

CONTENTS

SECTION 1 NEHODS- Northern England Haemato- Diagnostic Service

SECTION 2 Guidelines for Cytogenetic analysis in Haematological Malignancies

SECTION 3 North of England Cancer Network Guidelines and Indications for PETCT

SECTION 4 Guidelines for management of Acute Myeloid Leukaemia (AML)

SECTION 5 Guidelines for Management of Myelodysplastic Syndromes

SECTION 6 Guidelines for Management of Acute Lymphoblastic Leukaemia

SECTION 7 Guidelines for the Management of Chronic Myeloid Leukaemia

SECTION 8

Guidelines for Management of Myeloproliferative Disorders

Polycythaemia Vera (PRV)

Myelofibrosis (MF)

SECTION 9

Guidelines for Management of Chronic Lymphocytic Leukaemia (CLL) and Lymphoproliferative Disorders

Hairy Cell Leukaemia

T-Prolymphocytic Leukaemia

Waldenstrom Macroglobulinaemia

SECTION 10

Guidelines for the Management of Low-grade Non-Hodgkin Lymphoma

Mantle Cell Lymphoma

SECTION 11 Guidelines for the Management of High Grade B Cell Non-Hodgkin Lymphoma (NHL)

SECTION 12 Guidelines for the Management of Classical Hodgkin Lymphoma

SECTION 13 Guidelines for the Management of Mature T-Cell and NK-Cell Neoplasms

SECTION 14 Guidelines for Management of Plasma Cell Myeloma

SECTION 15 Indications for Haemopoietic Stem Cell Transplantation

SECTION 16 Clinical Guideline for the prophylaxis and treatment of tumour lysis syndrome in patients receiving treatment for haematological malignancies

SECTION 17 Blood Transfusion Guidelines

SECTION Appendix

Appendix 1 – Teenage and Young Adult Pathway for initial Management

Appendix 2 – Pathway for follow up on completion of First line treatment

Appendix 3- TYA Designated Hospitals

Appendix 4 – NHS Specialised Services Pathway

Appendix 5 – Local Referral Pathways and Levels of Care

Appendix 6 - Pathways

Appendix 7 – Inter-provider transfers

- Multiple Myeloma
- Non-Hodgkin Lymphoma
- Hodgkin Lymphoma

BLOOD TRANSFUSION GUIDELINES

NHSBT – local and national contact numbers

NHSBT Newcastle switchboard	0191 202 4400
North Duty Consultant 24/7	0191 261 5053
Dr Andrew Charlton	0191 202 4548

SELECTION OF RED CELLS FOR PATIENTS WITH HAEMATOLOGICAL MALIGNANCY

Chronically transfused haematology patients

It is prudent to phenotype as fully as possible prior to first transfusion – this needs to be specifically requested on the group and screen sample request form, ideally at first clinic attendance where a diagnosis requiring long-term transfusion support is being considered. In patients who have already been transfused, and therefore phenotyping may not be possible, a genotyping service is available via NHSBT in selected cases.

Units ideally should be matched for ABO and RhD, and it may also be prudent to match for the other Rh antigens, and K, to reduce the risk of red cell alloimmunisation.¹

Recipients of ABO/Rh-mismatched allogeneic haemopoietic stem cell grafts

Approximately 15-25% of HLA identical sibling donor/recipient pairs differ for ABO blood groups. The figure is higher for unrelated donor transplants. ABO incompatibility does not affect either graft rejection or GVHD since ABO antigens are not expressed on primitive stem cells.

Use the link below to access current NHSBT advice on selecting appropriate products for recipients of such transplants:

<http://hospital.blood.co.uk/media/2182/d4b11163-d079-4cf7-be1d-50baa5788066.pdf>

Patients with autoimmune haemolytic anaemia

Patients should have their correct ABO and D group determined and be tested for the presence of alloantibodies. It may be necessary to refer patients with AIHA to a red cell reference centre in view of the complexity of the investigations required.¹

¹BCSH Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories *Transfusion Medicine* 2013; 23, 3-35

PLATELET TRANSFUSIONS IN HAEMATOLOGICAL MALIGNANCY

Indications for transfusion

The 2016 National Comparative Audit (NCA) of platelet transfusions in haematology patients indicated a significant percentage of inappropriate use, mainly in the areas of prophylaxis and pre-procedure transfusion. In the context of chronic bone marrow failure syndrome patients, not undergoing any intensive treatment, just over 50% of prophylactic platelet transfusions may have been unnecessary.

<http://hospital.blood.co.uk/media/28915/2016-haematology-audit-report-national-results-1.pdf>

Note that prophylactic platelet transfusions are not indicated prior to bone marrow aspirate or trephine regardless of platelet count (in the absence of other risk factors for bleeding), with 14 patients in the NCA being transfused prophylactic platelets solely for this indication.

NHSBT has issued guidance and resources to help hospitals reduce inappropriate platelet transfusions, including posters and factsheets for ward staff, as well as information around transfusing across blood groups and tips for HTTs, accessible at this link:

<http://hospital.blood.co.uk/patient-services/patient-blood-management/platelet-resources/>

NICE guidelines on transfusion were published in November 2015 and include some recommendations on platelet transfusion and thresholds. In particular they advise against prophylactic platelet transfusion support in those with thrombocytopenia secondary to chronic bone marrow failure who are not bleeding or in need of higher thresholds for interventions. The document is found here:

<https://www.nice.org.uk/guidance/ng24/chapter/Recommendations>

National Blood Transfusion Committee indication codes for platelet transfusion can be used to audit reasons for transfusion / requesting and are available here:

<https://www.transfusionguidelines.org/document-library/documents/nbtc-indication-codes-june-2016v2>

BSH guidelines on platelet transfusion were published in 2016 and make recommendations with regards to transfusion thresholds in certain haem-oncology settings:

Reversible bone marrow failure:

- Give prophylactic platelet transfusions to those undergoing intensive chemotherapy or allogeneic HSCT to maintain a platelet count at or above $10 \times 10^9/L$
- Use only one adult dose of platelets routinely for prophylactic transfusions
- Consider not giving prophylactic platelet transfusions to well patients with no evidence of bleeding who have had an autologous HSCT
- Consider increasing the threshold for prophylactic platelet transfusions to between $10-20 \times 10^9/L$ for those with additional risk factors for bleeding

Chronic bone marrow failure, where recovery not expected:

- Use a 'no prophylactic platelet transfusion' strategy for asymptomatic patients with chronic bone marrow failure (including those taking low dose oral chemotherapy or azacitidine)
- Give prophylactic platelet transfusions to patients with chronic bone marrow failure receiving intensive treatment
- Manage patients with chronic bleeding of WHO grade 2 or above individually, according to the severity of their symptoms and signs. Consider a strategy of prophylaxis (e.g. twice a week)

The guideline can be found here:

<https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.14423>

Platelet refractoriness

This may be due to HLA or HPA alloimmunisation, but is more commonly due to non-immune factors such as sepsis or DIC, particularly in the haem-oncology setting.

Current guidance on testing and provision of products in this situation is provided at this link:

<http://hospital.blood.co.uk/media/2130/d5795605-7d36-40ce-8fb9-8c77254e24c6.pdf>

In brief, two or more episodes of poor increments after transfusion with random donor platelets should trigger investigations for refractoriness. It may be appropriate to use HLA-selected platelets while waiting for the results of the antibody screen, provided an HLA-typing sample has also been sent, and this should be discussed with the local H&I lab.

It is particularly important to return the 'Selected Platelets Follow-Up Form' that is supplied with each unit. This provides vital information to the H&I lab about the clinical effectiveness of the unit supplied, and assists with ongoing efforts to match units for the patient. Ordering clinicians are responsible for the return of this data.

The HLA-selected platelets product requires 24 hours' notice and although urgent requests can be made there is likely to be a delay of several hours before suitable units can be identified, transported and issued. Currently there is an H&I Consultant on call 24/7 who can take urgent requests out of hours for this product, but this is likely to be withdrawn in early 2019, such that it may be provided only between 06:00-23:00. Internal NHSBT audit data shows that the great majority of urgent requests are in fact non-urgent and the products are not used until well into the next working day.

Where HLA-selected platelets are not available within a clinically required timescale, random donor, group-specific apheresis platelet units should be requested instead, until HLA-selected units can be obtained.

Use of platelets in platelet additive solution (PAS) and minimal plasma (sometimes called “washed platelets”)

For this product, the majority of plasma is removed from apheresis platelets, which are then resuspended in 200mls of platelet additive solution. The clinical indications are: thrombocytopenic bleeding, or prophylaxis, in a patient who has a history of recurrent, severe allergic reactions to plasma-containing components. The shelf life is only 24 hours at present, and 24 hours' notice is usually required for preparation.¹ The first request must be made through an NHSBT Consultant.

References

¹NHSBT Portfolio of Blood Components and Guidance for their Clinical Use, version9
<http://hospital.blood.co.uk/media/29864/spn223.pdf>

GRANULOCYTE TRANSFUSIONS IN HAEMATOLOGICAL MALIGNANCY

Full guidance is available at the NHSBT Hospitals and Science website and this summary should be read together with the latest version of that guidance to ensure the most up to date guidelines are being followed. The current link is:

<http://hospital.blood.co.uk/media/28261/inf2764-clinical-guidelines-for-the-use-of-granulocyte-transfusions.pdf>

The preferred product “Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated” is derived from the buffy coat layer of whole blood donations. It is manufactured by pooling 10 donation buffy coats, removing red cells and plasma and then resuspending in SSP+ (platelet additive solution) and one male donor's plasma. These packs have the advantage of having a smaller volume and less red cell contamination than the same standard buffy coats, and are similar to an apheresis granulocyte collection.

Although the component contains fewer red cells (average haematocrit 15%), granulocytes should fulfil ABO and RhD compatibility requirements. More extensive matching or compatibility testing in the presence of red cell antibodies or to prevent their formation is not required.

Clinical Indications

It should be highlighted that randomised, controlled trials have so far failed to demonstrate clinical benefit of granulocyte infusions at the doses currently supplied through pooled donations. Higher doses yielded from steroid and G-CSF stimulated donors are not currently available from NHSBT.

Therapeutic granulocyte transfusions may be indicated for patients with severe neutropenia who fulfil all of the following criteria:

1. Severe neutropenia, defined as ANC $<0.5 \times 10^9/L$ due to congenital or acquired bone marrow failure syndromes.
2. Receiving active treatment in an attempt to achieve disease remission.
3. Proven or highly probable fungal or bacterial infection that is unresponsive to appropriate antimicrobial therapy as demonstrated by visible spreading lesions on skin, mucosa or radiological examination.
4. In whom neutrophil recovery is expected in the near future and / or in whom definitive therapy of curative potential is planned.

Therapeutic granulocyte transfusions may also be indicated for patients with a known congenital disorder of neutrophil function regardless of neutrophil count, with proven or highly probable fungal or bacterial infection unresponsive to appropriate antimicrobial therapy, demonstrated by visible spreading lesions on skin, mucosa or radiological examination.

Granulocyte transfusion should not be issued for therapeutic use in:

1. Patients with bone marrow failure where neutrophil recovery is not anticipated to occur spontaneously and no further active treatment is planned.
2. Sepsis in the absence of either neutropenia or known neutrophil dysfunction.
3. Pyrexia of unknown origin (PUO).

The component should be ordered through your hospital transfusion laboratory, using the OBOS online ordering system. This product can only be ordered following clinical discussion with an NHSBT Consultant.

Infusions should be given until one of the following events:

- Clear evidence of endogenous recovery, based on neutrophil count.
- Resolution of infection.
- Clinical deterioration despite a minimum of three days of transfusions.
- Severe reactions to granulocyte transfusions.

Granulocytes are manufactured specifically on a named patient basis so changes in the clinical condition of a patient, e.g. recovery or death, meaning they are no longer needed, should be relayed to NHSBT urgently to allow resources to be appropriately reallocated.

Dosing

For the pooled product:

A standard adult dose is 2 packs (derived from 20 donations), providing a dose of around 2×10^{10} which is considered to be an effective daily dose. The whole dose should be administered over 1-2 hours through a standard red cell giving set. Discuss alternative options with an NHSBT Consultant if intolerance of fluid load is a significant clinical issue.

Children (<30kg) should receive 10-20mL/kg (to a maximum of 2 packs).

CMV negative granulocytes should be used for recipients who are at risk of CMV disease (infants, pregnant women, CMV negative recipients of CMV negative

allogeneic bone marrow transplants). The SaBTO guidance (see below) recommends that all CMV negative recipients should receive CMV negative granulocytes.

Each pack contains 2.5 adult therapeutic doses of platelets so platelet transfusion requirements will be significantly diminished if not abrogated, and red cell transfusion requirement may also be diminished while receiving granulocytes.

The product has a 24 hour expiry shelf-life, and is generally available on Tuesdays-Saturdays due to red cell donation schedules.

INDICATIONS FOR CMV-SAFE CELLULAR BLOOD COMPONENTS

The advisory committee for the safety of blood, tissues and organs (SaBTO) issued a position statement on CMV-tested blood and components in 2012. Its main recommendations are:

- CMV seronegative red cell and platelet components should be provided for intra-uterine transfusions and for neonates (i.e. up to 28 days post expected date of delivery) and therefore all small-sized blood packs and other cellular components intended for neonates should be provided as CMV negative.
- CMV seronegative blood components should be provided where possible for pregnant women, regardless of their CMV sero status, who require repeat elective transfusions through the course of their pregnancy (not labour and delivery). This mainly applies to patients with haemoglobinopathies who are managed in specialist centres. However, CMV negative blood components are not expected to be generally available in all hospitals and therefore for emergency transfusions in pregnant women, leucodepleted components are recommended.
- All blood components, other than granulocytes, now undergo leucodepletion, which provides a degree of CMV protection considered equal to selection of CMV serologically-negative units.. This measure is considered adequate risk reduction for all patients requiring transfusion (including haemopoietic stem cell transplant patients, organ transplant patients, and immune deficient patients, including those with HIV) without the requirement for CMV negative components in addition.
- CMV PCR monitoring should be considered for all haemopoietic stem cell and solid organ transplant patients (even CMV negative donor/negative recipients) to allow early detection of any possible CMV infection (whether transfusion-transmitted or primary acquired infection)
- Transfusion-transmitted CMV should be reported via the SHOT (Serious Hazards of Transfusion) and SABRE (Serious Adverse Blood Reactions and Events) systems.

The full guidance can be accessed here:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215125/dh_133086.pdf

GUIDELINES ON THE USE OF IRRADIATED BLOOD COMPONENTS

The most recent BCSH guidelines (published 2010) can be accessed here:

<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08444.x/pdf>

Selected current indications in these guidelines:

Adult and paediatric

- All transfusions from a first or second-degree relative
- All HLA-matched transfusions
- All granulocyte transfusions
- All patients with Hodgkin's Disease at any stage - life long requirement
- All patients treated with purine analogue drugs (Fludarabine, Cladribine, Deoxycoformycin) and related drugs (Clofarabine, Bendamustine) - life long requirement
- Patients treated with Anti-thymocyte globulin (ATG) and Alemtuzumab. NB The ATG guidance was reinforced by EBMT (2013) and BCSH AA guidelines (2015). No firm recommendation was made for the length of time this should be adhered to following treatment, but it was suggested that it should be for at least as long as the CSA therapy is continued post-treatment. Similar recommendations were made following treatment with Alemtuzumab.
- All recipients of allogeneic bone marrow transplant from conditioning until GvHD prophylaxis is discontinued or lymphocytes are $>1 \times 10^9 /L$ (usually at least 6 months). If chronic GvHD is present or immunosuppression continues, irradiation should continue indefinitely.
- All patients undergoing bone marrow or peripheral blood stem cell harvesting for future autologous re-infusion: during and for 7 days before the harvest.
- All patients undergoing autologous stem cell transplant, from conditioning until 3 months post-transplant, or 6 months if TBI is used.
- All severe T-lymphocyte immunodeficiency syndromes, whether suspected or confirmed.

Patient Information

Patients at risk of TA-GvHD should be made aware of their need for irradiated blood components and provided with appropriate written information and an alert-card for clinical staff. An NHSBT information booklet is available to order that includes an alert card for the patient and stickers for the hospital medical notes. Initiatives to improve laboratory and clinical information management systems (including IT links with pharmacy and diagnostic services to highlight "at risk" patients) should be incorporated into local policies and regularly audited.

All cases of TA-GvHD and all episodes where non-irradiated components are transfused to high risk patients should be reported to the appropriate haemovigilance organisation (SABRE/SHOT).

OBTAINING CONSENT FOR BLOOD AND COMPONENT TRANSFUSION

It is a general legal and ethical principle that valid consent should be obtained from a patient before they are treated. In 2011, SaBTO issued the following recommendations on consent for blood transfusion:

- Valid consent should be obtained and documented in the patient's clinical record by the healthcare professional.
- There should be a modified form of consent for long-term multi-transfused patients, details of which should be explicit in an organisation's consent policy
- There should be a standardised information source for *clinicians* indicating the key issues to be discussed by the healthcare professional when obtaining valid consent from a patient for blood transfusion.
- There should be a standardised source of information for *patients* who may receive a transfusion in the UK.

NHSBT resources including patient information leaflets about red cell and platelet transfusion, and also unexpected transfusions, can be found here:

<http://hospital.blood.co.uk/patient-services/patient-blood-management/patient-information-leaflets/>

The full SABTO report can be accessed at:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216586/dh_130715.pdf

In 2014 the National Comparative Audit of Patient Information and Consent reported low levels of concordance with the SaBTO guidelines, and made further recommendations for improvements:

<http://hospital.blood.co.uk/media/27580/2014-audit-of-patient-information-consent.pdf>

HEPATITIS E SCREENED BLOOD COMPONENTS

Since May 2017, all blood components issued by NHSBT have been HEV-screened. There will no longer be any HEV-untested 'fresh' components in circulation. However, frozen plasma components can be stored for up to 36 months and there may be HEV-untested FFP and cryoprecipitate units in hospital blood banks.

Therefore clinical teams and hospital blood banks will need to remain vigilant about the indications for the use of HEV-negative frozen components, which affect a great number of haem-oncology patients, and were summarised by SaBTO in February 2018 as:

1. Patients with evidence of severe primary immunodeficiency
2. Patients currently being treated for malignant disease with immunosuppressive chemotherapy or radiotherapy, or who have terminated such treatment within at least the last six months.
3. Patients who have received a solid organ transplant and are currently on immunosuppressive treatment.
4. Patients who have received a haematopoietic stem and progenitor cell transplant for at least 12 months after finishing all immunosuppressive treatment or longer where the patient has developed graft versus host disease.
5. Patients receiving systemic high dose steroids until at least three months after treatment has stopped.
6. Patients receiving other types of immunosuppressive drugs, either alone or in combination with lower doses of steroids, until at least six months after terminating such treatment.
7. Patients who are immunocompromised due to Human Immunodeficiency Virus (HIV) infection with a CD4 count of <200/mm³.
8. Foetuses and neonates.
9. Patients who are within three months of a planned elective organ transplant and patients who may otherwise receive a solid organ transplant within three months due to being on the UK national transplant waiting list or are within three months of being placed on the waiting list.

This document is currently available at:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/680297/Hepatitis_E_Guidelines.pdf

Proposal for Antifungal Policy in Adults: Northern Region

Primary Prophylaxis

Primary prophylaxis will be considered in patients at highest risk of infection specifically those having the following treatments:

- AML induction
- ALL induction
- Allogeneic stem cell transplantation (pre-engraftment)
- GVHD therapy after allogeneic stem cell transplantation

Recommended Regimen:

i) ALL during initial induction

Ambisome® 2.5mg/kg twice weekly (rounded to nearest 50mg)

Or

Ambisome® 7mg/kg once weekly (rounded to nearest 50mg)

This regimen is recommended due to the need to avoid azoles when high doses of vinca alkaloids are prescribed and is consistent with national ALL protocols.

ii) Other indications including ALL therapy beyond initial induction

Voriconazole PO as dosed below

	Oral	
	Patients 40 kg and above	Patients less than 40 kg
Loading dose regimen (first 24 hours)	400 mg every 12 hours	200 mg every 12 hours
Maintenance dose (after first 24 hours)	200 mg twice daily	100 mg twice daily

LFTs should be monitored at least weekly for the first 3 weeks when voriconazole is commenced

This recommendation is an extrapolation of the ECIL 3 recommendations in which voriconazole is recommended for primary prophylaxis in allogeneic BMT recipients (ECIL Guidelines BMT 2011:46:7-9-718)

Monitoring Voriconazole Levels

It is essential to monitor voriconazole levels to ensure that levels therapeutic. We recommend testing a level approximately 5 days, 2 weeks and 4 weeks from commencement. Additional testing should only be done if there is a significant clinical change for the patient.

Trough levels to be checked aiming for a level of 2-6 mg/l

Treatment of Unresponsive Fever

In high risk febrile patients in whom the fever does not settle over 96 hours despite broad spectrum antibiotics, empiric antifungal therapy is often considered.

Where patients have been on voriconazole prophylaxis with acceptable drug levels, the risk of fungal infection is low and great care should be taken to try to reach a probable diagnosis of fungal infection before an antifungal is commenced.

We recommend that:

- All patients perceived to be at risk of fungal infection and who fail to defervesce despite appropriate antibiotics should have an urgent high resolution CT chest
- In general a change in antifungal therapy should be avoided in the absence of evidence of fungal infection. It may be necessary to repeat a high resolution CT chest after a week if clinical concern remains
- Any decision to discontinue voriconazole prophylaxis and use a different antifungal agent should be discussed with a consultant haematologist before an alternative agent is prescribed.

Treatment of Probable Fungal Infection After Voriconazole Prophylaxis

- i) First line therapy of choice is caspofungin IV (ECIL Guidelines BMT 2011:46:7-9-718)
- ii) In patients who fail to respond to caspofungin after 7 days we recommend Ambisome® 3mg/kg/day. Renal function must be monitored closely and attention paid to adequate hydration.

Step Down To Oral Agent

In some patients where there is good evidence of fungal infection, a prolonged antifungal course will be required. It is important to assess whether voriconazole levels were therapeutic at the time of the development of infection. In cases where levels were not therapeutic, it is reasonable to consider voriconazole as a step down drug but close monitoring of levels and dose adjustment is essential. An alternative would be to use posaconazole orally or to remain on an IV agent.

Where step down to an azole is considered after voriconazole prophylaxis, the patient clearly has to be closely monitored to ensure that response continues. If there is clinical concern then ongoing IV therapy with either an echinocandin or Ambisome® may be appropriate.

Secondary Prophylaxis

Where a high risk patient has developed a fungal infection and secondary prophylaxis is considered to cover further high risk episodes, we recommend voriconazole prophylaxis. If there is clear evidence of breakthrough fungal infection despite therapeutic levels of voriconazole previously then Ambisome® prophylaxis 2.5mg/kg twice weekly may need consideration.

EAG GUIDELINES FOR TEENAGE AND YOUNG ADULTS

Teenage and Young Adults Peer Review Measures

1. Teenage and Young Adult Pathway for initial Management

The EAG has received the document named 'NECN Teenage and Young Adult Cancer Pathway Guidance Paper' and agrees to follow the generic TYA Pathway with any site specific variations to be documented. Please see Appendix 1 for pathway.

2. Teenage and Young Adult Pathway for Follow up on completion of first line treatment

The Children and Young Peoples co-ordinating group have produced a pathway for follow up on completion of first line treatment, which was endorsed by the Haematology EAG. Please see Appendix 2 for more details.

If advice is required regarding the follow up care of a 19-24 year old patient, then the Lead TYA Clinician at the designated hospital or PTC should be contacted. Please see Appendix 3 for contact details.

3. Pathways for cases involving Specialised NHS services (Only Gynae and Sarcoma)

The Gynae EAG and SAG reviewed and agreed the Specialised NHS Service pathway for patient's age 16-24 years. This is attached in Appendix 4.