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MAJOR ARTICLE

Association Between Corticosteroids and Infection, Sepsis, and Infectious Death in Pediatric Acute Myeloid Leukemia (AML): Results From the Canadian Infections in AML Research Group

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Background. Infection continues to be a major problem for children with acute myeloid leukemia (AML). Objectives were to identify factors associated with infection, sepsis, and infectious deaths in children with newly diagnosed AML.

Methods. We conducted a retrospective, population-based cohort study that included children ≤18 years of age with de novo, non-M3 AML diagnosed between January 1995 and December 2004, treated at 15 Canadian centers. Patients were monitored for infection from initiation of AML treatment until recovery from the last cycle of chemotherapy, conditioning for hematopoietic stem cell transplantation, relapse, persistent disease, or death (whichever occurred first). Consistent trained research associates abstracted all information from each site.

Results. 341 patients were included. Median age was 7.1 years (interquartile range [IQR], 2.0–13.5) and 29 (8.5%) had Down syndrome. In sum, 26 (7.6%) experienced death as a first event. There were 1277 courses of chemotherapy administered in which sterile site microbiologically documented infection occurred in 313 courses (24.5%). Sepsis and infectious death occurred in 97 (7.6%) and 16 (1.3%) courses, respectively. The median days of corticosteroid administration was 2 per course (IQR, 0–6). In multiple regression analysis, duration of corticosteroid exposure was significantly associated with more microbiologically documented sterile site infection, bacteremia, fungal infection, and sepsis. The only factor significantly associated with infectious death was days of corticosteroid exposure (odds ratio, 1.05; 95% confidence interval, 1.02–1.08; $P = .001$).

Conclusions. In pediatric AML, infection, sepsis, and infectious death were associated with duration of corticosteroid exposure. Corticosteroids should be avoided when possible for this population.

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Children with acute myeloid leukemia (AML) are at substantial risk of mortality from invasive bacterial and fungal infections [1]. Efforts from multiple cooperative groups have attempted to quantify the infectious burden in pediatric AML and to identify factors associated with infections [2–8]. However, these reports are limited because of the inability to differentiate true infections versus likely contaminants, the inconsistent classification of clinically documented infection and sepsis, and because of the small number of explanatory variables collected. These issues are important if the goal is to accurately identify factors associated with infectious morbidity and mortality.

Identification of clinical variables that can predict the risk of invasive infection is important. First, knowledge of treatment variables associated with infection may provide data to support targeted prophylactic strategies. For example, prophylaxis could be used for children with a particular characteristic or during specific treatment courses. Second, this knowledge may aid in supportive care recommendations for future children with AML. Third, the study of genetic associations has increased greatly over the last few years. To confidently be able to determine if genotype has an independent contribution to outcomes, development of a robust model that adjusts for clinical covariates is critical.

To overcome the previous limitations in the literature, we conducted a population-based retrospective cohort study in Canada with careful collection and review of infection outcomes. Our primary objectives were to identify factors associated with infection, sepsis, and infectious deaths in children with newly diagnosed AML.

PATIENTS AND METHODS

We conducted a retrospective, population-based cohort study that included children with primary AML diagnosed and treated at all 15 Canadian centers that care for children with cancer in each province except for Saskatchewan. The Research Ethics Boards at The Hospital for Sick Children and all participating institutions approved the study.

Study Sample

We included children and adolescents diagnosed with de novo AML between 1 January 1995 and 31 December 2004 who were ≤18 years of age at diagnosis. Children with Down syndrome were included. We excluded those with acute promyelocytic leukemia, secondary AML, previous diagnosis of immunodeficiency, and children with Down syndrome receiving only low-dose cytarabine.

Patients were monitored for infection (time period at risk) from initiation of AML treatment until hematopoietic recovery from the last cycle of chemotherapy, conditioning for hematopoietic stem cell transplantation (SCT), relapse, persistent disease, or death (whichever occurred first). Consistent trained clinical research associates traveled to each site to abstract and code the relevant information.

Outcome Measures

All infections were reviewed by an adjudication subcommittee, and classification occurred by consensus. The rates of sterile site invasive infection, [9] clinically documented infection, and fever of unknown origin were expressed as number of events during the time period at risk. Similar to others [10, 11], positive cultures with common contaminants, such as coagulase negative *Staphylococcus,* were only considered true infection if there were ≥2 positive cultures within the same episode or if the infection was associated with sepsis. Sepsis was defined as systemic inflammatory response syndrome in the presence of suspected or proven infection and organ dysfunction according to international consensus guidelines [12, 13]. Classification of clinically documented infection was based on the Centers for Disease Control and Prevention (CDC) definitions of nosocomial infections [14]. Fever of unknown origin was defined as a fever occurring in the absence of a positive microbiology result or clinical infection.

Potential Predictors

Potential predictors were as follows: (1) Child characteristics at diagnosis (age, Down syndrome and obese vs nonobese); (2) Treatment characteristics (protocol type categorized as non-Down's specific Pediatric Oncology Group (POG), Children's Cancer Group (CCG) or UK Medical Research Council (MRC) protocols and Down syndrome–specific protocols, registration on AML trial, diagnosis prior to 1 January 2000, and cumulative dose of cytarabine in grams/m^2); (3) Course characteristics (neutropenia at the start of the course, neutropenia >15 days (threshold chosen a priori), days corticosteroids were administered for any reason, and dose of corticosteroids in 10 mg/m^2 of dexamethasone equivalents); and (4) Supportive care (co–trimoxazole and fluconazole prophylaxis). In the model of fungal infection, days of broad-spectrum intravenous antibiotics, meropenem and vancomycin, were also examined.

Only systemic (and not topical) corticosteroid exposure was examined. Corticosteroids, including hydrocortisone, prednisone, and methylprednisolone, were converted to dexamethasone equivalents by dividing the dose of corticosteroid administered by the equivalent pharmacologic dose (eg, 26.7 for hydrocortisone and 6.7 for prednisone) [15]. Obesity was defined as ≥95% percentile for age and sex according to the CDC for those at least 2 years of age [16]. The Children's Oncology Group protocol AAML03P1 [17] was classified as MRC-based.

Statistics

Regression analyses were conducted at the course level. In order to identify factors associated with rates of microbiologically documented sterile site infection, clinically documented infection and fever of unknown origin, we conducted a repeated measures Poisson regression using PROC GENMOD in SAS. Determination of factors associated with occurrence of gram-positive, gram-negative, and fungal infections from sterile sites was conducted with repeated logistic regression analysis using generalized estimating equations. These approaches were used because each child could experience multiple courses of chemotherapy. Variables significant in univariate analysis were included in multiple regression analysis. Because of high correlation, only corticosteroid duration and not dose and only Down syndrome and not Down syndrome–specific protocol were included if both met criteria for entry. Similarly, in the model of fungal infection, only days receiving broad-spectrum intravenous antibiotics were used and not the other measures of antibiotic exposure. All tests of significance were 2-sided, and statistical significance was defined as $P < .05$. Statistical analysis was performed using the SAS statistical program (SAS-PC, version 9.3; SAS Institute Inc, Cary, North Carolina).

RESULTS

Figure 1 illustrates the flow of patients; 395 patients were assessed for eligibility and 341 patients were included. Table 1 illustrates patient demographics. The median age was 7.1 years (interquartile range [IQR]: 2.0 to 13.5) and 29 (8.5%) had Down syndrome. The most common therapeutic protocols were POG followed by CCG and MRC. Of the 341 children,

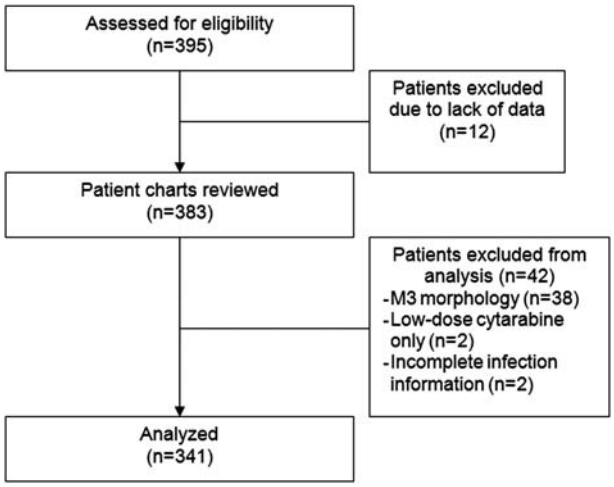

Figure 1. Flow diagram of patient evaluation.

Table 1. Demographics, Treatments, and Supportive Care of the Study Cohort (N = 341)

Demographic	Value
Child characteristics at diagnosis	
Male (%)	168 (49.3)
Median age in years (IQR)	7.1 (2.0, 13.5)
Down syndrome (%)	29 (8.5)
Body mass index (%) (n = 250)[a]	
Obese	30 (12.0)
Normal weight	199 (79.6)
Underweight	21 (8.4)
Median white blood cell count ($\times 10^9$/L) (IQR)	17.1 (5.9, 60.6)
Median absolute neutrophil count ($\times 10^9$/L) (IQR) (n = 326)	1.6 (0.4, 4.2)
FAB AML morphology (%)	
M0	7 (2.1)
M1	49 (14.4)
M2	81 (23.8)
M4	68 (19.9)
M5	60 (17.6)
M6	7 (2.1)
M7	42 (12.3)
Other[b]	27 (7.9)
Central nervous system involvement[c] (%) (n = 288)	75 (26.0)
Cytogenetics (%)	
t(8;21) (q22;q22) (AML1/ETO)	40 (11.7)
Inv16 (p13q22) or t(16;16)(p13;q22) (CBFβ/MYH11)	13 (3.8)
Normal karyotype	80 (23.5)
11q23 (MLL) abnormalities	41 (12.0)
Monosomy 7	10 (2.9)
Unknown	50 (14.7)
Treatment and supportive care	
Protocol (%)[d], non–Down syndrome specific	
POG	163 (48.3)
CCG	98 (29.1)
MRC	40 (11.9)
Other[e]	26 (7.7)
Down syndrome–specific protocol[d]	10 (2.7)
Registered on study (%)[d]	89 (26.4)
Median No. of chemotherapy courses started (IQR)	4.0 (2.0, 5.0)
Received G-CSF (any indication) (%)	166 (48.7)
Received intravenous immune globulin (%)	26 (7.6)

Abbreviations: AML, acute myeloid leukemia; CCG: Children's Cancer Group; FAB, French-American-British; G-CSF granulocyte-colony stimulating factor; IQR: interquartile range; MLL, mixed lineage leukemia; MRC: Medical Research Council; POG: Pediatric Oncology Group.

[a] Only available for children ≥2 years of age.

[b] Others were biphenotypia (n = 2), acute myeloid leukemia (AML) with multilineage dysplasia (n = 3), isolated granulocytic sarcoma (chloroma) (n = 2), and AML not further classified (n = 20).

[c] Unknown (n = 53).

[d] Four patients died before treatment started, and thus, n = 337.

[e] Other: Ekert (n = 12), in-house protocol (n = 13), and Cancer and Leukemia Group B (n = 1).

Table 2. Multiple Regression Analyses of Infection Outcomes[a]

Outcome and Potential Predictors	Estimate (95% CI)	*P* value
Microbiological sterile site infection	Rate ratio	
Down syndrome	0.75 (.37, 1.50)	.415
Treatment protocol, non–Down syndrome specific		
POG	Reference	
CCG	1.31 (.95, 1.80)	.096
MRC	1.72 (1.17, 2.52)	.006
Cumulative dose of cytarabine (g/m^2)	1.04 (1.02, 1.05)	<.0001
Greater than 15 d with neutropenia	1.19 (.87, 1.64)	.282
Days receiving corticosteroids	1.04 (1.03, 1.05)	<.0001
Clinically documented infection	Rate ratio	
Down syndrome–specific protocol	0.28 (.11, .75)	.011
Neutropenia (ANC $<0.5 \times 10^9$) at start of course	1.55 (1.21, 1.98)	.0005
Greater than 15 d with neutropenia	1.21 (.90, 1.62)	.211
Days receiving corticosteroids	1.02 (1.01, 1.03)	.002
Fluconazole prophylaxis	1.46 (1.06, 2.02)	.022
Fevers of unknown origin	Rate ratio	
Down syndrome	1.41 (1.00, 2.00)	.053
Obese vs nonobese[b]	1.44 (1.03, 1.99)	.031
Cumulative dose of cytarabine (g/m^2)	1.02 (1.00, 1.04)	.019
Greater than 15 d with neutropenia	0.68 (.51, .91)	.010
Days receiving corticosteroids	0.98 (.96, 1.00)	.090
Bacteremia	Odds ratio	
Down syndrome	0.59 (.25, 1.39)	.226
Treatment protocol, non–Down syndrome specific		
POG	Reference	
CCG	1.89 (1.29, 2.77)	.001
MRC	2.70 (1.72, 4.24)	<.0001
Cumulative dose of cytarabine (g/m^2)	1.05 (1.02, 1.07)	<.0001
Greater than 15 d with neutropenia	1.92 (1.35, 2.73)	.0003
Days receiving corticosteroids	1.06 (1.04, 1.09)	<.0001
Co-trimoxazole prophylaxis	1.13 (.75, 1.71)	.563
Sterile site gram-positive infection	Odds ratio	
Treatment protocol, non–Down syndrome specific		
POG	Reference	
CCG	1.22 (.78, 1.92)	.379
MRC	2.36 (1.37, 4.08)	.002
Diagnosed prior to 1 January 2000	0.90 (.59, 1.38)	.634
Cumulative dose of cytarabine (g/m^2)	1.05 (1.03, 1.08)	<.0001
Greater than 15 d with neutropenia	1.53 (1.04, 2.25)	.030
Days receiving corticosteroids	1.06 (1.04, 1.09)	<.0001
Sterile site gram-negative infection	Odds ratio	
Treatment protocol, non–Down syndrome specific		
POG	Reference	
CCG	2.18 (1.34, 3.56)	.002
MRC	1.46 (.73, 2.93)	.288
Greater than 15 d with neutropenia	2.55 (1.47, 4.43)	.001
Days receiving corticosteroids	1.04 (1.02, 1.07)	.001
Sterile site fungal infection	Odds ratio	
Diagnosed prior to January 1, 2000	2.30 (1.00, 5.28)	.050
Neutropenia (ANC $<0.5 \times 10^9$) at start of course	1.92 (.85, 4.34)	.117
Greater than 15 d with neutropenia	1.69 (.50, 5.72)	.400
Days receiving corticosteroids	1.05 (1.01, 1.09)	.013
Days receiving broad spectrum antibiotics	1.04 (1.00, 1.08)	.027
Sepsis		
Treatment protocol, non–Down syndrome specific	Odds Ratio	
POG	Reference	
CCG	1.37 (.73, 2.57)	.326
MRC	1.26 (.64, 2.46)	.506
Neutropenia (ANC $<0.5 \times 10^9$) at start of course	1.38 (.78, 2.44)	.271
Greater than 15 d with neutropenia	1.97 (1.04, 3.76)	.039
Days receiving corticosteroids	1.07 (1.04, 1.10)	<.0001
Co-trimoxazole prophylaxis	1.80 (.90, 3.61)	.095
Infection-related mortality[c]		
Days receiving corticosteroids	1.05 (1.02, 1.08)	.001

Abbreviations: ANC: absolute neutrophil count; CCG: Children's Cancer Group; CI: confidence interval; MRC: Medical Research Council; POG: Pediatric Oncology Group.

[a] Analyses were conducted using multivariable repeated measures Poisson or logistic regression.

[b] Obesity only available for children ≥2 years of age.

[c] Infection-related mortality is the univariate analysis because only one variable met entry criteria for multiple regression.

26 (7.6%; 95% confidence interval: 4.8%–10.4%) experienced death as a first event. Over the course of therapy, the cumulative incidence of any sterile site microbiologically documented infection was 218 (63.9%), bacteremia was 185 (54.3%), and a clinically documented infection was 263 (77.1%). Supplementary Appendix Table 1 illustrates the microbiologically documented infections on this study. Using the revised definition of invasive fungal infection (IFI) from the European Organization for Research and Treatment of Cancer/Mycosis Study Group [18], there were 38 proven IFIs, including 23 *Candida* species, 7 *Aspergillus* spp, and 8 other or unspecified IFIs. There were 8 probable IFIs.

There were 1277 courses of chemotherapy administered; Supplementary Appendix Table 2 illustrates the course characteristics and the infection outcomes. Non-co-trimoxazole antibacterial prophylaxis was very rare and only observed in 3 courses (0.2%). Fluconazole prophylaxis was administered in 693 courses (54.3%). There were 313 courses with at least one sterile site microbiologically documented infection (24.5%), 97

courses with sepsis (7.6%), and 16 infectious deaths (1.3%). The median number of days receiving any corticosteroid was 2 (IQR, 0–6). Supplementary Appendix Table 3 illustrates the median duration and dose in mg/m^2 of dexamethasone equivalents of corticosteroid exposure for those receiving POG-, CCG-, or MRC-based treatment. For those receiving MRC-based treatment, which does not include corticosteroids as chemotherapy, the median dose was 31.9 mg/m^2 of dexamethasone equivalents.

Supplementary Appendix Tables 4–6 illustrate the univariate models of infection, sepsis, and infectious death. In terms of patient characteristics, Down syndrome patients had a reduced risk of microbiologically documented infection and bacteremia. Obesity did not significantly influence the development of documented infection, sepsis, or infectious death. In terms of treatment variables, CCG- and MRC-based protocols were associated with more microbiologically documented infection compared with POG protocols, and sepsis was significantly more common with CCG- vs POG-based treatment. No differences in documented infection, sepsis, or death were seen when comparing CCG and MRC protocols (data not shown). The cumulative dose of cytarabine per course was specifically associated with microbiologically documented infection, bacteremia, gram-positive sterile site infection, and fever of unknown origin. In terms of nontreatment course characteristics, neutropenia at the start of the course was not associated with bacterial infections, sepsis, or infectious death but was significantly associated with clinically documented infection and sterile site fungal infection. Greater days of receiving corticosteroids was associated with a higher risk of microbiologically and clinically documented infection, bacteremia, sterile site gram-positive and gram-negative infection, sterile site fungal infection, sepsis, and infectious death. The only significant factor associated with infectious death was the duration of corticosteroid exposure. All measures of antibiotic administration were significantly associated with fungal infection.

Table 2 illustrates the multiple regression analyses of all outcomes. First, MRC protocols, in comparison to POG protocols, were associated with more microbiologically documented sterile site infection and more bacteremia. Second, cytarabine dose was independently associated with sterile site infection and bacteremia and more specifically, gram-positive infection. Third, duration of corticosteroid exposure was an independent risk factor for microbiologically documented sterile site infection, bacteremia, both gram-positive and gram-negative infection, fungal infection, clinically documented infection, and sepsis. Fourth, the 2 independent risk factors for sepsis were prolonged neutropenia and duration of corticosteroid exposure. Finally, only duration of corticosteroid was associated with infectious death.

DISCUSSION

In this large, population-based analysis including different treatment protocols, we made several key observations. First, corticosteroid exposure is an important risk factor for infection outcomes and, more specifically, is independently associated with both sepsis and infection-related mortality. Second, systemic corticosteroid exposure is common in pediatric AML, even when the treatment protocol does not include corticosteroids. Third, this study confirms that high-dose cytarabine is associated with bacteremia and, in particular, gram-positive infection, and that prolonged neutropenia continues to be an independent risk factor for bacterial and fungal infection in addition to sepsis.

We found that corticosteroid exposure was associated with higher rates of infection, sepsis, and infectious death. Although corticosteroid exposure has previously been determined to be a risk factor for IFI [19, 20], the relationship with other infection outcomes is less well recognized. In a randomized study of 147 patients receiving allogeneic SCT for hematological malignancy, those randomized to receive 35 days of methylprednisolone for graft-vs-host disease (GVHD) prophylaxis had a higher rate of infection, with bacteremia being the most common type of infection [21]. Conversely, another randomized study of methylprednisolone prophylaxis in allogeneic SCT found that there were fewer infections in the prophylaxis group although the study was difficult to interpret, given that the total amount of methylprednisolone received was similar in the 2 study arms because of more acute GVHD in the no prophylaxis group [22]. This study illustrates the importance of accounting for nonprotocol corticosteroid exposure in the evaluation of risk factors for infection outcomes.

Consistent with the literature, we found a higher risk of infection with longer duration of neutropenia [7, 23] and higher cumulative dose of cytarabine [24, 25]. However, we also found that obesity was not associated with infection outcomes, a finding distinct from those of the CCG [8, 26]. It is difficult to know whether these differences are related to a different population (predominately American vs Canadian) or different methodological approaches in infection and other outcome ascertainment.

In our study, Down syndrome was not associated with a higher risk of infection or sepsis. This finding is in contrast to most reports that have found Down syndrome to be an important risk factor for infection and infectious death [22]. In our cohort, 10 of 29 children with Down syndrome were treated on a Down syndrome–specific protocol. In univariate analysis, we found that Down syndrome–specific protocol was associated with a lower risk of infection outcomes. It is possible that our results may be explained by a lower dose intensity of Down syndrome–specific protocols compared with non–Down syndrome–specific protocols.

The major strength of our report is the rigor in identifying infections, given that a common group of trained personnel abstracted all infection data. Second, our findings are highly generalizable and allow the comparison of protocols from different cooperative groups. Another major advantage of our report is the approach; we examined factors associated with outcomes at the course level and not at the patient level. This approach has been advocated by others [25] and, very importantly, allowed us to evaluate factors that are expected to change between courses such as chemotherapy attributes, duration of neutropenia, and administration of corticosteroids.

However, our study must be interpreted in light of its limitations. First, the number of infectious deaths was limited. Second, there was heterogeneity in protocols and differences in supportive care throughout the centers. However, this heterogeneity is also a strength in terms of generalizability and the ability to identify how variability impacts on infection outcomes. In terms of protocol heterogeneity, because most cooperative groups build on previous studies in developing successor trials, protocols within a cooperative group should be more similar than protocols between different groups [27]. In terms of changes over time, we did not observe major difference in patients treated early vs late. Third, we do not know the reasons corticosteroids were used; corticosteroids may be used for a variety of reasons including for antiemetic control, transfusion reaction prophylaxis, and to treat cytarabine-related reactions. Corticosteroids may also be included as part of the treatment protocol, such as with CCG-based therapy. Although we attempted to control for confounding factors, it is possible that corticosteroid use is indicative of more ill patients, rather than causally related to outcomes. Finally, we conducted multiple analyses, and the *P* values must be interpreted cautiously in light of this repeated testing.

In conclusion, in pediatric AML, infection, sepsis, and infectious deaths were associated with duration of corticosteroid exposure. Our analysis suggests that corticosteroids should be avoided whenever possible for this population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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