Antecedent Hyperglycemia Is Associated With an Increased Risk of Neutropenic Infections During Bone Marrow Transplantation

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OBJECTIVE — To use bone marrow transplantation (BMT) as a model for testing the association between hyperglycemia and infection.

RESEARCH DESIGN AND METHODS — This cohort study included 382 adults (6.5% with diabetes) who had no evidence of infection before neutropenia during BMT. Mean glucose was calculated from central laboratory and bedside measurements taken before neutropenia; the primary outcome was neutropenic infections.

RESULTS — Eighty-four patients (22%) developed at least one neutropenic infection, including 51 patients (13%) with bloodstream infections. In patients who did not receive glucocorticoids during neutropenia, each 10 mg/dl increase in mean preneutropenia glucose was associated with an odds ratio of 1.08 (95% CI 0.98–1.19) ($P = 0.14$) for any infection and 1.15 (1.03–1.28) ($P = 0.01$) for bloodstream infections, after adjusting for age, sex, race, year, cancer diagnosis, transplant type, and total glucocorticoid dose before neutropenia. In those who received glucocorticoids during neutropenia ($n = 71$), the adjusted odds ratio associated with a 10 mg/dl increase in mean glucose was 1.21 (1.09–1.34) ($P < 0.0001$) for any infection and 1.24 (1.11–1.38) ($P < 0.0001$) for bloodstream infections. There was no association between mean glycemia and long length of hospital stay, critical status designation, or mortality.

CONCLUSIONS — In a BMT population highly susceptible to infection, there was a continuous positive association between mean antecedent glycemia and later infection risk, particularly in patients who received glucocorticoids while neutropenic. Tight glycemic control during BMT and glucocorticoid treatment may reduce infections.

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Observational studies in a variety of inpatient populations suggest that hyperglycemia is associated with an increased prevalence of nosocomial infections (1–4). However, in many such studies, the study design leaves open the possibility that hyperglycemia was the consequence and not the cause of the infections.

Patients undergoing bone marrow transplantation (BMT) constitute an excellent study population for using observational data to evaluate whether inpatient hyperglycemia predicts infections. During BMT, infection-free patients are rendered neutropenic, after which they are at risk for developing infections. Additionally, in-hospital glycemia can be assessed for over a week before the onset of neutropenia, allowing for an unbiased estimate of a patient's glycemic status.

BMT is also a good setting to explore the impact of glucocorticoid use on the relationship between hyperglycemia and infections, since some but not all patients receive glucocorticoids during the neutropenic period for treatment of graft-versus-host disease. Glucocorticoid treatment for graft-versus-host disease during BMT has been associated with increased infections (5), an association that could be mediated, at least in part, by glucocorticoid-induced hyperglycemia.

In this study, we analyze data from patients undergoing BMT at the Johns Hopkins Sidney Kimmel Cancer Center between 2002 and 2006 to determine whether hyperglycemia before neutropenia onset increases the risk of infection, as well as long length of stay, critical status designation, and in-hospital mortality.

RESEARCH DESIGN AND METHODS

— Adult patients who underwent allogeneic or autologous BMT at the Johns Hopkins Sidney Kimmel Cancer Center between 1 November 2002 and 1 November 2006 were identified from a database. Of 449 records for review, 67 patients were excluded because neutropenia (absolute neutrophil count $<500/mm^3$) occurred within 2 days of hospital admission ($n = 32$), neutropenia did not develop at all during the hospitalization ($n = 6$), or an infection was diagnosed before the onset of neutropenia ($n = 29$). The remaining 382 patients became the subjects of our study.

Each subject's age, sex, race, cancer diagnosis, BMT protocol used, and admission and discharge dates were obtained through the hospital billing database. The presence or absence of diabetes before hospital admission was determined by investigator review of the admission note and the list of home medications. The date of neutropenia onset was defined as the date during hospitalization when the absolute neutrophil count fell to $<500/mm^3$.

Glycemic assessment

Our subjects had a total of 20,026 glucose measurements during their hospital stays, which were downloaded from available databases, including results measured by

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the central laboratory (n = 17,139) and via point-of-care testing (n = 2,887). Central laboratory glucose measurements, available for 100% of the cohort, were typically performed daily in the early morning (between 12 and 3 A.M.). Capillary point-of-care glucose, available for 34% of the cohort, was routinely measured in patients with actual or suspected hyperglycemia; when ordered, it was usually performed by the nursing staff four times per day (before meals and at bedtime). The point-of-care glucose meter converted capillary glucose results to plasma glucose equivalents. If two glucose results were recorded for a single patient within 1 h, the latter result was excluded in order to avoid introducing bias from repeated testing of extreme glucose readings (n = 900). The primary exposure variable, mean glycemia between admission and neutropenia, was calculated for each patient by averaging all eligible glucose values measured between admission and 8 A.M. on the date of neutropenia. A secondary analysis was performed, in which preneutropenia mean glucose was calculated from central laboratory values only.

Clinical outcomes

Before the collection of patients' glucose records, the investigators abstracted clinical outcomes using the electronic patient record, which holds all laboratory, microbiology, and radiographic data. Clinicians routinely monitor patients closely for infections during the neutropenic period. Infections were included if they occurred between the onset of neutropenia and hospital discharge. The definition of bloodstream infection was one positive blood culture (two, in the case of coagulase-negative *Staphylcoccus*). Urinary tract infection required a positive urine culture with >100,000 colonies. Pneumonia was defined as a new infiltrate on a chest radiograph or computed tomography scan and either a positive sputum culture or information in the discharge summary indicating clinical improvement with antibiotic treatment. Sinusitis was diagnosed if there was computed tomography evidence of a sinus infection and documentation that the medical team suspected the infection was pathogenic. Finally, *Clostridium difficile* colitis was defined as stool toxin positivity. A subject was deemed as having "any infection" if any one of these infections was diagnosed in the period between neutropenia and discharge.

Other outcomes collected from the electronic record were hospital length of stay (days between admission and discharge or death) and mortality during hospitalization. Finally, critical status designation was recorded from the oncology center database and was defined as the need for arterial line monitoring, Swan-Ganz catheterization, continuous venovenous hemodialysis, or intubation during the hospital admission.

Statistical analysis

Mean glucose results for subgroups were reported as median and interquartile range (25th to 75th percentile) because their distributions were nonnormal. Nonparametric methods, the Wilcoxon rank-sum test, and the Kruskal-Wallis test were used to test the null hypothesis of no difference in mean glycemia between two subgroups and among multiple subgroups, respectively.

Analyses were conducted using a prospective approach, in which the independent variable was mean glucose and the dependent variable was infection. Based on nonparametric graphs (using Lowess Smoother techniques) that demonstrated a continuous relationship between mean preneutropenia glucose and the probability of neutropenic infections, rather than a threshold effect, mean preneutropenia glycemia was treated as a continuous variable in the analysis. Multiple logistic regression was used to test the null hypothesis of no association against the alternative of a linear relationship between inpatient glycemia and the log odds of infection, after controlling for potential confounders including age, sex, race, type of cancer, BMT type, and cumulative glucocorticoid dose given before neutropenia. Because glucocorticoids could exacerbate both hyperglycemia and infection risk, we tested whether glucocorticoid use during neutropenia modifies the effect of mean glycemia on infections. Multiple logistic regression was also used to evaluate the effect of hyperglycemia on the dichotomous outcomes long length of stay (defined as >75th percentile or >28 days), critical status designation, and in-hospital mortality.

RESULTS

Patient characteristics

Neutropenia developed after a mean of 9.3 days after admission. Subjects had a median of 11 (range 4–177) glucose readings during the preneutropenic period, and the median of subjects' average preneutropenia glucose was 108 mg/dl (83–255). Approximately half the patients were aged <50 years and had significantly lower mean preneutropenia glucose than those aged >50 years (Table 1). Few patients (6.5%) had a history of diabetes, and the median of these patients' mean preneutropenia glucose was 172 vs. 107 mg/dl in the group without diabetes. Nearly half of the patients underwent BMT for non-Hodgkins lymphoma, and the majority had an autologous transplantation. There was no statistically significant difference in mean preneutropenia glucose across diagnoses or transplant types. The vast majority of patients (94%) received some glucocorticoids during the preneutropenic period, with the most typical regimen being 20 mg/day dexamethasone on hospital days 5–8 (received by 63% of patients). However, glucocorticoid use during neutropenia was less common, with only 71 subjects (19%) receiving any glucocorticoids during this period. Those treated received a mean dose of 16 mg of dexamethasone for an average of 9.5 days.

Neutropenic infections and other adverse outcomes

After neutropenia developed, 84 patients (22%) had at least one documented infection (Table 2). Bloodstream infections were most common, occurring in 51 patients (13%). Thirty-four (67%) bloodstream infections were due to gram-negative organisms, 16 (31%) to gram-positive organisms, and one to a fungal pathogen. The most frequent bacteria cultured were *E. coli* (n = 17), coagulase negative *Staphylococcus* (n = 9), and *Pseudomonas aeroginosa* (n = 7). The diagnosis of infection was made an average (±SD) of 9.0 ± 9.1 days after neutropenia developed, supporting the notion that they were new, not previously established, infections.

The mean length of stay was 26.1 ± 9.7 days. Critical status was designated for only 15 patients (4%), for reasons including intubation (n = 12), need for arterial monitoring (n = 7), continuous venovenous hemodialysis (n = 3), and pulmonary artery catheterization (n = 1). Thirteen patients (3%) died during their hospital stay. In an unadjusted analysis, there was a statistically significant difference in mean preneutropenia glucose between affected and nonaffected patients for the outcomes any infection and bloodstream infections (P = 0.014 and P = 0.007, respectively) but not for other

types of infections, long hospital stay, critical status, and in-hospital death (Table 2).

Independent effect of hyperglycemia on infection risk

After adjusting for age, sex, race, cancer type, transplant type, year of transplant, and total glucocorticoid dose received before neutropenia, antecedent hyperglycemia was significantly associated with an increased rate of infection. The odds ratio for any infection was 1.11 (95% CI 1.01–1.21) ($P = 0.023$) for every 10 mg/dl increase in mean preneutropenia glycemia (Table 3). This relationship between mean glucose and neutropenic infections was modified by glucocorticoid treatment during neutropenia. For every 10 mg/dl increase in mean preneutropenia glucose, the odds ratio for any infection in 311 patients who did not receive glucocorticoids while neutropenic was 1.08 (0.98–1.19) ($P = 0.136$), whereas the odds ratio in 71 patients who did receive steroids was 1.21 (1.09–1.33) ($P < 0.00001$). Figure 1*A* depicts the results of applying our multivariate logistic regression model for a subject with the most frequently encountered characteristics. In patients who received glucocorticoids during neutropenia, a preneutropenia mean glucose of 200 vs. 100 mg/dl was associated with a 6.5 times higher (95% CI 2.0–21.2) risk of infection.

The adjusted odds ratio associated with a 10 mg/dl increase in mean preneutropenia glycemia was even higher for bloodstream infections than for any infection, at 1.17 (95% CI 1.06–1.30) ($P = 0.002$) (Table 3). Effect modification by glucocorticoids was also significant for bloodstream infection, with an odds ratio of 1.15 (1.03–1.28) ($P = 0.010$) and 1.24 (1.11–1.38) ($P < 0.00001$) associated with every 10 mg/dl increment in mean preneutropenia glucose for patients who did not and did receive glucocorticoids during neutropenia, respectively. The odds ratio for bloodstream infection comparing subjects with a mean glucose of 200 vs. 100 mg/dl was 8.5 (2.4–30.2) if glucocorticoids were received and 4.0 (1.4–11.2) if they were not (Fig. 1*B*). The effect of preneutropenia glycemia on bloodstream infections due to gram-negative bacteria only was not significant (1.02 [0.90–1.17]). In a sensitivity analysis, we found all our results to be minimally changed when the primary exposure variable, mean preneutropenia glucose, was calculated using central laboratory plasma glucose results only and no point-of-care measurements.

Table 1—*Mean preneutropenia glucose according to demographic and clinical characteristics*

Characteristic	*n* (%)	Mean preneutropenia glucose [median (interquartile range)]	*P* value
Age			<0.0001
<50 years	194 (51)	105 (97–115)	
≥50 years	188 (49)	111 (102–128)	
Sex			0.181
Male	223 (58)	108 (101–122)	
Female	159 (42)	107 (98–119)	
Race			0.630
White	315 (82)	108 (100–120)	
African American	51 (13)	109 (99–125)	
Other	16 (5)	109 (102–132)	
Diabetes			<0.0001
Yes	25 (7)	172 (136–203)	
No	357 (93)	107 (100–117)	
Type of cancer			0.096
Aggressive non-Hodgkin's lymphoma	117 (31)	109 (101–126)	
Indolent non-Hodgkin's lymphoma	56 (15)	105 (101–120)	
Hodgkin's lymphoma	57 (15)	103 (94–117)	
Multiple myeloma	35 (9)	113 (99–126)	
Acute Leukemia	82 (21)	109 (103–121)	
Chronic leukemia	23 (6)	103 (98–115)	
Myelodysplastic syndrome	10 (3)	111 (108–115)	
Other	2 (0.5)	125 (113–136)	
Type of BMT			0.064
Autologous	225 (59)	109 (101–126)	
Matched sibling	134 (35)	106 (99–116)	
Matched unrelated	23 (6)	109 (99–114)	
Glucocorticoid treatment after neutropenia onset			0.120
Yes	71 (19)	107 (100–120)	
No	311 (81)	111 (103–127)	

Stratification for diabetes history

Among 25 patients with previously identified diabetes, 9 (36%) were diagnosed with any infection and 7 (28%) were diagnosed with bloodstream infections. A history of prior diabetes was independently associated with any infection and bloodstream infections with an adjusted odds ratio of 2.48 (95% CI 1.01–6.13) ($P = 0.049$) and 3.30 (1.22–8.93) ($P = 0.018$), respectively. Given that only six patients with prior diabetes received glucocorticoids during neutropenia, the interaction between mean preneutropenia glucose and glucocorticoids could not be tested within the diabetic subgroup. Diabetes history was not related to longer length of stay, critical status designation, or in-hospital mortality in this population with a low prevalence of diabetes.

Of 357 patients without previously diagnosed diabetes, 65 received glucocorticoids during neutropenia. In these glucocorticoid-treated patients, but not in subjects not receiving glucocorticoids, mean glucose was significantly associated with developing neutropenic infections after adjustment; for every 10 mg/dl increase in mean preneutropenia glucose, the adjusted odds ratio was 1.17 (95% CI 1.02–1.34) ($P = 0.027$) for any infection and 1.19 (1.02–1.38) ($P = 0.029$) for bloodstream infections.

CONCLUSIONS — Many studies (6–8) have reported an increased risk of infections in outpatients with diabetes; here, we demonstrate that in-hospital glycemia is also related to the incidence of nosocomial infections in a susceptible inpatient population. We report that even relatively mild, preexisting hyperglycemia was associated with increased infec-

Table 2—*Unadjusted association between mean glucose and major clinical outcomes*

Outcome	*n* (%)	Mean preneutropenia glucose [median (interquartile range)]	*P* value
Any infection			0.014
Yes	84 (22)	111 (103–130)	
No	298 (78)	107 (99–119)	
Bloodstream infection			0.007
Yes	52 (14)	114 (103–134)	
No	330 (86)	107 (99–119)	
Pneumonia			0.318
Yes	29 (8)	111 (103–126)	
No	353 (92)	108 (100–120)	
Urinary tract infection			0.136
Yes	8 (2)	116 (109–134)	
No	314 (98)	108 (100–120)	
Clostridium difficile colitis			0.275
Yes	12 (3)	112 (106–128)	
No	370 (97)	108 (100–120)	
Sinusitis			0.210
Yes	5 (1)	99 (96–109)	
No	377 (99)	108 (100–121)	
Long hospital stay*			0.734
Yes	287 (75)	108 (100–116)	
No	95 (25)	108 (100–121)	
Critical status			0.240
Yes	15 (4)	111 (99–125)	
No	367 (96)	108 (100–125)	
In-hospital death			0.728
Yes	13 (3)	113 (104–125)	
No	369 (97)	108 (100–120)	

*Long hospital stay is defined as >75th percentile (>28 days).

tions during the neutropenic phase of BMT. This relationship was particularly prominent in patients who received glucocorticoids while neutropenic. In these patients, the association remained significant even after excluding patients with prior diabetes who experienced the most hyperglycemia.

Acute, short-term hyperglycemia affects all major components of innate immunity and impairs the ability of the host to combat infection (9). Hyperglycemia is well known to adversely impair neutrophil activity, including chemotaxis, formation of reactive oxygen species, and phagocytosis of bacteria (10), but these effects may be less deleterious in BMT patients who are already neutropenic. However, hyperglycemia also affects other components of the immune system, thus providing ample mechanisms for the observed association between hyperglycemia and neutropenic infections. The diabetic state increases lymphocyte apoptosis (11) and suppresses the proliferation of T-cells due to decreased expression of adenosine kinase (12). Also, the function of immunoglobulins and complement is attenuated due to their glycosylation in the setting of hyperglycemia (13,14). Finally, hyperglycemia may promote the exponential growth of bacteria and increase the virulence of bacteria (15). For example, detectable levels of glucose in bronchial aspirates, observed in hyperglycemic but not normoglycemic patients, correlates with the presence of pathogenic bacteria (15).

The relationship between glycemia and infections has rarely been studied in oncology patients, though it is a particularly relevant question for this population given their immunocompromised state and increased risk for hyperglycemia secondary to frequent glucocorticoid use. A recent study (16) from Japan failed to detect an effect of hyperglycemia on infection during BMT. They had, however, a far smaller sample size and a paucity of glucose measurements compared with our study. In addition, they did not analyze mean glycemia as a continuous variable, and glycemia was evaluated during neutropenia, raising the question of cause and effect. Another study in BMT patients reported that total parenteral nutrition increased the adjusted odds ratio for infection to 2.2 (95% CI 1.4–3.5), a relationship that became insignificant after correction for mean glucose (17). This suggests that the association between total parenteral nutrition and infections may have been driven by total parenteral nutrition–induced hyperglycemia. Finally, a study of patients with acute lymphocytic leukemia undergoing induction chemotherapy (not BMT) did show a relationship between in-hospital hyperglycemia (defined

Table 3—*Adjusted odds ratio (95% CI) for complications associated with every 10 mg/dl increase in mean glucose between admission and neutropenia*

Complication	All subjects	Glucocorticoids administered during neutropenia	
		No	Yes
n	382	311	71
Any infection ($n = 84$)	1.11 (1.01–1.21); $P = 0.023$	1.08 (0.98–1.19); $P = 0.136$	1.21 (1.09–1.33); $P < 0.00001$
Bloodstream infection ($n = 52$)	1.17 (1.06–1.30); $P = 0.002$	1.15 (1.03–1.28); $P = 0.010$	1.24 (1.11–1.38); $P < 0.00001$
Long hospital stay ($n = 92$)*	0.96 (0.85–1.09); $P = 0.535$	0.89 (0.78–1.02); $P = 0.094$	1.08 (0.95–1.23); $P = 0.229$
Critical status ($n = 15$)	0.69 (0.42–1.13); $P = 0.141$	0.80 (0.61–1.06); $P = 0.119$	1.03 (0.84–1.28); $P = 0.752$
In-hospital death ($n = 13$)	1.08 (0.88–1.33); $P = 0.447$	0.84 (0.64–1.11); $P = 0.213$	1.13 (0.92–1.40); $P = 0.224$

Adjusted for age, sex, race, cancer diagnosis, transplant type, year of transplant, and cumulative glucocorticoid dose before neutropenia onset. *Long hospital stay is defined as >75th percentile (>28 days).

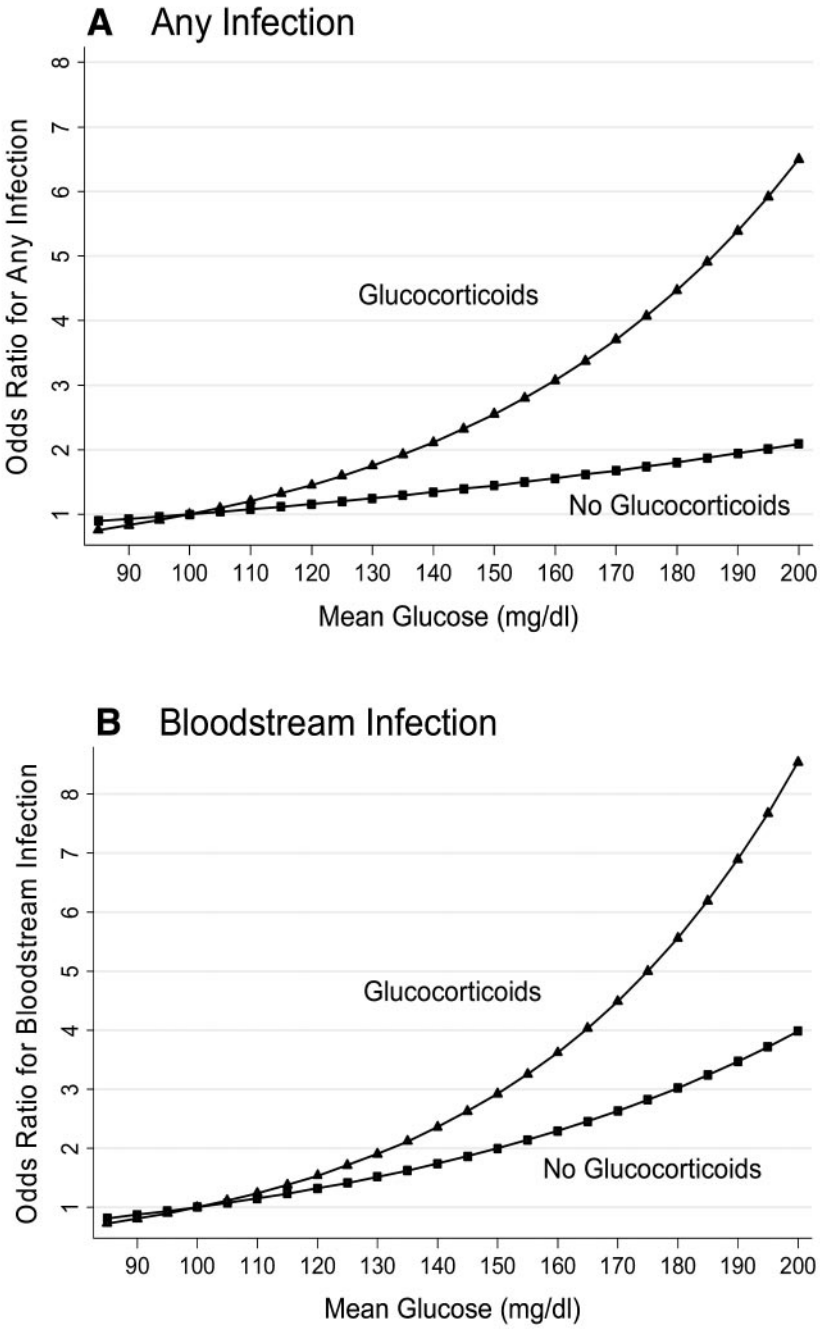

Figure 1—A: *Predicted odds ratios for any infection for increasing mean preneutropenia glucose compared with a mean glucose of 100 mg/dl.* B: *Predicted odds ratios for bloodstream infection. (▲), glucocorticoids received during neutropenia* (n = *71); (■), glucocorticoids not received during neutropenia* (n = *311). Odds ratios were calculated using multivariate logistic regression models, which included age, sex, race, cancer diagnosis, transplant type, year of transplant, and cumulative glucocorticoid dose before neutropenia onset. The values chosen for the covariates were the median in the case of continuous variables and the most frequent category in the case of categorical variables.*

as two or more glucose determinations >200 mg/dl) and infections (relative risk for any infection of 1.28) (*P* value = 0.009) (1).

Similar to results reported by Garg et al. (18), our data demonstrate a positive association between hospital length of stay and mean glucose readings performed throughout the entire course of BMT (*P* value <0.0001). However, when we focused on the preneutropenic period (before infection onset), we found that hyperglycemia was not associated with an increased length of stay (*P* = 0.351). Thus, it is likely that the association between higher mean glucose based on all hospital glucose values and longer length of stay is not causal but is observed because both result from more severe illness during neutropenia.

A main strength of our study is the study design, in which glycemic exposure was ascertained during a period of time when infections and other complications were not present, thereby increasing our ability to speculate that a causal relationship exists between hyperglycemia and infections. A second strength is our analysis of the interaction between hyperglycemia and glucocorticoid use on infections. While glucocorticoids are known to increase infection rates (19), the extent to which glucocorticoids modify the effect of hyperglycemia on infections has never before been examined.

Our study has some limitations. As with all observational studies, it is possible that unmeasured confounders affected the associations observed. However, we suspect such an effect would be minimal since we were able to adjust for many potential confounders and patients were otherwise relatively similar before neutropenia. Because the BMT population is relatively young and the prevalence of prior diabetes in our population was low, we were unable to evaluate whether the extent of hyperglycemia in patients with diabetes influences infection rates. Furthermore, in subjects without previously diagnosed diabetes, the lack of significant variation in preneutropenia mean glycemia likely decreased our ability to detect an association between glycemia and infections in this subgroup unless glucocorticoids were received. Additionally, our power to detect an effect of hyperglycemia on other outcomes (nonbloodstream infections, critical status designation, and death) was diminished by the low incidence of these outcomes in our study group.

In conclusion, our results suggest an important association between preneutropenia hyperglycemia and neutropenic infection rates during BMT, especially prominent in patients who receive glucocorticoids during neutropenia. The magnitude of this association is comparable with those seen with commonly utilized strategies for infection prevention during BMT, such as the use of prophylactic antibiotics, protective isolation, and high-efficiency particulate air filters (20–23). Our findings support the need

for trials that investigate whether intensive glycemic control improves infection rates in BMT patients and other high-risk populations.

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