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# Therapeutic granulocyte infusion for patients with severe neutropaenia and neutrophilic dysfunction: New Zealand experience

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## Abstract

**Background and Objectives:** Studies have shown granulocyte transfusions (GTXs) may be beneficial in neutropaenic patients with severe systemic infections. New Zealand Blood Service has a policy for provision of granulocytes to New Zealand's District Health Boards. We set out to explore utilization of therapeutic granulocyte infusions in New Zealand.

**Materials and Methods:** Patients who received GTXs in the 16-year period between 2000 and 2016 were identified by the New Zealand electronic blood management system, eProgesa. Information pertaining to recipient demographics, disease-related factors, methods of granulocyte collection and clinical outcomes was obtained by the review of electronic transfusion and clinical records.

**Results:** Forty-five septic patients received granulocyte support for a total of 263 days. The median age of the recipients was 16 (range 0–74) years. Seventy-nine percent of the recipients had an underlying haematological malignancy with 50% having acute leukaemia. The median neutrophil count on the last day of GTX was $0.02 \times 10^9$/L (range 0–16.32). Sixty-three percent (27/43 patients with available data) had persisting severe neutropaenia when the GTXs were stopped. The median duration of support was 3 (range 1–32) days. Forty-six percent of granulocyte collections were performed via apheresis. Of the 44 patients, for whom survival outcome was available, 18 (41%) survived the acute illness.

**Conclusion:** GTXs were infrequently used, most commonly in the setting of an underlying haematological malignancy. This may be explained by the current weak evidence base supporting this therapeutic modality. Procuring a sufficiently large dose of granulocytes for infusion remains an issue for adult recipients.

**KEYWORDS**
apheresis – donation, blood components, granulocyte concentrate

## INTRODUCTION

Cancer patients receiving intensive chemotherapy or those undergoing haematopoietic stem cell transplantation (SCT) often experience a prolonged period of severe neutropaenia, which predisposes them to invasive bacterial and fungal infections that are associated with high morbidity and mortality [1]. The strongest predictor of survival from these infections is improvement of the neutrophil count [2].

Granulocyte transfusion (GTX) has been around for many decades with the first documented GTX in 1934 [3]. Significant enthusiasm developed for GTX in the 1970s, but controlled trials in the 1970s and 1980s yielded mixed results [4], which were partially attributed to differences in qualities and doses of the granulocytes transfused. There was resurgence of interest in clinical application of GTXs in the 1990s with the advent of leukapheresis and clinical utilization of granulocyte colony stimulating factor (G-CSF). Granulocyte collection without stimulation of the donor may yield $0.1–1 \times 10^{10}$ granulocytes, but this yield can increase to $4–8 \times 10^{10}$ cells after stimulation with G-CSF and steroids [5]. A study has found that granulocytes obtained from donors stimulated by G-CSF retained immunological functions such as chemotaxis, respiratory burst, adhesion and bactericidal and antifungal activity, which remained unchanged even after storage of the granulocyte product for 24 hours [6].

The few published multicentre randomized controlled trials for GTX suffered from poor recruitment, and they were not able to show clinical benefit in the intervention arm [7, 8]. However, the RING study did show the subjects who received a higher dose of granulocytes (mean dose greater than $0.6 \times 10^9$/kg per transfusion) had superior outcomes in a subgroup analysis [8]. The latest Cochrane review recommends regarding the use of GTX as investigational, given the lack of sufficient evidence from randomized controlled trials to support or refute its use in patients with neutropaenia and severe infection to reduce mortality [9]. In the recent years, several single centres published retrospective analyses of their real-life experience with GTX therapy. In one such study, providing GTX to severe neutropaenic patients with treatment-refractory, life-threatening infections resulted in 15/27 (56%) patients surviving to hospital discharge [10]. In another, 18/22 (81.8%) patients with neutropaenia due to haematological malignancy survived severe refractory abdominal infection when treated with GTX until recovery of absolute neutrophil count (ANC $>1 \times 10^9$/L) or significant clinical improvement. The patients achieving control of the infection within 7 days of the first GTX had significantly better overall survival ($p < 0.001$) [11]. Nguyen et al. described use of GTX as a bridge to an urgent allogeneic SCT in 19 severe neutropaenic patients with severe uncontrolled infection, where 90% of the GTX recipients were able to proceed to SCT with 80% continuing on GTX support until neutrophil engraftment. Following the SCT, 10% of the patients eventually succumbed to the initial infection, for which they received GTX. They showed an association between delay in provision of GTX and delay in proceeding to HCT ($p < 0.0001$), suggesting a potential role for GTX in facilitating an urgent SCT [12]. In the current multicentre retrospective observational study, we report on New Zealand's real-life experience in use of GTX for treating paediatric and adult patients with severe infection in the setting of neutropaenia or neutrophil dysfunction associated with wide ranging haematological and non-haematological disorders over 16 years. This project was carried out as a quality improvement audit for New Zealand Blood Service (NZBS), and an ethics application was not required as per the local guidelines.

## New Zealand's policy and procedures for GTX

NZBS provides a 'vein-to-vein' transfusion service for the nation, and it is responsible for provision of all blood products. The national policy for provision of therapeutic granulocyte products states that GTX may be considered in patients with

1. persistent neutropaenia of less than $0.2 \times 10^9$/L, which is expected to persist for longer than 5 days,
2. either septicaemia or life-threatening local infection that is not responding to 72 h of appropriate antimicrobial therapy or proven or probable fungal or yeast infection that is refractory to appropriate antifungal therapy,
3. good long-term prognosis from the underlying disorder and
4. a suitable donor.

Contraindications include poor long-term prognosis of the underlying disorder, known as human leukocyte antigen (HLA) alloimmunization (relative), severe respiratory compromise and requirement for ventilatory support.

The granulocyte products can be provisioned within 24 h of a request through the on-call Transfusion Medicine Specialist on 6 days of the week, from Monday to Saturday. A donor search is made on a list of ABO- and RhD-compatible NZBS apheresis donors. Family members of the patient, who meet requirements of the NZBS Collection Standards as evaluated by a NZBS Medical Officer, may become donors, but directed family donation is relatively contraindicated if allogeneic SCT is being considered due to risk of HLA alloimmunization. Given the limited size of the donor pool, granulocytes are only matched for ABO and RhD types, unless the recipient is known to have HLA antibodies.

Apheresis units from single donors expose the recipients to a limited number of HLA antigens compared to buffy coat units from several donors. Collection of an apheresis unit, however, requires priming of the donor with recombinant G-CSF (5–10 µg/kg) with or without dexamethasone (8 mg) in the evening prior to the collection date, whereas buffy coat units are routinely set aside for platelet pooling at NZBS collection sites. Consequently, buffy coat units are used for GTX if an apheresis donation cannot be arranged in a timely manner. For procurement of buffy coat units, whole blood donations, collected into 'top-and-bottom' bags, are centrifuged at $3616g$ (using a Heraeus 6000i centrifuged at 3300 rpm for 11 min) at room temperature, and the bottom red cell layer and the top plasma layer are removed using a Macopress automated blood component separator. The remaining buffy coat is transferred to a bag that is suitable for transfusion. For apheresis collection, NZBS currently uses Spectra Optia®, which utilizes continuous-flow centrifugation and optical detection technology. Other machines that had been in use over the preceding years include Haemonetics MCS+® and Fresenius Kabi's COM.TEC®.

All granulocyte products are irradiated prior to infusion to prevent transfusion-associated graft-versus-host disease. The requirements for an adequate buffy coat unit are volume of 35–65 ml and granulocyte and platelet contents of $≥1 \times 10^9$ and $≥5 \times 10^{10}$ per unit, respectively. The volume of an apheresis unit is defined locally, and it is between 200 and 500 ml in practice. Each apheresis unit should

contain ≥1 × 10$^{10}$ of granulocytes. For quality control, each donation of granulocyte products is tested for volume and granulocyte content, and these data are entered into a statistical process control system, NWA, to identify trends and outliers. The collected granulocytes must be transfused as soon as possible but can be stored for up to 24 h from collection if they are kept at 20–24°C without agitation.

## METHODS

An electronic search was performed on eProgesa, the electronic blood management system used by NZBS since year 2000, to identify all recipients of buffy coat and/or apheresis granulocyte units during the 16-year period between 2000 and 2016. We collected data related to the recipient's demographic features, the underlying disease status (primary diagnosis, indication for GTX), the intervention (method of procurement of granulocyte products, number of infusions given per patient, dose of granulocytes given per patient) and the clinical outcome (neutrophil count post-GTX, survival). The Transfusion Nurse Specialists working for the eight largest District Health Boards (DHBs) around New Zealand reviewed the electronic records of the GTX recipients belonging to their respective DHBs and other smaller DHBs supported by their DHBs and collected the pre-specified set of data. The authors analysed the data and prepared the manuscript.

## STATISTICAL ANALYSIS

Pearson's chi-squared test with Yates' continuity correction was used for the correlation between increment in the neutrophil count during treatment and survival to the time of discharge from hospital. Kaplan–Meier analysis was used to estimate survival. The statistical software used was R (R Foundation for Statistical Computing, Vienna, 2018).

## RESULTS

Between 2000 and 2016, 45 patients received GTX for a total of 263 days in New Zealand. Twenty-eight (62%) patients were females. The median age of the recipients was 16 with a range between zero and 74 years (Figure 1). Fifty-six percent of the recipients had underlying acute leukaemia, and another 22% had other haematological malignancies including large granulocytic leukaemia (two patients), chronic lymphocytic leukaemia (one patient), classic Hodgkin lymphoma (one patient), Burkitt lymphoma (one patient), chronic myeloid leukaemia (one patient), Juvenile myelomonocytic leukaemia (one patient) and T-cell lymphoproliferative disorder, NOS (one patient). Four patients had underlying aplastic anaemia. Four recipients did not have a primary haematological diagnosis. These included two paediatric patients with chronic granulomatous disease leading to granulocyte dysfunction and two patients with solid organ malignancy (Figure 2). All patients had documented bacterial or fungal infections that were refractory to conventional therapy. None received GTX as a secondary prophylaxis to prevent progression or recurrence of chronic infection.

Eleven out of the 20 DHBs in New Zealand have a dedicated Haematology Department, and the remaining DHBs are served by neighbouring DHBs with a Haematology Service. The majority of the GTXs (21 patients, 47%) were carried out by Starship Hospital, the largest tertiary paediatric service in New Zealand. Auckland City Hospital, the adult equivalent, was the second biggest user of GTX during the study period, but their usage was much less than that of Starship Hospital, with only six cases comprising 13% of the total number. This was slightly more than that seen in the rest of the country. Other haematology centres in both North and South Islands of New Zealand had one to four cases of GTX therapy in the 16-year period. There did not appear to be any apparent regional variation in the clinical practice; for example, Wellington Hospital Haematology
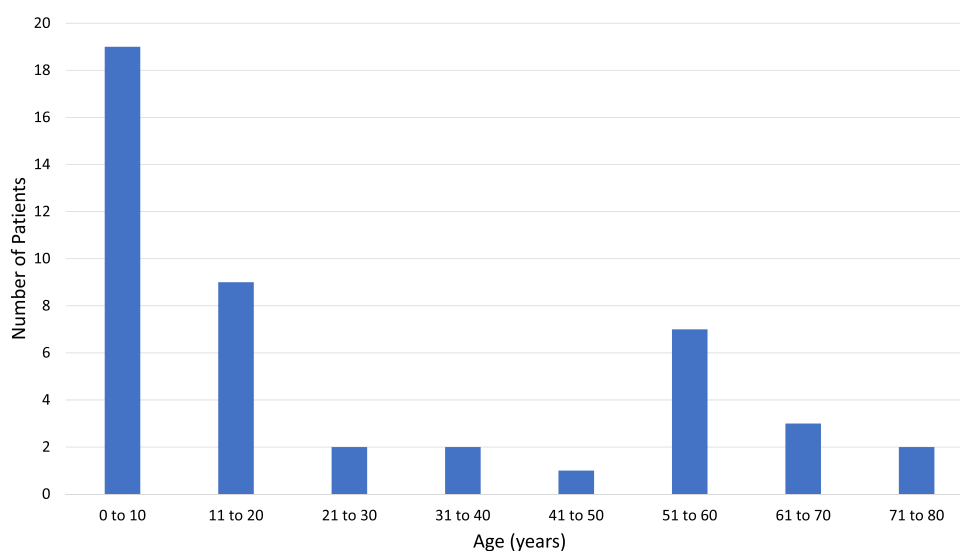


**FIGURE 1** Age distribution of recipients. This graph illustrates the number of recipients of therapeutic granulocyte infusion in each age bracket
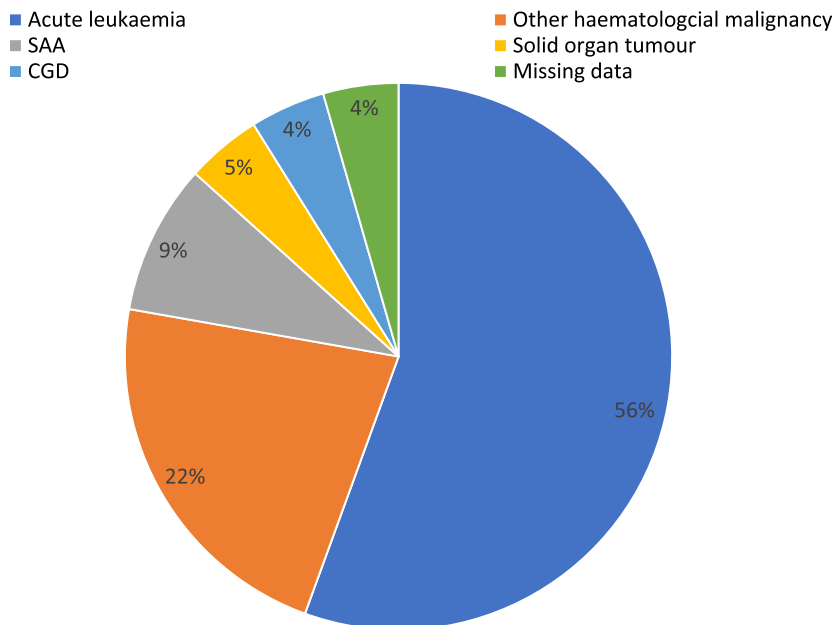
**FIGURE 2** Underlying primary diagnoses of granulocyte transfusion (GTX) recipients. This graph illustrates the underlying primary diagnoses of the patients who received therapeutic granulocyte infusion for neutropaenia or neutrophil dysfunction in this series

Centre, serving Capital and Coast, Hutt Valley and Wairarapa DHBs in the lower end of the North Island (a population of 525,910 people by the Ministry of Health 2020/21 estimate), used GTX on four occasions, whereas Dunedin Hospital Haematology Department, serving the lower end of the South Island (a population of 344,900 people by the same estimate) used it for three patients.

Thirty-four out of the 40 recipients with available data (85%) had severe neutropaenia (defined as a neutrophil count of less than $0.5 \times 10^9$/L) at baseline and three (7.5%) had moderate neutropaenia (defined as a neutrophil count between 0.5 and $1 \times 10^9$/L). Four of the five patients with missing data had only the total white blood cell (WBC) count without differentials reported on the day. Three of the 44 patients with available data (6.8%) had a neutrophil count above $1 \times 10^9$/L. Only one patient had a missing data for this latter category because all of the patients who had a WBC reported without differentials had a WBC of less than 1. The patients with a starting neutrophil count of $1 \times 10^9$/L or greater included a patient with an underlying chronic granulomatous disease (ANC $16.32 \times 10^9$/L), a paediatric acute leukaemia patient with typhlitis and abdominal wall cellulitis (ANC $3.29 \times 10^9$/L) and an adult patient with a bone marrow failure syndrome and *Escherichia coli* bacteraemia (ANC $1.1 \times 10^9$/L). The median neutrophil count at baseline was $0.02 \times 10^9$/L with a range between 0 and $16.32 \times 10^9$/L.

One hundred thirty-nine (139/303, 45.9%) therapeutic doses of granulocytes were collected via apheresis, and 164 (164/303, 54.1%) doses were derived from buffy coats (10–12 buffy coats per one therapeutic dose). The median number of GTXs given per patient was four with a range between one and 37 doses (Figure 3). The patient who received the highest cumulative dose of GTX was a 7-year-old female with a brain stem glioma, who had chemotherapy-induced

neutropaenia and invasive pulmonary aspergillosis. Despite receiving 23 therapeutic doses of buffy coats and 14 apheresis units of GTX, she eventually succumbed to the acute infection. Her WBC at the commencement of GTX was $0.14 \times 10^9$/L, and the peak WBC during the course of GTX was $0.44 \times 10^9$/L (no differentials available).

The survival outcome data were available for all but one recipient. Twenty-six (58%) recipients were alive at the time of discharge from hospital. Eighteen (40%) died from severe infection.

The information on the granulocyte dose per kilogram body weight was available for a subset of 30 patients. Fifteen patients received $0–100 \times 10^8$/kg of granulocytes, and 40% of them survived the acute infection. Of the 11 patients who received $100–200 \times 10^8$/kg of granulocytes, 55% survived. All four patients who received greater than $200 \times 10^8$/kg of granulocytes were alive at the time of discharge from hospital ($p = 0.1014$).

Based on the available data, the post-GTX neutrophil count could be determined for a subset of 42 patients. During the time interval between the first GTX and the day after the last GXT, 27 (64%) patients had a rise in their neutrophil count of $0.2 \times 10^9$/L or greater, and 14 (52%) of these patients survived to hospital discharge. Out of the 15 patients who had less than $0.2 \times 10^9$/L increase in their neutrophil count, only five (33%) survived ($p = 0.4055$). All but six patients had an increment in their neutrophil count at one or more measurements while receiving GTX. Of the six patients who failed to have any rise in their neutrophil count during the treatment course, only one patient (17%) was alive at the time of discharge from hospital, in comparison to 18 out of the 36 patients (50%) who had at least a transient rise in their neutrophil count ($p = 0.282$).

Eight GTX incidents were associated with a reported transfusion reaction according to the NZBS haemovigilance record. The
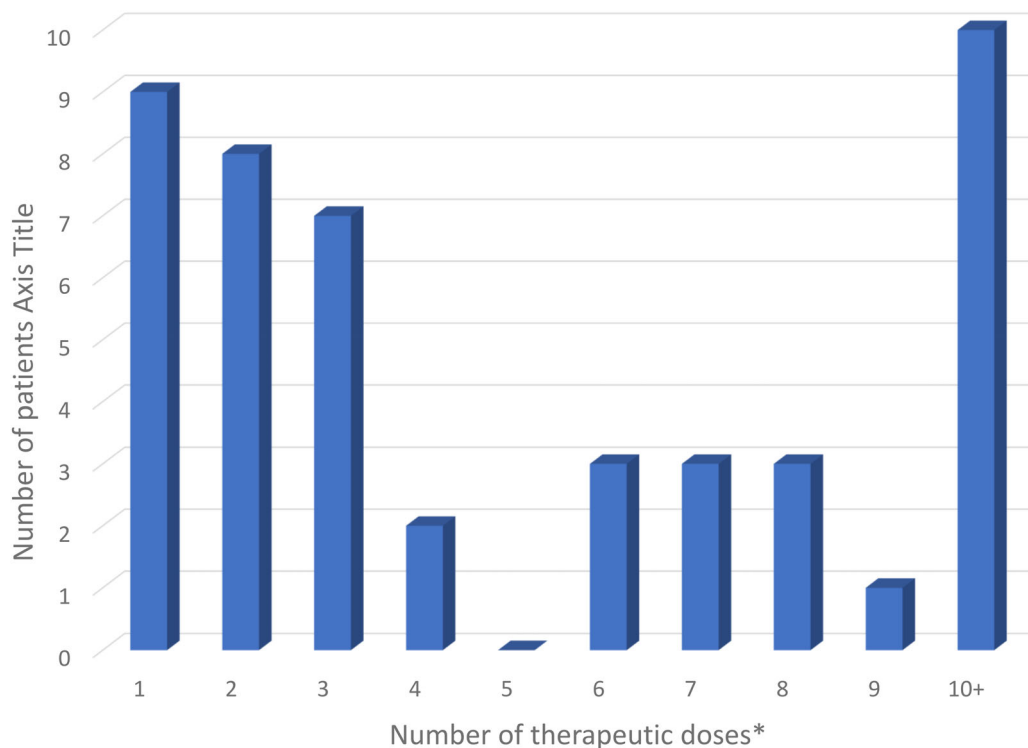
**FIGURE 3** Number of therapeutic granulocyte doses given per patient. This graph illustrates distribution of the number of therapeutic doses of granulocytes given per patient. Each therapeutic dose of granulocytes consists of either one apheresis unit or 10–12 buffy coats

commonest transfusion reaction was mild to moderate allergic reaction (four patients; two patients with buffy coat units and two patients with apheresis units). Two patients experienced non-haemolytic febrile transfusion reaction (one with buffy coat unit and one with apheresis unit) and one patient developed transfusion-associated circulatory overload after receiving an apheresis unit. There was one reported case of transfusion-associated polycythaemia in a paediatric patient who received a cumulative sum of 23 buffy coat units and 14 apheresis units over the treatment course.

## DISCUSSION

In our retrospective study, we reviewed the GTX usage in New Zealand over a 16-year period between 2000 and 2016 and explored the associated clinical practice and patient outcomes. Although the NZBS protocol suggests GTX be given to patients with a neutrophil count of less than $0.2 \times 10^9$/L, 11 (24.4%) recipients had a neutrophil count of $0.2 \times 10^9$/L or greater at the time of treatment. This is because NZBS allows the requesting clinicians to make the decision to access GTX support for a septic patient after careful consideration of the patient's underlying disease, neutrophil function, anticipated trajectory of the neutrophil count and severity of the acute infection, in addition to the absolute neutrophil count.

There was little fluctuation in the demand for GTX over the years. The maximum number of cases was seen in 2008 and 2012, with five

patients receiving GTX in each. The number of cases varied between one and four in other years, except for in 2002, when GTX was not given at all. This is not surprising as there has not been any groundbreaking improvement in the process of granulocyte collection or a major publication providing stronger evidence for benefit of GTX over this time. The majority of the recipients were paediatric patients located at Starship Hospital, the country's largest tertiary children's hospital. This may be partially because GTX is perceived to be more efficacious in paediatric patients, who are able to receive a higher number of granulocytes per kilogram body weight due to their smaller size. It may also be because doctors and the parents, who often are the surrogate decision-makers for paediatric patients, are more likely treat the very young patients aggressively and/or explore alternative therapeutic options when conventional measures are failing. Cost may also be an issue favouring paediatric recipients. Although all blood components are free of charge to the patient, NZBS operates on a cost recovery model, with the government-funded DHBs paying for each component. A single apheresis granulocyte component costs approximately €500, while a buffy coat from a single whole blood donation costs approximately €145.

New Zealand is a small country, hence, therapeutic granulocytes can generally be transported from a collection site to where a patient is situated by land or air in a timely manner. Provision of all blood products in New Zealand is coordinated by a single crown-owned, non-profit entity, NZBS, so there are insignificant variations in the cost or logistic complexities related to GTX provision around the country. Consequently, there does not appear to be any regional

variation in the usage of GTX. The overall number of cases has been low from all parts of the country. This is likely reflective of the clinicians' uncertainty or scepticism towards the therapeutic benefit of GTX in treating severe infections in immunocompromised patients, given the lack of clear evidence based on large well-conducted randomized controlled trials.

It is interesting to note that at 42 days (the RING trial's endpoint), our survival was over 70%, which is in keeping with the RING trial's expected indicator of success [8]. We have failed to demonstrate improved survival in patients who received a higher dose of granulocytes in the subgroup analysis, but it could be attributable to the small sample size and the incomplete data set. We were not able to determine the granulocyte dose per kilogram body weight for patients who received GTX prior to 2008 due to missing data on the granulocyte content in the infusion products in our current electronic quality assurance database. We also did not find statistically significant difference in survival in patients who had a rise in their neutrophil count of at least $0.2 \times 10^9$/L compared to those who did not ($p = 0.4055$), but in order to have a 95% chance of detecting a statistically significant difference, around 144 patients were needed in each group. Likewise, there was no statistically significant difference in survival between the patients who had any rise in the neutrophil count during the course of GTX and those who did not ($p = 0.282$), but we would have needed 24 patients in each arm to detect a statistically significant difference (50% vs. 16.7%) with 80% certainty.

GTX has a number of challenges. It is mandatory to have specialized expertise and facility, such as leukapheresis and HLA matching, to produce the granulocyte products and the manufactured granulocyte products need to reach the intended recipients within 24 hours. This may be particularly challenging in peripheral centres where the manufacturing expertise and facility are not available. The NZBS protocol considers a minimum therapeutic dose of granulocytes to be $1 \times 10^{10}$, although $>2 \times 10^{10}$ is desirable. Each bag of buffy coat unit should contain at least $1 \times 10^9$ of granulocytes, and at least 10 bags of buffy coat are given per infusion to achieve the therapeutic dose. Currently, there is no formal requirement to adjust the number of buffy coat units to be given based on the patient's weight although this does happen in practice. The recommended granulocyte dose from the 2009 Cochrane review is $3 \times 10^8$/kg, which equates to 2.1 $\times 10^{10}$ per infusion for a 70 kg individual. As the average weight of the population increases in the current obesity pandemic, provision of a sufficient dose of therapeutic granulocytes will likely become more and more challenging.

There are concerns over treatment-related adverse effects, particularly pulmonary events, CMV transmission and HLA alloimmunization. GTX appears safe in our study. During the 16-year period where 45 patients received a total of 303 therapeutic doses, only eight transfusion incidents were reported to have caused a transfusion reaction. The commonest transfusion reaction was an allergic reaction, and none was life-threatening. This is significantly less than what was reported in the RING study, where 41% of the 114 participants and 28% of the transfusions were associated with grade 1–2 transfusion reactions, the commonest of which were fever, chills and/or modest changes in the blood

pressure [8]. In the same study, 20% of the recipients and less than 5% of the transfusions were associated with grade 3–4 reactions, such as hypoxia, tachycardia, hypotension and allergic reaction. There were no deaths attributable to GTX and no significant association between the granulocyte dose administered and the occurrence of a transfusion reaction. In New Zealand, reporting of transfusion reactions is voluntary, which may lead to under-reporting. Our observed rate of transfusion reactions for fresh components is 2% from audits of over 1000 transfusion episodes, whereas our reported rate via the haemovigilance program is 0.3%. Transfusion reactions associated with GTX are, however, less likely to have been unreported compared with those associated with other fresh components as provision of therapeutic granulocyte products demands close communication among the treating clinicians, the transfusion medicine specialists and the NZBS staff during the treatment course.

There are potential ethical and safety concerns pertaining to exposing healthy volunteer donors to medications, such as G-CSF and dexamethasone, for mobilization of granulocytes. Quillen et al. followed 83 out of 92 apheresis granulocyte donors who received three or more doses of G-CSF at 5 mcg/kg and 8 mg of oral dexamethasone between 1994 and 2002 for a median follow-up period of 10 years. They compared the health outcomes of these granulocyte donors with matched control platelet donors and found there was no difference in the incidence of malignancies, coronary artery disease and thrombosis [13]. To our knowledge, there is no definite evidence in the current literature that a short-term use of G-CSF and dexamethasone leads to any significant long-term morbidity or mortality. These medications, however, still have potential side effects, such as bone pain, tenderness at the injection site, transient hyperglycaemia and so forth. Therefore, it is important to counsel the potential donors carefully before obtaining their informed consent.

Improvements in diagnostic strategies, antimicrobial therapy and supportive care in modern medicine have reduced the perceived need for GTX, and there is lack of strong evidence for GTX in treating neutropaenic patients with severe infection; a limited number of published randomized trials were underpowered to demonstrate potential benefit of GTX owing to small sample sizes and slow recruitment. As the latest 2015 Cochrane review has concluded, there is also not enough evidence to refute the benefit of GTX, and there are case series and anecdotal evidence that show potential benefit of GTX; hence, it seems premature and scientifically unjustified to dismiss therapeutic utility of GTX entirely [9, 14]. We believe GTX should be considered in critically unwell patients with severe neutropaenia or neutrophil dysfunction who fail to respond to conventional antimicrobial or antifungal therapy and surgical measures to control an infective source but otherwise have good long-term prognosis from their underlying diagnoses. Without firm evidence directing the clinicians and patients in one way or another, full discussion should be held with regards to the potential benefits and risks of GTX, and the controversial nature of the treatment before a consensus decision is reached for each patient. It is essential that such a decision is made promptly so that the search for suitable donors can begin without delay and GTX can be delivered in a timely manner at an appropriate dose, before the patient is in extremis.

Our study has a number of limitations. It is a retrospective data analysis, and the data quality was dependent on the availability and completeness of historic documentation. The number of subjects included in this study is small although we were able to capture all patients who received GTX during the study period by virtue of the presence of a single national electronic platform for patient blood management. There is no comparison group because we anticipated it would be difficult to define a matched historic control group as the GTX recipients included in this analysis were a heterogeneous group with varying underlying diagnoses, different types of infections and a wide range of baseline neutrophil counts.

In order to prove or refute the clinical benefit of GTX in septic patients with severe neutropaenia or neutrophil dysfunction, a randomized controlled trial with an adequate power is needed. Such efforts to date have been hindered by failure to enrol enough participants to achieve an adequate power. The next best approach would be to set up an international prospective registry of therapeutic GTX, so the outcome data can be collected in a much larger scale. The Biomedical Excellence for Safer Transfusion (BEST) Collective has set up a web-based international collaborative registry of GTX [15]. NZBS has been working with this international registry to establish participation since 2018. It is anticipated that as the Registry data matures over time, more information will become available to shed more light on real-life experience in therapeutic use of GTX and trend in clinical outcome.

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