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Little is known about the impact of enrollment on therapeutic clinical trials on adverse event rates. Primary objective was to describe the impact of clinical trial registration on sterile site microbiologically documented infection for children with newly diagnosed acute myeloid leukemia (AML). We conducted a multicenter cohort study that included children aged ≤18 years with *de novo* AML. Primary outcome was microbiologically documented sterile site infection. Infection rates were compared between those registered and not registered on clinical trials. Five hundred seventy-four children with AML were included of which 198 (34.5%) were registered on a therapeutic clinical trial. Overall, 400 (69.7%) had at least one sterile site microbiologically documented infection. In multiple regression, registration on clinical trials was independently associated with a higher risk of microbiologically documented sterile site infection [adjusted odds ratio (OR) 1.24, 95% confidence interval (CI) 1.01–1.53; $p = 0.040$] and viridans group streptococcal infection (OR 1.46, 95% CI 1.08–1.98; $p = 0.015$). Registration on trials was not associated with Gram-negative or invasive fungal infections. Children with newly diagnosed AML enrolled on clinical trials have a higher risk of microbiologically documented sterile site infection. This information may impact on supportive care practices in pediatric AML.

Key words: infection, bacteremia, children, acute myeloid leukemia, clinical trial

Abbreviations: AML: acute myeloid leukemia; ANC: absolute neutrophil count; CCG: Children's Cancer Group; CI: confidence interval; COG: Children's Oncology Group; CRA: clinical research associate; G-CSF: granulocyte colony-stimulating factor; HSCT: hematopoietic stem cell transplantation; IQR: interquartile range; MRC: Medical Research Council; OR: odds ratio; POG: Pediatric Oncology Group; UK: United Kingdom

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What's new?
Clinical trials often test more intensive treatment strategies than standard regimens. Consequently, it's important to evaluate adverse event rates. In this study, the authors found that pediatric patients with acute myeloid leukemia (AML) who were enrolled in clinical trials had a higher risk of several types of infection than patients who were not. These results are worth considering when offering patients enrollment in clinical trials, and may impact supportive care practices in pediatric AML.

Clinical trials evaluating different treatment approaches to improve disease control in pediatric cancer often test more intensive strategies compared to standard regimens.[1] Consequently, clinical trials may be associated with more adverse events compared to standard treatments. Infections are one of the most common and important adverse events for children and adolescents receiving intensive chemotherapy such as treatment for acute myeloid leukemia (AML).[2,3] Bacteria and fungi have the biggest impact on morbidity and mortality.[4] While consideration of the effect of clinical trial registration has been directed at survival outcomes,[5] almost no attention has been paid to adverse event rates. If present, differences in adverse event rates may be important to disclose when offering children enrollment onto clinical trials.

Reasons why children enrolled onto clinical trials may have better disease outcomes compared to those who do not enroll on trials may be related to the following: (*i*) treatment effect in which the intervention results in better outcomes compared with standard approaches; (*ii*) participation effect where enrollment in the trial results in better outcomes due to the effect of the protocol, changes in healthcare professional behavior, changes in patient/family behavior and/or a placebo effect; (*iii*) confounding if patients enrolled on trials are systematically different than patients not enrolled on trials and (*iv*) bias related to how outcomes are collected or reported.[5]

The first step in determining whether a trial effect may be present for adverse events would be to compare the rate of events in those with the same disease registered and not registered on a clinical trial. We recently conducted two successive observational trials of infection outcomes in pediatric AML that included both children enrolled and not enrolled on clinical trials, thus giving us an ideal platform to evaluate this question. Consequently, the primary objective was to describe the impact of clinical trial registration on sterile site microbiologically documented infections for children with newly diagnosed AML. Secondary objectives were to evaluate the impact of registration on trials on Gram-positive and -negative sterile site infections, viridans group streptococcal infection and proven or probable invasive fungal infection.

Material and Methods

We conducted a retrospective and prospective cohort study focused on infections in pediatric AML.[2] Children and adolescents with *de novo* AML in Canada and the United States were included. Institutional review board approval was obtained from each participating site. For the retrospective component, the need for informed consent was waived. For the prospective component, participants/guardians provided informed consent and assent as appropriate.

Study sample

Inclusion criteria were: (*i*) diagnosis of *de novo* AML and (*ii*) age ≤ 18 years at diagnosis. Exclusion criteria were: (*i*) previous antineoplastic therapy, radiotherapy, myelodysplastic syndrome or immunodeficiency diagnosis and (*ii*) juvenile myelomonocytic leukemia. Enrolled participants excluded from analysis were those with acute promyelocytic leukemia and Down syndrome patients receiving only low-dose cytarabine.

Procedure

Infections were collected from the time of AML diagnosis until the first of the following events: patients recovered from the last cycle of chemotherapy, began conditioning for hematopoietic stem cell transplantation (HSCT), relapsed, had persistent disease or died. A single group of clinical research associates (CRAs) conducted site visits in order to abstract and code the outcomes and demographic information.

Definitions for infection outcomes were standardized.[2,6] The primary outcome was microbiologically documented sterile site infection, defined as one or more cultures positive for a pathogen obtained from a usually sterile site.[7] Positive cultures with common contaminants such as coagulase negative *Staphylococcus* and *Propionibacterium acnes* required two positive cultures for the same organism or association with sepsis syndrome to be categorized as a true infection.[8,9] Secondary outcomes were Gram-positive and Gram-negative infections and viridans group streptococci infection from sterile sites. Another secondary outcome was proven or probable invasive fungal infection defined according to standard criteria.[10]

Analysis

Baseline characteristics were compared between those registered and not registered on clinical trials using χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables.

In order to evaluate whether registration on clinical trials was associated with infection rates, we conducted repeated measures logistic regression with generalized estimating equations where the unit of analysis was each chemotherapy

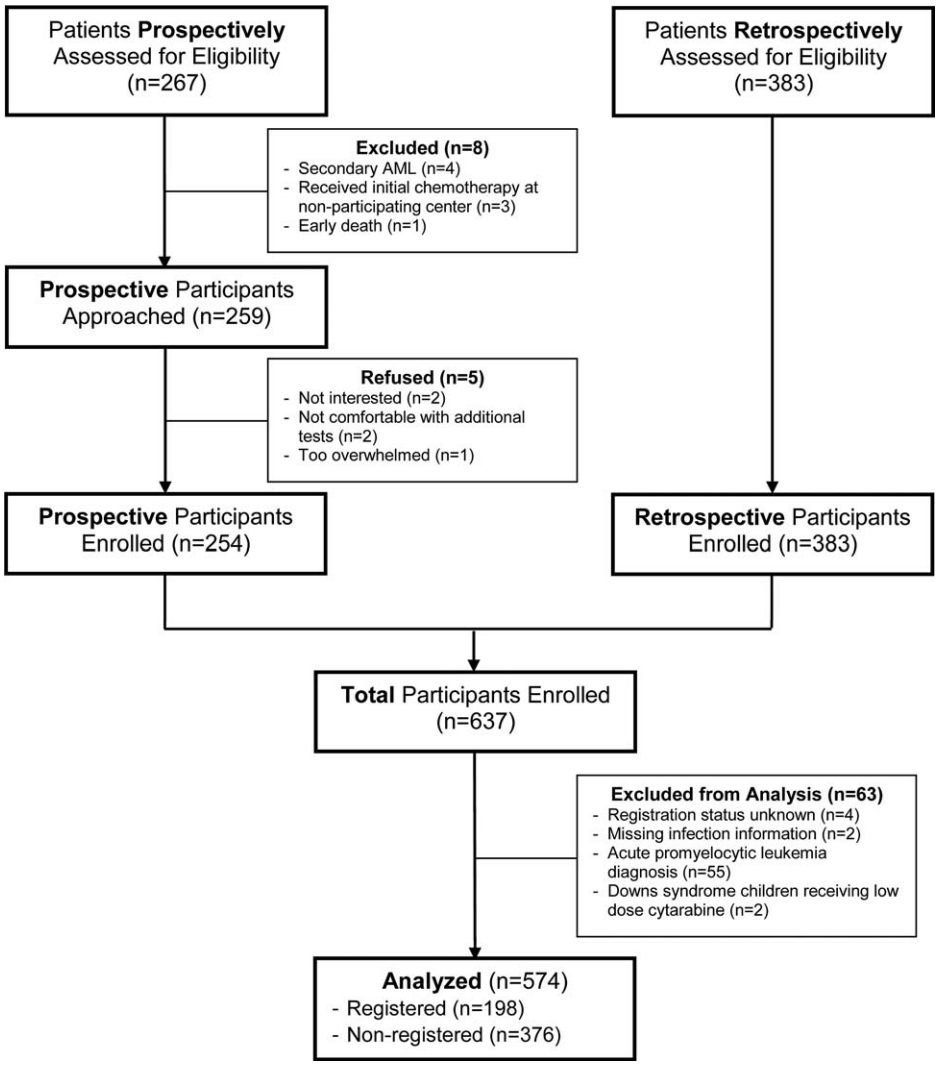

Figure 1. Flow diagram of patient identification and selection.

course. This approach allowed us to explicitly incorporate course-level factors such as cytarabine dose and to allow each child to contribute multiple courses of chemotherapy. Co-interventions evaluated included age at diagnosis, Down syndrome, obesity at diagnosis, diagnosed before January 1, 2000, treatment protocol according to UK Medical Research Council (MRC)-based approach (yes or no), course-specific cumulative dose of cytarabine, neutropenia (absolutely neutrophil count $< 0.5 \times 10^9$/L) at start of course, >15 days of neutropenia, days receiving corticosteroids and corticosteroid dose. Obesity was defined as $\geq$95th percentile for age and gender according to the Centers for Disease Control and Prevention for those at least 2 years of age.[11] For the analysis of invasive fungal infection, days of broad-spectrum antibiotics and fluconazole prophylaxis were also included. Variables significant in univariate analysis were included in multiple regression analysis.

As diagnosis before January 1, 2000 and treatment with a MRC-based approach were highly correlated ($r = -0.80$; $p < 0.0001$), only protocol type was included if they were both significant in univariate analysis. Similarly, only days of corticosteroid and not dose was included if both were significant in univariate analysis. Comparison of first event deaths was by the Fisher's exact test. Event-free survival and overall survival were described using the Kaplan–Meier approach and compared using the log-rank test. In order to compare cytarabine dose and duration of neutropenia in those registered and not registered on trials, repeated measures linear regression was conducted using Proc Mixed in SAS. All tests of significance were two-sided, and statistical significance was defined as $p < 0.05$. Statistical analysis was performed using the SAS statistical program (SAS-PC, version 9.3; SAS Institute, Cary, NC).

Results

Figure 1 illustrates the flow diagram of patient identification and enrollment. Between January 1995 and September 2012, 650 children and adolescents with AML were identified. The

Table 1. Demographics of the study cohort

	Registered on study ($N = 198$)	Nonregistered on study ($N = 376$)	p Value
Child characteristics at diagnosis			
Male (%)	90 (45.5)	193 (51.3)	0.211
Median age in years at diagnosis (IQR)	8.2 (2.0, 13.1)	7.9 (2.2, 13.6)	0.740
Down syndrome (%)	20 (10.1)	23 (6.1)	0.120
Body mass index (%)[1]			0.166
Obese	15 (10.2)	40 (13.9)	
Normal weight	114 (77.6)	229 (79.5)	
Underweight	18 (12.2)	19 (6.6)	
Median white blood cell count ($\times 10^9$/L) (IQR)	15 (5.7, 51.0)	18 (7.1, 61.0)	0.062
Primary AML morphology (%)			0.153
M0	5 (2.5)	12 (3.2)	
M1	31 (15.7)	49 (13.0)	
M2	42 (21.2)	93 (24.7)	
M4	31 (15.7)	73 (19.4)	
M5	44 (22.2)	67 (17.8)	
M6	8 (4.0)	4 (1.1)	
M7	25 (12.6)	43 (11.4)	
Other	12 (6.1)	35 (9.3)	
Central nervous system involvement (%)	56 (30.8)	98 (30.1)	0.948
Diagnosed before January 1, 2000 (%)	88 (44.4)	227 (60.4)	0.0004
Treatment characteristics			
Protocol (%)			0.294
MRC (non-Down's specific)	99 (50.0)	163 (43.4)	
CCG	38 (19.2)	61 (16.2)	
POG	48 (24.3)	116 (30.9)	
Down's specific	13 (6.6)	9 (2.4)	
Other	0 (0.0)	27 (7.2)	
Received G-CSF for any indication (%)	75 (37.9)	136 (36.2)	0.755
Ever received intravenous immune globulin (%)	12 (6.1)	33 (8.8)	0.323

Abbreviations: AML: acute myeloid leukemia; G-CSF: granulocyte colony-stimulating factor; IQR: interquartile range; MRC: Medical Research Council; CCG: Children's Cancer Group; POG: Pediatric Oncology Group.
[1]For the calculation of body mass index percentile, those <2 years of age were excluded. Obesity was defined as ≥95th percentile for age and gender according to the Centers for Disease Control for those at least 2 years of age while underweight was defined as <5th percentile.[11]

retrospective component extended until December 2004 while the prospective component began April 2005. Patients diagnosed between January 2005 and March 2005 were not included. Of the 637 participants enrolled, 63 were excluded from analysis (Fig. 1) leaving 574 analyzed patients. Patient characteristics are shown in Table 1 stratified by registration on trials. In total, 198 (34.5%) were registered on clinical trials while 376 (65.5%) were not registered on a clinical trial. The specific protocols used (whether registered on not registered on trials) were CCG 213 ($n = 2$), CCG 2891 ($n = 40$), CCG 2941 ($n = 3$), CCG 2961 ($n = 54$), CCG 2971 ($n = 11$), AAML0431 ($n = 11$), AAML03P1 ($n = 31$), AAML0531 ($n = 162$), UK MRC-10 ($n = 41$), UK MRC-12 ($n = 5$), AAML1031 ($n = 23$), POG 9421 ($n = 140$), POG 8821 ($n = 7$), POG 9822 ($n = 17$) and other protocols ($n = 27$). Demographic variables were similar between the groups except that nonregistered patients were more likely to be diagnosed earlier in the study period (Table 1).

The number of first event deaths was 6 (3.0%) for those registered on trials and 22 (5.9%) for those not registered on trials ($p = 0.157$). The number of infection-related first event deaths was four (2.0%) for enrolled patients *versus* 14 (3.7%) for nonenrolled patients ($p = 0.322$). The number of first events that were relapse was 107 (54.0%) for those registered on trials and 196 (52.1%) for those not registered on trials. Event-free survival at 3 years for those registered and not

Table 2. Factors associated with at least one microbiologically documented sterile site infection

	Odds ratio	95% CI	*p*
Registered on study	1.31	1.06–1.62	0.011
Treatment protocol MRC-based	1.91	1.57–2.32	<0.001
Course cumulative dose of cytarabine (g/m^2)	1.04	1.03–1.06	<0.0001
Age in years	1.03	1.01–1.04	0.003
Down syndrome	0.37	0.24–0.56	<0.0001
Obese *vs.* nonobese	1.17	0.83–1.64	0.370
Diagnosed before January 1, 2000	0.62	0.51–0.76	<0.0001
Neutropenia (ANC $< 0.5 \times 10^9$/L) at start of course	0.87	0.67–1.15	0.332
Greater than 15 days with neutropenia	1.97	1.60–2.43	<0.0001
Days receiving steroids	1.05	1.04–1.07	<0.0001
Steroid dose[1]	1.02	1.00–1.03	0.029

Abbreviations: ANC: absolute neutrophil count; MRC: Medical Research Council; CI: confidence interval.
[1]Presented as 10 mg/m^2 of dexamethasone equivalents.

Table 3. Factors associated with at least one Gram-positive and Gram-negative sterile site infection

	Gram-positive infection		Gram-negative infection	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Registered on study	1.36 (1.06–1.73)	0.014	1.05 (0.75–1.46)	0.792
Treatment protocol MRC-based	2.24 (1.78–2.82)	<0.0001	1.38 (1.01–1.87)	0.041
Course cumulative dose of cytarabine (g/m^2)	1.04 (1.02–1.05)	<0.0001	1.05 (1.03–1.06)	<0.0001
Age in years	1.02 (0.99–1.04)	0.150	1.04 (1.01–1.06)	0.013
Down syndrome	0.45 (0.28–0.73)	0.001	0.34 (0.17–0.70)	0.003
Obese *vs.* nonobese	1.00 (0.69–1.45)	0.998	1.52 (0.94–2.46)	0.091
Diagnosed before January 1, 2000	0.51 (0.41–0.64)	<0.0001	0.83 (0.61–1.13)	0.242
Neutropenia (ANC $< 0.5 \times 10^9$/L) at start of course	0.86 (0.63–1.19)	0.372	0.49 (0.30–0.80)	0.004
Greater than 15 days with neutropenia	1.47 (1.16–1.86)	0.001	3.17 (2.15–4.66)	<0.0001
Days receiving steroids	1.03 (1.01–1.05)	0.0003	1.05 (1.03–1.07)	<0.0001
Steroid dose[1]	1.00 (0.99–1.02)	0.617	1.01 (1.00–1.03)	0.061

Abbreviations: ANC: absolute neutrophil count; MRC: Medical Research Council; CI: confidence interval.
[1]Presented as 10 mg/m^2 of dexamethasone equivalents.

registered on trials was $56.9 \pm 3.9\%$ and $57.3 \pm 2.8\%$ ($p = 0.614$). Overall survival at 3 years was $70.7 \pm 3.5\%$ and $65.4 \pm 2.7\%$ ($p = 0.258$).

Overall, 400 (69.7%) patients had at least one sterile site microbiologically documented infection during any course of chemotherapy. In total, there were 2,222 courses of chemotherapy delivered. Median days of neutropenia were 21 [interquartile range (IQR) 14–29]. Median days of fever were 4 (IQR 1–9). Median days receiving intravenous broad-spectrum antibiotics were 13 (IQR 5–22). The number of courses with at least one sterile site, microbiologically documented infection was 638 (28.7%) and the number with at least one bacteremia was 547 (24.6%).

Tables (2–4) illustrate that in univariate analysis, registration on clinical trials was associated with a higher risk of microbiologically documented sterile site infection [odds ratio (OR) 1.31, 95% confidence interval (CI) 1.06–1.62; $p = 0.011$], Gram-positive sterile site infection (OR 1.36, 95% CI 1.06–1.73; $p = 0.014$) and viridans group streptococcal infection (OR 1.58, 95% CI 1.17–2.14; $p = 0.003$). Registration on trials was not associated with Gram-negative sterile site infection or invasive fungal infection.

Table 5 illustrates the effect of clinical trials registration in multiple regression models. In adjusted models, registration on trials was significantly associated with more microbiologically documented sterile site infection, Gram-positive sterile site infection and viridans group streptococcal infection.

In order to evaluate treatment intensity, duration of neutropenia and cytarabine dose were compared between those registered and not registered on trials using repeated measures linear regression. The effect of registration on trials on cytarabine dose per course was $\beta = 0.58$ (standard error = 0.32); $p = 0.072$ while the effect of registration on duration of neutropenia was $\beta = 2.03$ (standard error = 0.67);

Table 4. Factors associated with at least one viridans group streptococcal microbiologically documented and invasive fungal infection

	VGS infection		Invasive fungal infection	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Registered on study	1.58 (1.17–2.14)	0.003	1.05 (0.61–1.81)	0.866
Treatment protocol MRC-based	3.35 (2.47–4.55)	<0.0001	0.62 (0.35–1.08)	0.089
Course cumulative dose of cytarabine (g/m^2)	1.03 (1.02–1.05)	<0.0001	1.00 (0.97–1.04)	0.968
Age in years	1.02 (0.98–1.05)	0.082	1.01 (0.96–1.06)	0.804
Down syndrome	0.35 (0.19–0.67)	0.001	0.30 (0.08–1.21)	0.092
Obese *vs.* nonobese	0.92 (0.54–1.56)	0.765	1.43 (0.58–3.52)	0.432
Diagnosed before January 1, 2000	0.38 (0.28–0.51)	<0.0001	1.97 (1.11–3.50)	0.022
Neutropenia (ANC $< 0.5 \times 10^9$/L) at start of course	1.02 (0.69–1.51)	0.909	3.60 (2.08–6.23)	<0.0001
Greater than 15 days with neutropenia	1.41 (1.06–1.86)	0.017	2.07 (1.08–3.97)	0.028
Days receiving steroids	0.99 (0.97–1.02)	0.594	1.09 (1.06–1.12)	<0.0001
Steroid dose[1]	1.00 (0.99–1.20)	0.577	1.04 (1.02–1.05)	<0.0001
Days receiving broad-spectrum antibiotics			1.07 (1.05–1.08)	<0.0001
Fluconazole prophylaxis			0.64 (0.38–1.08)	0.091

Abbreviations: ANC: absolute neutrophil count; MRC: Medical Research Council; CI: confidence interval.
[1]Presented as 10 mg/m^2 of dexamethasone equivalents.

Table 5. Influence of registration on trials on study outcomes when adjusted in multiple regression analysis

	Adjusted odds ratio	95% CI	Adjusted *p*
Microbiologically documented sterile site	1.24	1.01–1.53	0.040
Gram-positive sterile site	1.28	1.01–1.64	0.044
Gram-negative sterile site	0.97	0.68–1.37	0.852
Viridans group streptococci	1.46	1.08–1.98	0.015
Invasive fungal infection	0.99	0.55–1.78	0.961

$p = 0.002$. The median days of neutropenia in the registered and not registered groups were 22 (IQR 15–30) and 20 (IQR 12–28), respectively.

Discussion

In this large pediatric AML cohort, we demonstrated that registration on clinical trials is associated with higher infection rates and specifically more viridans group streptococcal infection. This finding is important as viridans group streptococci is a common cause of sepsis and mortality in pediatric AML.[12,13] This finding may also be important when considering implementation of clinical trials and may impact on supportive care practices.

Higher infection rates for children enrolled on clinical trials may occur by a multiple of mechanisms. First, if clinical trials are comparing a more aggressive regimen to standard regimens, as has been the case in the most recent Children's Oncology Group trials,[14,15] then the observed higher rate of infections may be a direct consequence of more aggressive chemotherapy. Second, providers of those enrolled on trials may be more adherent to protocol therapy and less likely to dose reduce or delay chemotherapy, thus resulting in more intensive treatment. Both of these possibilities are supported by the finding of more prolonged neutropenia in those enrolled on trials. Third, differential practice in testing and obtaining blood cultures is a theoretical possibility but unlikely to be true. Finally, there may be other confounders not captured by our study to explain the effect.

It is important to note that not all of the listed studies are randomized trials. For example, AAML03P1 was a pilot study that evaluated the feasibility of adding Gemtuzumab ozogamicin onto a standard MRC backbone.[14] Consequently, we cannot conduct a meaningful comparison between those randomized to the experimental *versus* the standard arm of trials as not all trials were explicitly comparative.

This study is limited to patients with *de novo* AML, most of whom received treatment according to phase 3 clinical trials. If increased infections for children enrolled on clinical trials are due to more cytotoxic chemotherapy, then the same effect may occur in children enrolled on early-phase studies. Such an impact would be important to document to facilitate decision making for phase 1 trial enrollment.

It is uncertain whether this information should impact on the decision-making process for enrollment onto clinical trials or supportive care practices. As the effect on infection outcomes may still be due to residual, unmeasured confounding, it is probably premature for this information to be explicitly included in the consent process. However, further evaluation of adverse event rates in general is important to provide insight into the influence of trial registration. Similarly, it is uncertain whether this information should impact on supportive care practices. It is hard to envision that institutions should have differential practices depending on whether children are enrolled on trials or depending on treatment arm. However, heighted awareness and early

implementation of empiric therapy could be appropriate depending on the magnitude of the difference in infection rates.

The strengths of this report are the multiinstitutional nature and meticulous collection of infection outcomes. However, our results need to be interpreted in light of its limitations. First, practices have changed over time and this study does not capture the influence of changing supportive care practices. Second, some of our infection outcomes were rare such as invasive fungal infection and consequently, we had limited power to illustrate an effect of trials on infection rates. Third, we did not capture how long children were enrolled on protocol therapy and if duration on protocol therapy is important, we may have underestimated the trial effect.

In conclusion, we observed more microbiologically documented sterile site infection and viridans group streptococcal infection in children with newly diagnosed AML enrolled on clinical trials compared to those not registered on trials. Multiple factors may contribute to this observation. This information may impact on supportive care practices in pediatric AML.

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References

1. Adamson PC. The Children's Oncology Group's 2013 five year blueprint for research. *Pediatric Blood Cancer* 2013;60:955–6.
2. Dix D, Cellot S, Price V, et al. Association between corticosteroids and infection, sepsis, and infectious death in pediatric acute myeloid leukemia (AML): results from the Canadian infections in AML research group. *Clin Infect Dis* 2012;55:1608–14.
3. Sung L, Lange BJ, Gerbing RB, et al. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. *Blood* 2007;110:3532–9.
4. Hann I, Viscoli C, Paesmans M, et al. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol* 1997; 99:580–8.
5. Peppercorn JM, Weeks JC, Cook EF, et al. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 2004; 363:263–70.
6. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.
7. Santolaya ME, Alvarez AM, Becker A, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. *J Clin Oncol* 2001;19:3415–21.
8. Bouza E, Cobo-Soriano R, Rodriguez-Creixems M, et al. A prospective search for ocular lesions in hospitalized patients with significant bacteremia. *Clin Infect Dis* 2000;30:306–12.
9. Chirouze C, Schuhmacher H, Rabaud C, et al. Low serum procalcitonin level accurately predicts the absence of bacteremia in adult patients with acute fever. *Clin Infect Dis* 2002;35:156–61.
10. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002;34:7–14.
11. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* 2002;109:45–60.
12. Gassas A, Grant R, Richardson S, et al. Predictors of viridans streptococcal shock syndrome in bacteremic children with cancer and stem-cell transplant recipients. *J Clin Oncol* 2004;22:1222–7.
13. Lewis V, Yanofsky R, Mitchell D, et al. Predictors and outcomes of viridans group streptococcal infections in pediatric acute myeloid leukemia: from the Canadian infections in AML research group. *Pediatr Infect Dis J* 2014;33: 126–9.
14. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. *Cancer* 2012;118:761–9.
15. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. *J Clin Oncol* 2014;32:3021–32.