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Are Granulocyte Transfusions Helpful in Treating and Preventing Infections?

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A. Introduction

"Can granulocyte transfusions (GTX) treat and prevent infections?" Clearly, the answer is "yes"! Should all patients, then, with severe neutropenia (< 500 neutrophils/μl blood) receive therapeutic GTX to treat bacterial infections – or if free of infections, receive prophylactic GTX to prevent infections? Most emphatically, the answer is "no"! In this report, the literature will be reviewed as it pertains to the use of therapeutic and prophylactic GTX as supportive care for severely neutropenic patients. Conclusions of the review are:

1. Therapeutic GTX definitely should be used to treat episodes of gram-negative septicemia that have failed to respond to optimal, combination antibiotics.
2. Therapeutic GTX probably should be used to treat documented bacterial or fungal infections of other types under similar circumstances.
3. Prophylactic GTX should not be used except in investigational settings. However, renewed considerations might be given to conducting studies of prophylactic GTX in certain clinical settings.

B. Therapeutic Granulocyte Transfusions

A total of 24 papers pertaining to the use of therapeutic GTX in neutropenic patients were analyzed [1–24]. The role of therapeutic GTX has been extensively reviewed recently [25–30], and this paper will not reiterate an exhaustive discussion. Instead, data will be combined and analyzed collectively. Patients from all 24 papers who were treated with GTX for specific types of infections are displayed in Table 1 together with the results of therapy. When drawing conclusions, several limiting factors must be kept in mind: (a) except for patients with culture-proven septicemia, diagnostic criteria for each type of infection varied; (b) only the index infections which prompted GTX are listed (additional infections recognized during therapy or postmortem were not tabulated); (c) with the exception of septicemia, it was impossible to study the response of individual categories of infections caused by specific types of organisms; and (d) criteria to judge clinical response varied and eventual outcome could not always be ascribed to the course of the index infection. All patients who received therapeutic GTX were tabulated in the "treated" column (Table 1), but only those whose course and mortality could be clearly documented were included in the "evaluable" column. Criteria for "favorable response" included absence of fever, sterile blood cultures, clearing of chest roentgenograms, disappearance of skin inflammation, and survival.

Many patients with septicemia have been reported (Table 1). Important information has been learned from the study of gram-negative sepsis in recipients of therapeutic GTX. Investigators agree that most septic patients will recover with antibiotics alone

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Table 1. Pooled results of 24 studies of therapeutic GTX

Types of infections	Treated	Evaluable	Favorable response[a]
Total septicemias[b]	435	247	146/247 (59)
Gram-negative sepsis	238	172	103/172 (60)
Gram-positive sepsis	44	18	16/18 (89)
Polymicrobial sepsis	15	15	7/15 (47)
Fungemia	6	3	–
Sepsis organism unspecified	132	39	18/39 (46)
Total pneumonias	130	45	23/45 (51)
Gram-negative	3	–	–
Gram-positive	1	–	–
Polymicrobial pneumonia	1	–	–
Fungal pneumonia	10	9	1/9 (11)
Pneumonia organism unspecified	115	11	7/11 (64)
Total localized infections[c]	142	48	–
Cellulitis-abscess	76	38	32/38 (84
Genitourinary	11	8	6/8 (75)
Total fever of unknown origin	184	85	64/85 (75)

[a] Number with favorable response/total number evaluable (percentage)
[b] All septic patients included (patients with septicemia plus a localized infection are listed here, not under the localized infection)
[c] Infections of skin, pharynx, genitourinary and gastrointestinal systems. Detailed data tabulated only for cellulitis–abscess and genitourinary categories

if they experience bone marrow recovery during the early days of infection [1, 10, 11, 23, 24]. Such patients do not require GTX. In contrast, patients with persistent, severe neutropenia due to continuing marrow failure may [11] or may not [24] benefit when GTX are added to antibiotics. It should be noted that only 36% of nontransfused, control patients (antibiotics only) in the first study [11] survived, whereas, 72% of controls survived in the last [24]. Thus, it was fairly easy in the first [11], and impossible in the last [24], to demonstrate a significant benefit from the added effects of therapeutic GTX. The greatest benefit of therapeutic GTX is apparent in patients with persistent marrow failure [1, 11, 23].

Regarding other types of septicemia and other kinds of infection (Table 1), information published to date is insufficient to determine whether therapeutic GTX offer advantages over antibiotics alone. Patients with pneumonia, localized infections, and fever of unknown origin responded well to GTX. However, comparable responses have been reported using antibiotics alone.

Because of the clinical complexity of these heterogeneous patients, seven controlled studies were performed (Table 2). The response of infected, neutropenic patients to treatment with GTX plus antibiotics was compared with that of nontransfused, control patients given antibiotics alone and evaluated concurrently. Three of the seven studies found a significant overall benefit for GTX [11, 12, 23]. A fourth study [1] found a significant improvement in survival only for the subgroup of GTX recipients who did not have early endogenous marrow recovery. It must be emphasized, however, that patients in these reports were selected by study design to be unusually ill. Thus, information provided may not be directly applicable to many neutropenic patients encountered in practice. For example, in three studies [7, 12, 23] patients were eligible to receive GTX only after failing 48–72 h of antibiotic

Table 2. Seven controlled therapeutic granulocyte transfusion trials

Reference	Randomized	Patients entered		Percentage septic	Percentage survival	
		Transfused	Controls		Transfused	Controls
[8]	No	39	37	100	46	30
[11]	Yes	13	14	100	75[a]	36
[12]	Yes	17	19	31	76[a]	26
[7]	No	17	22	34	78	80
[23]	Yes	17	13	67	59[a]	15
[1]	Yes	12	19	39	82[b]	62
[24]	Yes	48	47	80	63	72

[a] Survival of transfused patients significantly ($P < 0.05$) greater than controls
[b] Survival was improved in the subgroup of patients who did not have endogenous marrow recovery

therapy. As another factor, many patients had cancer resistant to therapy and, as expected, GTX were able to prolong life in these terminal patients with persistent marrow failure. In practice, however, it is difficult to justify therapeutic GTX as a routine part of palliative therapy offered to terminal patients for whom there is no effective anticancer therapy. Finally, antibiotic therapy in the controlled studies may not have been optimal by current standards. Antibiotics chosen and doses employed were recorded, but in only one study [24] was there an indication that proper precautions (antibiotic blood levels, serum bacteriostatic/bactericidal activity, or sensitivity testing designed to detect antibiotic synergism) were employed to ensure adequate antibiotic therapy. As reviewed in references [25] and [26], the survival of cancer patients with sepsis is significantly better in patients receiving antibiotics deemed appropriate than it is in those given ineffective therapy. Perhaps GTX are most likely to benefit patients whose infecting bacteria are being inadequately treated by antibiotics [31, 32]. Certainly (Table 2), survival of the nontransfused controls was inferior in the studies showing an overall benefit for GTX [11, 12, 23] when compared with the better survival of controls in the studies unable to demonstrate an advantage for GTX.

Despite these reservations, a number of conclusions can be drawn from the therapeutic GTX trials published to date. Clearly, some neutropenic patients die from bacterial infections, despite the most skilled use of combination antibiotics. Among these patients, therapeutic GTX have improved the survival of those with persistent, severe neutropenia who have gram-negative sepsis that fails to respond to antibiotics. It is likely that similar patients with other types of documented bacterial infections will also benefit from GTX, but efficacy has not been proven. On the other hand, therapeutic GTX have never been shown to be efficacious for treating nonbacterial infections or for fever of unknown origin. Unquestionably, the return of bone marrow function early in the course of a bacterial infection is usually associated with resolution of that infection, whether or not GTX are added to appropriate antibiotics. However, nearly all patients with persistent marrow disease eventually die, either from the index infection or from a later one.

C. Prophylactic Granulocyte Transfusions

Eleven studies that pertain to prophylactic GTX were reviewed (Table 3). Five were randomized studies attempting to prevent infections in leukemic patients [33–37]; three additional studies of leukemic patients were controlled, but not randomized [5, 38, 39]. Three reports were randomized studies of bone marrow transplant recipients [40–42]. One published report [43] was

not included because it was presumed to include the same patients reported by Clift et al. [40]; abstracts and letters were not included.

Data from the 11 studies are presented in Tables 3 and 4. Several qualifying statements are required for proper interpretation. The precise number of subjects in each group was difficult to determine in some studies because: (a) patients occasionally failed to complete the trial; (b) some "nontransfused" controls received therapeutic GTX; (c) patients may have been counted more than once if they experienced more than one course of remission induction therapy; (d) tabulation of infections varied considerably among investigators; and (e) authors' judgments regarding overall benefit were not always based on statistical significance, and contrasting results were sometimes noted when subpopulations of patients were analyzed separately.

Prophylactic GTX are considered by nearly all investigators to be of marginal value because the benefits are few while the risks and expenses are substantial (reviewed in references [26–30]). However, in two studies [34, 40], prophylactic GTX undeniably decreased the incidence of infections in severely neutropenic patients (Table 4). Of note, fairly large doses of granulocytes were infused daily in these studies, and efforts were made to optimize donor–recipient compatibility by HLA typing and/or leukocyte cross-matching (donors were excluded if recipient sera reacted with donor lymphocytes). Although

Table 3. Eleven studies of prophylactic granulocyte transfusions

Reference	Patients entered	GTX recipients	No GTX
Randomized leukemia			
[33]	18	9	9
[34]	50	22	28
[35]	92	49	43
[36]	65	29	36
[37]	24	13	11
Not randomized leukemia			
[38]	63	38	25
[5]	27	7	20
[39]	45	18	27
Randomized bone marrow transplants			
[40]	69	29	40
[41]	38	19	19
[42]	182	92	90
Total patients	673	325	348

Table 4. The success of prophylactic granulocyte transfusions

Reference	Dose	Matching
Definite success		
[34]	2.1 × 10 daily	LCT-negative[a]
[40]	1.5 – 2.2 × 10 daily	LCT-negative, HLA[b]
Partial success		
[35]	0.7 × 10 daily	None
[5]	0.07 × 10 ?	HLA
[39]	1.6 × 10 daily	HLA
[42]	? daily	HLA
Lack of success		
[33]	1.2 × 10 alternate day	None
[37]	1.5 × 10 alternate day	None
[36]	0.9 × 10 daily	None
[38]	2.6 × 10 twice weekly	LCT-negative, HLA
[41]	1.2 × 10 daily	None

[a] LCT-negative = Recipient sera negative for lymphocytotoxic antibody

[b] HLA = Donor and recipient at least haploidentical for HLA-A and HLA-B

Table 5. Incidence of immediate, nonhemolytic, febrile transfusion reactions

Reference	HLA matching	Reactions/course	Reactions/individual GTX
[35]	No	39/53 (72%)	158/987 = (16%)
[45]	No	Not reported	1233/6020 = (18%)
[37]	No	12/13 (92%)	Not reported
[33]	No	7/10 (70%)	Not reported
[36]	No	23/31 (74%)	Not reported
[41]	No	19/48 (40%)	Not reported
[23]	Yes[a]	0/17 (0%)	Not reported

[a] Donor-recipient compatible by leukocyte cross-match; recipients premedicated with diphenhydramine and acetaminophen

overall success could not be documented in four reports [5, 35, 39, 42], partial success was demonstrated when certain groups of patients were examined separately. Prophylactic GTX were found to decrease the incidence of bacterial sepsis [35], clinical infections (but not those proven by culture) [5], and pneumonia [39]. Success was implied in another study [42] since prophylactic GTX were equally effective as a comprehensive program of protected environment (laminar flow, etc.) in decreasing infections in bone marrow transplant recipients.

Five studies [33, 36–38, 41] failed to show benefit (Table 4). None of these studies provided both large numbers of granulocytes and granulocytes from matched donors. Among the nine studies that found only partial or no success, only one [39] provided at least 10^{10} granulocytes daily from donors selected by leukocyte matching (Table 4). Thus, the failure of prophylactic GTX trials published to date might be explained, at least in part, by transfusion of suboptimal granulocyte concentrates.

The other major deterrent to the widespread use of prophylactic GTX is concern for the risks involved. The use of GTX exposes both granulocyte donors and recipients to potential risks. The majority of granulocyte donors do not experience adverse effects, and even when they occur, they usually are of little consequence [44]. Despite their importance, hazards to donors will not be discussed further in this paper. Instead, the adverse effects of GTX experienced by recipients will be reviewed.

Immediate, nonhemolytic, febrile transfusion reactions occur during or within a few hours after transfusion, and are characterized by fever and chills. Other findings include cyanosis, dyspnea, wheezing, nausea, vomiting, itching, urticaria, anxiety, and fluctuations in blood pressure. The majority of patients can be expected to experience a reaction if they receive a course of several GTX from random donors (Table 5). The chance that an individual GTX will provoke a reaction is fairly small. Alloimmunization to leukocyte antigens is the most likely causative mechanism with transfused leukocytes interacting with anti-leukocyte antibodies in recipient sera. The lack of reactions in Table 23 of reference [23] supports this mechanism since donors were selected by HLA typing and by compatibility with leukocyte cross-match. However, reactions may have been masked as recipients were premediated prior to each GTX.

The incidence of alloimmunization following GTX, and the importance of emerging antibodies are only partly defined. Reports indicating the detection of anti-leukocyte antibodies in patients following GTX are listed in Table 6. At the present time, it is impossible to predict accurately the likelihood that an individual patient might become immunized during a course of GTX, or whether the antibody would have clinical importance. Several methods exist to detect anti-leukocyte antibodies and difficulties arise in comparing data from different laboratories. For example (Table 6), none of the patients of Cooper et al. [38]

Table 6. Prevalence of anti-leukocyte antibodies following GTX

Reference	HLA-matched donors	Antibodies detected[a]	(%)
[34]	No	7/23	(30)
[33]	No	7/10	(70)
[38]	Yes	0/14	(0)
[46]	No	23/26	(88)
[54]	No	13/22	(59)

[a] Subjects with antibody/total subjects studied (percentage)

were alloimmunized after receiving GTX from HLA-matched donors when antibodies were measured only by lymphocytotoxicity – a technique detecting primarily anti-HLA antibodies. In contrast, nearly all patients evaluated by Thompson et al. [46] produced anti-leukocyte antibodies in response to random donor GTX when studied by a battery of assays that were designed to detect antibodies directed against multiple lymphocyte and granulocyte antigens. Based on current knowledge, it seems likely that the majority of patients receiving a series of GTX from random donors will develop anti-leukocyte antibodies if their sera are evaluated by a battery of tests.

The importance of such antibodies is unclear. In animals [47, 48], immunization with blood products decreases the effectiveness of subsequent GTX. Post-transfusion increments of blood leukocyte counts were diminished, granulocyte function was impaired, thrombocytopenia was induced, and survival of immunized animals was decreased. Studies in humans are not as definitive, but data suggest that anti-leukocyte antibodies mediate transfusion reactions, adversely affect post-transfusion increments of blood leukocyte counts, alter the circulating kinetics of infused granulocytes, and decrease the antimicrobial effects of GTX. For example, Goldstein et al. [49] observed transfusion reactions following 90% of GTX administered to immunized recipients, while only 11% of GTX given to patients without anti-leukocytic antibodies evoked reactions. In contrast, Ungerleider et al. [50] studied 187 donor –recipient pairs with a battery of anti-leukocyte antibody assays. They were unable to establish a significant relationship between the presence of antibodies and either transfusion reactions or postinfusion neutrophil recovery. McCullough et al. [50] found the intravascular kinetics of transfused granulocytes to be altered adversely (decreased recovery, half-life, and migration to sites of infection with increased liver sequestration) by granulocyte agglutinating antibodies, but not by granulocytotoxic or lymphocytotoxic antibodies. Dutcher et al. [52] found transfused neutrophils to be sequestered in the lungs of alloimmunized patients. In additional studies, this same group [53] observed that radiolabeled leukocytes obtained from random donors failed to reach sites of infection in alloimmunized patients (defined by refractoriness to random donor platelets and the presence of lymphocytotoxic antibodies reacting against more than 20% of a lymphocyte panel). Dahlke et al. [6] noted decreased survival of patients with gram-negative septicemia, who received therapeutic GTX deemed to be incompatible by a granulocyte indirect immunofluorescence antibody assay, when compared with similar patients given more compatible GTX. Finally, pulmonary infiltrates are a serious complication that may be related to alloimmunization [3, 24, 35]. However, they can occur in patients not receiving GTX [24], and the exact mechanisms involved in individual patients are often unclear. Whether immediate, nonhemolytic, febrile transfusion reactions and pulmonary reactions can be consistently eliminated in individual recipients by HLA matching and leukocyte compatibility testing remains to be shown.

Other potential hazards of GTX do not pose major barriers to prophylactic GTX. The concern over fatal pulmonary reactions due to the interaction of GTX and amphotericin B [55] simply has not been confirmed by several other investigators (reviewed in reference [27]). However, it may be a useful practice to infuse amphotericin B during the morning and GTX during the late afternoon in patients receiving both agents. Graft-versus-host disease can be eliminated by irradiating granulocyte concentrates with 1500–5000 rads prior to

transfusion. Finally, transfusion-associated cytomegalovirus infections that arise in seronegative patients can be avoided by selecting donors who are likewise seronegative for anti-cytomegalovirus antibodies.

The following recommendations can be made. Based on current evidence, prophylactic GTX cannot be recommended for treating neutropenic cancer patients (except on an investigational basis) because the benefits are few and the risks and costs are substantial. Although still investigational because of the multiple complex issues involved, an argument can be made to support bone marrow transplant recipients with prophylactic GTX when granulocyte concentrates are obtained from HLA closely matched donors. Since many earlier prophylactic GTX trials can be criticized for transfusing small numbers of neutrophils, too infrequently, and without regard for leukocyte compatibility, consideration probably should be given to renewed investigations in this area using HLA-matched donors who produce good *platelet* increments (as a sign of compatibility). In such trials, prophylactic GTX should be discontinued if anti-leukocyte antibodies appear and/or if immediate, febrile transfusion reactions occur that cannot be eliminated with premedications. Granulocyte concentrates should contain $\geqq 1.5 \times 10^{10}$ and be given daily. Patients seronegative for anti-cytomegalovirus antibody should receive GTX from seronegative donors, and granulocyte concentrates should be irradiated. Obviously, careful comparisons of the costs of prophylactic GTX versus alternative therapies (e.g., protected environments) must be made, in addition to observations of efficacy and toxicity.

Note added in proof: Gomez-Villagran et al. (Cancer 54:734–738, 1984) reported prophylactic GTX to successfully decrease infections in leukemic patients when given as 1.24×10^{10} per day.

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