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LETTER TO THE EDITOR

Risk of serious bloodstream infections is low in pediatric hematopoietic stem cell transplant (HSCT) recipients with fevers due to antithymocyte globulins and alemtuzumab

Owing to their immunomodulatory effects, antithymocyte globulins and alemtuzumab, commonly referred to as serotherapy (ST), are a common component of allogeneic hematopoietic stem cell transplant (HSCT) conditioning regimens.[1,2] Although the majority of patients receiving ST develop fevers and other adverse events (AE), there are no well-established practice guidelines for the management of ST-related fevers. We hypothesize that few ST-related fevers represent true bloodstream infection (BSI) and propose an evidence-based approach to antibiotic use in this population.

After obtaining IRB approval, we retrospectively collected data on 94 children receiving ST at our institution between July 2012 and April 2015. Data included transplant characteristics, ST-related AE (ST-AE), use of antibiotics and positive blood cultures (BC) during ST.

ST-AE were defined as new events starting during ST or within 72 h of its completion and comprised the following:

ST-related fever and rash: axillary temperature of $\geqslant 38\,°C$ starting within 24 h after any ST dose; hives starting on any day ST was given and resolving within 72 h of the last dose.

ST-related cardiovascular (CV) and respiratory AE: these were documented only if they required medical management (for example, fluid bolus, albuterol, pediatric intensive care unit (PICU) transfer, and so on). CV AE included heart rate or blood pressure, which were 2 s.d. outside of the normal for age, and were not related solely to elevated temperature. Respiratory AE included new upper (for example, angioedema) or lower (for example, wheezing) respiratory symptoms occurring on the days ST was used.

We documented all positive BC and antibiotics used from 48 h before ST until 30 days post HSCT. Following published Center for Disease Control/National Healthcare Safety Network (CDC/NHNS) criteria, a patient with a positive BC was considered to have a BSI if either a recognized pathogen was isolated or if two BC collected on the same or consecutive days were positive for the same commensal organism.[3]

All patients received standard pre-medication for ST consisting of dexamethasone, diphenhydramine, acetaminophen and ranitidine. Additional medications used as clinically indicated for the management of ST-related symptoms included hydrocortisone, methylprednisolone, albuterol, epinephrine and normal saline boluses.

All HSCT patients had indwelling central venous catheters (CVC), and management of fevers during ST followed published guidelines,[4,5] including daily BC from all CVC lumens and physical examination to determine the source of fever. If no localized signs of infection were found and ANC was $\geqslant 500\,/\mu L$, daily ceftriaxone was administered and continued until the patient was afebrile and the last obtained BC was negative for 48 h. If a patient had an ANC $< 500/\mu L$, broad-spectrum monotherapy or a combination of antibiotics was initiated per the treating physician's preference and continued until ANC recovery. In cases of documented BSI, antibiotic selection and length of therapy was guided by BC results in consultation with the infectious disease service.

ST regimens: Most (87/94) patients received one of the following four standard ST regimens, in combination with other chemotherapy or radiation therapy:

Alemtuzumab (Campath), used in 39.4% of patients, total dose of 1.5 mg/kg or 46 mg, whichever was lower, given over 3 days. Depending on the protocol, alemtuzumab was started between days − 14 and − 12.

Rabbit ATG (rATG) (Thymoglobulin), used in 26.6% patients, total dose 8 mg/kg over 4 days, on days − 4 to − 1.

Low dose rATG, used in 18.8% of patients, total dose 3.5 mg/kg over 4 days, on days − 4 to − 1.

Horse ATG (Atgam), used in 9.6% of patients, total dose 90 mg/kg, given on days − 3 to − 1.

Four other regimens, used in a total of 6 patients (6.4%), consisted of different doses of one of the above three agents.
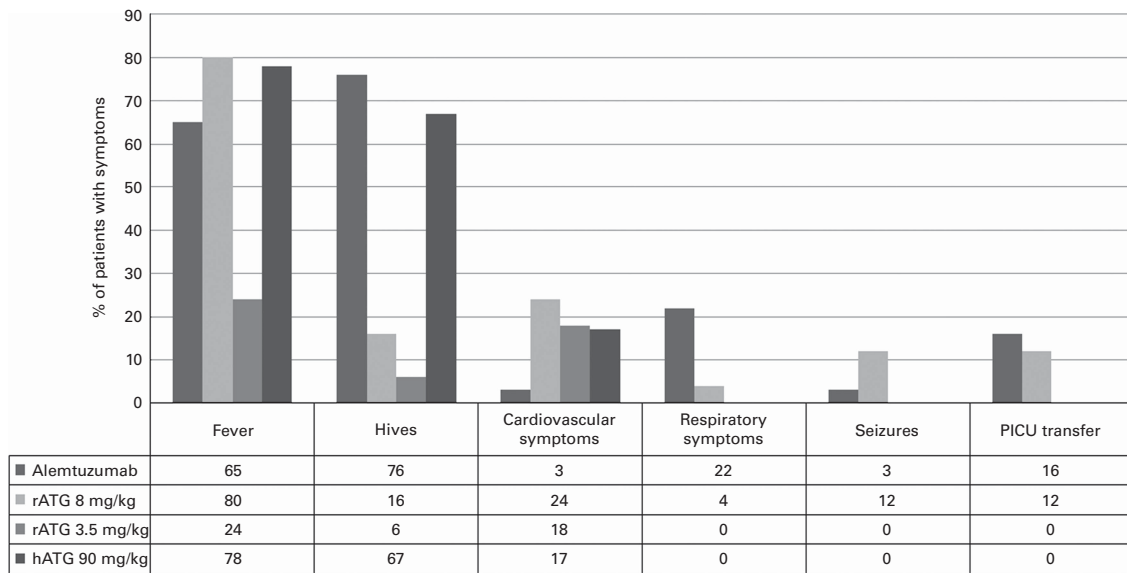
We used IBM SPSS version 23 statistical program for data analysis. Descriptive statistics and odds ratios with 95% CI are presented. Newcombe's[6] method was used for calculating confidence intervals for the single proportion.

Eighty-six patients were included in this study; eight patients received two different ST and conditioning regimens, resulting in a total of 94 ST and transplant episodes. Diagnoses included hematologic malignancies (47%), bone marrow failure syndromes (22%) and primary immune deficiencies (31%). Stem cell sources comprised bone marrow (33%), peripheral blood (62%) and cord blood (5%). Related or unrelated unmodified ($\geqslant 9/10$ HLA matched) HSCT was used in 85% and T-cell-depleted haploidentical HSCT from related donors in 15% of the cases. Three varieties of CVC were used: double-lumen tunneled CVC (81%), peripherally inserted CVC (8%) and multiple CVC (11%).

The most common AE by ST regimen are depicted in Figure 1. Sixteen (17%) patients had no AE during ST. Patients receiving low-dose rATG were less likely to have fevers or hives than other patients (odds ratio (OR) for fever 0.1 (95% CI 0.03-0.36), OR for hives 0.05 (95% CI 0.007-0.5)). Nine patients (10%) were transferred to the PICU during ST.

Thirty-two (34%) patients did not have any fever during ST, 3 (3%) were febrile prior to the first use of ST and 59 (63%) patients developed fever after the start of ST. Table 1 summarizes the characteristics, duration of fever and antibiotic use in 59 patients who developed a new fever during ST. The mean highest temperature during ST was $39.2 \pm 0.7\,°C$. The fever resolved within 48 h in 80% of patients; however, 54/59 (92%) received > 48 h of antibiotics. In 38/59 (64%) patients whose fever started during ST, antibiotics were discontinued before the ANC recovery, with a median length of antibiotic use of 72 h (range 24–120). Ceftriaxone was the most common empiric antibiotic coverage, used in 59% of ST-related fevers.

In patients with ST-related fevers, there were four true BSI and three false positive BC obtained during ST days. There were no episodes of Gram-negative BSI during ST. Only two of seven positive BC were obtained at the start of ST-related fever while five of seven positive BC were obtained on repeated daily cultures due

	Fever	Hives	Cardiovascular symptoms	Respiratory symptoms	Seizures	PICU transfer
■ Alemtuzumab	65	76	3	22	3	16
■ rATG 8 mg/kg	80	16	24	4	12	12
■ rATG 3.5 mg/kg	24	6	18	0	0	0
■ hATG 90 mg/kg	78	67	17	0	0	0

Figure 1. The most common adverse events by serotherapy regimen are depicted. Only 17% of patients did not have any adverse events. Patients receiving low-dose rATG were less likely to have fevers or hives than other patients.

Table 1. Fevers and antibiotic use during serotherapy

	N	%
Timing of new fever during serotherapy		
Started after the 1st dose of serotherapy	56	95
Started after the subsequent dose of serotherapy	3	5
Duration of serotherapy-related fever		
< 24 h	33	56
24–48 h	14	24
49–72 h	4	7
> 72 h	8	13
Length of antibiotic therapy initiated during serotherapy-related fever		
48 h	5	8
72 h	18	30
96 h	11	19
> 96 h but antibiotics discontinued	4	7
Antibiotics continued until the recovery of neutrophils after transplant	21	36
Type of antibiotic coverage		
Single agent (ceftriaxone)	35	59
Single agent (cefepime, vancomycin, piperacillin/tazobactam, cefotaxime)	8	14
Multiple antibiotics	16	27
Absolute neutrophil count on the 1st day of serotherapy		
< 500/μL	14	24
⩾ 500 /μL	45	76

to continued fevers. Among all episodes of ST-related fevers, new BSI was detected in 4/59 patients (6.7% (95% CI 2.7 – 16%)). In patients with ANC ⩾ 500/μL on the first day of ST, 2/45 (4.4% (95% CI 1.2 – 15%)) developed BSI during ST fevers, both caused by coagulase-negative staphylococci (CNS). Among 14 patients with fever and ANC < 500/μL, 2 (14% (95% CI 4 – 40%)) developed BSI during ST: one was caused by CNS and the other by nutritionally variant streptococci. There was a non-statistically significant trend toward greater odds of BSI in febrile patients during ST with ANC < 500/μL, compared with patients with ANC ⩾ 500/μL (OR 3.6 (95%CI 0.5 – 28)).

In all febrile patients, daily incidence of positive BC on ST days was 1.9% (95% CI 0.8–4.9%) for true BSI and 1.5% (95% CI 0.5–4.2%) for BC contaminants. In patients with ANC ⩾ 500/μL on the first day of ST, the daily incidence of true BSI was 1.3% (95% CI 0.4 – 4.5%), as opposed to 4.1% (95% CI 1.1 – 14%) in patients with ANC < 500/μL.

Data on the best management of fevers during ST infusion are scant.[7,8] In 95% of ST-related fevers, the fever started after the first ST dose. Fever resolved within 48 h in 80% of cases. The majority of patients (76%) had an ANC of ⩾ 500/μL at the time of initiation of ST. The daily incidence of BSI on ST days in patients with ST-related fever was 1.9% (95% CI 0.8 – 4.9%), with the daily incidence of false-positive BC at 1.5% (95% CI 0.5 – 4.2%). These findings were consistent with previously described incidences of new BSI obtained with repeat BC in persistently febrile neutropenic patients.[9] There were two true BSI among 14 patients with an ANC < 500/μL at the time of ST-related fever (14% (95% CI 4 – 40%)), which is similar to the 10 – 20% rate of BSI described in neutropenic oncology patients with a new onset of fever.[10,11] Regardless of the ANC at the start of ST, the majority of organisms identified as causing BSI in patients receiving ST were of low virulence, dominated by CNS, which is also a common BC contaminant.

In 1998, Dearden et al.[7] observed that febrile patients receiving anti-thymocyte globulin for therapy of aplastic anemia were less likely to have positive BC than febrile neutropenic patients with acute leukemia, and suggested that it may be reasonable to discontinue intravenous antibiotics early in clinically stable patients who have not had proven sepsis. We agree with Dearden's conclusion that it is reasonable to discontinue intravenous antibiotics early in HSCT recipients with ST-related fever, with a caveat that the number of patients with ANC < 500/μL at the start of ST was very small in our study.

In conclusion, the majority of organisms causing BSI in children receiving ST were of low virulence, dominated by CNS. No Gram-negative BSI were identified in our patient cohort. ST-related AE are often indistinguishable from sepsis, resulting in initiation of antibiotics in patients who develop fever during ST. However, once fever resolves, if the initial BC is negative and patients are clinically stable, empiric antibiotics could be discontinued, without waiting for the last BC to be negative for 48 h. If applied to our

historic cohort, this approach would have resulted in $\leqslant 48\,h$ of antibiotic use in ~80% as opposed to 8% of patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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