Joint UKBTS Professional Advisory Committee [1]

Position Statement

Granulocyte Therapy

November 2015

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Introduction

Granulocyte transfusions are 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 have steadily increased in the UK (particularly in England and Wales during the last five years). This has been driven by 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). Recent 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).

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). However 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 by one of two means:

- by apheresis (from stimulated donors – see below), or
- as a component 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. The Table below summarises information on cell counts for the main sources of granulocytes.

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Properties of different granulocyte concentrates
(data provided by the UK National Blood Services: Edwin Massey, Rebecca Cardigan, Saber Bashir, Fred Goddard)

	Single buffy coat (n=21) (mean, SD)	**10 buffy coats** (dose typically transfused for adults)	**Pooled granulocytes from 10 whole blood donations** (n=99) (mean, SD)	**Unstimulated apheresis collection** (n=20) (mean, SD)	**Stimulated apheresis collection** (n=5) (median, range)
Volume (ml)	59 (3)	590	207 (12)	276 (26)	299 (214-333)
Neutrophils (10^{10}/U)	0.105 (0.04)	1.05	1.0 (0.3)	0.54 (0.2)	6.37 (3.69 – 8.47)
Haematocrit (%)	45 (6)	45	15 (5)	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	499 (112)	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)

Data in italics from a pilot study on 13 units

Collections of granulocytes by apheresis in UK

The UK Blood Services have 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). In some hospitals in UK, granulocyte collections are obtained from directed G-CSF and/or steroid stimulated donors who are 'family and friends' of patients. Leitner *et al* (2010) provide a recent update on international approaches to obtaining the granulocyte concentrate by apheresis. In view of the poor yield and lack of availability of a licenced anticoagulant solution, unstimulated granulocytes are no longer produced in the UK.

The process in UK involves multiple steps, including:

- Identifying and selecting potential 'family and friends' of patients
- Checking suitability and eligibility in keeping with national requirements and guidelines for blood collection (including medical examination)
- Counselling donors, and obtaining consent
- Microbiological screen testing (including e.g. HIV, as for any blood donation)
- Immunohaematological testing (e.g. for atypical red cell antibodies)
- Administering G-CSF and steroids to the donor
- Apheresis
- Post- collection processing (if appropriate)

Whilst on paper this appears feasible and even straightforward, there are a number of potentially significant constraints in this process which can (and do) limit provision of apheresis products on a regular and timely basis in the UK in response to all potential requests from hospitals:

- Hospitals managing granulocyte collections by apheresis now have a requirement for meeting 'blood establishment status', as a consequence of EU legislation, enacted in the UK as the Blood Safety & Quality Regulations 2005.
- There are often (major) resource limitations at already overstretched apheresis units, alongside, for example, pre-booked stem cell collections, yet requests for granulocytes are unpredictable
- Ensuring all volunteer 'family and friends' of patients are given time and adequate explanation of the (potential small) risks they are exposed to by both taking specific drugs (steroids and G-CSF) to mobilise granulocytes into the peripheral blood (see Ghodsi & Strauss 2001; Gutierrez-Delgado & Bensinger, 2001; Bennett *et al*., 2006; Goldman *et al*., 2006) and by undergoing an apheresis procedure.
- UK blood services do not recommend the collection of whole blood or other component donations from directed donors, for well established reasons of blood safety (Pink et al., 1994).
- The risks of delay in collecting and administering apheresis granulocytes for transfusion, given all the above steps (Hubel et al. 2002), which could be very important in cases of severe life-threatening infection (Sachs et al., 2006)
- Unexpected variation in collection yield – sometimes very low doses are obtained by apheresis (Strauss 2005)
- The use of hydroxyethyl starch or dextran to sediment red cells during processing (Poon & Wilson, 1980, Rock et al., 1984) may have deleterious effects on chemotactic and

oxidative killing activity of neutrophils (Hofbauer et al., 1999, Jaeger et al., 2001), as well as having a risk of allergic reactions in recipients

There are also remote, but presumably finite, risks of developing life-threatening haematological malignancies even after short courses of G-CSF (Bennett *et al*., 2006; Goldman *et al*., 2006). This very important issue of potential, albeit very low, risk to healthy donors needs to be considered alongside the uncertain benefits of granulocyte transfusions to patients, as summarised in the section on the evidence base (see below).

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.

There has been a significant increase in requests for the buffy coat granulocyte component over the last five years. As mentioned, usually 10 buffy coats are transfused to give a dose of approximately 1×10^{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

There has been a general resurgence of interest in granulocyte transfusion therapy over the last decade largely as a consequence of using G-CSF and steroids to 'prime' donors for apheresis, which has permitted 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 evaluated for efficacy in a 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/presumed 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 54.9x109 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 >0.6x109 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; Stanworth *et al*., 2010, Massey *et al* 2009), 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

Recent work in the National Blood Service Components Development Laboratory (CDL) has 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 2×10^{10} cells may be transfused to patients, which is considered by many physicians a clinically 'meaningful' yield for transfusion.

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.

Compatibility testing

Granulocyte components should be treated as whole blood when compatibility testing is performed. 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, the guidance for red cell significance should be followed (Daniels *et al*. 2002). For some antigens it would be purely IAT crossmatch compatibility (e.g. Cw, Kp^a or M detectable at 22^oC only); for other antigens, antigen negative donations crossmatched by IAT technique would be recommended (e.g. Rh, K, Jk, Fy). This is a cautious standard based upon the available components with the greatest volume of red cells from each individual donor. The risks posed by red cell incompatibility of the optimised component would be less than apheresis granulocytes or unprocessed standard buffy coats because in less than 250ml there will be less than 50ml of red cells i.e. less than 5ml from each donor.

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. If available, antigen matched granulocytes would be preferable but logistically are rarely available (Elebute *et al*. 2004).

Summary

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 standard, but a number of logistic and other constraints currently limit wider provision in UK. The pooled granulocyte component is now available from NHS Blood & Transplant but not yet from the other UK Blood Services. 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. Possible future clinical studies of this component to address efficacy in patients with neutropenia will need to evaluate how

best to use the component alongside granulocytes for transfusion collected by apheresis from GCSF/steroid stimulated donors. New studies to definitively address the issue of effectiveness are required.

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

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