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Granulocyte Transfusions For Patients With Neutropenia: Current Status

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History: Polymorphonuclear leukocytes (PMN), commonly referred to as granulocytes, are critical for controlling bacterial and fungal infections, the risks of which rise steeply at PMN levels ≤500/μL. Thus, the theoretical rationale for providing granulocyte transfusion (GTX) to neutropenic patients is clear. The historic limitation of GTX was the inability to collect physiologically relevant doses, and proof of efficacy has been elusive. This shortcoming was first addressed in the early 1970s by using continuous flow centrifugation apheresis, donor stimulation with corticosteroids, and efficient cell separation facilitated by hydroxyethyl starch (HES) as a red blood cell (RBC) sedimenting agent. By then, doses of ~2-3 x 10^{10} PMN were attainable. Controlled trials and observational studies (both of generally low power and/or rigor) had conflicting outcomes, with clinically relevant responses limited by the actual doses transfused and recipient side effects, e.g., fevers, pulmonary toxicity, and CMV transmission. With the exception of a few centers, GTX was essentially abandoned in the face of increasingly potent antimicrobial regimens and increasingly effective basic supportive care.[1-3]

Interest in GTX revived after the advent of granulocyte colony stimulating factor (G-CSF), which induces marked increases in PMN counts and leukapheresis yields, along with the evolution of increasingly drug resistant pathogens. Using large-volume leukapheresis of donors stimulated with G-CSF and steroids generally allows collection of 6-8 x 10^{10} PMN/procedure, and their infusion results in significant increments in circulating PMN counts. The Resolving Infection in Neutropenia with Granulocytes trial (RING) was a randomized controlled trial of antimicrobial therapy vs. antimicrobial therapy + GTX in patients with neutropenia from chemotherapy or hematopoietic stem cell transplant (HSCT). The primary outcomes measured were survival and blinded adjudication of antimicrobial responses. No overall benefit from GTX was apparent, but low accrual (half of that planned) compromised the study's power. Post-hoc secondary analyses suggested that higher doses were effective. Significant improvement in a composite primary endpoint and in survival ($p<0.01$ and 0.02 respectively) were seen when high-dose transfusions (mean ≥0.6 x 10^9/kg) were compared to lower mean doses; however, the transfused dose was not independent of the enrollment site, so these data are confounded.[4] We remain at clinical equipoise after RING and it is unlikely that a definitive trial is forthcoming—thus, the use of GTX remains a risk-benefit exercise based on clinical judgment.

Key Points

- The best available data (RING Trial), while NOT establishing the efficacy of granulocyte transfusion (GTX), were compromised by inadequate study enrollment.
- *Post-hoc* secondary endpoints from RING suggest that "high" doses (in the range actually targeted for use) were clinically useful in recipients enrolled in that study.
- In patients with time-limited neutropenia and bacterial or fungal infection unresponsive to optimal antimicrobial therapy, GTX from stimulated donors may be considered.
- Prophylactic GTX is not generally recommended absent evidence of effectiveness.
- The agents used to stimulate and enhance the efficiency of collections are safe for qualified donors.

Indications: Requests for GTX optimally involve the attending physician along with infectious disease and transfusion medicine consultation in close coordination. Healthy donors of PMN require rigorously timed and expensive stimulation and collection procedures, so requests for GTX must be scrutinized critically. Recipients should have a PMN count of ≤500/μL (with an exception for PMN functional defects like chronic granulomatous disease, not further considered herein). There also must be: (1) clear evidence of bacterial or fungal infection after comprehensive clinical, imaging, microbiologic and/or pathologic evaluation, and (2) an inadequate response to appropriate empiric or definitive antimicrobial therapy over an interval dictated by clinical urgency (e.g., 48 hours in hemodynamically stable patients). Recipients not expected to recover marrow function generally should not be considered as candidates for GTX. Most recipients have hematologic malignancy being treated with aggressive chemotherapy and/or have undergone HSCT. There is significant experience in aplastic anemia demonstrating the feasibility of GTX, with outcomes closely associated with hematologic recovery under immunosuppressive therapy.[5] Septic neonates develop neutropenia from "storage pool depletion" and have received GTX, though the evidence for their efficacy is of generally low quality and they are impractical in this setting.[6]

Prophylactic GTX is in general disfavor due to lack of confirmed clinical advantages sufficient to balance risks to both donors and recipients, but the quality of the evidence is

suboptimal.[7]

Donor stimulation: Given consistent, if not rigorous, evidence that clinical outcomes are correlated with the transfused dose, donor stimulation is a cornerstone of contemporary GTX.[1,4] When done optimally, this allows collection of doses up to ~1 x 10^{11} cells, approaching normal daily production—though still well short of production under the stress of active infection—and dictates the use of G-CSF (with or without corticosteroids) for all collections (with a possible exception for some neonatal/pediatric indications where unstimulated donors may be adequate). Stimulatory doses have been empirically chosen based on the kinetics of granulocyte release from the bone marrow. They result in ~10-fold and greater increases in PMN counts compared to unstimulated donors. Combining G-CSF with steroids is additive. Stimulated donors often experience self-limited headache, arthralgia, bone pain, fatigue, and difficulty sleeping. No long-term side effects are recognized. HES is associated with modest fluid retention, headaches, pruritus, and a prolongation of the aPTT.

Of unknown clinical significance are observations that stimulated PMNs survive longer and have improved functional performance compared to cells from unstimulated donors on assays of antimicrobial activity, e.g., migration, respiratory burst in response to agonists, phagocytic ability, and bacterial killing.[1]

Donor selection and collection: Donors must make a substantial time commitment and be ABO/RhD compatible (GTXs contain 20-50mL of RBCs). They are recruited from experienced, recently tested (ideally within 30 days of collection) repeat donors (generally apheresis). This minimizes procedures lost to donor reactions and reactive donor tests and facilitates timely availability of the product. Alternatively, qualified friends and family of the intended recipient are used as donors. Human leukocyte antigen (HLA) and/or human neutrophil antigen (HNA) matching is not routinely performed, but may be of use in sensitized recipients known to be alloimmunized to leukocytes or with poor responsiveness to platelet transfusion. Stimulation with one 480 µg vial of G-CSF subcutaneously, along with ~8 mg of oral dexamethasone, was administered in RING, anticipating maximal neutrophilia after about 12 hours. Continuous flow centrifugation apheresis was performed at 8-16 hours after stimulation in RING. Given this sequence, GTX is clearly not a stat procedure.[1] RING collections were targeted to collect a dose of ~0.6 x 10^9 cells/kg (4 x 10^{10} for a 70 kg recipient) during procedures lasting 2.5-3 hours, processing 7-10 liters of whole blood. Cytomegalovirus (CMV)-seronegative donors were used for CMV-negative recipients.[2] GTX products must be irradiated for graft-vs.-host disease prophylaxis. The final volume, including anticoagulants and residual plasma, is generally 200-300 mL (sometimes somewhat higher depending on the apheresis instrument used).

Donor side effects, other than those noted above related to G-CSF stimulation and sedimentation agents, are generally the same as those for plateletpheresis. The most common is symptomatic hypocalcemia related to citrate anticoagulants. Vascular and nerve injuries from needles are rare, but do occur. The time burdens—e.g., often separate trips for initial donor education and routine donor testing, one for administration of G-CSF and the third for the collection and recovery—multiply when a donor is used for repeated collections over days or weeks.

Storage and transfusion: Granulocytes are not licensed by the Food and Drug Administration. They are stored at 20-24ºC without agitation.[8] GTX, using a standard blood infusion set, is performed as soon as possible after collection and irradiation, but in all cases before 24 hours after collection to avoid deterioration of PMN function. Pre-transfusion testing is performed as for RBCs. 2500 cGy of gamma or x-ray irradiation must be applied to inactivate contaminating lymphocytes that can engraft and cause transfusion-associated graft-vs.-host disease (this dose does not affect PMN function). Leukocyte reduction and microaggregate filters must not be used as they remove PMNs. Daily GTX is generally continued until recovery of peripheral PMN counts to >500/µL, usually for 5-7 days, but sometimes for weeks. Monitoring includes in-product PMN counts and pre- and post-transfusion PMN counts from recipients.

Recipient side effects: As many as half of GTX recipients have mild to moderate reactions, most often fever, chills, and/or allergic signs and symptoms. Accordingly, many clinicians pre-medicate using antipyretics with or without antihistamines. Respiratory reactions, including TRALI and TACO, may occur, but the previously alleged association of these reactions with amphotericin B infusions appears to have been spurious. Alloimmunization to HLA and HNA antigens can occur and complicate future transfusion therapies. Transfusion-transmitted infections are rare with contemporary testing and monitoring and preemptive treatment for CMV infection.

Assessing response and discontinuing GTX therapy: PMN increments are used to assess the immediate response and to plan for future doses. The clinical, laboratory, and radiographic studies used to justify GTX should be repeated at appropriate intervals to assess the status of the infection being treated. Stopping GTX is a clinical judgment based on evidence of control and resolution of the target infection and return of the recipient's endogenous PMN count to ≥500/µL. If the patient worsens despite GTX and/or the clinical team opts for palliative care, as opposed to active treatment of the underlying disease, transfusions should be stopped. Lack of donors can complicate provision of GTX as well.

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