**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 x 10^9/L
- Receipt of allogeneic BMT with active GvHD on immunosuppressant’s including corticosteroids
- Leukaemia patients with an absolute neutrophil count less than 0.5 x 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

Although 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 of proven efficacy to reduce the risk of pneumonia and death.\

**Diagnosis**
All HRPG (<100 days and those >100 days with continued immunosuppression) with symptoms suggestive of RTI (nasal discharge, congestion, sneezing, sore throat, cough etc) should have a throat swab taken, ideally at the onset of symptoms. This does not preclude testing of other patient groups.

**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.
- Nasopharyngeal aspirate (NPA) or nasopharyngeal wash (NPW) are alternative methods of specimen collection in the absence of a flocked swab. See Appendix for nasopharyngeal specimen collection.

**Investigations:**
- Swabs should be sent in the usual way to the Microbiology Department at the John Radcliffe Hospital and the clinical details should clearly indicate that this is a BMT/Leukaemia patient.
- On EPR, request **Influenza/RSV PCR** (performed daily) and **Respiratory virus screen PCR** (performed 1-2x/week). If influenza or RSV is detected, the full viral panel will not be performed unless specifically indicated. (Full viral panel includes: Influenza A/B, H1N1; coronaviruses HKU, 299, 43, 63; parainfluenza 1,2,3,4; human metapneumovirus; rhinovirus; respiratory syncytial viruses A,B; enterovirus; parechovirus; bocavirus; adenovirus; **Mycoplasma pneumonia**).
- Results of the Influenza/RSV PCR should be available on same day please contact lab if results not in EPR.
Minimising spread

- Inpatients with confirmed viral RTI should be nursed on the Haematology Ward in a negative pressure side room with the door closed.
- In suspected cases, the patient should be nursed in a side room, with the door closed (no pressurisation). In high risk patients, where initial screening is negative, the patient should remain in isolation until the second more sensitive PCR result is available.
- Strict isolation is required in both cases. The patient should be confined to their room to avoid social contact with other immunocompromised patients. Standard precautions plus vigilant hand washing or alcohol hand rub is essential. Patients should remain isolated until discharge.
- These infections are spread by close contact with infected secretions, by large particle aerosols and by fomites. Health care workers are most likely the main vectors in this setting.\(^5\)
- 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.
- Multiple, confirmed cases should be cohort nursed, in a 2-bedded bay with the door closed.

Visitors should be advised to be vigilant about hand washing or alcohol hand rub and avoid contact with other immunocompromised patients on the ward. They should not use the day room or other ward facilities.

Outpatients should be advised to avoid prolonged contact with other immunocompromised patients, in waiting/treatment areas, i.e. they should wait and be seen in a side room, until their symptoms are no longer present, 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.\(^4\)

   Investigations: RSV PCR, CXR, Serum Ig’s and electrophoresis and CT chest

   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 and signs of lower respiratory tract infection (clinical, imaging)
   - Positive molecular test for RSV
   - High risk for RSV disease progression

   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).
**Ribavirin**

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

**Summary of Ribavirin Use**

| Oral dose | 15-20mg/kg/day divided into TDS administration for 7-10 days
|           | Dose should be rounded to the nearest 200mg
|           | To be taken with food
| Intravenous dose | Day 1: 600mg loading dose, then 200mg every 8 hours
|                 | Day 2: 400mg every 8 hours
|                 | Day 3: Increase the dose to a maximum of 10mg/kg every 8 hours
| Renal Dose adjustments (European Guidelines) | Original maximum dosing regimen (IV/PO): 10mg/kg/dose Q8h
|                                                                 | Dose adjustments:
|                                                                 | CrCl 30-50ml/min – 200mg Q8h
|                                                                 | CrCl 10-30ml/min – 200mg once daily with close clinical and laboratory monitoring.
|                                                                 | *Note: Specific renal dose adjustments for 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.*
| Monitor | 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 one week after completing Ribavirin.** In a recent series of Oxford patients (December 2015/January 2016) 3/8 BMT patients were admitted with 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.
2. **Influenza A & B**
   Testing as per above
   On positive result commence Oseltamivir. Oseltamivir may also be indicated for patients with laboratory confirmed Influenza A or B infection after 48 hours of symptoms (discuss with Consultant Microbiologist).

3. **Parainfluenza (PIV)**
   There is no licensed antiviral therapy for the treatment of PIV, although Ribavirin has antiviral effects against PIV in cell culture and has been used in immunocompromised hosts. Discuss with Consultant Microbiologist.

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 the Consultant Microbiologist. Antiviral therapy particularly Cidofovir may be advised.

**References:**


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
Audit
These processes are subject to the OxBMT audit programme

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

Circulation
NSSG Haematology Website

Review

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<td>Reduction in duration of oral ribavirin administration to 7 days. Changes to patient follow up guidance</td>
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