Nottingham University Hospitals NHS Trust

Bone Marrow Transplant Programme Guideline

***Clinical Guidelines** are "policy and/or guideline" documents.*

They do not require a competency, but each document must be registered with the Trust.

Title: Screening, Pre-emptive Therapy and Treatment of Viral Infections.

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Amendments to Version:

Version	Amendment	Released	Implemented	Archived
3.0	Early Review Contents page updated Sections 2 & 3: updated Section 6: Updates throughout text. **NOTE:** **CMV and EBV units and parameters for intervention have been updated.** **Instruction added for Hep C screening, diagnosis and treatment.** **Instruction added for intravesical Cidofovir for BK virus–related Haemorrhagic cystitis** Section 9 : References updated	07-Nov-2017	07-Nov-2017	01 Nov 19
4.0	• Appendix 2 Pro forma for Monitoring and Dosing Foscarnet added • Appendix 2 becomes appendix 3 • 6.3.2 failure to respond – sentence added The pro forma in Appendix 2 may be used to help monitor the patient's creatinine • 6.6.2 medication name changes Probenicid becomes Probenecid Cidofivir becomes Cidofovir Appendix 2 Foscarnet dose changes from give over 1 hour to mg/kg instructions • Appendix 3 added: Cidofovir will be prepared in the Pharmacy Cytolab during normal working hours	07 Nov 2019	07 Nov 2019	17/05/2023
5.0	• Addition of use of IV letermovir • Addition of use of Maribavir for refractory CMV • Addition of Hep E screening • Addition of use of BK CTLs for haemorrhagic cystitis	17/05/2023	17/05/2023	16/08/2023
6.0	Include reference to SOP PRB52	16/08/2023	16/08/2023	19/09/2023
7.0	DCR297 implemented – acyclovir start date amended	19/09/2023	19/09/2023	20/11/2023
8.0	DCR310 Page 3- updated to letermovir	20/11/2023	20/11/2023	30/4/2025
9.0	Added SARS-CoV2 section and refer to NUH Guidleine Added references to Shingrix vaccination and use of IVIG in RSV and Influenza A	30/4/2025	30/4/2025	

CONTENTS page

1. Principles and Purpose / Objective:

Infection is a major cause of morbidity and mortality after Haematopoietic Progenitor Stem Cell Transplant (HSCT) due to the immunosuppression that follows conditioning therapy. CMV is the major viral cause of infection in HSCT patients, and other viruses may also cause problems due to reactivation or new infection.

There is increased risk of viral infection for up to at least one year after allogeneic HSCT, particularly if there is GvHD and / or prolonged immunosuppressive therapy.

All patients receive anti-viral prophylaxis with Aciclovir, and allograft patients have weekly screening for CMV and EBV. Allograft recipients that are seropositive for CMV should start prophylactic letermovir from Day +12 post transplant (or from day +1 if at very high risk of reactivation) and then have a lower dose of acyclovir. Screening for Hepatitis B and adenovirus infection is undertaken if clinically indicated – *see sections 6.5 and 6.6 below.*

Respiratory virus infections may cause outbreaks during the winter months. Attention must be given to control of infection policies as well as treatment of the individual patient.

This document gives guidance on the screening, pre-emptive therapy and treatment of the viral infections that are most likely to be seen post-transplant.

N.B. Aciclovir, Valaciclovir and Ganciclovir given as indicated should not be given concomitantly. Use with caution in patients with renal impairment.

2. Related Documentation:

- Appendix 1 - Dosing regimens for Valganciclovir, Ganciclovir and Foscarnet for treatment of CMV.
- Appendix 2 – Pro forma for Monitoring and Dosing Foscarnet
- Appendix 3 - Guideline for the Administration of Cidofovir for CMV, adenovirus or BK virus infections.
- BMT Conditioning protocol in patient's medical record.
- NUH Clinical guideline 1407 – Infection guidelines.
- NUH Clinical guideline 2027 – Treatment guideline for adult patients with influenza.
- SOP PRB45 - Guideline for the Management of Haemorrhagic Cystitis
- SOP PRB62 – Clinical Guidelines for the Nursing Care of the Patient Receiving Nebulised Pentamidine.
- SOP PRB67 – Administration of Ribavirin via Aiolos Nebuliser
- NUH intranet page for Ribavirin http://nuhnet/diagnostics_clinical_support/antibiotics/Pages/A-Z/Ribavirin.aspx
- NUH Treatment guideline for adult patients with influenza
- SOP PRB52 Guideline for the Administration of Donoe Lymphocyte Infusions Post Allogeneic Transplantation

3. Terminology, Abbreviations and Definitions:

See Glossary in current Bone Marrow Transplant Programme Operational Policy and Quality Manual.

ACV	Aciclovir
BAL	Broncho-alveolar lavage

BK virus	A papovavirus named from the initials of the first known patient.
COVID	Novel coronovirus 2019 (also known as SARS-CoV-2)
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
EBV	Epstein Barr virus
CTLs	Cytotoxic T Lymphocyte therapy - given for EBV-driven PTLD.
HepBsAg	Hepatitis B virus surface antigen
HepBcAb	Hepatitis B core antibody
HepCAb	Hepatitis C antibody
HHV6	Human Herpes Virus 6
HSCT	Haematopoietic (Progenitor) Stem Cell Transplant
HSV	Herpes simplex virus
NPA	Naso-pharingeal aspirate
RSV	Respiratory syncytial virus
RTI	Respiratory tract infection
PTLD	Post Transplant Lymphoproliferative Disease
PCT	Primary Care Trust
qPCR	quantitative Polymerase Chain Reaction. An assay that amplifies a specific DNA sequence to enable measurement of the original levels presentation the sample. In this case, a method of measuring the levels of a specified virus present in the blood.
SpR	Specialist Registrar, ST3 or above.
URTI	Upper Respiratory Tract Infection
VZV	Varicella-zoster virus (chickenpox and shingles)
VZIG	anti-VZV immunoglobulin

4. Personnel and Training Requirement:

- Clinical Haematology medical and nursing staff.
- BMT Coordinators

5. Equipment:

See instructions under ‘Diagnosis’ in relevant sections.

6. Procedure / Method:

6.1. ANTI-VIRAL (HSV, VZV) PROPHYLAXIS

6.1.1. Autograft patients receive oral Aciclovir 400mg qds from Day 0 until Day + 90 post-transplant.

6.1.2. Allograft patients on myeloablative protocols receive IV Aciclovir 10mg/kg from Day -2 until engraftment when they can be switched to PO Aciclovir 800mg qds. Allograft patients on non-myeloablative protocols receive PO Aciclovir 800mg qds from day -2. CMV seropositive patients are started on Letermovir form Day +12 when the dose of acivlovir can be reduced to 400 mg po bd.

- Continue aciclovir to at least 100 days then reduce the dose to 400mg bd and continue until at least 12 months post-transplant to reduce risk of Herpes zoster infection.

-Ensure that the patients starts their Shingrix vaccinations at 6 months post transplant

- If the patient remains on immunosuppressive therapy after 12 months post-transplant continue prophylactic Acyclovir.

For adults unable to tolerate oral medication, IV Aciclovir 250mg tds should be given.
(usual dose 5mg/kg)

6.2 ANTI-VIRAL (CMV PROPHYLAXIS)

6.2.1 Allograft recipients who are **CMV IgG SEROPOSITIVE** prior to their transplant are eligible for CMV prophylaxis with **LETERMOVIR.** This must be started before day 28 post-transplant and at NUH it will normally be started on day +12 post transplant **and continued until day +100.**

- A **Blueteq** form must be completed prior to the prescribing of letermovir prophylaxis

- The usual dose of letermovir will be 240 mg po od since the majority of allograft recipients will be taking cyclosporine as GVHD prophylaxis. If patients are NOT taking cyclosporine (eg are on tacrolimus instead or stop cyclosporine earlier than day +100) then the increased dose of 480 mg po od will be used instead

- If CMV reactivation requiring treatment occurs despite the letermovir prophylaxis then the letermovir will be discontinued and CMV treatment will be started. Letermovir cannot be restarted after CMV reactivation has occurred however.

- If letermovir has to be stopped for up to 2 weeks due to the oral route not being available then IV letermovir should be considered. Oral letermovir can be restarted provided it has not been stopped for > 2 weeks unless CMV reactivation has already occurred

- The use of letermovir prophylaxis is ADDITIONAL to acyclovir prophylaxis for other herpes viruses since it is only specific for CMV but a lower dose of acyclovir is usually given

- There is no dose adjustment required for letermovir in the presence of renal or hepatic impairment

- There currently is no liquid or IV formulation of letermovir and the tablets cannot be crushed but an IV formulation is now available if the oral route is not possible (D/W pharmacy) and is given at the same dose of 240 mg IV over 1 hour

- Letermovir may reduce the blood levels of voriconazole and some other drugs eg dabigatran.

- Letermovir may be able to be continued longer than 100 days if there is good reason to prolong it

6.3 ROUTINE SCREENING

6.1.3. Pre-transplant

Pre-transplant screening of patients and donors is described in the following documents:

- SOP PRB03 Procedure for Donor Selection and Work Up for Allogeneic Transplantation
- SOP PRB60 Procedure for the Work Up of Patients for Autologous Transplantation.
- NUH BMT Conditioning Protocols
- SOP PRB52 Guideline for the Administration of Donoe Lymphocyte Infusions Post Allogeneic Transplantation

6.1.4. Post-transplant

6.1.4.1. CMV

All allogenic transplant recipients (relative, MUD, cord) weekly screening for CMV by qPCR on peripheral blood.
Screening should be continued for 4 months for all patients. It may be discontinued if patient is not on steroids at Day +100, and no CMV reactivation has been seen over the following 3 weeks of sampling (to day +120).
Re-start screening if a patient requires prednisolone therapy >20mg for GVHD or starts on Ruxolitinib and has a previous history of CMV reactivation.

BMT Coordinator CNS staff coordinate sample collection for both inpatients and outpatients. Samples are taken from inpatients on Wednesday, and stored overnight in the sample fridge. Outpatient samples are taken on Thursday morning.
The samples are placed in a single dedicated insulated box and sent to QMC Main reception on B floor who ring Microbiology for urgent collection to be processed on Thursday.
Microbiology ring all abnormal results through to BMT CNS team on Friday morning to enable dose alterations to be prioritized. The BMT CNS then review the rest of the results to double-check that no action is required.

6.1.4.2. EBV

EBV reactivation has an associated risk of developing PTLD. The risk is greater to patients receiving T-cell depletion with Campath or ATG as part of the conditioning protocol.

All allogenic transplant recipients (relative, MUD, cord), **and autograft patients receiving ATG**, should have EBV qPCR levels monitored weekly post-transplant for a minimum of 4 months.

Sampling arrangements are as for CMV, above.

Patients receiving autografts do not need to be monitored unless they have received ATG as part of the conditioning protocol.

6.1.4.3. Hepatitis

Hep-B - Patients who are HepBcAb +ve will usually receive anti-viral prophylaxis, (eg lamivudine) until they are off immune suppression– check current practice with Infectious Diseases Consultant. They will require screening monthly for reactivation by HepB qPCR from Day +28 to 4 months post-transplant. *See Section 6.5.for treatment*

Hep-C - Patients who are HepCAb +ve will require screening monthly for reactivation by HepC qPCR from Day +28 to 4 months post-transplant. *See Section 6.5. for treatment.*

Hep E screening – An unexpected ALT rise post transplant should be investigated with a Hep E PCR test and chronic Hep E infection may occur in immune suppressed individuals and should be excluded. Hepatitis E can be spread through undercooked pork and so patients should be encouraged to ensure all pork dishes are properly cooked.

Adenovirus – abnormal LFTs should also result in screening for adenovirus PCR in the blood. This virus can also sometimes be identified in eye swabs / sputum/ throat swabs / stool samples and should be followed up by blood PCR

6.1.5. Screening List

A list of patients to be screened is maintained by the BMT Coordinators.
The list is reviewed periodically by the Transplant Consultants to ensure that only necessary screening is undertaken.

6.2. CMV DIAGNOSIS AND TREATMENT

6.2.1. Diagnosis (routine screening)

Sampling: coordinated by the Bone Marrow Transplant Coordinators. See section 6.2.2.1, above.

Timing and Duration:

Pre-Transplant - All allograft patients to be screened on Thursday, pre-transplant (D -6). This is in addition to the requirements of patient and donor screening pre-transplant.
Post-Transplant: All allograft patients should be screened weekly on Thursday mornings from day +21 until at least four months post-transplant by qPCR.
Testing will continue if the patient still requires immunosuppression at this stage or if they require steroid treatment. See section 6.2.2.1, above

If any patient has a qPCR positive result then samples should continue to be sent weekly: Screening can be stopped when the patient has at least 3 weeks with a negative qPCR.

Samples To Be Sent: EDTA sample to Microbiology at QMC, sent by the BMT Coordinators as described in 6.2.2.1, above. **In-patient samples should be sent via the BMT Coordinators – not via the pod system.**

Results The BMT Coordinators receive results from the laboratory and confirm as described in 6.2.2.1, above.
If any results are outstanding at 16:00 the BMT Co-ordinators must handover for results to be chased by on-call Haematology SpR.

If any patient becomes PCR positive when both patient and donor were CMV seronegative pre-transplant, then this seroconversion must be submitted as a SHOT report.

Action Required The decision concerning treatment with Valganciclovir is normally made by the consultant. However patients will normally be treated if they have a qPCR result >2000 iu/ml [source: Dr Radia Oct 2017]

6.2.2. Treatment – should be commenced if CMV-PCR is >2,000 iu/ml *[source JLB Oct 2017]*

Conversion factors CMV: 1 copy/ml => 0.29 iu/ml 1 iu/ml => 3.11 copies/ml

First Line Treatment will be with oral Valganciclovir 900mg bd for at least 2 weeks with a dose reduction for renal dysfunction *(see Appendix 1).* If the oral route is not available use IV ganciclovir 5 mg/kg bd.

If CMV is non-detectable after 2 weeks stop Valganciclovir / ganciclovir.

Continue for a 3rd week of therapy of still positive but <500 copies/ml.

Side-effects include cytopenias – G-CSF may be required. Discuss with Consultant if patient is cytopenic before treatment is initiated.

If there is a high level PCR result (>20,000) then treatment may be initiated with Ganciclovir 5mg/kg bd (iv) to ensure rapid achievement of therapeutic levels. After 7 days switch to oral Valganciclovir or once daily Ganciclovir increased to 6mg/kg (iv)

If there is significant renal impairment then the dose of Valganciclovir / Ganciclovir may have to be reduced *(see Appendix 1).*

If the patient fails to respond to Valganciclovir, there is a contra-indication to Valganciclovir or a patient has known resistance to Ganciclovir, then consider switching to Foscarnet (iv) dose adjusted to renal function *(see Appendix 1).*

Side-effects of Foscarnet include renal toxicity and electrolyte imbalance – monitor U&E, Mg, Ca^{2+} regularly. Adjust Foscarnet dose if creatinine levels are elevated. The pro forma in Appendix 2 may be used to help monitor the patient's creatinine.

If a patient has recurrent CMV reactivation or fails to respond to treatment contact Microbiology and request a mutation screen.

Maribavir is now approved by NICE for refractory CMV (defined as documented failure to achieve > 1 log depletion decrease in CMV DNA level in whole blood or plasma after 14 days of treatment with valganciclovir, IV ganciclovir, foscarnet or cidofovir. Blueteq must be done.

Other Third Line Treatments for recurrent CMV reactivation include Cidofovir *(see Appendix 3)* .

6.3. EBV DIAGNOSIS AND TREATMENT

EBV is a member of the herpes virus family and one of the most common human viruses. EBV also establishes a lifelong dormant infection in some cells of the

body's immune system. Reactivation of EBV in an immunocompromised patient can lead to PTLD.

6.3.1. Diagnosis

Sample – coordinated by the Bone Marrow Transplant Coordinators

Timing: to be taken either in the Bone Marrow Transplant Clinic on a Thursday or if patient is an inpatient sample to be taken on the ward.

Samples To Be Sent EDTA blood sample (x1) to be sent to Microbiology with ***"EBV PCR request"*** clearly marked on form.

Results The Bone Marrow Transplant Coordinators will check all available results on Friday morning. If any results are outstanding at 16:00 the BMT Co-ordinators must ring the laboratory to check if there has been a problem and handover for results to be chased by on-call Haematology SpR.

Action Required Any result above 10 000 iu /ml *[source: Dr Radia Oct'17]* must be reported to one of the transplant consultants, who will make a decision with regards to pre-emptive therapy.
All patients with an EBV level of 12,000 iu /ml *[source: Dr Radia Oct'17]* should be treated with Rituximab even if asymptomatic.
If the patient has clinical features suggestive of EBV reactivation or PTLD treatment should be initiated regardless of screening result.

Conversion factors EBV: 1 copy/ml => 1.02 iu/ml 1 iu/ml => 0.98 copies/ml

6.3.2. Treatment

Weekly Rituximab 375mg/m^2 (iv) for up to 4 weeks depending on response. Often only 1 or 2 doses will be needed to bring EBV to < 10,000 copies/ml.

If there is persistent EBV reactivation assess for clinical features of PTLD eg CT / PET scan / LDH

Consider stopping immunosuppression and giving donor-specific EBV CTL therapy for EBV-related PTLD not responding to treatment with Rituximab. These can be obtained by the Scottish blood transfusion service or by compassionate use.

6.4. HEPATITIS B and C DIAGNOSIS AND TREATMENT

All patients will have pre-transplant serology testing for:
Hep B Surface Antigen (HepBsAg)
Hep B Core Antibody (HepBcAb)
Hep C

Patients who are HepBcAb +ve will require screening monthly for reactivation by HepB qPCR from Day +28 to 4 months post-transplant
and should receive oral Lamivudine 100mg o.d.
from Day +28 to Day +100 as prophylaxis.

If patients have rising HepB qPCR levels post-transplant discuss with Consultant Microbiologist and consider referral to Hepatology or infectious diseases.

Patients who are HepC +ve will require screening monthly for reactivation by HepC qPCR from Day +28 to 4 months post-transplant. They should be referred to Hepatology for consideration of Hep C eradication therapies.

6.5. ADENOVIRUS DIAGNOSIS AND TREATMENT

Adenovirus is responsible for many types of infections in patients undergoing HSCT. It should be considered as a potential pathogen in cases of pneumonitis, hepatitis, encephalitis, haemorrhagic cystitis, gastroenteritis and colitis.

6.5.1. Diagnosis. Appropriate samples (NPA, sputum, BAL, CSF and stool) should be sent for direct immunofluorescence, PCR testing and viral culture.
Adenovirus viraemia is potentially life-threatening, and blood samples should be sent for adenovirus qPCR if adenovirus is identified in sputum or stool samples or if there is clinical concern. (Blood sample in EDTA).

Positive stool samples in patients having undergone an allogeneic HSCT indicate a high risk of infection.
The risk is lower in patients who have undergone an autologous HSCT and have adenovirus only in their stool.

6.5.2. Treatment threshold for treating adenovirus in blood is when the viral load in the blood is 1000 or more copies/ml irrespective of the severity or presence of diarrhoea.
Depending on the severity of infection, the following are recommended therapies:

Intravenous immunoglobulin 500mg/kg daily for 4 days

Cidofovir 5mg/kg once weekly for 2 –3 doses and then once every 14 days.
(reduce dose in renal impairment)
NB: Patients will require Probenecid prior to having Cidofovir as per protocol. See Appendix 3

Ribavirin can also be considered in severe cases of adenovirus pneumonia
- use the same dose as for RSV *(see below)*.

Brincidofovir – is no longer available

6.6. RSV, PARAINFLUENZA 3 and 4, AND METAPNEUMOVIRUS DIAGNOSIS AND TREATMENT

RSV, Paraflu and Metapneumovirus may cause severe, even fatal lower respiratory tract infections in HSCT patients, especially those within 4 months of transplant, those on immunosuppression longer than 3 months, before engraftment or with chronic GVHD of the lungs.

6.6.1. Diagnosis - by immunofluorescence and viral culture on NPA, sputum, throat swab or BAL samples. Paraflu infections tend to follow a seasonal pattern and patients should have an NPA as soon as the first upper respiratory tract infections develop.

6.6.2. Infection Control Measures
Patients should be isolated from other immunocompromised patients for several weeks preferably in a negative pressure room or non-pressurised room but never in one with positive pressure.

Strict hand washing with alcohol based solutions by staff is necessary to reduce cross-infection.

Staff involved in the patient's care who develop respiratory symptoms should be screened for RSV and Paraflu with an NPA or throat swab.

6.6.3. Treatment should be considered as soon as infection is diagnosed *(hypoxia, crackles, and clinical evidence on chest X-ray)*, and if possible before progression to lower respiratory tract infection.

If URTI only: consider oral Ribavirin - see Clinical Haematology Guideline for the Treatment of Specific Infections including Mucositis, Enterocolitis and Respiratory Viral Infections in Clinical Documents Library on NUH web site (shortcut is 'Specific Infections Management in Haematological Patients') .

RSV Patients with LRTI: These patients may be eligible for a single dose of IVIG as per the IVIG on-line request form, but this must be approved. Treat with oral ribavirin.

Haemolysis is a well-described side effect of Ribavirin requiring regular monitoring of the Hb, bilirubin, LDH and blood film appearances.

Oral Ribavirin dosing - refer to NUH antibiotic website. *IV Ribavirin should be considered if nebulised therapy is not practical,refer to NUH antibiotic website*

6.7. INFLUENZA A and B DIAGNOSIS AND TREATMENT

Influenza viruses cause flu in humans and can progress to pneumonitis in patients undergoing HSCT. They should receive treatment immediately and should be isolated from other immunocompromised patients for several weeks - preferably in a negative pressure room.

6.7.1. Diagnosis may be made on throat swab , sputum sample or NPA should be sent qPCR testing and viral culture.

6.7.2. Treatment - to commence as soon as possible
refer to NUH Clinical guideline 2027 – Treatment guideline for adult patients with influenza.

Option 1. Oseltamivir (Tamiflu ®): a neuraminidase inhibitor recently licensed for the treatment and prevention of Influenza A and B. It has a similar spectrum of activity to Zanamivir but resistance is common in H1N1 strains where Zanamavir should be used (see below). It has the advantage of being taken orally as opposed to inhaled. It can also reach therapeutic levels in sites such as the middle ear and sinuses that Zanamivir does not penetrate well.

Dose 75mg bd po for 5 days

Caution is required in patients with significant liver impairment.

Dose reductions are required in renal impairment

Option 2. Zanamivir

Dose 10mg BD by inhaler for 5 days

For critically ill patients unable to use inhaled Zanamivir – IV Zanamivir may be obtained. Refer to the Trust treatment of influenza guideline for advice on dosing and how to obtain IV zanamivir as this is only available on a named patient basis.
Dose may need to be reduced in renal dysfunction- consult product specification.

Treat for 5 days, but may continue longer if ongoing severe symptoms.

IVIG – patients post HSCT with Influenza A may be eligible for a single dose of IVIG – see IVIG website and on-line request form on the intranet

6.8. SARS-CoV-2 (COVID 19) Diagnosis and Treatment

SARS-CoV-2 can cause a potentially fatal pneumonitis in immune suppressed individuals.

6.8.1 **Screening** – all patients are screened with viral throat swabs for potential COVID-19 infection prior to admission for any transplant procedure – transplant to be delayed until there have been 2 consecutive negative swabs at least 48 hours apart.

Patients are advised to isolate and avoid exposure to possible COVID for 1 week prior to planned admission

No patients to be admitted to Fletcher ward if testing positive for COVID-19

6.8.2 **Prevention** – all immune suppressed patients are strongly advised to have their COVID vaccinations, including re-vaccination at 3 months post-transplant and annual boosters. Facemasks are still to be worn by patients and staff in clinical areas. Patients with any respiratory symptoms should be isolated where possible until throat swabs results are made available.

6.8.3 **Treatment** – for immune suppressed patients testing positive for COVID but clinically not requiring admission they should be referred to the COVID Medicines Delivery Unit (CMDU) for assessment and treatment with antivirals if they meet the criteria.

For transplant patients admitted with suspected or proven COVID-19 symptoms the NUH COVID-19 Guideline (nhs.sharepoint.com/sites/RX1_SpecialistReceivingUnit/Shared Documents/Forms/AllItems.aspx?id=%2Fsites%2FRX1_SpecialistReceivingUnit%2FShared Documents%2FInfectious Diseases Guidelines%2FCOVID 19 Guideline for Adults%2Epdf&parent=%2Fsites%2FRX1_SpecialistReceivingUnit%2FShared Documents%2FInfectious Diseases Guidelines) should be followed. CXR and high-resolution CT scans should be performed. Hypoxic patients should be started on dexamethasone. Baricitinib, Sotrovimab, Paxlovid and / or remdesivir may be indicated. Consideration to addition of standard antibiotics should also be given.

6.9. BK VIRUS DIAGNOSIS AND TREATMENT

Haemorrhagic cystitis (HC) presents with painful haematuria, frequently with clots leading to retention of urine and possible renal impairment if BK nephritis occurs.

6.9.1. Diagnosis Urine should be sent for viral culture / qPCR for BK virus, JC, CMV and adenovirus. Peripheral blood should be sent for qPCR for CMV, BK virus and adenovirus.

6.9.2. Treatment - severe BK virus-associated haemorrhagic cystitis can be treated with low-dose cidofovir (0.5-1mg/kg IV weekly) until symptom resolution. *(See Appendix 3)*

Note that probenecid cover is not required due to the low dose of cidofovir used.

If patient fails to respond after 2 weeks, discuss with Consultant.

Intravesical Cidofovir

Where treatment with low-dose intravenous cidofovir is contra-indicated e.g. Severe cytopenias, intravesical cidofovir can be considered. This must be discussed with a consultant. The systemic absorption of intravesical cidofovir is variable.

Prescribe as:

Cidofovir 5mg/kg bladder instillation in 100ml sodium chloride 0.9%.
Administer via urinary catheter and clamp catheter for a minimum of 1 hour.
To be retained in the bladder for 2 hours.
Dose may be repeated after 1 week.

BK virus CTLs –may be available in clinical trials or via compassionate use for severe haemorrhagic cystitis due to BK virus (Allovir study)

6.10. HHV6 DIAGNOSIS AND TREATMENT

There are currently eight known members of the herpes virus family. Although all these viruses share some similar traits, such as latency and potential for reactivation, HHV-6 differs from other herpes viruses in the diseases it causes.

HHV-6 commonly reactivates in the peripheral blood post-transplant but only a small number of patients develop signs of infection. HHV6 present in the CSF indicates HHV6 encephalitis. Active infection can cause fever and encephalitis which may be manifest as confusion, neurological signs or fits.
HHV-6 infection may also be a cause of secondary graft failure.

6.10.1. Diagnosis HHV-6 should be tested for in patients with unexplained fever, fits, confusion, graft failure or falling blood counts. No routine monitoring is required. Liaise with Microbiology to send a CSF specimen for HHV-6 qPCR testing.

6.10.2. Treatment may be started on clinical grounds **or** if a positive CSF result is obtained but **should be discussed with transplant consultant** before implementing.

- Foscarnet IV should be considered
  (dose as for CMV i.e. 90 mg/kg bd if normal renal function).

6.11. VZV DIAGNOSIS AND TREATMENT

Varicella-zoster virus (chickenpox and shingles) can cause devastating disseminated disease in immunocompromised patients, especially post-transplant.

6.11.1. Contact with VZV

Immunocompromised HSCT patients who are VZV negative who come into contact with VZV should receive high titre anti-VZV immunoglobulin.

Dose: VZIG 1gm by intramuscular injection *as soon as possible and not later than 7 days after exposure.*

In addition give Aciclovir 800mg orally 5 times a day for 2 weeks.

VZIG does not prevent infection with VZV and can increase the incubation period. Therefore inpatients who have received VZIG should be isolated for up to 28 days after exposure to protect susceptible patients and staff.

If a second exposure occurs after 3 weeks, a second dose is needed. After this period, the patient should have their VZV IgG status re-tested.

Contacts with bleeding disorders who cannot receive intramuscular injections should be given intravenous normal immunoglobulin 0.2g/kg. *(ie 4ml/kg of 5% solution)*

6.11.2. Infection with VZV

Diagnosis – suspected cases should have blood sent for VZV-qPCR and /or viral swabs from vesicles sent for culture.

Treatment Patients with disseminated VZV should be isolated from other immunocompromised patients, admitted to hospital and given Aciclovir (iv).

Dose:

Localised VZV Aciclovir 800mg orally 5 times per day for 7 days
or Valaciclovir 1gm tds orally

Disseminated VZV Aciclovir 10mg/kg tds(iv) for at least 5 days, or until lesions have crusted and are healing - whichever is later.

Following this, responding patients should receive
Aciclovir 800mg orally 5 times per day
or Valaciclovir 1gm tds orally, for a period of 2-3 weeks.

The dose should then be reduced to Aciclovir 400mg tds
or Valaciclovir 500mg bd as maintenance.

6.11.3 Shingrix Vaccination

All SCT patients should receive 2 doses of Shingrix vaccine at 6 months post transplant. If patients have had a recent attack of Zoster they should wait 3 months before receiving Shingrix

At 2 years a test for VZV immunity should be requested

6.12. HSV DIAGNOSIS AND TREATMENT

6.12.1. Diagnosis - viral swabs from lesions sent for culture.

6.12.2. Treatment

For non-neurological HSV infections use Aciclovir 5mg/kg tds iv
or if non-severe, Aciclovir 400mg po x5 daily.

Consider Foscarnet 40mg/kg iv 8 hourly if severe HSV infection is resistant to Aciclovir on clinical or virological grounds.

If good clinical response after 5 days of iv Aciclovir, patients can be changed to oral preparations using the following treatment guidelines:

Adults: Aciclovir 400mg orally 5 times per day or Valaciclovir 1gm tds.

The dose should be reduced to the prophylactic dose after 2 – 3 weeks providing the infection has resolved.

**For suspected or proven HSV encephalitis use iv Aciclovir 10mg/kg tds.
for a minimum of 14 - 21 days.**

6.13. PARVOVIRUS DIAGNOSIS AND TREATMENT

Parvovirus is a small DNA virus. It is usually spread by infected respiratory droplets but can be passed on via blood transfusion or HSCT. Parvovirus can lead to significant red blood aplasia and the virus is associated with a haemophagocytic syndrome, which put the HSCT patient at risk of graft failure.

6.13.1. Diagnosis -where the HSCT patient has an undiagnosed pyrexia or falling blood counts a blood specimen should be sent for Parovovirus qPCR. Any positive result should be treated irrespective of level.

6.13.2. Treatment

IV- Immunoglobulin to a total of 2g/kg iv once only then repeat Parvovirus qPCR.

7. Endpoints, Expected Results and Limitations of Procedure:

7.1. ~~Endpoint and Expected Results~~ *- not applicable for this document.*

7.2. Limitations

7.2.1. Aciclovir, Valaciclovir and Ganciclovir given as indicated should not be given concomitantly. Use with caution in patients with renal impairment.

7.2.2. If any patient becomes qPCR positive for CMV when pre-transplant samples for both patient and donor were negative, then this seroconversion must be submitted as a SHOT report.

8. Audit:

Incidents and near misses in the care of patients must be reported via the Trust Datix system.

- Incident reports and deviations from this protocol will be copied to the BMT Quality Management Group.
- Infection data will be reviewed at least annually by the BMT Quality Manager

9. Evidence Base of Policies / References:

- EBV/CMV conversion factors – email communication from NUH pathology laboratories July 2015
- 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. Dignan F, Clark A, Aitken C et al. Br J Haematol, 173: 380–393. 2016
- Infections after HSCT. Rovira M, Mensa J and Carreras E. 2012. Haematopoietic Stem Cell Transplantation EMBT Handbook J Apperley *et al* (eds.) 6th Edition pp196-215.Genoa: Forum Service Editore.
- British National Formulary BMJ Group and Pharmaceutical Press October 2017
- Guidelines for EBV management in patients with leukaemia and other haematological disorders. 2009 update of ECIL2. Styczynski J, Einsele H, De la Camara R, et al. 3rd European Conference on Infections in Leukemia, 2009.
- Targeted monitoring of patients at high risk of post-transplant lymphoproliferative disease by quantitative Epstein-Barr virus polymerase chain reaction. Omar H, Hägglund H, Gustafsson-Jernberg A, et al. Transpl. Infect. Dis. 2009 Oct;11(5):393-9. Epub 2009 May 26
- Low-dose cidofovir in the treatment of symptomatic BK virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation: a retrospective analysis of an algorithmic approach. Ganguly N, Clough LA, Dubois LK, Mcguirk JP, Abhyankar S, Aljitawi OS, O'Neal N, Divine CL, Ganguly S. *Transpl Infect Dis. 2010 Oct;12(5):406-11*.
- Bone Marrow Transplant Programme Operational Policy and Quality Manual for Nottingham University Hospitals NHS Trust BMT Programme.

- FACT-JACIE International Standards For Cellular Therapy Product Collection, Processing, And Administration, Edition 6.01, available at http://www.jacie.org

10.Training and Competency:

Clinical Guidelines *are "policy and/or guideline" documents. They do not require a competency, but still require a record that staff have read the document.*

Once they have read the SOP, relevant staff members are acknowledge the SOP on Q Pulse

APPENDIX 1

Dosing regimens for Valganciclovir, Ganciclovir and Foscarnet for treatment of CMV

VALGANCICLOVIR

Induction PO 900mg bd 21/7

Maintenance PO 900mg od

Renal impairment:

Induction

Creatinine clearance	Dose
> 60ml/min	900mg bd
40-59ml/min	450mg bd
25-39ml/min	450mg od
10-24ml/min	450mg every 2 days

On consultant recommendation only.

Side effects:

Myelosuppresive
- causing neutropenia and thrombocytopenia. Severe myelosuppression may necessitate a dose reduction or discontinuation. Myelosuppression can sometimes be delayed and persist up to 1 month after discontinuing.

Other less frequent side effects include: fever, rash, headache, abnormal LFT, mild renal impairment.

GANCICLOVIR

Induction IV 5mg/kg bd over 1 hour

Maintenance IV 5mg/kg od

Renal impairment:

Induction dose

Creatinine Clearance	Dose
≥70 ml/min	5mg/kg bd
50 – 69ml/min	2.5mg/kg bd
25 – 49ml/min	2.5mg/kg od
10 – 24ml/min	1.25mg/kg od
<10ml/min	1.25mg/kg 3x/week after haemodialysis

Refer to Renal Drug Database for advice on maintenance doses in patients with renal impairment and discuss with consultant.

On consultant recommendation only.

Side effects:

Myelosuppresive
- causing neutropenia and thrombocytopenia. Severe myelosuppression may necessitate a dose reduction or discontinuation. Myelosuppression can sometimes be delayed and persist up to 1 month after discontinuing.

Other less frequent side effects include: fever, rash, headache, abnormal LFT, mild renal impairment.

FOSCARNET	Calculate Creatinine clearance in ml/min/kg using $\frac{1.04 \times (140-age)}{Scr}$ for females $\frac{1.23 \times (140-age)}{Scr}$ for males Then select dose from table : Induction IV 90mg/kg **bd** 2/52 Maintenance IV 90mg/kg **od** 2/52 **Creatinine clearance — Dose** >1.6 - 90mg/kg bd 1.6 – 1.4 - 82mg/kg bd 1.4 – 1.2 - 73mg/kg bd 1.2 – 1.0 - 63mg/kg bd 1.0 – 0.8 - 53mg/kg bd 0.8 - 0.6 - 42mg/kg bd 0.6 – 0.4 - 31mg/kg bd <0.4 - Avoid Round to a convenient volume (24mg/ml injection) Give undiluted via Hickman line If peripheral access dilute to 12mg/ml Give doses ≤60mg/kg over at least 1 hour and doses >60mg/kg over 2 hours	**On consultant recommendation only.** **Side effects:** **Causes renal toxicity** **- monitor U+Es daily and adjust dose**

Aciclovir, Valaciclovir and Ganciclovir

given as indicated should **not** be given concomitantly.

Use with caution in patients with renal impairment.

APPENDIX 2
Pro Forma for Monitoring and Dosing Foscarnet

Affix patient addressograph	**Ward:**
	Date:
	Weight:
	Allergies:
Indicate the type of line the patient has in place:	**□ Peripheral** **□ Central**

Day / Date	Creatinine	CrCl (ml/min/kg)	Dose of Foscarnet (mg)	Prescriber to sign if dose has been amended on the drug chart
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				

Appendix 3: Guideline for the Administration of Cidofovir for CMV, adenovirus or BK virus infections.

Cidofovir may be used in the treatment of patients with CMV reactivation and retinitis, adenovirus infection or severe BK virus-associated haemorrhagic cystitis.

Indications for Use of Cidofovir

- Third- line treatment for CMV reactivation in patients post allogeneic bone marrow or stem cell transplant.
- First-line treatment of CMV retinitis.
- May be used for adenovirus infection.
- Severe BK virus-associated haemorrhagic cystitis – note different 'Low Dose' and schedule needed.
  Intravesical Cidofovir may be considered where 'low dose' cidofovir is contraindicated e.g. cytopenias, renal impairment.

Initiation of Treatment with Cidofovir

Initiation of treatment with cidofovir must be authorised by a consultant haematologist.

Cidofovir can only be administered on Fletcher ward or on the Haematology Day Case Unit. When administered on the Day Case unit a bed is not required for treatment.

Prior to each administration:

Check serum creatinine and urine protein levels (by dipstick).

Treatment with cidofovir is **contraindicated** in patients if:

- the serum creatinine is >133 micromol/L,
- the creatinine clearance is <55ml/min
- or there is ++ or more of proteinuria.

FBC should also be monitored as cidofovir can cause reversible neutropaenia.

Renal Cover – to minimise the nephrotoxicity of full-dose cidofovir, oral probenecid and intravenous saline prehydration must be administered with each cidofovir infusion.
This is not required for low dose or intravesical cidofovir
(i.e. when treating BK virus-associated haemorrhagic cystitis)

Probenecid - given orally:
2g given 3 hours prior to cidofovir infusion
1g given at 2 hours after the completion of the cidofovir infusion
1g given at 8 hours after the completion of the cidofovir infusion
(Total dose 4g probenecid).

To reduce nausea give probenecid after food or use an anti-emetic.
If allergic or hypersensitivity reactions to probenecid occur, give antihistamine and/or paracetamol as appropriate.
~ Hydration details overleaf ~

Hydration – given intravenously. Total of 2 litres 0.9% saline given as follows:

First litre 0.9% saline infused over one hour immediately prior to cidofovir infusion.

Second litre 0.9% saline infused over a 1-3 hour period beginning simultaneously with the cidofovir infusion or starting immediately after the infusion.

CIDOFOVIR - supplied as vials containing 375 mg cidofovir anhydrous

Reconstitution

Dilute appropriate dose in 100ml 0.9% saline prior to administration.

Cidofovir will be prepared in the Pharmacy Cytolab during normal working hours.

Administration

Intravenously through a central or a peripheral line.

Dose Schedule 1

Induction treatment for CMV/Adenovirus:

Recommended dose is 5mg/kg/body weight, given as an intravenous infusion at a constant rate over one hour, and administered once weekly for two consecutive weeks.

Maintenance treatment for CMV/Adenovirus:

Beginning two weeks after the completion of induction, recommended dose is 5mg/kg body weight given over one hour, once every two weeks.

Dose Schedule 2

Low-Dose Cidofovir for BK virus-associated haemorrhagic cystitis

0.5-1mg/kg (iv) weekly until symptom resolution.
If patient fails to respond after 2 weeks, discuss with Consultant.
Probenecid cover is not required, but hydration is recommended.

Side Effects The most frequently reported side effects include proteinuria and increased creatinine, fever, asthenia, nausea and vomiting, rash and neutropaenia.

Intravesical Cidofovir may be considered for BK cystitis

Cidofovir 5mg/kg bladder instillation in 100ml sodium chloride 0.9%. Administer via urinary catheter and clamp catheter for a minimum of 1 hour. Dose may be repeated after 1 week.

Post Treatment Monitoring - Weekly U+E and FBC at the BMT clinic.