

CLINICAL GUIDELINES FOR THE USE OF GRANULOCYTE TRANSFUSION

Prepared by the Granulocyte Working Group:

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Purpose

This document outlines:

1. The clinical indications for the use of granulocyte transfusions
2. The options in England for the provision of granulocytes
3. A referral system for provision of granulocytes in England

These guidelines are not meant to be prescriptive and the decision for each request for granulocyte transfusions should be made following detailed assessment of the clinical details, in conjunction with the referring Consultant (or their designated deputy).

Method

Recommendations are based on review of the literature and review of accepted current clinical practice. The definitions of the types of evidence and the grading of recommendations used in this document originate from the US Agency for Health Care Policy and Research and are provided in Appendix 1.

Consultation

NHSBT consultants

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Summary

Granulocyte transfusions continue to be used as supportive therapy in patients with life-threatening neutropenia caused by bone marrow failure or in patients with neutrophil dysfunction. With the advent of potentially curative intensive chemotherapy regimens used alone or in combination with stem cell transplantation, there has been an increase in patients with fungal infections during periods of prolonged neutropenia and on-going interest in the use of granulocyte transfusions to support these patients, often with refractory infection. The current standard of care portfolio component in England. is “Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated”. This component has replaced the old non-pooled component, “Leucocytes, Buffy Coat, Irradiated” except in exceptional circumstances.

Adverse events such as febrile reactions, HLA alloimmunisation and transfusion related acute lung injury (TRALI) are well recognized complications following granulocyte transfusions. The use of granulocyte transfusions should, like all blood components, be limited to patients in whom the possible benefits are thought to outweigh the risks. Granulocytes should always be irradiated as they contain a large number of white blood cells which can, like a bone marrow donation, establish themselves in the recipient and form an immune system or “graft”. This unmatched, unintended graft may cause Transfusion Associated Graft Versus Host Disease (TA-GVHD), affecting the host’s liver, blood, gut and skin. TA-GVHD is almost universally fatal.

There is limited published literature on the *in vivo* efficacy of whole blood derived granulocyte concentrates and as part of an on-going initiative, routine data on indications, dose and outcomes is collected on all patients for whom granulocytes are requested (ProGrES).

1. BACKGROUND

Functioning white blood cells (WBCs) are a vital component of the defence system against infection. Neutrophils are a subtype of granulocytes and are the most numerous circulating WBC in healthy adults. Granulocytes in general and neutrophils in particular are crucial in protection against bacterial and fungal infection. Neutropenia (a persisting reduction in neutrophil numbers) severity has been classified by the World Health Organisation [WHO 1999]. As the peripheral blood count falls below 0.5×10^9 /litre there is an exponential increase in risk of severe infection (the normal neutrophil count ranges from 2.0 to 7.5×10^9 /litre in adults).

Neutropenia usually occurs as a result of impaired production of neutrophils in the bone marrow. Diseases occupying the bone marrow, such as leukaemias, or drugs that are toxic to the bone marrow, such as chemotherapy, are typical reversible causes of neutropenia. Even if the numbers of neutrophils are normal, patients may suffer from a similar inability to fight infections if there is an impairment of neutrophil function. Such disorders may be congenital and suspected from family history or by demonstrating the inability of neutrophils to function normally on laboratory testing [Kuijpers et al 1999]. Despite the use of specific and appropriate antibiotic and antifungal drugs, infection in patients with neutropenia can lead to hospital admission, organ damage, and death.

Component availability

There are two methods for collecting granulocytes for transfusion; a pooled, buffy-coat derived component, and by apheresis.

The currently available granulocyte component is “Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated”. The NHSBT Components Development Laboratory (CDL) has reported good in-vitro functionality of a pooled granulocyte component derived from whole blood donations [Bashir et al 2008]. The method involves the addition of platelet additive solution but without the need for hydroxyethyl starch or

dextran to sediment red cells during processing. A clinical study undertaken in the UK has demonstrated acceptable in-vivo safety of this component [Massey et al 2012].

Each bag contains buffy coats from 10 whole blood donations which are then processed to remove excess red cells and platelets. Nonetheless red cell and platelet content remains high (the haematocrit of a bag of pooled granulocytes is 0.15 and each bag contains 15g haemoglobin) and usually render the recipient independent of additional transfusions of red cells and platelets for the duration of the granulocyte transfusions. Each pool contains at least 5×10^9 granulocytes with a mean of 9×10^9 per pool. The standard adult dose is 2 pools per day or 10-20 mL/kg in children (usually one pool, mean 207 mL). Due to the red cell 'contamination' the red cells must be ABO compatible for transfusion to the recipient (see further detail below regarding compatibility). It should be noted that a typical dose of apheresis granulocytes is higher, with a median dose of 54.9×10^9 granulocytes per dose being achieved in the most definitive randomised controlled trial to be published, the RING study [Price et al., 2015].

Granulocytes expire at midnight the day following donation, and therefore are only available the day following large scale blood donation. Currently granulocytes are available routinely from Tuesday to Saturday, with 2 pools of O D positive, high titre negative (HT neg), granulocytes available from each of Manchester and Colindale on Mondays. Granulocytes should ideally be requested the day prior to transfusion to allow diversion of appropriate donations for testing and manufacture. However, given the nature of the clinical circumstances under which granulocytes are usually transfused, the patient should be discussed with the NHSBT patient-facing consultant as soon as granulocytes are considered, and efforts will be made to source same-day granulocytes if available when there is clinical need.

On rare occasions, when the pooled component is not available, single buffy coats may be issued (see section 3 below). The standard dose for an adult is 10 buffy coats per day, which equates to approximately half the number of granulocytes provided by 2 pools.

Apheresis granulocytes are usually collected after stimulation of the donor with steroids and granulocyte colony stimulating factor (G-CSF). The exposure of a healthy volunteer donor to any form of medication with potential side effects does however present ethical and safety issues [Gutierrez-Delgado & Bensinger 2001, Bennett et al 2006, Goldman et al 2006]. This practice is not considered ethical for unrelated/non-directed donations in England and constraints on granulocyte collection (including inability to obtain appropriate sedimenting agents) mean that apheresis granulocytes ceased to be available in England from 2018.

Evidence of clinical effect

Although there is evidence that donated granulocytes are functional [Bashir and Cardigan 2003, Bashir et al 2008], published controlled trials have reported conflicting results of clinical effect. A number of these issues have been raised in systematic reviews [Estcourt et al 2015 and 2016, Vamvakas et al 1996 and 1997]. Studies with

promising but overall inconclusive results have been reported both in adults and children [Oza et al 2006, Sachs et al 2006, Seidel et al 2008, Price et al 2015]. More recent studies have suggested that the efficacy of granulocyte transfusions in neutropenic patients is proportional to the dose of granulocytes transfused. Doses of at least 1×10^{10} granulocytes per transfusion appear to be required to treat or prevent infection [Estcourt et al 2015 and 2016] and if there is benefit from giving granulocytes, it is likely derived from higher doses e.g. above $0.6 \times 10^9/\text{kg}$ per dose [Price et al. 2015].

Adverse events such as febrile reactions, occasional severe pulmonary reactions and HLA (human leucocyte antigen) alloimmunisation are well recognized complications in the recipients of granulocyte transfusions.

The RING study [Price et al., 2015] is the largest and most recent randomised controlled trial of granulocyte transfusions, despite fewer patients than expected being recruited, and target granulocyte doses not being achieved in 31% of transfusions. Reported rates for the primary composite outcome of survival and resolution of infection were 42% and 43% in the granulocyte and control groups respectively ($p > 0.99$), and in the intention-to-treat analysis the outcome was reached in 49% and 41% respectively ($p = 0.64$). The authors described a range of factors that contributed to the challenges of conducting randomised trials to evaluate the effectiveness of granulocyte transfusions. These included difficulty consenting patients due to strongly held clinician perception of either benefit or lack of benefit of transfusion; discrepancy between study protocol and physicians' decision to transfuse granulocytes; failure to achieve target doses of granulocytes; fewer patients meeting the strict inclusion criteria in the protocol than anticipated. Many of the other randomised trials identified in systematic reviews [Estcourt et al., 2015 and 2016] were undertaken over 30 years ago, with the general quality of the available evidence being reported to be low, and the sample sizes often too small to evaluate clinical outcomes robustly.

Given the established challenges of conducting randomised trials in this area, and the need to understand indications, safety and outcomes, a registry of all cases of granulocytes was established in England in 2017, the PROspective Granulocyte usage and outcomES Survey (ProGrES). This database provides a resource to enable exploration of evidence of benefit of granulocyte transfusions. Clinicians requesting granulocytes for patients in England will be asked to provide clinical information for the study, which is ongoing. At the initial time of request, the NHSBT consultant should collect a minimal (anonymised) dataset of information about the case.

2. CLINICAL INDICATIONS FOR GRANULOCYTE TRANSFUSIONS

The following recommendations are based on the available evidence to date. However, there are additional circumstances under which it may be reasonable to transfuse granulocytes which can be discussed with the NHSBT patient-facing consultant on call (contact through Hospital Services). Although the evidence base is inadequate to provide definitive guidance, it is recognised that granulocytes for therapeutic use are usually given to patients where other evidence-based interventions have proven ineffective and where death due to infection is considered otherwise almost certain.

All requests for granulocyte transfusions should be referred to the NHSBT patient-facing consultant on call.

- 2.1 Therapeutic granulocyte transfusions may be indicated for patients who fulfil **all** of the following criteria:
 - 2.1.1 Severe neutropenia, defined as ANC $<0.5 \times 10^9/L$ [WHO 1999] due to congenital or acquired bone marrow failure syndromes.
 - 2.1.2 Receiving active treatment in an attempt to achieve disease remission.
 - 2.1.3 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 [Ascioglu et al 2002].
 - 2.1.4 In whom neutrophil recovery is expected in the near future (weeks)
- 2.2 Therapeutic granulocyte transfusions may also be indicated for patients with a known congenital disorder of neutrophil function [Kuijpers et al 1999] 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.
- 2.3 There is little evidence to guide the use of granulocyte transfusions in patients with acquired neutrophil dysfunction e.g. myelodysplasia. Refractory infection can be just as problematic in these circumstances, and ongoing infection may preclude delivery of more chemotherapy aimed at increasing the neutrophil function and/or count. Granulocytes may be considered if **all** of the following criteria are met:
 - 2.3.1 Receiving active treatment in an attempt to achieve disease remission (including if treatment has been paused due to refractory infection)
 - 2.3.2 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 [Ascioglu et al 2002].
 - 2.3.3 Neutrophil (numerical or functional) recovery is expected if treatment can be delivered
- 2.4 Granulocyte transfusion should **not** be issued for therapeutic use in:
 - 2.4.1 Patients with bone marrow failure where neutrophil recovery is not anticipated to recur spontaneously and no further active treatment is planned
 - 2.4.2 Sepsis in the absence of either neutropenia or known neutrophil dysfunction
 - 2.4.3 Pyrexia of unknown origin (PUO)
 - 2.4.4 Viral infection in the absence of additional proven or highly probable fungal or bacterial infection unresponsive to appropriate antimicrobial therapy
- 2.5 There are insufficient data to support the use of granulocytes as primary prophylaxis for infection [Estcourt et al., 2015] and thus their use in these circumstances is not recommended.

2.6 Granulocytes have been used as secondary prophylaxis for patients with ongoing infection in whom further definitive myelosuppressive treatment is required for disease control, where there is concern over development of life-threatening infection during subsequent predictable severe neutropenia. Such cases will be considered on an individual basis.

3. SOURCE OF GRANULOCYTES

3.1 Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated (“pooled granulocytes”). This component **MUST** be irradiated for all patients.

3.1.1 A standard adult dose is considered to be two pools or 20 donations (each pool contains approximately 9×10^9 granulocytes). Larger adults or those able to tolerate higher volumes may receive up to three pools per day. For reference the mean volumes for administration are 207 mL per pool).

3.1.2 Children less than 30 kilograms should receive 10-20 mL/kg to a maximum of two packs.

3.1.3 As the haematocrit is <20%, venesection is unlikely to be required but red cell transfusion requirements may be diminished.

3.1.4 Each pack contains the equivalent of 3 adult therapeutic doses of platelets so platelet transfusion requirements will be significantly diminished if not abrogated.

3.2. Leucocytes, Buffy Coat, Irradiated (“buffy coats”): This component **MUST** be irradiated for all patients: This component will only be used if the component in 3.1 above, (Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated) is not available.

3.2.1 A dose of ten packs for adults and 10-20ml / kg for children less than 50kg (to a maximum of 10 packs) is suggested. Each pack of Leucocytes, Buffy Coat, Irradiated is approximately 50 mL, has a haematocrit of 0.45, contains $1-2 \times 10^9$ white cells, 90×10^9 platelets and 9.5g of haemoglobin.

3.2.2 Clinicians should be warned of the high haematocrit of buffy coats, can result in a significant rise in the patients’ haematocrit, reducing the need for top-up red cell transfusions. Venesection may be needed if given daily to patients who are not heavily red cell dependent.

3.3.3 Ten packs contain the equivalent of 3 adult therapeutic doses of platelets so platelet transfusion requirements will be significantly diminished if not abrogated.

4. GRANULOCYTE STORAGE, RELEASE AND TRANSPORTATION

- 4.1 Granulocytes are stored at $22\pm 2^{\circ}\text{C}$ ideally without agitation. If granulocytes are agitated in error this does not preclude their transfusion as there is limited evidence that agitation affects them functionally [McCullough 1980, Sasakawa & Miyamoto 1987].
- 4.2 Granulocytes MUST be irradiated to prevent transfusion associated graft versus host disease [Treleaven et al 2011, Bashir and Cardigan 2003].
- 4.3 All testing for mandatory microbiological markers must be completed before granulocytes are issued for transfusion with the exception of HCV PCR and HTLV testing.
- 4.4 In view of the residual red cell and plasma content, granulocyte preparations should fulfil the compatibility requirements outlined in section 6.1.
- 4.5 Granulocytes should be infused as soon as possible after collection. The times of dispatch and infusion should be recorded. Traceability and all other regulatory aspects relating to transfusion of blood components apply to granulocytes.
- 4.6 Granulocytes expire at midnight the day following donation. The short expiry is on account of granulocyte activity (as opposed to concerns around bacterial contamination). Due to testing and manufacturing requirements, the component usually arrives in the hospital blood bank in the evening of the day of transfusion. If there is inability to complete the transfusion prior to midnight, the clinicians caring for the patient should discuss with the NHSBT consultant on call to review whether the risks and benefits are in favour of transfusing a short time past expiry, or of discarding the component.

5. DOSE ADMINISTRATION & COURSE OF GRANULOCYTE TRANSFUSIONS

- 5.1 There is currently no consensus on the specified effective dose required (see section 3). However, larger numbers of cells transfused result in higher increments (in the absence of HLA allo-immunisation) [Price et al., 2015].
- 5.2 Granulocytes should be transfused through a standard red cell giving set. The whole dose should be infused over 1-2 hours. Other than the screen filter present in a red cell giving set no further filter should be used.
- 5.3 Infusions should be given until one of the following events:
 - 5.3.1 Clear evidence of endogenous recovery, based on neutrophil count occurs. Neutrophil increment due to granulocyte transfusions is unlikely to exceed $1.0 \times 10^9/\text{L}$. It is therefore reasonable to continue until the absolute neutrophil count is $>1.0 \times 10^9/\text{L}$ on 2 consecutive days.
 - 5.3.2 Resolution of infection occurs.
 - 5.3.3 Clinical deterioration despite a minimum of three days of transfusions.

5.3.4 Severe reactions to granulocyte transfusions occur.

5.4 Granulocytes are manufactured specifically on a named patient basis so changes in clinical condition of 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.

6. COMPATIBILITY TESTING

6.1 In view of the residual red cell and plasma content, granulocyte preparations should fulfil the following compatibility requirements:

6.1.0 ABO compatible with the recipient's plasma and crossmatch compatible by immediate spin (for ABO incompatibility) in those not eligible for electronic issue.

6.1.1 ABO compatible for ABO antibodies in the donor against recipient antigens i.e. low titre for anti-A or B if group O granulocytes are provided for A, B or AB recipients.

6.1.2 RhD negative granulocytes should ideally be provided for RhD negative people of childbearing potential who have not formed immune anti-D.

6.1.3 More extensive matching or compatibility testing in the presence of red cell antibodies or to prevent their formation is not required. i.e. IAT crossmatch. Attempts to provide granulocytes that are negative for antigens other than ABO and RhD are not required. A decision regarding risks and benefits needs to be made by the clinician caring for the patient and the NHSBT consultant where the patient has non-ABO alloantibodies and there is a risk of delayed haemolytic transfusion reactions. A pool of granulocytes contains 15g haemoglobin; each pool equates to around 30 mL red cells. See section 7.4.

6.2 As granulocytes are not leucocyte reduced, there is a risk of CMV transmission from CMV IgG positive donors. CMV IgG negative granulocytes should ideally be provided for recipients who are at risk of CMV disease (infants, pregnant women, CMV negative recipients (or recipients whose CMV status is unable to be determined) of allogeneic bone marrow transplants). CMV negative granulocytes should be issued where possible for CMV negative recipients at risk of CMV disease. (See section 7 for potential substitutions).

6.3 HLA alloimmunisation:

6.3.1 HLA compatible granulocytes can only be provided by apheresis and as such are not available in England.

6.3.2 It is recommended that the following investigations should be requested on a pre-granulocyte transfusion sample taken from the recipient in order to establish aetiology of new HLA antibodies (10% of granulocyte transfusions [Massey et al., 2012]):

6.3.2.1 HLA typing

6.3.2.2 Anti-HLA class I and II antibody screening

- 6.3.3 HLA antibody screening as defined in 6.3 should be repeated if:
- 6.3.3.1 Platelet transfusion refractoriness occurs
 - 6.3.3.2 Severe reactions occur (hypoxia / TRALI and/or hypotension)
- 6.3.4 Human neutrophil antibody (HNA) antibody screening should also be undertaken if severe reactions occur (TRALI and/or hypotension)
- 6.3.5 Careful monitoring for refractoriness and reactions such as TRALI should be undertaken both in the presence and absence of incidentally identified antibodies.

7. POTENTIAL SUBSTITUTION STRATEGIES

7.1 Volume:

- 7.1.1 Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated: One pack for adults or 10 mL/kg for children under 30 kg may be used if the recipient has difficulty tolerating larger volumes or if larger volumes are not available. It should be noted that the available evidence suggests that if there is benefit from giving granulocytes, it is likely derived from higher doses e.g. above 0.6 x10⁹/kg per dose [Price et al. 2015].

7.2 ABO blood group compatibility (see table 1 for hierarchy of donation selection):

- 7.2.1 Residual red cells in the pack: As stated in section 6, compatibility rules for ABO provision of red cells MUST be complied with for all patients as the haematocrit for all available components is high enough to cause an acute haemolytic transfusion reaction as a result of ABO incompatibility.
- 7.2.2 Plasma compatibility: If giving donations that may contain ABO lysins against the recipient (the greatest risk being a group O donor to group A recipient) then the component must be negative for high titres of anti-A and / or anti-B as appropriate (HT neg). Only the donor of the resuspending plasma strictly needs to be HT neg for Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated). **Group B and AB granulocytes are not available.**

Table 1: Hierarchy for selection of granulocytes by ABO blood group

Recipient group	1st choice donation	2nd choice donation
O	O	N/A
A	A	O HT neg
B	O HT neg	N/A
AB	A HT neg	O HT neg

7.3 RhD

7.3.1. Recipients with pre-formed anti-D antibodies should receive RhD negative granulocytes. If a suitable number of RhD negative donors are not available, consideration can be given to transfusing pooled granulocytes from RhD positive donors. The risk of haemolysis is low as a result of the small volumes of red cells present in pooled granulocytes. See section 7.4.

7.3.2 RhD negative recipients who do not have pre-formed anti-D

7.3.2.1 People of child-bearing potential should receive RhD negative donations. If RhD positive donations are given due to lack of availability of RhD negative donors, consideration would need to be given to giving anti-D prophylaxis. This should be given in accordance with manufacturers' instructions and following British Society for Haematology Guidelines [Qureshi et al. 2014].

To calculate the number of red cells transfused use this equation:

$$\text{RBC} = \text{Hct} \times \text{Vol} \times n$$

Where RBC = volume of donor red cells transfused

Hct = haematocrit of pack(s)

Vol = average volume of the pack(s)

n = number of packs transfused

e.g. $0.15 \times 207 \text{ mL} \times 2$

7.3.2.2 People who do not have child-bearing potential should receive RhD negative granulocytes. However, if these are not available, RhD positive granulocytes may be given and anti-D prophylaxis is not indicated.

7.4. Other red cell antibodies

7.4.1 There is no need to provide granulocytes from donors who are matched for red cell antigens other than ABO and RhD as outlined in section 6.1 if the recipient has antibodies or to prevent formation of antibodies. Acute intravascular haemolysis leading to significant symptoms is unlikely for antibodies other than ABO as a result of the small volumes present in pooled granulocytes. More rapid turnover of the red cells present in a granulocyte pack is not an issue as unlike red cell concentrates transfused for anaemia the "contaminating" red cells are not an intentional therapy. Attempts to provide more extensive matching will lead to delay and potentially to the supply of less optimal transfusion support (e.g. reduced granulocyte content, increased volume, red cell and platelet content, and exposure to female plasma if relying on individual buffy coats).

7.5 Cytomegalovirus (CMV)

- 7.5.1 As for red cell antigen negative donations, the risk of failure to supply against morbidity / mortality from bacterial or fungal infection would need to be balanced against a risk of subsequent CMV disease. Discussion between an NHSBT consultant and the consultant looking after the patient would be required if there were inadequate supplies to support the issue of CMV negative components to a patient in the at-risk groups defined in 6.2.

8. REQUESTING PROCEDURE (see flow chart on page 11)

Requests for granulocyte transfusions should be made in the same manner as other blood components using the Online Blood Ordering System (OBOS). In view of the logistics required to manufacture and supply doses such requests will need to be referred to the on call patient-facing NHSBT consultant (smart divert number available through Hospital Services). It is expected the clinician (NHS consultant or registrar) contacting NHSBT should discuss the request with a consultant or suitably experienced haematology registrar. The NHSBT consultant will:

- 8.1 Take a detailed clinical history from the referring clinician to define indications for the request.
- 8.2 If there is consensus that granulocyte transfusion is indicated, agree with the referring clinician when granulocytes would best be supplied depending on the clinical circumstances.
- 8.3 Advise the referring clinician that their hospital transfusion laboratory should order the granulocytes from NHSBT Hospital Services on the Online Blood Ordering System (OBOS).
- 8.4 Liaise with the NHSBT Hospital Services department to determine if and when the provision of the component(s) is possible.
- 8.5 Report back to the referring clinicians on availability of the component(s) and agree start date and duration.
- 8.6 If a referral is received but there is no clear indication for granulocytes, discuss with referring clinician.
- 8.7 Submit anonymised details of the request to the ProGrES database by completing form A Part 1.

PROCEDURE FOR MANAGING REQUESTS FOR GRANULOCYTE CONCENTRATES

A HOSPITAL REQUESTS GRANULOCYTES FOR TRANSFUSION

REFER TO ONCALL CONSULTANT FOR PATIENTS DURING THE DAY AND OUT OF HOURS

ON CALL CONSULTANT takes a detailed clinical history from the referring clinician to define indications for request.

Agree on clinical indication as outlined in section 2

Yes

No

Agree to provide granulocytes if operationally possible. Advise the referring clinician to place an order with NHSBT Hospital Services via their Hospital Transfusion Laboratory on the Online Blood Ordering System (OBOS).

Discuss with referring clinician

Granulocytes not provided

Choose appropriate granulocyte component

1. Granulocytes, Pooled, Buffy Coat Derived, in Platelet Additive Solution and Plasma, Irradiated: 2-3 packs (adult) 10-20ml/kg (child), ABO compatible available Tues-Sat
2. A limited supply of O RhD pos, HT neg granulocytes are be available on Mondays
3. Substitutions agreed as dictated by availability and clinical need (e.g. CMV positive, red cell antibody positive)

Liaise with NHSBT Hospital Services. Regional Hospital services may additionally need to liaise with Filton/Colindale/Manchester.

Report back to the referring clinicians on the availability of component and agree start date and duration.

Request an HLA type and antibody screen.

REFERENCES

Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*. 2002;34:7-14.

Bashir S, Cardigan R. Granulocyte concentrates: how can we assess their quality? *Transfusion Medicine* 2003;13:245-258.

Bashir S, Stanworth S, Massey E, Goddard F, Cardigan R. Neutrophil function is preserved in a pooled granulocyte component prepared from whole blood donations. *British Journal of Haematology*. 2008;140(6):701-11.

Bennett CL, Evens AM, Andritsos LA, et al. Haematological malignancies developing in previously healthy individuals who received haematopoietic growth factors: report from the Research on Adverse Drug Events and Reports (RADAR) project. *Br J Haematol*. 2006 Dec;135(5):642-50

Dale DC, Liles WC. Return of granulocyte transfusions. *Curr Opin Pediatr*. 2000;12:18-22.

Estcourt LJ, Stanworth S, Doree C, Blanco P, Hopewell S, Trivella M, Massey E. Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No: CD005341. DOI:10.1002/14651858. CD005341.pub3.

Estcourt LJ, Stanworth SJ, Hopewell S, Trivella M, Massey E. Granulocyte transfusions for treating infections in patients with neutropenia or neutrophil dysfunction *Cochrane Database of Systematic Reviews* 2016 in press.

Freireich EJ, Levin RH, Whang J, Carbone PP, Bronson W, Morse EE. The function and fate of transfused leukocytes from donors with chronic myeloid leukaemia in leukopenic recipients. *Annals of the New York Academy of Sciences*. 1964;113:1081-1090.

Goldman JM, Madrigal JA, Pamphilon D. Possible harmful effects of short course granulocyte colony-stimulating factor in normal donors. *Br J Haematol*. 2006 Dec;135(5):651-2

Gutierrez-Delgado F, Bensinger W. Safety of granulocyte colony-stimulating factor in normal donors. *Curr Opin Hematol*. 2001;8:155-160.

Hubel K, Dale DC, Engert A, Liles WC. Current status of granulocyte (neutrophil) transfusion therapy for infectious diseases. *J Infect Dis*. 2001;183:321-328.

Hubel K, Carter RA, Liles WC, et al. Granulocyte transfusion therapy for infections in candidates and recipients of HPC transplantation: a comparative analysis of feasibility and outcome for community donors versus related donors. *Transfusion*. 2002;42:1414-1421.

Kerr, J. P., Liakopolou, E., Brown, J., Cornish, J. M., Fleming, D., Massey, E., Oakhill, A., Pamphilon, D. H., Robinson, S. P., Totem, A., Valencia, A. M. P. I. and Marks, D. I. (2003), The use of stimulated granulocyte transfusions to prevent recurrence of past severe infections after allogeneic stem cell transplantation. *British Journal of Haematology*, 123: 114–118.

Kuijpers TW, Weening RS, Roos D. Clinical and laboratory work-up of patients with neutrophil shortage or dysfunction. *J Immunol Methods*.1999;232:211-229.

Massey E, Harding K, Kahan B C, Llewelyn C, Wynn R, Moppett J, et al (2012) The Granulocytes in Neutropenia 1 (GIN 1) Study: A Safety Study of Granulocytes Collected from Whole Blood and Stored in Additive Solution and Plasma. *Transfusion Medicine*; DOI: 10.1111/j.1365-3148.2012.01152.x

McCullough J. Liquid preservation of granulocytes. *Transfusion* 1980. 20(2) 129-37.

Oza A, Hallemeier C, Goodnough L, Khoury H, Shenoi S, Devine S, Augustin K, Vij R, Trinkaus K, DiPersio JF, Adkins D. Granulocyte-colony-stimulating factor-mobilised prophylactic granulocyte transfusions given after allogeneic peripheral blood progenitor cell transplantation result in a modest reduction of febrile days and intravenous antibiotic usage. *Transfusion* 2006;46:14-23.

Peters C, Minkov M, Matthes-Martin S, et al. Leucocyte transfusions from rhG-CSF or prednisolone stimulated donors for treatment of severe infections in immunocompromised neutropenic patients. *Br J Haematol.* 1999;106:689-696.

Price TH, Bowden RA, Boeckh M, et al. Phase I/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation. *Blood.* 2000;95:3302-3309.

Price TH, Boeckh M, Harrison RW, McCullough J, Ness PM, Strauss RG, Nichols WG, Hamza TH, Cushing MM, King KE, Young JA, Williams E, McFarland J, Holter Chakrabarty J, Sloan SR, Friedman D, Parekh S, Sachais BS, Kiss JE, Assmann SF. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. *Blood* 2015 Oct 29;126(18):2153-61.

Sachs UJH, Reiter A, Walter T, Bein G, Woessmann W. Safety and efficacy of therapeutic early onset granulocyte transfusions in pediatric patients with neutropenia and severe infections. *Transfusion* 2006;46:1909-1914.

Sasakawa S and Miyamoto M. Studies on granulocyte preservation III. Effect of agitation on granulocyte concentrates. *Transfusion* 1987. 27(2): 165-6

Seidel MG, Peters C, Wacker A, Northoff H, Moog R, Boehme A, Silling G, Grimminger W, Einsele H. Randomized phase III study of granulocyte transfusions in neutropenic patients. *Bone Marrow Transplantation* 2008; 42(10) 679–84

Treleaven, J., Gennery, A., Marsh, J., Norfolk, D., Page, L., Parker, A., Saran, F., Thurston, J. and Webb, D. (2011), Guidelines on the use of irradiated blood components prepared by the British Committee for Standards in Haematology blood transfusion task force. *British Journal of Haematology*, 152: 35–51.

Vamvakas EC, Pineda AA. Determinants of the efficacy of prophylactic granulocyte transfusions: a meta-analysis. *J Clin Apheresis.* 1997;12:74-81.

Vamvakas EC, Pineda AA. Meta-analysis of clinical studies of the efficacy of granulocyte transfusions in the treatment of bacterial sepsis. *J Clin Apheresis.* 1996;11:1-9

WHO. International Statistical Classification of Diseases and Health Related Problems (The) ICD-10. Geneva: 1999.