Hyperglycemia requiring insulin during acute lymphoblastic leukemia induction chemotherapy is associated with increased adverse outcomes and healthcare costs.

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Hyperglycemia Requiring Insulin during ALL Induction Chemotherapy Associated with Increased Adverse Outcomes and Healthcare Costs

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Abstract

Background:

Hyperglycemia is a complication of induction chemotherapy in 10–50% of pediatric patients with acute lymphoblastic leukemia (ALL). Though hyperglycemia in ALL patients is usually transient, it may be associated with adverse health outcomes. However, the risk factors for and consequences of hyperglycemia are poorly understood. We hypothesized that hyperglycemia significant enough to require insulin therapy during induction chemotherapy would be associated with increased morbidity and mortality in pediatric ALL patients during induction chemotherapyandin subsequent care.

Methods:

We abstracted clinical and resource utilization data from the Pediatric Health Information System (PHIS) database utilizing ICD-9 codes and medication charges. We used logistic regression analysis to predict the development of hyperglycemia. The effects of hyperglycemia on binary and count adverse outcomes following induction chemotherapy were modeled using mixed effect regression models.

Results:

An increased risk of hyperglycemia requiring insulin was associated with older age, female sex, higher-risk group and Trisomy 21. Patients on insulin for hyperglycemia had increased mortality following induction chemotherapy. These patients were more likely to have subsequent infectious complications, need for bone marrow transplant and risk of disease relapse. They also had greater length of inpatient stay, higher cost of care and were more likely to require ICU admission during induction chemotherapy.

Conclusions:

Hyperglycemia requiring insulin during induction chemotherapy in pediatric ALL is associated with an increased risk of short and long-term complications. Prospective studies are needed to analyze formal screening, preventive measures and optimal management practices for hyperglycemia during ALL induction chemotherapy.

Keywords: Hyperglycemia, Leukemia, Clinical Outcomes, Pediatrics, Retrospective Study

Background and Objectives:

Hyperglycemia is a recognized complication of induction chemotherapy in children with Acute Lymphoblastic Leukemia (ALL). Hyperglycemia is most common during the induction phase of therapy likely due in part to the use of medications including glucocorticoids and asparaginase products.[1–3] Typically, patients with standard-risk ALL (defined by the National Cancer Institute as having white blood cell count <50,000/μL and age 1–10 years at presentation) undergo a three-drug induction phase with vincristine, steroids (prednisone or dexamethasone), and asparaginase; patients designated under National Cancer Institute (NCI) high-risk category (white blood cell count ≥50,000/μL and/or 10 years of age or older at presentation)receive a four-drug regimen with doxorubicin or daunorubicin in addition to the above. Although it has been reported that 10–50% of pediatric patients with ALL develop any degree of hyperglycemia, only 4–8% have severe hyperglycemia necessitating insulin therapy.[1–7]

Prior studies have uniformly identified older age, co-existing diagnosis of Trisomy 21 and the presence of CNS disease as potential risk factors for hyperglycemia.[1,4,6–8] However, these studies report conflicting results or no data with regards to other important risk factors, including sex, socioeconomic status and type of steroid received during induction. In addition, there is limited evidence in the literature on how hyperglycemia during induction chemotherapy influences short- and long-term outcomes. Three retrospective, single-center analyses of relatively small cohorts of patients generated conflicting results on the association between hyperglycemia and the risk for adverse health outcomes, such as subsequent hospitalizations, infectious complications, and mortality.[7–9] Finally, there is no published data quantifying healthcare utilization in these patients.

In this study, we utilized a multi-center database to evaluate a large, diverse population of pediatric patients undergoing treatment for ALL to elucidate the associated risk factors for hyperglycemia during induction chemotherapy and the association of hyperglycemia during induction chemotherapy

with short-term and long-term clinical outcomes. We hypothesized that the incidence of adverse outcomes including hospitalization, infectious complications and mortality would be greater in patients who required insulin during induction chemotherapy compared to patients who did not require insulin.

Methods:

Data Collection

We extracted data from the Pediatric Health Information System (PHIS) database for the period 01/01/2004 through 10/31/2015. We included patients 1 – 21 years of agewith an encounter for acute lymphoblastic leukemia as a primary or secondary ICD-9 diagnosis from 1/01/2004 through 12/31/2011. Weidentified patients in induction chemotherapy by selecting the first encounter with acute lymphoblastic leukemia as a primary or secondary ICD-9 diagnosis code and medication charges for vincristine, peg-as paraginase or L-as paraginase, and dexamethasone or prednisone during the encounter. Patients with medication charges for insulin on two or more calendar days in the 30-day period following the first day of the initial encounter were included in the cohort of patients requiring insulin. We classified patients as higher risk if they were ten years or older during the first encounter or if they received doxorubicin or daunorubicin (identified by medication charges) during this admission. NCI high risk designation is based on presenting age and white blood cell count. Since we do not have access to lab values as part of PHIS, we used patient's age and doxorubicin/daunorubicin administration as a proxy for higher risk status. We then collected data from all subsequent encounters in the four-year time period following initial hospital admission to track data on outcomes of interest. The study period end date was selected due tochanges fromtheICD-9 to ICD-10systemin October 2015. We felt this change would impact certain coding practices and thus reliability of follow-up data.

We abstracted the following information from the included initial encounter: demographic data, medication charges (insulin and doxorubicin or daunorubicin), household income, payer source, length of stay, cost of the encounter, mortality, Intensive Care Unit (ICU) admission, encounter severity level, and associated ICD-9 codes for pancreatitis, dyslipidemia, acanthosis nigricans, obesity and Trisomy 21. Household income is estimated by the database using the average income data for the patient's reported zipcode, based on United States census data. Encounter costs are calculated by summing all of the encounter's billed services and adjusting for the hospital's ratio of costs to charges (based on each hospital's official cost report submitted to the Center for Medicare and Medicaid Services (CMS)) and the cost of living within the geographic area of the hospital (based on the CMS wage index). The variable 'encounter severity level' represents a relative score determined by computerized algorithm which takes into account All Patient Refined Diagnosis Related Group(APR-DRG), principal and secondary diagnoses, patient age and operative procedures during the encounter. This algorithm stratifies patient acuity into a four-point scale with 1 being least and 4 being the greatest severity level.

We collected data from all subsequent encounters in the four-year time period following initial hospital admission to track data on outcomes of interest. Data abstracted from subsequent encounters included: ICU admission, mortality, procedure codes forbone marrow transplantation (BMT) and ICD-9 codes for central line infection, bacteremia, sepsis, candidemia, aspergillosis, osteonecrosis, pancreatitis and relapsed leukemia. Study approval was obtained from the institutional review board for all study procedures.

PHIS Database

The PHIS database collects clinical and resource utilization data from 52 freestanding children's hospitals throughout the United States. All data are de-identified at the time of submission. We included data from the 30 member hospitals which contributed complete data throughout the entire duration of our study period.

Statistical Analysis

We performed data analysis using Stata 15.1 (College Station, TX). Two-sided p-values of <0.05 were considered significant. We compared categorical outcomes using Chi-squared test or Fisher's Exact test based on expected cell counts. We compared continuous outcomes by two-sample t-test for difference of means. We linked records from the initial qualifying encounter with subsequent encounters through a unique patient identifier corresponding to the patient's PHIS record. We conducted a univariate and multi variate mixed effect logistic regression analysis with a random hospital effect to predict the development of hyperglycemia using the following baseline characteristics: age, sex, ethnicity, income, trisomy 21,pancreatitis, higher risk group, prednisone use and encounter severity level. All baseline characteristics analyzed in the univariate model were adjusted for in the multivariate model. For outcomes following the initial hospitalization, we conducted a mixed effect logistic regression model with a random hospital effect to model the effects of hyperglycemia on binary adverse outcomes and mixed effect negative binomial regression model with a random hospital effect to model the effects of hyperglycemia/insulin use on count outcomes (i.e., number of encounters for infectious complications). Models were controlled for the effect of age, sex, ethnicity, income, trisomy 21, pancreatitis, higher-risk group, Prednisone use, and severity level. One hundred sixteen patient encounters were excluded from analysis of income data due to missing information. All regression models excluded

patients who had received both prednisone and dexamethasone from analysis (n=231) as the type of steroid use (dexamethasone vs. prednisone) was a predictor of interest in our model. This did not change the significance of any results apart from modelling results for ALL relapse.

Results:

In total 6,213 patients met inclusion criteria. 453 of these patients (7.3%)required insulin according to our predetermined definition (Table 1). Patients who required insulin during induction chemotherapy were older (mean age 11.2 years versus 6.2 years), were more likely to identify as Hispanic, and were more likely to have a co-existing diagnosis of Trisomy 21. There were a greater proportion of higher risk patients in the group requiring insulin therapy. Additionally, patients requiring insulin were more likely to experience pancreatitis during the first thirty days of induction therapy. On univariate analysis all examined variables appeared to be associated with increased odds of developing hyperglycemia requiring insulin (Table 2). On multivariate analysis, older age (OR 1.17, 95% CI 1.14 – 1.21), female sex (OR 1.94, 95% CI 1.56 – 2.42), the presence of trisomy 21 (OR 4.72, 95% CI 3.10 – 7.18), higher risk group (OR 2.17, 95% CI 1.47 – 3.20), greater level of encounter severity(OR 1.64, 95% CI 1.45 – 1.86), and occurrence of pancreatitis (OR 6.51, 95% CI 3.72 – 11.37)were significantly associated with hyperglycemia. Patients who received insulin during induction chemotherapy had increased hospitalization costs and length of stay as well as increased likelihood of ICU admission and mortality (Table 3). Patients also had a greater utilization of hospital resources during subsequent encounters with a significantly greater number of overall hospital admissions per patient (13.4 versus 11.7 encounters per patient, p<0.001) (Table 3).

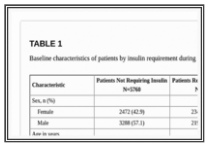

TABLE 1

Baseline characteristics of patients by insulin requirement during induction therapy.

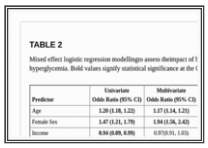

TABLE 2

Mixed effect logistic regression modellingto assess theimpact of baseline characteristics on risk of developing hyperglycemia. Bold values signify statistical significance at the 0.05 level.

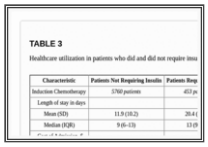

TABLE 3

Healthcare utilization in patients who did and did not require insulin therapy during induction therapy.

With regression modelling, hyperglycemia requiring insulin use was associated with significantly increased odds of mortality following induction (OR1.61, 95% CI 1.17 – 2.23)and ICU admission during induction (OR 1.40, 95% CI 1.07 – 1.85), as well as increased odds of later ALL relapse (OR 1.39, 95% CI 1.01 – 1.91) and bone marrow transplantation (OR 1.52, 95% CI 1.11 – 2.08) (Table 4). Negative binomial regression modelling found associations between hyperglycemia and an increased incidence rate ratio (IRR) of encounters complicated by ICU admission (IRR 1.55, 95% CI 1.28 – 1.88), bacteremia (IRR 1.26, 95% CI 1.02– 1.57), central line infection (IRR 1.54, 95% CI 1.12 – 2.11), and sepsis (IRR 1.48, 95% CI 1.21 – 1.82)(Table 5).

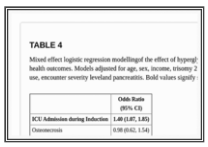

TABLE 4

Mixed effect logistic regression modellingof the effect of hyperglycemia during induction therapy on adverse health outcomes. Models adjusted for age, sex, income, trisomy 21, ethnicity, higherrisk group, prednisone use, encounter severity leveland pancreatitis. ...

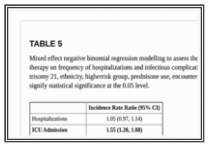

TABLE 5

Mixed effect negative binomial regression modelling to assess the impact of hyperglycemia during induction therapy on frequency of hospitalizations and infectious complications. Models adjusted for age, sex, income, trisomy 21, ethnicity, higherrisk group, ...

Discussion:

The results of this study suggest that hyperglycemia requiring insulin administration during induction chemotherapy is associated with increased morbidity and mortality, as well as increased short and long-term complications in pediatric patients with ALL. The major strength of our study lies in its analysis of over 6,000 patients from 30 different children's hospitals across the United States. The PHIS database, and by extension our study cohort, provides information from a large, diverse patient population with representation from most metropolitan areas in the United States. This study represents the only multi-center study to evaluate the impact of hyperglycemia on pediatric patients during induction chemotherapy for leukemia.

Despite the existence of several prior published studies evaluating the prevalence of hyperglycemia during induction chemotherapy, the true prevalence is not known due to variations in the methods used for monitoring glycemic status. Retrospective chart reviews rely on plasma blood glucoses documented in the patient's clinical record, which may not reflect the full picture of dysglycemia. It is unclear whether the development of mild or moderate hyperglycemia that resolves without the need for insulin therapy is associated with higher risk for adverse outcomes. On the other hand, patients who develop severe persistent hyperglycemia are typically started on insulin during induction chemotherapy and are thus likely to be at a higher risk for additional complications. There are no standardized guidelines on monitoring for hyperglycemia or protocols to guide insulin initiation. However, the proportion of patients requiring insulin for hyperglycemia during induction chemotherapy for ALL reported in the literature is fairly consistent across studies (Table 6).[1,4,7,9–11]

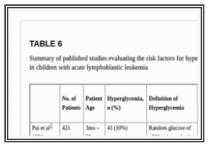

TABLE 6

Summary of published studies evaluating the risk factors for hyperglycemia and its associated complications in children with acute lymphoblastic leukemia

Pediatric patients undergoing induction chemotherapy are at high risk for hyperglycemia due to a variety of factors. Acute stress, critical illness, and the direct effect of certain chemotherapeutic agents used during induction phase have been shown to increase blood glucose concentrations.[1–6,12–18] In addition, certain patient characteristics including trisomy 21, female sex, pancreatitis, increased age and higher risk group appear to be associated with the development of hyperglycemia requiring insulin. Prior studies have noted an increased risk of hyperglycemia with many of these characteristics, though no previous work has comprehensively evaluated all within the same cohort.[1,4,6–11,19]While modelling results did identify an association between prednisone use and increased odds of hyperglycemia on univariate analysis, this relationship was not significant on multivariate analysis. In many currently used treatment protocols, older children are treated with prednisone rather than dexamethasone. Thus, the disappearance of an association between hyperglycemia and prednisone use on multivariate analysis may represent confounding by the influence of age and higher risk status. Of note, prior studies have demonstrated an association between dexamethasone use and increased rates of hyperglycemia, steroid myopathy, osteonecrosis, and infection-related mortality.[20–22] Dexamethasone use has also been associated with lower relapse rates and higher rates of event-free survival compared to prednisone use.[20,22,23] We found the association between hyperglycemia and disease complications to be significant even after controlling for the type of steroid administered in our regression analysis.

In our cohort of patients, insulin treatment during induction chemotherapy was associated with increased infectious and non-infectious complications. These results support previously published findings of increased mortality, decreased relapse-free survival, decreased overall survival and increased risk of infectious complications in patients that developed hyperglycemia during induction chemotherapy.[4,7,9, 10]While we found an increased rate of bacteremia, central line infection and sepsis in patients with hyperglycemia, we are unable to derive causal inference about these outcomes. It is certainly possible that infectious complications were an inciting factor for hyperglycemia. Infectious events are also associated with an increased risk of ICU admission and mortality. In addition, hospitalization costs will vary dramatically in the setting of infection, critical illness requiring ICU admission or therapy for relapsed disease. Prospective studies will be better able to isolate the effect of hyperglycemia on infectious complications and resource utilization.

There are several limitations to this study. The PHIS database is an administrative database and therefore patients and outcomes of interest can only be identified if the correct ICD-9 codes have been selected by hospital staff. Thus, some conditions of interest may be under-estimated. Certain patient characteristics which have been cited in prior works as risk factors for the development of hyperglycemia (including increased body mass index and family history of diabetes) were unable to be analyzed in our study due to the limited information available in an administrative (PHIS) database. We were unable to adjust for patient race and payer in our multivariate analysis due to the large number of encounters with missing data. In addition,

laboratory and pathology data, such as leukemia subtype (B or T cell ALL), cytogenetics, minimal residual disease status or the presence of genomic modifiers influencing medication metabolism and the risk of chemotherapy-associated toxicity, are not collected in this database. These features both affect treatment decisions as well as impact other outcomes of interest and are an important consideration in the application of our results.

Our study is the first to define hyperglycemia in terms of severity in order to capture patients at maximum risk due to severe persistent hyperglycemia necessitating insulin therapy. Most patients with mild or moderate hyperglycemia during induction chemotherapy will not require insulin. While our study may underestimate the total number of patients with hyperglycemia of any degree, we were able to isolate and describe the risk factors and complications associated with severe persistent hyperglycemia requiring insulin therapy, which we believe is ultimately a strength of our work. We chose to define our patient cohort as those who received two or more calendar days of insulin to limit the inadvertent inclusion of patients who received insulin for alternate reasons, such as the management of hyperkalemia due to tumor lysis syndrome. As we do not have access to the rationale for insulin use or the ability to review correlative lab values, we cannot confirm this with complete certainty.

We also chose to identify higher risk status using age and anthracycline administration during induction chemotherapy. Approximately one-third of children with B-ALL are high-risk by NCI risk group at the time of presentation.[24] In comparison, 45.9% of patientsin our cohort were classified as higher risk, likely due to several factors. Patients with T-ALL typically receive anthracyclines during induction therapy. ICD-9 diagnosis codes do not differentiate between B-ALL and T-ALL, and therefore patients with T-ALL would be included in the higher risk group. While T-ALL was previously considered to be higher risk due to poor overall prognosis, treatment with more intensive chemotherapy protocols have resulted in excellent outcomes.[25]In addition, on Children's Oncology Group (COG) protocols only patients with NCI high-risk B-ALL receive anthracyclines during induction therapy. However, other consortium groups in the United States administer anthracycline therapy to all children with B-ALL during initial chemotherapy. Some members of these consortium groups contribute data to the PHIS database. However, over 90% of children with malignancies are treated within COG member institutions.[26] Therefore, the definition used will apply for most contributing hospitals. We believe that the association between higher risk group and development of hyperglycemia is especially notable when it is considered that many children with NCI standard-risk disease, who are considered to have better prognosis, were allocated to our higher risk group.

We found that a significantly greater proportion of the patients in our study requiring insulin therapy compared to those not requiring insulin experienced pancreatitis during early therapy as a complication(7.7% vs 0.7%, $p<0.001$). Severe pancreatitis considered related to asparaginase administration is an indication to hold further doses of asparaginase. Several studies have demonstrated an associated with an increased risk of relapse and death in patients who have had asparaginase withheld due to intolerance or toxicities.[27–29]Though we controlled for this factor in our multivariable regression analysis, only 1.2% of our overall cohort was documented to experience this complication, which may underrepresent its prevalence. Other asparaginase-associated toxicities, such as asparaginase hypersensitivity, may lead to the decision to change medication formulation or withhold doses as well. The majority of asparaginase doses following induction therapy are administered on an outpatient basis, which is also the setting in which most hypersensitivity reactions are managed. Data on outpatient visits are contributed to the PHIS database for only few member hospitals, and therefore we were unable to further explore the relationship of asparaginase substitution on outcomes.

The work presented herein contributes important information to this field as it represents a large cohort of children treated in diverse settings. In the past decade, there have been dramatic improvements in survival for childhood leukemia, with 5-year survival rates of 75–90% in patients with newly diagnosed childhood ALL. As outcomes have improved, many have started to focus on minimizing the toxicities associated with therapy. Our findings suggest that hyperglycemia during induction chemotherapy may be associated with an increased risk of short and long-term complications. As hyperglycemia can be easily identified through routine screening measures, the development of surveillance protocols for early recognition of hyperglycemia in pediatric patients undergoing chemotherapy induction for ALL may be of benefit. Additional studies are needed to further characterizeand determine whether the identification and management of hyperglycemia results in improved health outcomes for this patient population.

Conclusions:

In this multi-center study of a large, diverse patient cohort, hyperglycemia requiring insulin use during induction chemotherapy for Acute Lymphoblastic Leukemia was associated with high utilization of healthcare resources and increased morbidity and mortality in pediatric patients. Further studies are needed to identify patients at highest risk of developing hyperglycemia, to determine optimal protocols for glycemic monitoring and treatment during chemotherapy, and to evaluate whether these interventions impact patient outcomes.

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Abbreviation

ALL	Acute Lymphoblastic Leukemia
APR-DRG	All Patient Refined Diagnosis Related Group
BMT	Bone Marrow Transplantation
CMS	Center for Medicare and Medicaid Services
ICU	Intensive Care Unit
IRR	Incidence Rate Ratio
NCI	National Cancer Institute
OR	Odds Ratio
PHIS	Pediatric Health Information System

Footnotes

This manuscript was presented in poster format as: Adverse Outcomes in Patients with Hyperglycemia Requiring Insulin during Induction Chemotherapy for Pediatric Acute Lymphoblastic Leukemia at the 2019 American Society of Pediatric Hematology Oncology Meeting in New Orleans, LA. Abstract published in: *Pediatr Blood Cancer*. 2019; Volume 66 (Supplement 2).

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Ramasubramanian Kalpatthi and Sri priya Raman conceptualized and designed the study and reviewed and revised the manuscript for important intellectual content.

James Zullomade substantial contributions to acquire the data and critically reviewed and revised the manuscript.

Nursen Gurtunca made substantial contributions to the conception and direction of the manuscript as well as interpreted the data. She reviewed and revised the manuscript in all forms.

Jun Zhang and Robert Krafty analyzed and interpreted the data and revised and reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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