Bone Marrow Transplant Programme Standard Operating Procedure

Title: **Guideline for the Management of Haemorrhagic Cystitis**

Index Code: SOP PRB45

Version: 7.0

Area of Application: Clinical Unit

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Number of Pages: 7

Date of next review: July 2027

Amendments to Version:

Version	Amendment	Released	Implemented	Archived
6.0	Section 6.3.1: Change to dose of premarin Section 9: inclusion of reference for premarin dose Reference to SOP B68 at 7.2 and 7.3	10-Feb-2020	14-Feb-2020	11-Nov-2022
6.1	Remove reference to Alumina Add Bedi grading scale Add section on use of CTLs	11-Nov-2022	11-Nov-2022	13/08/2025
7.0	Transferred onto new template, removed staff training table.	13/08/2025	13/08/2025	

Contents

1. Principles and Purpose / Objective:

Haemorrhagic cystitis (HC) is caused by direct toxicity of drugs used in the conditioning regimen on the urothelium OR by viral infections developing post-BMT. Classically HC due to direct drug toxicity occurs early (days +1 to +14) and is associated with the use of myeloablative conditioning regimens particularly cyclophosphamide, TBI and high dose etoposide. Viral HC appears later after d +30 and can be due to a number of viruses including human polyoma virus (BK), adenovirus (type 11) JC virus or CMV.

The purpose of this document is to provide guidelines on the management of haemorrhagic cystitis post-BMT.

2. Related Documentation:

- BMT Conditioning protocol in patient's notes.
- PRB18 Nursing Guidelines for the Care and Monitoring of Patients Undergoing Allogeneic Stem Cell Transplantation

3. Terminology, Abbreviations and Definitions:

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

HC - haemorrhagic cystitis

4. Personnel and Training Requirement:

- Nursing and clinical staff in Clinical Haematology

5. Equipment:

- Not Applicable

6. Procedure / Method:

6.1 Prophylaxis

Prophylaxis is with hyper-hydration and Mesna. For details see the BMT schedules for patients receiving high-dose cyclophosphamide.

Nursing Interventions – patients receiving high dose cyclophosphamide must have urinalysis to check for haematuria each time the patient passes urine. Evidence of haematuria of any kind to be reported to medical staff. *[Source HH July 2017]*

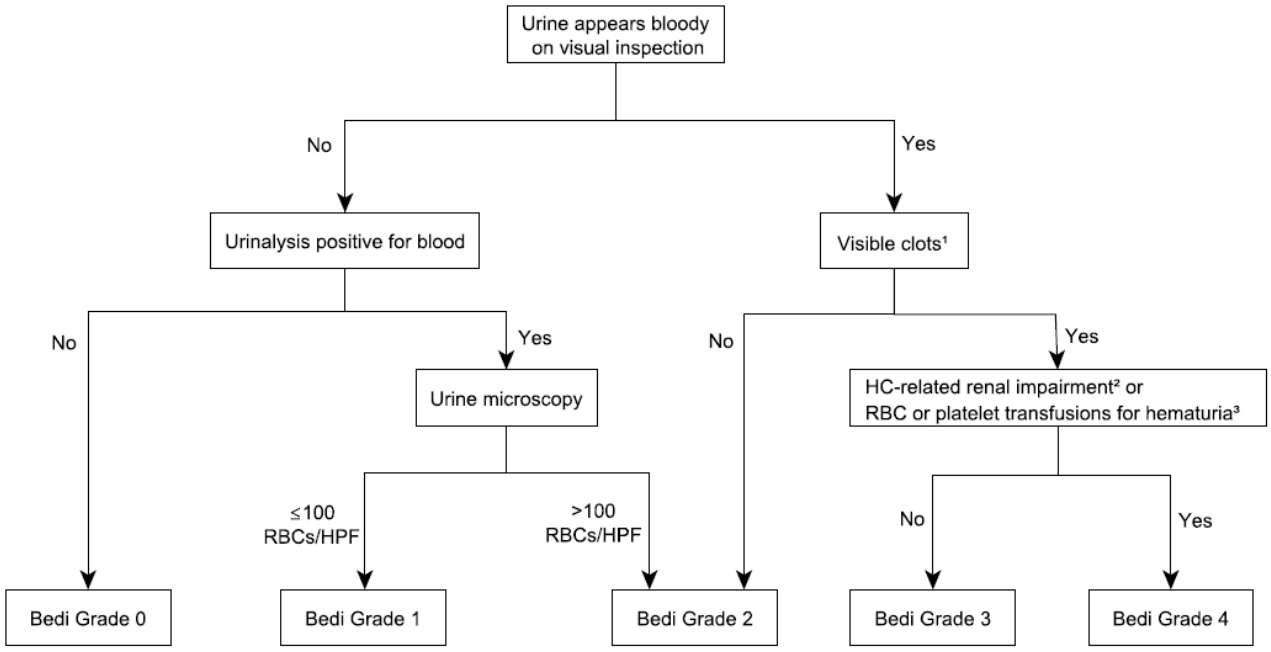
6.2 Diagnosis

HC presents with painful haematuria, frequently with clots leading to retention of urine. Urine should be sent for viral culture / PCR for BK virus, JC, CMV and adenovirus. Peripheral blood should be sent for CMV PCR.

Renal function should be monitored, and USS renal tract done to visualise renal tract and ensure that there is no hydronephrosis due to clot retention.

6.3 Grading of Haematuria

Haematuria can be graded using the Bedi criteria by sending urine samples for microscopy and checking renal function (see below)



The same urine sample should be used for the HCP's urine visual assessment and the urinalysis. Bedi grading should not be performed on days on which the participant is receiving continuous bladder irrigation or has nephrostomy tubes. However, if a participant has nephrostomy tubes that are capped, Bedi assessments may be performed, including for the purpose of assessing for resolution.

1. If a participant has visible clots in the urine, the Bedi grade is ≥3 even if the urine does not appear bloody (ie, if the liquid component is yellow or clear).
2. HC-related renal impairment is defined as a new elevation of creatinine to ≥1.5 × ULN that is considered by the investigator to be HC-related (ie, from urinary obstruction due to clots).
3. If a participant is requiring packed RBC or platelet transfusions for hematuria, the Bedi Grade is a 4 even if no clots are present.

HC: hemorrhagic cystitis; RBC: red blood cell; HPF: high-powered field; HCP: healthcare provider; ULN: upper limit of normal.

6.4 Treatment of established HC

A 3 step approach is recommended.

6.4.1. Forced hydration plus intensive platelet support to maintain platelets > 50 and Hb >10 gm/dl.
There is some evidence that oestrogens may be of value (Heath et al 2006) so start premarin 2.5 mg bd up to max 5 mg tds

Tranexamic acid is contraindicated as increases the risk of clot retention

6.4.2. Continuous bladder irrigation with saline solution. Discuss this with the Urology team at NUH as a special 3 way catheter is required. This is particularly important for patients passing large clots because of the risks of retention.

6.4.3. If these approaches have failed, selective embolisation
OR
suprapubic cystostomy and installation of formalin along with ureteric catheterisation to rest the bladder.
Cystectomy is a last resort.

6.5 Viral Induced Haemorrghagic Cystitis

6.5.1. **Diagnosis** Although BK virus is the most common virus causing haemorrhagic cycsttis, urine should be sent for viral PCR for BK, JC, CMV and adenovirus virus. If high levels of BK are found in the urine and patients are symptomatic then specific antiviral treatment may be advisable with cidofovir. Peripheral blood should also be sent for BK viraemia which may cause BK virus associated nephritis and renal impairment

6.5.2. **IV Cidofovir Treatment** severe BK virus-associated haemorrhagic cystitis can be treated with low-dose cidofovir (1mg/kg IV weekly) for 4 weeks until symptom resolution provided renal function is adequate. (See SOP B 68)

Note that probenecid cover is not required due to the low dose of cidofovir used. Hydration is recommended, as per SOP B68.

If patient fails to respond after 4 weeks, discuss with consultant.

6.5.3. **Intravesical Cidofovir.** Alternatively, if the counts are low or the renal function is deranged intra-vesical cidofovir can be considered. 5mg/kg in 100 ml N saline instilled into the bladder via a catheter which is clamped for 1 hour. Repeat weekly. Can be very painful and require Entonox (see SOP PRB68).

6.5.4. **Third party BK specific Cytotoxic T lymphocytes (CTLs)** may be available commercially or via clinical trials eg Allovir study for patients with severe haemorrhagic cystitis and discussion with the attending Consultant to source / request these may be undertaken. Usually 1-2 doses of the CTLs will be required.

7. Endpoints, Expected Results and Limitations of Procedure:

7.1 Endpoint and Expected Results

7.1.1. Diagnosis and appropriate treatment of Haemorrhagic Cystitis**.**

7.2 Limitations

7.2.1. Incidents must be reported via the NUH Trust Datix system

8. Audit:

8.1 Incident reports and deviations from SOP (whether planned or unplanned) are reviewed at the monthly BMT Quality Management Group meeting.

9. Evidence Base of Policies / References:

- **Evidence for use of premarin Section 7.3.1 above.**

  Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation.
  Heath et al, BMT 2006

- **Evidence for use of selective embolization Section 7.3.3 above.**
  Selective embolization of the internal iliac arteries was performed with gelatin sponge to confirm the occlusion of the vesical hyperva haemorrhagic cystitis (HC) vascularization. Eight patients achieved complete response (CR), their hematuria and symptoms ceased after embolization treatment, including six from first

treatment of embolization and two from second treatment.
Sun et al, BMT 2008.

- **Evidence for CTLs Section 7.4**
  Third party BK virus specific xytotoxicT lymphocyte therapy for haemorrhagic cystitis following allotransplantation. Olson et al JCO 2021 April 30
- PL6 Haemopoietic Stem Cell Transplantation and Cellular Programme Operational Policy and Quality Manual
- PL1 FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration , 8th Edition
  - also available at *http://www.ebmt.org/jacie-accreditation*
- PL13 Human Tissue (Quality and Safety for Human Application) Regulations 2007, Licensing Standards, also available at *http://www.hta.gov.uk*
- PL7 HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment –also available at *http://www.hta.gov.uk*
- PL14 HTA Code of Practice A - Guiding Principles and Fundamental Principle of Consent - also available at *http://www.hta.gov.uk*
- PL15 HTA Code of Practice G - Donation of allogeneic bone marrow and peripheral blood - also available at *http://www.hta.gov.uk*

10. Training and Competency:

10.1 Training: Read SOP only

10.2 Competency Assessment: Not Applicable

10.3 Training & Competency Record

Once they have read the SOP, relevant staff members are to acknowledge the in use SOP on QPulse.