CLINICAL TRIALS AND OBSERVATIONS

Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the Children's Oncology Group

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Key Points

- Systemic antibacterial and granulocyte colony-stimulating factor prophylaxis appear to reduce bacterial infection rates.
- Mandatory hospitalization during profound neutropenia did not reduce infection or significantly reduce nonrelapse-related mortality.

Objective was to describe the effect of antibiotic and granulocyte colony-stimulating factor (G-CSF) prophylaxis and discharge policy on infection risk and nonrelapse-related mortality (NRM) during chemotherapy for children with acute myeloid leukemia. Patients were non–Down syndrome children enrolled on Children's Oncology Group (COG) trial AAML0531. We surveyed sites to determine institutional standards for systemic antibacterial, antifungal, and G-CSF prophylaxis, and mandatory hospitalization during neutropenia. COG institution survey response rate was 180 of 216 (83.3%). Of 1024 patients enrolled on AAML0531, 897 were non-Down patients from survey-responding institutions. In multiple regression, antibacterial prophylaxis reduced any sterile-site bacterial infection (incidence rate ratio [IRR] 0.85; 95% confidence interval [CI], 0.72-1.01; $P = .058$) and Gram-positive sterile-site infection (IRR 0.71; 95% CI, 0.57-0.90; $P = .004$). Prophylactic G-CSF reduced bacterial (IRR 0.79; 95% CI, 0.67-0.92; $P = .004$) and *Clostridium difficile* infections (CDIs; IRR 0.46; 95% CI, 0.25-0.84; $P = .012$). Mandatory hospitalization did not reduce bacterial/fungal infection or significantly reduce NRM but did increase CDI (IRR 1.96; 95% CI, 1.34-2.87; $P < .001$). Antibacterial and G-CSF prophylaxis reduced infection rates while mandatory hospitalization did not reduce infection or significantly affect NRM. This trial was registered at www.clinicaltrials.gov as #AAML0531. (*Blood*. 2013;121(18):3573-3577)

Introduction

Current therapies for pediatric acute myeloid leukemia (AML) are intensive and infections are responsible for considerable morbidity and most treatment-related deaths.[1,2] These factors have led to much interest in supportive care recommendations designed to reduce infections and infectious mortality. Three prophylactic strategies that have garnered much attention are prophylactic antibiotics with antibacterial and antifungal agents, prophylactic granulocyte colony-stimulating factor (G-CSF), and mandatory hospitalization during profound neutropenia.

Multiple randomized controlled trials of prophylactic antibiotics and G-CSF have been conducted in primarily adult cancer patients and have been summarized by meta-analyses. For example, Gafter-Gvili et al found that antibiotic prophylaxis decreased the risk of death (relative risk [RR] 0.67; 95% confidence interval [CI], 0.55-0.81), infection-related death (RR 0.58; 95% CI, 0.55-0.81), and microbiologically documented infection (RR 0.54; 95% CI, 0.49-0.60).[3] Another systematic review found that prophylactic colony-stimulating factors reduced all documented infection (rate ratio 0.85; 95% CI, 0.79-0.92), and microbiologically documented infection (rate ratio 0.86; 95% CI, 0.77-0.96).[4]

However, there are at least 2 sources of uncertainty in how to apply these results to children. First, there are far fewer studies conducted in children and it is unclear whether results of adult trials are applicable to pediatric patients. For example, there may be important differences between adult and pediatric fever and neutropenia.[5,6] Second, there are concerns that randomized trials may not be generalizable; observational studies may better reflect the impact of interventions on patients in real-world clinical practice, although they are susceptible to several sources of bias.[7,8] Consequently, results of both randomized and observational studies may be informative.

AAML0531 was a randomized phase 3 clinical trial conducted by the Children's Oncology Group (COG) that included children with de novo AML. Infections were collected and monitored prospectively to optimize reporting accuracy. Midway through the trial, we surveyed institutions to determine institutional supportive care policies. Consequently, we had an "intention-to-treat" measure of supportive care practices by COG institution and sought to determine how institutional policies toward antibacterial, antifungal, and G-CSF prophylaxis and mandatory hospitalization through profound neutropenia affected infections and nonrelapse-related mortality (NRM).

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Table 1. Characteristics in children with de novo AML enrolled on AAML0531 and treated at institutions who responded to the survey

	All patients, N = 897		Antibacterial prophylaxis, N = 115		Antifungal prophylaxis, N = 730		No discharge,* N = 573	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gender								
Female	455	51	72	63	370	51	277	48
Male	442	49	43	37	360	49	296	52
Age, y								
0-1	184	21	23	20	152	21	125	22
2-16	624	70	83	72	507	69	390	68
≥17	89	10	9	8	71	10	58	10
Race								
White	642	81	83	86	512	80	402	81
Asian	45	6	2	2	34	5	26	5
African American	105	13	10	10	88	14	67	13
Other	5	1	1	1	3	1	3	1
Unknown	100		19		93		75	
Weight group†								
Underweight	64	8	6	6	54	8	32	7
Middleweight	584	74	79	78	471	73	363	73
Overweight	139	18	16	16	117	18	100	20
Unknown	110		14		88		78	
FAB classification								
M0	18	2	2	2	18	3	16	3
M1	93	12	6	6	70	11	60	12
M2	180	24	30	32	142	23	104	21
M4	184	24	25	27	149	24	116	24
M5	167	22	24	26	135	22	116	24
M6	13	2	1	1	9	1	6	1
M7	42	6	3	3	39	6	29	6
AML NOS	48	6	2	2	43	7	29	6
Other/	12	2	1	1	10	2	9	2
Unknown	140		21		115		88	
Cytogenetic group†								
Favorable	210	24	24	22	161	23	121	22
Standard	621	72	84	76	512	73	411	75
Unfavorable	31	4	3	3	26	4	19	3
Unknown	35		4		31		22	

FAB, French-American-British; NOS, not otherwise specified.

*No discharge indicates institutions that never discharge patients prior to count recovery vs those who always or sometimes discharge patients early.

†See Materials for details of weight and cytogenetic- risk groups.

Materials

Trial description

This report used data collected from AAML0531 which enrolled patients between August 14, 2006 and June 15, 2010.[9] The study was approved by each institutional review board and all parents/participants provided written informed consent or assent as appropriate in accordance with the Declaration of Helsinki. Inclusion criteria were those ⩾1 month to ⩽30 years with de novo AML. Infants aged <1 month with progressive disease, and children with isolated chloromas and Down syndrome >4 years were also eligible. There were no organ function requirements. Exclusion criteria were patients with acute promyelocytic leukemia, AML as a second malignancy, or myelodysplastic syndrome unless there were karyotypic abnormalities characteristic of de novo AML or unequivocal presence of megakaryoblasts. Patients included in this analysis were eligible non-Down syndrome patients treated by institutions who participated in a survey focused on supportive care practices (see "Survey administration").

Therapy consisted of 5 cycles of intensive chemotherapy based on the UK Medical Research Council 12 study,[10] and patients were randomized to receive or not receive gemtuzumab ozogamicin (GMTZ) at 3 mg/kg per dose once on day 6 during induction I and intensification II. Induction I consisted of cytarabine 100 mg/m^2 per dose intravenously every 12 hours on days 1 through 10; daunorubicin 50 mg/m^2 per dose intravenously on days 1, 3, and 5; and etoposide 100 mg/m^2 per dose intravenously daily on days 1 through 5 (ara-C, daunorubicin, etoposide 10 + 3 + 5). Induction II consisted of the same chemotherapy as induction I except that cytarabine was administered for 8 days (ara-C, daunorubicin, etoposide 8 + 3 + 5).

Intensification courses were as follows. Intensification I: cytarabine 1 g/m^2 per dose intravenously every 12 hours on days 1 through 5 and etoposide 150 mg/m^2 per dose intravenously daily on days 1 through 5. Intensification II: cytarabine 1 g/m^2 per dose intravenously every 12 hours on days 1 through 4 and mitoxantrone 12 mg/m^2 per dose intravenously daily on days 3 through 6. Intensification III: cytarabine 3 g/m^2 per dose intravenously every 12 hours on days 1, 2 and 8, 9 and *Escherichia coli* L'asparaginase 6000 international units (IU)/m^2 dose intramuscularly on days 2 and 9. Indications for best allogeneic donor hematopoietic stem cell transplantation (HSCT) were >15% bone marrow blasts after induction I in those without favorable-risk cytogenetics and poor-risk cytogenetics irrespective of response following induction I. Those with good response after induction I without favorable-risk cytogenetics received HSCT if a matched family donor was available.

Uniform guidelines for supportive care were provided. Empiric systemic antibiotics were initiated in patients with fever and neutropenia. The use of broad-spectrum antibiotics with activity against viridians group streptococci, *Pseudomonas aeruginosa*, and other Gram-negative organisms was suggested. No guidance was provided related to antibacterial or G-CSF prophylaxis. Fluconazole prophylaxis was recommended to prevent invasive fungal infection. Hospitalization following chemotherapy until the absolute neutrophil count was rising and at least 200/μL was suggested but not mandated.

For weight group classification, body mass index (BMI) percentile at diagnosis for patients 2 years of age and older was as follows: underweight, BMI ⩽ 10th percentile; overweight, BMI ⩾ 95th percentile; and middleweight, BMI > 10th to < 95th percentile.[11] Patients 1 to 2 years old were classified using weight-for-length percentiles. Patients unknown for weight group consisted of infants (<1 year) and patients missing either weight or height information. Cytogenetic-risk groups were defined by

Table 2. Poisson regression evaluating the influence of any antibacterial prophylaxis (N = 115) or penicillin/vancomycin prophylaxis (N = 70)

		Any antibacterial prophylaxis				Penicillin or vancomycin prophylaxis			
Infection	**N**	**IRR (95% CI)**	***P***	**Adjusted IRR* (95% CI)**	**Adjusted *P****	**IRR**	***P***	**Adjusted IRR* (95% CI)**	**Adjusted *P****
Any sterile-site bacterial infection	612	0.84 (0.71-0.98)	.028	0.85 (0.72-1.01)	.058	0.87 (0.72-1.05)	.150	0.92 (0.75-1.12)	.398
Gram-positive sterile-site bacterial infection	512	0.72 (0.58-0.90)	.004	0.71 (0.57-0.90)	.004	0.73 (0.56-0.95)	.021	0.76 (0.58-1.01)	.054
Gram-negative sterile-site bacterial infection	78	1.39 (0.78-2.47)	.258	1.39 (0.75-2.60)	.297	1.03 (0.48-2.23)	.940	1.07 (0.46-2.48)	.872
C difficile infection	123	0.77 (0.46-1.30)	.330	0.65 (0.38-1.13)	.126	1.09 (0.63-1.88)	.769	0.88 (0.48-1.59)	.674
Sterile-site fungal infection	49	1.07 (0.49-2.38)	.860	1.11 (0.47-2.63)	.812	1.47 (0.63-3.43)	.378	1.50 (0.59-3.81)	.399

*Analysis adjusted for age, race, and weight group.

Table 3. Poisson regression evaluating the influence of any antifungal prophylaxis (N = 722) or antimold prophylaxis (N = 62)

		Any antifungal prophylaxis				Any antimold prophylaxis			
Infection	N	IRR (95% CI)	*P*	Adjusted IRR (95% CI)	Adjusted *P**	IRR	*P*	Adjusted IRR (95% CI)	Adjusted *P**
Any sterile-site bacterial infection	612	0.96 (0.84-1.09)	.514	0.94 (0.82-1.07)	.371	0.88 (0.71-1.09)	.244	0.94 (0.75-1.18)	.584
Gram-positive sterile-site bacterial infection	512	0.85 (0.73-0.99)	.041	0.82 (0.70-0.97)	.021	0.70 (0.52-0.95)	.023	0.70 (0.50-0.98)	.036
Gram-negative sterile-site bacterial infection	78	1.02 (0.59-1.79)	.932	1.21 (0.64-2.31)	.560	1.36 (0.63-2.95)	.433	1.46 (0.63-3.39)	.379
C difficile infection	123	1.28 (0.83-1.98)	.263	1.24 (0.80-1.94)	.339	0.38 (0.14-1.03)	.056	0.40 (0.15-1.09)	.074
Sterile-site fungal infection	49	1.06 (0.52-2.18)	.865	1.62 (0.69-3.83)	.271	1.59 (0.63-4.01)	.321	1.62 (0.58-4.56)	.361

*Analysis adjusted for age, race, and weight group.

cytogenetic data only: favorable, inv(16) or t(8;21); unfavorable, monosomy 7 or −5/5q−; and standard, all others with cytogenetic data.

Outcomes

The outcomes were microbiologically documented Common Terminology Criteria for Adverse Events version 3.0 grade 3 to 5 infection and NRM during chemotherapy. Outcomes were limited to those that occurred 10 days or more after beginning induction I because events occurring earlier were unlikely to be influenced by prophylactic strategies. Infections occurring between day 10 of induction I and initiation of conditioning for HSCT, completion of protocol therapy (recovery after the last cycle of chemotherapy), relapse, or date taken off study (whichever occurred first) were included in the analysis. Infection data were collected prospectively by institutional clinical research associates and the data were monitored by 2 central reviewers (L.S. and R.A.) in real time to optimize reporting accuracy. Specific infections examined were sterile-site bacterial, gram-positive, gram-negative, and fungal infections, and *Clostridium difficile* infection (CDI) from any site. Sites were instructed not to report isolates that were believed to be contaminants or colonizing organisms. We also examined the risk of NRM during chemotherapy, defined as (1) any induction death on or after day 10 of induction I or (2) death during intensification or within 30 days of being taken off study due to nondisease-related causes.

Survey administration

We surveyed 216 COG institutions in the United States, Canada, Switzerland, Australia, and New Zealand as previously reported.[12] The survey content and format were developed by the investigators and pilot tested prior to dissemination. The themes addressed in the survey related to: (1) systemic antibacterial prophylaxis, (2) systemic antifungal prophylaxis, (3) G-CSF prophylaxis, and (4) routine discharge from hospital prior to evidence of bone marrow recovery. If antibiotic prophylaxis was used, the specific agent(s) were recorded. We evaluated penicillin or vancomycin prophylaxis separately because there is a specific concern regarding viridans group streptococci in children with AML[13,14] and the role of gram-positive agents is controversial. Similarly, antimold antifungal prophylaxis was evaluated separately. Routine discharge was categorized as "no discharge" (in other words, mandatory hospitalization through profound neutropenia) vs "routinely discharge" or "sometimes discharge" prior to marrow recovery.

The survey was e-mailed to 1 investigator from each institution. Typically, the respondent was the COG principal investigator for that site although for some centers, individuals with a particular interest in AML and/or supportive care completed the survey. In the case of nonresponse, up to 2 reminder e-mails were sent. The survey was administered between November 25, 2008 and December 12, 2008.[12]

Statistical analysis

The data were analyzed by T.A.A. and R.B.G., and all authors had access to the primary survey data. The COG investigators had access to all patient data. Poisson regression was performed to evaluate the relationship between demographic characteristics and supportive care practices, and the number of infections occurring during the time period at risk. Univariate and multivariable regression analyses were performed and incidence rate ratios (IRRs) and 95% CIs were calculated. In order to evaluate the association between demographic characteristics and supportive care strategies and NRM, a Cox proportional hazards model was used to estimate hazard ratios (HRs) of NRM during the time period at risk where patients were censored at date of HSCT, relapse, 30 days after date taken off study, or date of last contact. For both infection and NRM outcomes, multiple regression analyses adjusted for age, race, and weight category. All statistical analysis was performed using the SAS statistical program (SAS-PC, version 9.2; SAS Institute, Inc). All tests of significance were 2-sided and the α level was set at 0.05.

Results

There were 216 COG sites that were sent the survey; 180 (83.3%) responded. Of 1024 children and young adults enrolled on AAML0531, 897 were non-Down syndrome patients treated at

Table 4. Poisson regression evaluating the influence of any G-CSF prophylaxis (N = 116) or no discharge policy (N = 563)

		Routine G-CSF prophylaxis				No discharge policy			
Infection	N	IRR (95% CI)	*P*	Adjusted IRR (95% CI)	Adjusted *P**	IRR (95% CI)	*P*	Adjusted IRR (95% CI)	Adjusted *P**
Any sterile-site bacterial infection	612	0.82 (0.70-0.96)	.016	0.79 (0.67-0.92)	.004	0.91 (0.82-1.01)	.083	0.91 (0.82-1.01)	.084
Gram-positive sterile-site bacterial infection	512	0.87 (0.72-1.06)	.167	0.83 (0.68-1.02)	.082	0.96 (0.84-1.09)	.500	0.95 (0.83-1.10)	.502
Gram-negative sterile-site bacterial infection	78	0.89 (0.46-1.73)	.732	0.69 (0.32-1.52)	.362	1.01 (0.64-1.58)	.974	1.07 (0.65-1.77)	.778
C difficile infection	123	0.52 (0.29-0.94)	.031	0.46 (0.25-0.84)	.012	1.88 (1.30-2.72)	<.001	1.96 (1.34-2.87)	<.001
Sterile-site fungal infection	49	1.08 (0.49-2.41)	.844	1.13 (0.50-2.53)	.772	0.56 (0.32-0.99)	.045	0.68 (0.37-1.23)	.198

No discharge indicates institutions that never discharge patients prior to count recovery vs those who always or sometimes discharge patients early.
*Analysis adjusted for age, race, and weight group.

Table 5. Association between prophylaxis and discharge policies and NRM (N = 883)

Predictor	n/N*	HR (95% CI)	P	Adjusted HR (95% CI)	Adjusted P†
Institution policy					
Prophylaxis					
Any antibacterial	3/115	0.84 (0.25-2.77)	.770	0.69 (0.16-2.97)	.618
Penicillin or vancomycin	3/70	1.36 (0.41-4.51)	.613	1.24 (0.29-5.33)	.775
Any antifungal	22/722	0.80 (0.33-1.98)	.633	0.79 (0.29-2.12)	.635
Antimold	1/62	0.58 (0.08-4.24)	.294	1.04 (0.14-7.83)	.973
G-CSF	3/116	0.80 (0.24-2.67)	.722	0.89 (0.27-3.02)	.857
Discharge policy‡					
No discharge after chemotherapy	15/563	0.62 (0.30-1.31)	.211	0.60 (0.26-1.36)	.220

Risk of any death during induction on or after day 10 of induction 1 or death without relapse or progressive disease during intensification. Patients censored at conditioning for stem cell transplantation. Fourteen patients not included for death or withdrawal <10 days after starting induction I. REF, reference.

*Denominator is the number who received the intervention while the numerator is the number who experienced NRM among that those receiving the intervention.

†Analysis adjusted for age, race, and weight group.

‡No discharge indicates institutions that never discharge patients prior to count recovery vs those who always or sometimes discharge patients early.

institutions that responded to the survey. Demographics of patients from institutions that routinely administer antibacterial or antifungal prophylaxis, and do not discharge patients before count recovery are described in Table 1. Supplemental Appendix Tables 1 to 3 illustrate the association between age, race, and weight group and outcomes.

Tables 2 to 4 summarize the associations between antibacterial, antifungal, and G-CSF prophylaxis and mandatory hospitalization during profound neutropenia and infection outcomes. These tables also illustrate the number of infection events. In multiple regression analysis, antibacterial prophylaxis reduced any sterile-site bacterial infection (IRR 0.85; 95% CI, 0.72-1.01; $P = .058$) and gram-positive sterile-site infection (IRR 0.71; 95% CI, 0.57-0.90; $P = .004$). Antimold prophylaxis did not reduce sterile-site fungal infection (IRR 1.62; 95% CI, 0.58-4.56; $P = .361$). Prophylactic G-CSF reduced any sterile-site bacterial infection (IRR 0.79; 95% CI, 0.67-0.92; $P = .004$) and CDI (IRR 0.46; 95% CI, 0.25-0.84; $P = .012$). In evaluating the impact of prophylactic G-CSF, because antibacterial prophylaxis may affect sterile-site bacterial infection and CDI, we also performed multiple regression analyses for these outcomes that adjusted for antibacterial prophylaxis in addition to age, race, and weight category. In these multiple regression models, prophylactic G-CSF was independently associated with infection reduction; the adjusted IRR (95% CI) was 0.78 (0.66-0.92; $P = .003$) for any sterile-site bacterial infection and 0.45 (0.24-0.83; $P = .010$) for CDI. Mandatory hospitalization did not reduce sterile-site bacterial or fungal infection but did increase CDI (IRR 1.96; 95% CI, 1.34-2.87; $P < .001$).

There were 28 NRM events among patients included in this analysis. Table 5 illustrates that supportive care practices, including mandatory hospitalization did not influence NRM in univariate or multiple regression.

Discussion

By combining results of a survey and a phase 3 COG clinical trial, we made several important observations. First, we found that administration of systemic antibacterial and G-CSF prophylaxis is effective at reducing sterile-site bacterial infection. Second, we did not demonstrate a benefit of antifungal or antimold prophylaxis. Finally, we could not demonstrate a statistically significant benefit of mandatory hospitalization during profound neutropenia.

Our findings that antibacterial and G-CSF prophylaxis are effective at reducing the risk of sterile-site bacterial infection is in keeping with results of systematic reviews which included primarily adult trials and thus, confirms the effectiveness of these interventions in the pediatric setting.[3,4] However, whether these interventions should be incorporated into routine clinical practice also depends on the downsides associated with administration. For example, antibacterial prophylaxis has been reported to be associated with bacterial resistance, drug toxicity, CDI, and fungal infection[15] although we did not demonstrate the latter 2 outcomes in our analysis. Furthermore, 1 analysis suggested that prophylactic G-CSF may increase the risk of relapse in a subgroup of children with AML[16] although a similar adverse influence on disease control was not observed in a meta-analysis of G-CSF administration in AML.[17] In addition, a randomized trial of G-CSF in pediatric AML failed to show a beneficial impact on microbiologically documented infection.[18]

We did not observe a benefit of antifungal or antimold prophylaxis on sterile-site fungal infection rates or NRM. This finding is in direct contrast to 2 meta-analyses that demonstrated that antifungal and antimold prophylaxis are associated with a reduction in invasive fungal infection and invasive aspergillosis.[19,20] There are at least 3 possibilities that may explain these results. First, we used an ecological measure of antifungal prophylaxis, and there are likely to be confounders that influenced this analysis. Indeed, centers with a higher rate of mold infection may be more likely to adopt a strategy of antimold prophylaxis. Second, our analysis may have been underpowered to demonstrate an effect of prophylactic strategy. This consideration is important because only 6.9% of patients were analyzed in the antimold prophylaxis group. Finally, it is possible that the results of trials are not generalizable to every day clinical practice and that the efficacy observed in trials is not replicated outside of the trial setting. In part, this finding could be related to poor compliance with institutional standards.

We did not observe a statistically significant benefit of mandatory hospitalization during profound neutropenia. It is important to note that this strategy is directed at NRM rather than infection outcomes and our analysis may have been underpowered to demonstrate an effect. However, we did note a downside of mandatory hospitalization, namely an increased CDI rate. Hospitalization duration is a well-recognized risk factor for CDI.[21]

This report has unique strengths. To our knowledge, this is the first integration of treatment-center-level practice data with cooperative group clinical trial data. This approach results in an intention-to-treat measure of supportive care practices. This data combination enables the description of the effectiveness of prophylaxis in the real-world care of children with cancer in a manner that reduces bias from confounding by indication. For example, this approach is probably the only way in which the effectiveness of discharge policies can be measured. Randomized trials are almost certainly not feasible and observational studies conducted at the individual level would be confounded by comorbidities and performance status.

However, our study has important limitations. These merged data may still be limited by center-level confounding and unmeasured covariates, such as in the case of antimold prophylaxis.

In other words, institutions that use prophylaxis may be systematically different than institutions that do not use prophylaxis. Also, despite the availability of individual institution prophylaxis standards of care, individual patients may have received care that differs from these standards. We did not have the ability to validate cases by on-site review given the large number of institutions that enrolled children onto AAML0531 and were included in this analysis. Furthermore, the rates of sterile-site fungal infection and NRM are low and thus, these analyses had limited power. Finally, other supportive care measures such as empiric antibiotics that provide coverage against virulent organisms in pediatric AML such as viridans group streptococci and gram-negative organisms such as *P aeruginosa* are also important,[22] and we did not include these aspects in our study.

In conclusion, systemic antibacterial and G-CSF prophylaxis as measured by institutional survey responses appear to reduce infection rates while mandatory hospitalization during profound neutropenia did not reduce infection or significantly reduce NRM. However, it is not clear whether the benefits of these interventions are outweighed by downsides such as increased antibacterial resistance in the case of antibacterial prophylaxis and a potential impact on leukemia control in the case of G-CSF prophylaxis. Our results will need to be evaluated against future data from randomized trials conducted in children with cancer.

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Authorship

Contribution: L.S., R.A., T.A.A., R.B.G., T.L., and A.S.G. designed the study, contributed to obtaining study materials, contributed to drafting the manuscript, and gave their approval of the final manuscript.

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