

# Hyperglycemia increases the complicated infection and mortality rates during induction therapy in adult acute leukemia patients

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**Objective:** To determine the prevalence of hyperglycemia during induction therapy in adult patients with acute leukemia and its effect on complicated infections and mortality during the first 30 days of treatment.

**Methods:** An analysis was performed in a retrospective cohort of 280 adult patients aged 18 to 60 years with previously untreated acute leukemia who received induction chemotherapy from January 2000 to December 2009 at the Hemocentro de Pernambuco (HEMOPE), Brazil. Hyperglycemia was defined as the finding of at least one fasting glucose measurement > 100 mg/dL observed one week prior to induction therapy until 30 days after. The association between hyperglycemia and complicated infections, mortality and complete remission was evaluated using the Chi-square or Fisher's exact tests by the Statistical Package for Social Sciences (SPSS) in the R software package version 2.9.0.

**Results:** One hundred and eighty-eight patients (67.1%) presented hyperglycemia at some moment during induction therapy. Eighty-two patients (29.3%) developed complicated infections. Infection-related mortality during the neutropenia period was 20.7% (58 patients). Mortality from other causes during the first 30 days after induction was 2.8%. Hyperglycemia increased the risk of complicated infections (OR 3.97; 95% confidence interval: 2.08 - 7.57; p-value < 0.001) and death (OR 3.55; 95% confidence interval: 1.77-7.12; p-value < 0.001) but did not increase the risk of fungal infections or decrease the probability of achieving complete remission.

**Conclusion:** This study demonstrates an association between the presence of hyperglycemia and the development of complicated infections and death in adult patients during induction therapy for acute leukemia.

**Keywords:** Leukemia; Infection; Hyperglycemia; Mortality; Neutropenia; Fever

## Introduction

Hyperglycemia has been associated with nosocomial infections and mortality in a variety of inpatient populations<sup>(1-4)</sup>. Stress hyperglycemia is the elevation of blood glucose in the presence of acute illness. Factors contributing to hyperglycemia in critical illnesses include the release of stress hormones (e.g., epinephrine and cortisol), the use of medications such as exogenous glucocorticoids and catecholamines, and the release of inflammatory mediators in cases of sepsis or surgical trauma. All these conditions inhibit insulin release and action, thereby enhancing gluconeogenesis, inhibiting glycogen synthesis, and impairing insulin-mediated glucose uptake by peripheral tissues. Intravenous dextrose, commonly used in parenteral nutrition and antibiotic solutions, also contributes to hyperglycemia<sup>(5)</sup>.

Intensive glucose control has been shown to reduce infection rate and complications in critically ill patients in the intensive care unit (ICU) and after heart surgery<sup>(6,7)</sup>. However, a recent large-scale randomized trial indicated that such glycemic control is not effective in reducing ICU mortality and that glycemic control with intensive insulin therapy increases the risk of hypoglycemia and complications arising from hypoglycemia<sup>(8)</sup>.

It is well known that hyperglycemia adversely impairs neutrophil activity, including chemotaxis, formation of reactive oxygen species and the phagocytosis of bacteria<sup>(9)</sup>. It also affects other components of the immune system, increasing lymphocyte apoptosis and suppressing the proliferation of T cells due to the decreased expression of adenosine kinase<sup>(10)</sup>. The function of immunoglobulins and complement is attenuated due to their glycosylation in the hyperglycemia environment<sup>(11,12)</sup>.

The relationship between hyperglycemia and infections has rarely been studied in oncohematological patients, though it is a relevant issue in this population given their immunocompromised state and increased risk of hyperglycemia (eg. glucocorticoid use, chemotherapy induced hyperglycemia, stress induced hyperglycemia) and infections. Induction therapy for acute leukemias is performed using intense chemotherapy regimens with a high risk of neutropenic infections. In fact, neutropenic

fever, an early sign of infection requiring empiric therapy, occurs almost uniformly in patients undergoing induction chemotherapy for acute leukemias, and despite aggressive treatment, progression to a more complicated infection occurs in up to 15% of these patients<sup>(13)</sup>.

There are also few studies evaluating the incidence of hyperglycemia during induction therapy of acute leukemias, and those that have been published show a range of 10% to 56% depending on the glucose level considered as hyperglycemia<sup>(14-19)</sup>.

The aim of this study was to determine the prevalence of hyperglycemia during induction therapy for acute leukemias in adult patients and to determine the effect of hyperglycemia on complicated infection, mortality and complete remission rates.

## Methods

A retrospective cohort analysis was performed of newly diagnosed 18- to 60-year-old acute leukemia patients [including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) and biphenotypic acute leukemia] treated from January 2000 through December 2009 at the Hemocentro de Pernambuco (HEMOPE), a hematology reference center in the northeast of Brazil.

Medical records were reviewed to obtain demographic information, a description of the treatment protocol, leukemia risk category, date of diagnosis, comorbidities, use of prophylactic antibiotics, duration of neutropenic fever, documented infections, remission status and death during the first 30 days of induction treatment.

Patients were excluded if they had less than two fasting glucose measurements in the first 30 days of therapy.

To determine the occurrence of hyperglycemia, all serum fasting glucose values obtained during one week prior to the beginning of chemotherapy until 30 days after therapy induction were assessed. No capillary glucose values were included in this analysis.

Hyperglycemia was defined as one or more fasting glucose values of > 100 mg/dL during remission induction therapy. 'Early hyperglycemia' was considered when hyperglycemia occurred one week prior to the first day of induction chemotherapy or before the development of neutropenic fever or any documented infection and 'late hyperglycemia' when it occurred after the development of neutropenic fever or any documented infection.

Complicated infections were defined as sepsis, microbiologically documented or not, associated with hemodynamic failure requiring vasoactive drugs, the need of mechanical ventilation for respiratory failure or renal failure necessitating hemodialysis.

Complete remission was defined as a bone marrow aspirate with less than 5% blasts and restoration of normal hematopoiesis.

The frequency of glucose level measurements and glycaemic control, and the use of antibiotics or antifungal therapy were defined by the attending physician.

Outcomes were evaluated for patients with hyperglycemia during the first 30 days of induction chemotherapy and compared

with those of patients without evidence of hyperglycemia during the same time interval.

Primary endpoints included comparisons of the rates of complicated infections and mortality between patients who did or did not experience one or more episodes of hyperglycemia in the first 30 days of remission induction therapy.

The secondary endpoints were a comparison of these rates between patients who experienced 'early hyperglycemia' and 'late hyperglycemia' or hypoglycemia (defined as any glucose value < 60 mg/dL) and comparison of number of fungal infections and complete remission rates in those with or without hyperglycemia.

Differences with regard to rates of complicated infections, mortality, fungal infections and complete remission were analyzed using a Chi-square or Fisher's exact test when appropriate. Comparisons were considered significant when the type I error rate was greater than 5% (p-value < 0.05).

Multivariate logistic regression models (for complicated infections and mortality) were used to control for the effect of patient and leukemia characteristics on the association between hyperglycemia and clinical outcomes. Significant factors with a p-value < 0.05 in univariate analysis were entered into the multivariate models.

All statistical tests were performed using the Statistical Package for Social Sciences (SPSS) using the R software package (version 2.9.0).

## Results

Two hundred and eighty-five patients were admitted for remission induction therapy. Five were excluded (one because there was no available information about induction therapy and four because they had less than two glucose measurements during the first 30 days). Of the 280 patients evaluated, 188 (67.1%) experienced hyperglycemia during the first 30 days of remission induction therapy, of which 134 (47.8%) presented 'early hyperglycemia' and 148 (52.8%) presented 'late hyperglycemia'. Only 11 patients (3.9%) had previous diagnosis of diabetes mellitus. Patients had a median of five fasting glucose measurements in the first 30 days of treatment (range: 2-12).

Baseline characteristics according to hyperglycemia status are demonstrated in Table 1. Patients with hyperglycemia were found to be slightly older and more commonly of female gender than patients without hyperglycemia.

Eighty-two patients (29.3%) experienced complicated infections. The relationship between hyperglycemia during remission induction and treatment-related complicated infections during the first 30 days is shown in Table 2. On unadjusted univariate analysis, patients who experienced hyperglycemia had an odds ratio of 3.97 (95% confidence interval: 2.08-7.57; p-value < 0.001) for the development of complicated infections. The risk was also increased for older patients, 'early hyperglycemia', 'late hyperglycemia', hypoglycemia, more than six days of febrile neutropenia and a positive blood culture. On multivariate analysis, 'late hyperglycemia', hypoglycemia and a positive blood culture

Table 1 - Patients baseline characteristics by hyperglycemia status

Characteristic	Hyperglycemia		p-value
	Yes n (%)	No n (%)	
<b>Age (years)</b>			
18 - 29	56 (49.1)	58 (50.9)	< 0.001
30 - 39	52 (73.2)	19 (26.8)	
40 - 60	80 (84.2)	15 (15.8)	
<b>Gender</b>			
Female	103 (73.0)	38 (27.0)	0.034
<b>Body mass index</b>			
18.5 - 25	101 (67.8)	48 (32.2)	0.745*
25.1 - 30	27 (60.0)	18 (40.0)	
30.1 - 40	8 (66.7)	4 (33.3)	
< 18.5	4 (5.1)	3 (42.9)	
<b>Race</b>			
White	73 (68.9)	33 (31.1)	0.617*
Black	5 (71.4)	2 (28.6)	
Mulatto	79 (68.1)	37 (31.9)	
Indian	0 (0.0)	1 (100.0)	
<b>Diabetes</b>			
Yes	11 (100.0)	0 (0.0)	0.018
No	176 (65.7)	92 (34.3)	
<b>Comorbidity</b>			
Yes	46 (75.4)	15 (24.6)	0.120
No	142 (64.8)	77 (35.2)	
<b>Diagnosis</b>			
AML	109 (69.9)	47 (30.1)	0.534*
ALL	76 (63.3)	44 (36.7)	
Biphenotypic	3 (75.0)	1 (25.0)	
<b>White blood cell count</b>			
< 30 x 10 <sup>9</sup> /L	110 (68.3)	51 (31.7)	0.676
30 x 10 <sup>9</sup> /L	48 (63.2)	28 (36.8)	
> 100 x 10 <sup>9</sup> /L	30 (69.8)	13 (30.2)	
<b>Immunophenotype</b>			
AML	76 (68.5)	35 (31.5)	0.806*
Mature B ALL	24 (68.6)	11 (31.4)	
Precursor B ALL	32 (66.7)	16 (33.3)	
T - ALL	12 (54.5)	10 (45.5)	
T precursor ALL	5 (55.6)	4 (44.4)	
Biphenotypic	3 (75.0)	1 (25.0)	
<b>CNS involvement</b>			
Yes	13 (65.0)	7 (35.0)	0.969
No	106 (65.4)	56 (34.6)	
<b>AML prognosis</b>			
Favorable	6 (46.2)	7 (53.8)	0.485
Intermediate	17 (65.4)	9 (34.6)	
Unfavorable	17 (63.0)	10 (37.0)	
<b>B-ALL prognosis</b>			
Low risk	10 (71.4)	4 (28.6)	1.000*
High risk	10 (71.4)	4 (28.6)	
Very high risk	2 (66.7)	1 (33.3)	
<b>T-ALL prognosis</b>			
Low risk	5 (45.5)	6 (54.5)	0.477
High risk	12 (60.0)	8 (40.0)	
<b>Corticosteroid use</b>			
Yes	79 (63.2)	46 (36.8)	0.207
No	109 (70.3)	46 (29.7)	

\*p-value Fisher exact test

AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; CNS: central nervous system;

Table 2 - Risk of complicated infection according to risk factors

Risk factor	Complicated infection		OR (95% CI)	p-value
	Yes n (%)	No n (%)		
<b>Age (years)</b>				
18 - 29	23 (20.2)	91 (79.8)	1.47 (0.88 - 2.45)	0.007
30 - 39	21 (29.6)	50 (70.4)		
40 - 60	38 (40.0)	57 (60.0)		
<b>Hyperglycemia at any time</b>				
Yes	73 (38.8)	115 (61.2)	3.97 (2.08 - 7.57)	< 0.001
No	9 (9.8)	83 (90.2)		
<b>Early hyperglycemia</b>				
Yes	53 (39.6)	81 (60.4)	2.05 (1.38 - 3.03)	< 0.001
No	28 (19.9)	117 (80.1)		
<b>Late hyperglycemia</b>				
Yes	67 (45.3)	81 (54.7)	3.34 (1.96 - 5.71)	< 0.001
No	13 (13.5)	83 (86.5)		
<b>Hypoglycemia</b>				
Yes	5 (83.3)	1 (16.7)	2.97 (1.98 - 4.45)	0.009*
No	77 (28.1)	197 (71.9)		
<b>Days of febrile neutropenia</b>				
≤ 10 days	27 (13.0)	180 (87.0)	2.12 (1.45 - 3.11)	< 0.001
> 10 days	25 (58.1)	18 (41.9)		
<b>Positive blood culture</b>				
Yes	45 (47.4)	50 (52.6)	2.37 (1.66 - 3.39)	< 0.001
No	37 (20.0)	148 (80.0)		

\*Fisher exact test; OR: odds ratio; CI: confidence interval.

proved to be independent risk factors for the development of complicated infections.

Infection-related mortality during neutropenia was 20.7% (58 patients). Other causes of mortality during the first 30 days comprised 2.8% of the patients (three lung hemorrhage, four brain hemorrhage and one cardiogenic shock).

The odds ratio for death of patients presenting hyperglycemia was 3.55 (95% confidence interval: 1.77-7.12; p-value < 0.001). Other variables associated with mortality on univariate analysis included age, 'early hyperglycemia', 'late hyperglycemia', hypoglycemia, days with febrile neutropenia and a positive blood culture (Table 3). On multivariate analysis the variables 'early hyperglycemia', 'late hyperglycemia', hypoglycemia and positive blood culture remained independent risk factors for mortality.

Patients who experienced hyperglycemia did not exhibit significant differences in number of fungal infections (4.8% vs. 4.3%; p-value = 1.0) and complete remission rates (57.4% vs. 61.2%; p-value = 0.581).

Table 3 - Risk of death according to risk factors

Risk factor	Death		OR (95% CI)	p-value
	Yes n (%)	No n (%)		
<b>Age (years)</b>				
18 – 29	19 (16.7)	95 (83.3)		
30 – 39	17 (23.9)	54 (76.1)	1.44 (0.80-2.57)	
40 - 60	30 (31.6)	65 (68.4)	1.89 (1.14 - 3.14)	0.041
<b>Hyperglycemia at any time</b>				
Yes	58 (30.9)	130 (69.1)	3.55 (1.77 - 7.12)	<0.001
No	8 (8.7)	84 (91.3)		
<b>Early hyperglycemia</b>				
Yes	45 (33.6)	89 (66.4)	2.33 (1.47 - 3.71)	<0.001
No	21 (14.4)	125 (85.6)		
<b>Late hyperglycemia</b>				
Yes	53 (35.8)	95 (64.2)	3.13 (1.72 - 5.67)	<0.001
No	11 (11.5)	85 (88.5)		
<b>Hypoglycemia</b>				
Yes	4 (66.7)	2 (33.3)	2.95 (1.61 – 5.40)	0.029*
No	62 (22.6)	212 (77.4)		
<b>Days of febrile neutropenia</b>				
≤ 10 days	47 (19.8)	190 (80.2)		
> 10 days	19 (44.2)	24 (55.8)	2.56 (1.43 - 4.58)	<0.001
<b>Positive blood culture</b>				
Yes	34 (35.8)	61 (64.2)	2.07 (1.37 - 3.13)	0.001
No	32 (17.3)	153 (82.7)		

\*Fisher's exact test; OR: odds ratio; CI: confidence interval.

## Discussion

In this retrospective cohort, hyperglycemia was frequent among adult hospitalized patients with acute leukemia submitted to a remission induction therapy. Patients presenting hyperglycemia even at a low threshold (fasting glucose > 100 mg/dL) were at an increased risk of complicated infections and mortality, but not for fungal infections, neither for a decreased probability of complete remission.

In this study hyperglycemia was considered as at least one fasting glucose measurement > 100 mg/dL because of the most recent guidelines for the diagnosis of diabetes mellitus / impaired glucose tolerance<sup>(20)</sup>.

This study is consistent with two other studies in acute leukemia patients. Weiser et al. found that adult patients with ALL who experienced hyperglycemia (defined as  $\geq 2$  random glucose determinations  $\geq 200$  mg/dL) during remission induction therapy using the Hyper-Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone (CVAD) regimen had a shorter median survival (29 months vs. 88 months; p-value = 0.001) and were more likely to develop sepsis (16.5% vs. 8.0%; p-value = 0.03) or any complicated infection (sepsis, pneumonia, or fungal) (38.8% vs. 25.1%; p-value = 0.016) compared with patients without hyperglycemia<sup>(19)</sup>. Ali et al. examined the relationship between hyperglycemia and mortality during the hospitalizations of adult

AML patients and found that hyperglycemia during a patient's hospitalization was associated with increased hospital mortality (OR: 1.38; 95% confidence interval: 1.23-1.55; p-value < 0.001) after adjusting for covariates including disease state, treatment type and response. The rise in mortality was evident at even mild hyperglycemia levels (110-150 mg/dL). The odds of developing severe sepsis (OR: 1.24; 95% confidence interval: 1.13-1.38; p-value < 0.001) or severe sepsis with respiratory failure (OR: 2.04; 95% confidence interval: 1.44-2.91; p-value < 0.001) were also increased with hyperglycemia<sup>(14)</sup>.

In pediatric patients with ALL, Roberson et al. found similar outcomes with or without hyperglycemia during remission induction therapy<sup>(17)</sup>.

The results of this study demonstrated that this association of hyperglycemia and adverse outcomes persisted when the analysis was restricted to hyperglycemia occurring before neutropenic fever or documented infections. This suggests that hyperglycemia may be important early in the hospitalization of acute leukemia patients and not only during sepsis.

Derr et al. found an association between pre-neutropenia hyperglycemia and infections during the neutropenic period after bone marrow transplantation with an odds ratio of 1.11 (95% confidence interval: 1.01-1.21; p-value = 0.023) for each 10 mg/dL increase in mean glucose<sup>(21)</sup>. Another study from Japan failed to detect any effect of hyperglycemia on infection during bone marrow transplantation<sup>(22)</sup>.

Other important risk factor for mortality in the current study was the presence of hypoglycemia (< 60 mg/dL). This finding is consistent with several studies in critically ill patients and is the most probable cause of the negative results of tight glycemic control (80-110 mg/dL) in patients with sepsis in the ICU<sup>(23-25)</sup>.

## Conclusion

The findings of this study are limited in part by its retrospective, single institution nature. Also, glucose levels were not sampled in a standardized fashion and there was no standard for glucose control. The diagnosis of diabetes was based on past medical history in the medical record, which may have underestimated the actual number of patients with diabetes in this cohort.

However, the results are compelling and provide a strong rationale for studying this question prospectively as well as on the issue of whether tight glycemic control improves infection and mortality rates during treatment of acute leukemia in adults.

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