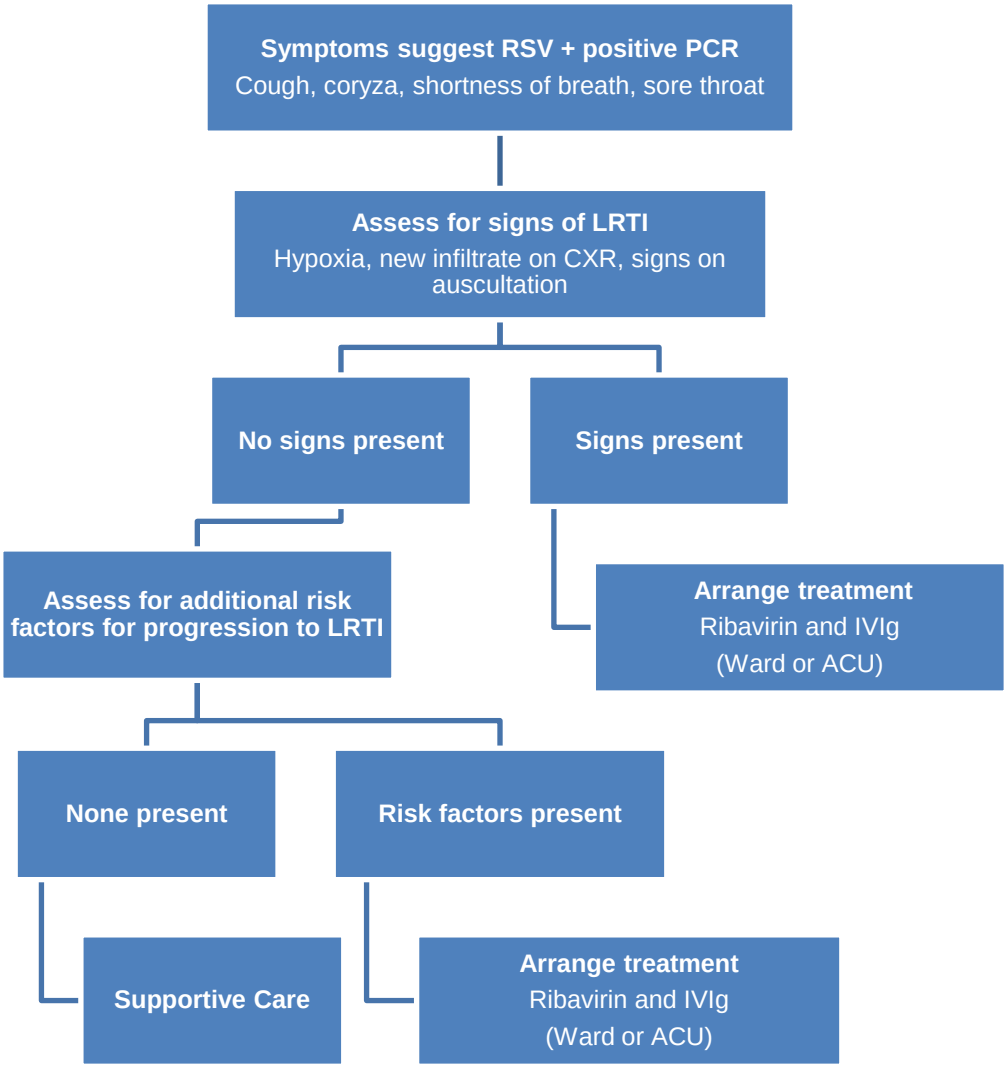
Empiric use of ribavirin is not recommended; only patients who have a positive molecular test for RSV and meet one of the two criteria below should be considered for ribavirin therapy:

1. Symptoms and signs of lower respiratory tract infection (clinical, imaging).
2. Treatment may be considered occasionally in patients with upper respiratory tract infection (URTI). The following are associated with high risk for progression from URTI to LRTI:
    - Pre-engraftment lymphopenia < 0.3 x 10^9/l
    - > 60 years old
    - GvHD
    - Mismatched, haploidentical related or umbilical cord blood donor transplant

- Neutropenia < 0.5 x 10^9/l.

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

4.4. Treatment algorithm



An Oxford study was 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).

4.5. Immunoglobulin for RSV – post BMT patients only

Consider commencement of IV Immunoglobulin (IVIg), in combination with ribavirin, at a total treatment dose of 1 - 2 g/kg administered in divided doses.

All cases should be discussed with Dr Siraj Misbah (Consultant Immunologist) or if Dr Misbah is unavailable, Dr Brian Angus (contactable via email).

Requests need to be accompanied by an electronic IVIg application submitted via the national database (link on NSSG frontpage). This should be accessed via an NHS/HSCN network connection.

Pharmacy will be unable to order and supply treatment without the electronic case ID.

This is NHS commissioned as treatment for “Viral pneumonitis post-transplantation: HSCT and solid organ”.

4.6. Ribavirin (unlicensed)

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

Unfortunately, as of 2019 there is no intravenous formulation available within the UK.

Ribavirin dosing
15 - 20 mg/kg/day given in 3 divided doses (TDS) for 7 - 10 days (Rory Sallach, 2014). Maximum recommended dose is 600mg TDS. Dose should be rounded to the nearest 200 mg and should be taken with food **Impaired renal function (CrCl < 50 ml/min):** Ribavirin accumulates in patients with decreased renal function; substantial increases in ribavirin plasma concentrations have been reported. Consider the risk vs. benefit of treatment and monitor closely for side effects, particularly haemolytic anaemia. **Renal dosing recommendation** (EUCIL4, 2013) CrCl 30 - 50 ml/min – Maximum 200 mg TDS CrCl 10 - 30 ml/min – 200 mg once daily with close clinical and laboratory monitoring. **Monitoring** Pregnancy test in appropriate patients. Blood monitoring: FBC (if Hb is falling add a reticulocyte count), U&E, serum creatinine, LFTs, LDH, monitor for signs/symptoms of adverse effects. Repeat bloods twice weekly in the first of treatment, 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 an analysis of Oxford patients (Balassa K, J. Infection 2019) 4/24 BMT patients (16.7%) were admitted with haemolytic anaemia following Ribavirin. **Warnings/precautions:** Haemolytic anaemia can occur. Avoid use in patients with significant or unstable cardiac disease due to the potential for haemolytic anaemia precipitating 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.

Pregnancy

Teratogenic effects have been observed in animal studies.

Exclude pregnancy before treatment; effective contraception is essential during treatment and for 4 months after treatment in women and for 7 months after treatment in men and female partners of male patients treated with ribavirin.

Hazardous agent

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

4.7. Influenza A & B

4.8. 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.

4.9. Treatment

See OUH Eolas Influenza guidance or local Trust policy.

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.

4.10. 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).

4.11. Immunoglobulin for parainfluenza – post BMT patients only

Consider immunoglobulin administration at a dose of 1 – 2 g/kg in divided doses in the presence of some, or all, of the following risk factors:

1. Older age
2. Graft-versus- host disease
3. Lymphopenia $\leq$ 0.2 x 10^9/L
4. Neutropenia
5. Mismatched/unrelated donor
6. Immediate aftermath of HSCT (< 1 month)

All cases should be discussed with Dr Siraj Misbah (Consultant Immunologist) or if Dr Misbah is unavailable, Dr Brian Angus (contactable via email).

Requests need to be accompanied by an electronic IVIg application submitted via the national database (link on NSSG frontpage). This should be accessed via an NHS/HSCN network connection.

Pharmacy will be unable to order and supply treatment without the electronic case ID.

This is NHS commissioned as treatment for "Viral pneumonitis post-transplantation: HSCT and solid organ".

4.12. Adenovirus

Adenovirus infection post BMT may be asymptomatic or present as an URTI, enteritis or cystitis. Adenovirus can be detected in blood, stool, urine, throat swab or NPA/NPW.

Adenovirus is now recognised as a significant pathogen in children following BMT with reported mortality rates as high as 60% in disseminated infection. Patients should be referred to Oxford BMT team for treatment.

Confirmed cases should be discussed with Consultant Microbiologist / Churchill Infection consult team (bleep 5039).

Antiviral therapy may be advised. Duration of anti-viral treatment will depend on clinical course, viral titres, and degree of immunosuppression.

4.13. Cidofovir (micro approval required)

Cidofovir is aseptically manufactured by Baxter. Orders cannot be placed out of hours or over the weekend. Doses have only 24-hour expiry once made.

Cidofovir stock can be difficult to obtain, and ribavirin may be considered in selected high-risk patients with LRTI, based on anecdotal reports.

Cidofovir **must** be co-prescribed with probenecid and fluids. The recommended dose of probenecid is 2 g (4 x 500 mg tablets) administered **three hours before** each dose of cidofivir and 1 g (2 x 500 mg tablets) **two and eight hours after the completion** of the infusion.

At OUH, we recommend prescribing hydration/probenecid using the cidofovir Powerplan. Please consult Eolas monograph for full prescribing information including dose adjustment advice in organ dysfunction.

There are 2 separate cidofovir dosing schemes, selection is discretional however use of the split dose regimen may need to be informed by the national availability of cidofovir. Treatment needs accompanied by hydration and probenecid administration to prevent toxicity.

Induction	5 mg/kg once a week for approx. 2 weeks **OR** (where renal concerns) 1 mg/kg 3 times a week for approx. 2 weeks.

Proceeding to maintenance: It should be a consultant decision to proceed to maintenance, informed by the latest PCR result.	
Maintenance	5 mg/kg every two weeks according to response **OR** (where renal concerns) 1 mg/kg every two weeks according to response
Stopping treatment: Treatment should continue until two consecutive negative PCR results	

4.14. SARS-CoV-2 (COVID-19)

HSCT recipients within the last 12 months, CAR-T recipients within the last 24 months (or until lymphocyte count within range), patients with haematological malignancy receiving SACT or radiotherapy within the last 12 months or those with myeloma (excluding MGUS), AL amyloidosis, chronic B-cell lymphoprofilerative disorders (e.g. CLL, follicular lymphoma), myelodysplastic syndrome (MDS), myelofibrosis or any mature T-cell malignancy are at at increased risk for COVID-19 associated morbidity and mortality.

Prompt treatment of patients meeting the criteria outlined within NICE TA878 or admitted to hospital and requiring supplemental oxygen should be promptly treated with NHS commissioned anti-viral treatments.

Follow local Trust COVID-19 guidance (For Oxford - OUH Eolas COVID guidelines)

Consult local infectious disease/microbiology team if advice required (OUH Churchill Infectious consult team (bleep 5039)).

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Original authors

Tim Littlewood, BMT Programme Director, Version 1, 2004
Claire Humphries, Cancer Pharmacist, Version 1, 2004

Audit

These processes are subject to the OxBMT/IEC audit programme

Circulation

NSSG Haematology Website

Document Review

Name	Revision	Date	Vers	Review
Dr Katie Jeffrey, Consultant Virologist Denise Wareham, BMT Coordinator	No detail available.	2008	2.0	Jan 2013
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 amendments	Feb 2017	4.3	2017 TBC
Lara Rowley BMT Nurse Practitioner Dr Katalin Balassa, BMT Fellow Dr Katie Jeffery, Consultant Virologist	Additions and amendments: HRPG, BCSH guidelines Ribavirin dosing, IVIG Generic changes	Apr 2018	4.4	Apr 2020
Dr Katie Jeffery, Consultant Virologist	Minor amendments Addition of guidance for staff with respiratory infection	Jun 2019	4.5	Jun 2020
Prof Katie Jeffery, Consultant Virologist	Addition of SARS-CoV_2	Apr 2023	4.6	Apr 2025
Donna Constantine, Advanced Haematology Pharmacist	IV ribavirin unavailable since 2019 and no parallel import, removed from document. Contact details for IVIg updated. Adjusted RSV flowchart to remove nebulised ribavirin (used IV prep). New information flow & formatting. Added new cidofovir info to adenovirus section.	Nov 2024	5.0	Apr 2025
Donna Constantine, Advanced Haematology Pharmacist	Clarification added that immunoglobulin only permitted in post-BMT indications. Few clarifications in text for external Trusts. Added the recommendation for use of hydration and probenecid with cidofovir. Max ribavirin dose.	Dec 2024	5.1	Apr 2025