Joint UKBTS Professional Advisory Committee ([1])

Position Statement

Granulocyte Therapy

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Introduction

Granulocyte transfusions continue to be requested by clinicians for use in patients with refractory infection or at high risk of developing severe infection (Strauss 2003). Most patients prescribed granulocyte transfusions are those with cancer related neutropenia, who are receiving myeloablative chemotherapy with or without haemopoietic stem cell rescue. Interest in the use of granulocytes remains high (Van Burik & Weisdorf, 2002; Price 2006), and requests for granulocyte components for transfusion in the UK continue to rise. Although randomised data are sparse, there are several publications describing transfusion in neutropenic patients both for *therapeutic* indications, when they have an infection refractory to antimicrobials (Hubel et al. 2002) and for secondary *prophylaxis*, in patients who have had severe bacterial or fungal infections previously but who require a further cycle of chemotherapy or haemopoietic stem cell rescue (Kerr et al. 2003, Oza et al., 2006). A number of studies with variable or promising, but overall inconclusive, results have been reported both in adults (Oza et al. 2006, Seidel et al, 2008) and children (Sachs et al., 2006). More recently, a further trial in North America was published: The Resolving Infection in Neutropenia with Granulocytes (RING) study (Price et al, 2015); this is discussed in more detail below.

Requests for use of granulocyte transfusions in other clinical groups of patients (e.g. neonates) are much less common, and will not be discussed further in this article (Baley et al., 1987; Wheeler et al., 1987). Similar broad principles of treatment apply, although in the case of neonates (or very small children), much higher doses of granulocytes can be provided per kg body weight.

Methods of collection in UK

In the UK, granulocytes for transfusion are produced as a component derived from whole blood donations. Since 2018, apheresis granulocytes have not been available in the UK although these continue to be the main source of granulocytes in many other countries. Of interest, some countries eg France and Netherland are now currently actively exploring options to provide a source of granulocytes derived from whole blood donations.

The administration of Granulocyte Colony Stimulating Factor (G-CSF) and steroids to donors increases the circulating granulocyte count prior to apheresis, enabling greater yields of granulocytes to be collected for transfusion. However, the UK Blood Services had made a decision not to permit G-CSF and steroid administration to volunteer unrelated donors for the purpose of collecting granulocytes (Guidelines for UK Transfusion Services), in view of the paramount need to ensure absolute safety of volunteer donors (see below for details of

specific although small risks). The provision of stimulated directed donations for granulocytes is challenging, due to infrequent requirement for the product, and complex logistics and resource implications

The Table below summarises information on cell counts for the main sources of granulocytes.

Properties of different granulocyte concentrates
(Data provided by the UK National Blood Services: Edwin Massey, Rebecca Cardigan, Saber Bashir, Fred Goddard. Information on yields in pooled granulocytes from 10 whole blood donations has been updated by reference to NHSBT 2013/14 Quality Monitoring: Simon Procter)

	Single buffy coat (n=21) (mean, SD)	**10 buffy coats** (dose typically transfused for adults)	**Pooled granulocytes from 10 whole blood donations** (n=1595) (mean, SD)	**Unstimulated apheresis collection** (n=20) (mean, SD)	**Stimulated apheresis collection** (n=5) (median, range)
Volume (ml)	59 (3)	590	211 (11)	276 (26)	299 (214-333)
Neutrophils (10^{10}/U)	0.105 (0.04)	1.05	0.81 (0.2)	0.54 (0.2)	6.37 (3.69 – 8.47)
Haematocrit (%)	45 (6)	45	19 (3)	23 (7)	9 (7-20)
Lymphocytes (10^9/U)	0.88 (0.41)	8.80	6.72 (0.75)*	5.90 (1.38)	N/A
Monocytes (10^9/U)	0.18 (0.07)	1.80	1.22 (0.37)*	0.95 (0.39)	N/A
Platelets (10^9/U)	75 (17)	750	447 (90)	111 (25)	160 (82 – 293)
Red cells (10^{12}/U)	0.27 (0.04)	2.70	0.57 (0.06)*	0.71 (0.23)	0.3 (0.28 – 0.61)

*lymphocytes, monocytes and red cell counts are not routinely reported as QM, and so are drawn from initial validation work in 2012

Granulocytes derived from whole blood

The alternative source of granulocytes, derived from whole blood donations, has been available for many years and has some immediate advantages of availability, but the component has not been evaluated in any detail (Poon & Wilson, 1980, Rock *et al*., 1984). These donations are commonly described as "buffy coats" as they are derived from the buffy coat layer between red cells and plasma in centrifuged whole blood. The main disadvantage of this source of granulocytes is the lower yield, by comparison to apheresis collections. Risks of "buffy coats" granulocyte transfusion also include alloimmunisation and transfusion transmitted infection associated with multiple donor exposure, given that 10 buffy coats are typically transfused for an adult dose (Schiffer *et al*., 1979). Such risks would extend to vCJD. However, patients for whom granulocyte transfusions are considered are often acutely ill and unwell, with life-threatening infection, and these patients require extensive transfusion support with other blood components. As mentioned, usually 10 buffy coats are transfused to give a dose of approximately 1 x 10^{10} neutrophils for an adult. In addition to the low cell dose, the current buffy coats are also heavily contaminated with red cells and platelets, and repeated transfusion can result in polycythaemia necessitating venesection.

Evidence Base

A general resurgence of interest in granulocyte transfusion therapy was strengthened with the recognition that using G-CSF and steroids to 'prime' donors for apheresis supported the collection of significantly greater yields of granulocytes for transfusion (Dale et al., 2000; Yeghen & Devereux, 2001; Hubel et al., 2001, Robinson & Marks 2004, Murphy et al., 2000). These higher yields for transfusion are considered clinically important and the transfusion of these components is associated with definite post-infusion increments and appropriate localisation in vivo (Adkins et al., 1997). However, the apheresis granulocyte component for transfusion has not to date been successfully evaluated for efficacy in a sufficiently large prospective randomised controlled trial, perhaps in part because of the major logistic difficulties required in the planning and design of such a trial which would require significant resources and hundreds of enrolled patients (Price et al., 2006). A group in Europe published a randomised controlled trial of granulocytes collected by apheresis from GCSF and steroid stimulated donors. For a number of methodological and logistic reasons however, this trial of therapeutic granulocytes failed to establish evidence of benefit (Seidel et al, 2008).

More recently, an important trial in North America was published. The RING (Resolving infection in neutropenia with granulocytes) study described a multi-centre randomized controlled trial designed to address the question of efficacy of granulocyte transfusions. Eligible subjects were those with neutropenia (ANC<500/uL) and proven/probable infection. Subjects were randomized to receive either 1) standard antimicrobial therapy or 2) standard antimicrobial therapy plus daily granulocyte transfusions from donors stimulated with G-CSF and dexamethasone. The primary end point was a composite of survival plus microbial response at 42 days after randomization. Microbial response was determined by a blinded adjudication panel. The target sample size was 118 patients per arm, to provide 80% power

to detect a treatment difference if the true response rate with antimicrobial therapy alone was 50%, and with granulocytes was 70%.

Fifty six subjects were randomized to the granulocyte arm and 58 to the control arm. Transfused subjects received a median of 5 transfusions. Mean transfusion dose was $54.9x10^9$ granulocytes. Overall success rates were reported as 42% and 43% for the granulocyte and control groups, respectively (p> 0.99), and 49% and 41%, respectively, for subjects who received their assigned treatments (p=0.64). Success rates for granulocyte and control arms were not reported to differ within any infection type. In a post-hoc analysis, subjects who received an average dose per transfusion of $>0.6x10^9$ granulocytes/kg tended to have better outcomes than those receiving a lower dose.

This trial does not unfortunately answer (again) the question of whether granulocytes have benefit for clinical outcomes. Enrolment was half that planned; the low accrual rate reflects multiple issues, which have been well described in other attempts at studies of granulocytes, including uncertainty in the state of clinical equipoise for clinicians (and patients). There is also a concern about selection bias and whether the sickest patients were included. Finally, there was variability in doses of granulocytes received, and around a quarter of all patients received doses that were less than defined in the protocol.

The exact role for granulocyte transfusions (whether derived from whole blood or collected by apheresis) therefore remains unclear. Potential efficacy including a dose dependent effect has been raised by systematic reviews/meta-analyses (Vamvakas *et al*. 1996; Vamvakas *et al*. 1997; Estcourt et al *et al*., 2015 and 2016), and in animal studies. The existing literature is, perhaps not surprisingly otherwise heavily dominated by case reports and small case series, with the significant attendant risk of publication bias. However, it should be acknowledged that anecdotal evidence of benefit in selected patients from physicians in the UK and abroad can be found, and that a number of very recent publications have again pointed to evidence of benefit, including one study based on biological randomisation - although this study was underpowered to detect an effect on mortality (Oza *et al*., 2006).

Developments in UK Blood Transfusion Services: A better component of granulocytes derived from whole blood: Granulocytes, pooled, buffy coat derived, in platelet additive solution and plasma

Work in the NHS Blood and Transplant Components Development Laboratory (CDL) has previously reported the characterisation of a purer pooled granulocyte component derived from whole blood donations. The method involved the addition of platelet additive solution but without the need for hydroxyethyl starch or dextran to sediment red cells during processing (Bashir *et al*., 2008). In addition to cell content, a range of *in vitro* tests for measures of neutrophil function were determined during storage (Bashir & Cardigan, 2003; Bashir *et al*., 2008). The volume and red cell contamination of this product is vastly reduced compared to standard buffy coats and is similar to an apheresis granulocyte collection. The results for pH, viability and neutrophil function indicated well maintained function during storage up to 24 hours and some measures of neutrophil function were preserved for longer (for comparison

see Schwanke *et al*., 2005). There were no statistically significant differences when this optimised granulocyte component was compared to either the standard buffy coat or fresh whole blood. Therefore the method for producing a pooled granulocyte component derived from whole blood donations described above appears to provide granulocytes whose in vitro function is maintained for up to 24 hours of storage.

The component has advantages of ready availability for transfusion on a daily basis if adequate whole blood donations have been collected the day before which may be clinically important given that there is some evidence that provision of granulocytes at early onset of severe infection may be critical (Sachs *et al*., 2006). In addition, by providing a standard adult component derived from two pools of 10 donations, a consistent daily cell dose of around 1.6 x 10^{10} cells (current NHSBT process capability) may be transfused to patients, which is considered by many physicians a clinically 'meaningful' yield for transfusion. The Red Book granulocyte specification has been revised in 2019 to state that 95% or more pooled granulocyte units should have >5x10^9/unit per month, and production processes should be reviewed if any component has <3.8x10^9/unit. It is not felt to be clinically appropriate to have a 'concessionary release limit' below which a granulocyte pool would not be issued for use, as this would add complexity to the system. A key consideration is to ensure rapid provision to patients often with life-threatening illness and there is no robust evidence to indicate what is an effective dose of granulocytes. The main limiting factor for dose remains the volume; for patients able to tolerate the volume transfusions of three (or even four) pooled bags per day may be offered in an attempt to achieve greater increments and enhanced clinical response.

A clinical study has been undertaken in the UK which has assessed the outcome from infusing 221 packs of the product (each being from a pool of 10 donations) in 30 patients with neutropenia and sepsis (Massey et al 2012). The recipients were tested prior to and 1 to 6 months following transfusion for leucocyte antibodies. The rate of antibody formation was consistent with findings in historic studies of multiply transfused patients. The transfusions were well tolerated but this dose did not produce a measurable increment in granulocyte count 12-18 hours post infusion in the patients studied in the trial (Massey et al. 2012).

The pooled granulocyte component is now available from NHS Blood & Transplant but not yet from the other UK Blood Services. There continues to be a demand for this buffy coat granulocyte component across England.

Compatibility and other requirements for testing

In view of the residual red cells still present in the final component granulocytes need to be ABO and RhD compatible with the recipient. If the recipient is eligible for electronic issue, crossmatching is not required. If not eligible for electronic issue for technical reasons in the absence of an antibody specificity, granulocytes should be crossmatched against recipient plasma by IAT technique (British Committee for Standards in Haematology, 2004).

If there is a specific antibody present there is no need to select granulocytes from donors who are negative for the antigen other than ABO and D as the numbers of donor red cells are relatively small.

If ABO compatible but non-identical granulocytes are used (e.g. O donor, A recipient) the plasma should not have high titres of anti-A and anti-B using the laboratory standards defined for platelets. The plasma used for resuspension of the optimised component should ideally be from a male contributor to the pool (to reduce risk of TRALI). The risk of immunological complications occurring as a result of donor derived antibodies is least for the optimised component as a substantial proportion of the suspending fluid is an additive solution rather than plasma.

It is advised that all patients receiving granulocyte transfusions are screened for HLA class I and II antibodies when granulocytes are requested. In the absence of transfusion reactions or previously identified refractoriness to platelet transfusion, the significance of the positive antibody screen is very unclear. The development of platelet or granulocyte refractoriness or severe transfusion reactions would prompt repeat screening for HLA, HPA and granulocyte antibodies. In the event of severe reactions in the presence of HLA antibodies in the recipient the provision of antigen matched granulocytes may ameliorate future reactions but they are unlikely to be available (Massey *et al*. 2016).

As granulocytes cannot be leucodepleted and are usually given to immunocompromised patients it is essential that they are irradiated prior to transfusion to avoid graft-versus-host disease.

Summary and the "ProGreS" study

The issue of efficacy of granulocytes (either therapeutically for refractory infection or as secondary prophylaxis for high risk groups of patients with prior severe infection) is still very much an open question. Provision of granulocytes by apheresis collection from G-CSF and steroid stimulated donors remains the international standard, but logistic and other constraints now preclude UK provision of apheresis granulocytes. The pooled granulocyte component is now available from NHS Blood & Transplant but not yet from the other UK Blood Services. The pooled component is available only five days per week (Tuesday to Saturday) due to the short shelf life and dependence on weekday blood donation. However buffy coats may be provided on Sundays and Mondays when specifically requested and buffy coats from suitable donors are available, and planning work may increase the availability at weekends in the future. Any additional risks associated with high donor exposure for this component including alloimmunisation and vCJD would need to be considered in the context of the use of this component in very sick and immunosuppressed patients.

Although new studies to definitively address the issue of effectiveness are required, researchers and clinicians recognise the challenges of completing RCTs. An additional issue is the very limited prospective data available on actual patterns of use, follow-up and outcomes for granulocyte products in UK and elsewhere. This is a key objective of an on-going UK (and

international) 'registry'. PROspective GRanulocyte usage and outcomEs Survey (ProGRES) describes a prospective study (registry) of outcomes following transfusion of granulocytes. Data collection on all patients for whom granulocytes are "authorised" by the NHSBT patient facing team commenced in March 2017. Data are being collected on indications, dose and outcomes following use of granulocytes administered to children and adults. (Morton et al 2017 – Trial website).

Primary outcome measure:

- to understand how granulocytes are being used (this includes patient demographics, underlying conditions and treatment received, e.g. type of leukaemia, chemotherapy treatment, concomitant treatment for infection, indication for transfusion, dose and schedule)

Secondary outcome measure:

- outcomes at 28 days and 6 months
- to assess granulocyte transfusion practice with reference to local or relevant national guidelines on appropriate indications, dose and frequency of transfusion.
- to inform further research.

Preliminary results for the first 128 patients were presented in 2019 (Morton et al, 2019). 19.7% patients were under the age of 16 years. The most common cause of neutropenia was acute myeloid leukaemia (n = 75; 59.1%). Thirty one (24.4%) patients were undergoing stem cell transplant (90.3% allogeneic, 9.7% autologous). Median dose of granulocytes per transfusion was only 0.2 x 10^9/kg. The most common reason for stopping GTX was due to recovery of neutropenia. Granulocyte transfusions were stopped due to adverse reactions in 3 cases. Clinicians reported granulocyte transfusions had a positive effect on the patient's outcome in 42.9% and no difference in 35.1%.

Granulocytes are commenced for 8.6 patients per month, with the number remaining static over a 2 year period. Accepting a positive bias in data return for deceased patients, 28 day mortality is estimated at 34% (95% CI: 24-47%) (unpublished data).

Further information is available by contacting: ProGrES@nhsbt.nhs.uk.

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