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Approval Sheet

Intravenous immunoglobulin supplementation during pediatric B-cell acute lymphoblastic leukemia treatment – Associations with receipt and outcomes

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Abstract Cover Page

Intravenous immunoglobulin supplementation during pediatric B-cell acute lymphoblastic leukemia treatment – Associations with receipt and outcomes

By

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MD, University of Toledo College of Medicine and Life Sciences, 2015

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An abstract of

A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research 2021

Abstract

Intravenous immunoglobulin supplementation during pediatric B-cell acute lymphoblastic leukemia treatment – Associations with receipt and outcomes

By: Holly Edington, MD

Background: Children with B-cell acute lymphoblastic leukemia (B-ALL) experience severe infections during treatment, which intravenous immunoglobulin (IVIG) supplementation may mitigate. IVIG supplementation currently occurs in approximately 30% of children with B-ALL, but evidence for its indications and benefits is sparse.

Objective: To compare disease and demographic characteristics by receipt of IVIG amongst children with B-ALL, and to evaluate outcomes following IVIG supplementation.

Methods: A retrospective cohort analysis examined children age 1-21 years with B-ALL treated at Children's Healthcare of Atlanta from 2010 to 2017. Demographic, disease, treatment, and outcome data were collected from the electronic medical record. Patient characteristics were compared between patients with an immunoglobulin G (IgG) level checked vs. not checked, and by IVIG receipt among those with an IgG level checked. Multivariable logistic regression models identified factors associated with IVIG receipt. For IVIG recipients, general estimating equation modeling with Poisson distribution was used to compare rates of outcomes between IVIG supplemented and non-supplemented days.

Results: In total, 373 patients met inclusion criteria. IVIG was administered to 114 (30.5%) patients. An IgG level was checked in 251 (67.3%) patients. Median IgG nadir was lower for IVIG recipients vs non-recipients (404 vs 675mg/dL, $p<0.01$). IVIG recipients were younger at diagnosis (4 vs 6 years, $p<0.01$) and had more severe infections per 1,000 treatment days (4.2 vs 2.5, $p<0.01$). The odds of IVIG administration were lower for Non-White patients (Odds ratio (OR) 0.43, 95% Confidence interval (CI) 0.22-0.83), higher for patients with more than 2 severe infections during treatment (OR 2.57, 95% CI 1.28-5.18) and higher for National Cancer Institute standard risk patients with IgG nadir <500mg/dL (OR 7.45, 95% CI 3.54-15.70), adjusting for covariates. Rates of emergency department (ED) visits, hospitalization days, febrile neutropenia episodes and severe infections were lower during IVIG supplemented days vs. non-supplemented days (Rate ratio (RR) 0.52, CI [0.42-0.63]; RR 0.35, CI [0.26-0.46]; RR 0.29, CI [0.19-0.43]; RR 0.37, CI [0.27-0.49], respectively).

Conclusion: Patient characteristics differed by IVIG receipt status. IVIG supplementation can be beneficial in children with B-ALL to reduce infection-related outcomes. Prospective studies can help establish guidelines for IVIG supplementation and IgG monitoring.

Cover Page

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INTRODUCTION

More than 80% of children with acute lymphoblastic leukemia (ALL) will experience at least one severe viral, bacterial, or fungal infection during their multi-year treatment course, and as a result, experience significant morbidity and mortality (1). Severe infections can lead to increased hospitalizations, exposure to antibiotics, delays in chemotherapy, and risk of end organ damage (1). Enhanced supportive care approaches such as rapid antibiotic initiation with fever and antibiotic prophylaxis have decreased infection-related morbidity and mortality, but the factors that predispose certain patients to severe infections, and which interventions can best prevent infections, remain incompletely understood (2, 3).

B-cell acute lymphoblastic leukemia (B-ALL) results from malignant clones of B-lymphocytes. Immunoglobulin G (IgG) production is a key component of normal B-lymphocyte function and plays a critical role in humoral immunity and susceptibility to infections (4). Curative chemotherapy approaches are aimed at eliminating B-cells and likely impact the entire B-cell compartment beyond the malignant clone (5, 6). The impact of low levels of IgG, known as hypogammaglobulinemia, is of particular interest in children with B-ALL as intravenous immunoglobulin (IVIG) is available to treat hypogammaglobulinemia and reduces the incidence of infection in several diseases (7). IVIG is approved through the United States Food and Drug Administration for primary hypogammaglobulinemia caused by primary immunodeficiency (7-9). IVIG has shown some benefit in adults with chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) for infection prevention (10). While IVIG is used off-label in approximately 30% of pediatric patients with B-ALL for secondary hypogammaglobulinemia, there have only been two, small pediatric studies evaluating the use of IVIG in this population - neither of which suggested that IVIG is effective for infection prevention during standard chemotherapy approaches (8, 9). There are no published guidelines about when and why to initiate IVIG

supplementation in children with B-ALL and there is limited clinical evidence as to the benefit of IVIG supplementation (8, 9). Ultimately, the decision to begin IVIG supplementation is based on the medical provider's discretion and has largely been extrapolated from the experience of IVIG in primary immunodeficiency and in CLL.

We aimed to address several gaps in the literature regarding IVIG supplementation in pediatric B-ALL. Within a single institution retrospective cohort, we first described the associations between patient characteristics and receipt of IVIG supplementation. We conceptualized based on biologic mechanisms that hypogammaglobulinemia and frequent, severe infections would influence a medical provider's decision to begin IVIG supplementation. We considered other factors that may be associated with hypogammaglobulinemia and severe infections when conceptualizing their relationship with IVIG supplementation (**Figure 1**).

Second, we examined the effect of IVIG on rates of outcomes by comparing these outcomes during IVIG-supplemented vs non-supplemented days. We selected severe infection episodes and febrile neutropenia episodes as outcomes of interest as they are obtainable from medical chart review and are of inherent clinical and biologic interest. We also selected emergency department (ED) visits and hospitalization days as outcomes since they are important infection-related factors that influence health utilization, morbidity and quality of life. By analyzing the effect of IVIG on these outcomes, this study can provide more evidence to inform physician decision making and future studies of IVIG supplementation.

BACKGROUND

B-ALL develops when B-lymphocytes undergo malignant transformation. Under normal physiologic conditions, B-lymphocytes are responsible for humoral immunity, which involves antigen recognition and binding as well as immunoglobulin production (4). IgG is multifunctional, playing a role in the first line of immune response, including opsonization and agglutination for phagocytosis of bacteria, cell-mediated cytotoxicity, complement activation, and neutralization of toxins and viruses (4). Serum IgG levels differ by age, starting at a mean peak of 1121 mg/dL (95% Confidence Interval (CI) 636-1606 mg/dL) at birth and decreasing to a nadir of 334 mg/dL (95% CI 176-581 mg/dL) around 3 months of age, then slowly increasing until reaching mean adult levels of 994 mg/dL (95% CI 636-1349 mg/dL) by 9-10 years of age (11). There is evidence that serum IgG levels differ by race, with Black and Asian adults having higher mean IgG levels than White adults (12). Patients can experience low IgG levels, also known as hypogammaglobulinemia, due to either primary or secondary causes.

Primary immunodeficiency (PID) is a heterogeneous group of innate disorders of immune regulation characterized by impaired immune response, with more than half of diagnoses being B-cell-related disorders that can result in hypogammaglobulinemia (13). Patients with B-cell PID generally have increased rates of sinopulmonary infections (13). Treatment of primary hypogammaglobulinemia may include immunoglobulin replacement therapy (IGRT) with either IVIG or subcutaneous immunoglobulin to reduce the rates of infections (7).

Secondary hypogammaglobulinemia has a heterogeneous etiology, but can be broadly categorized into malignancy-associated and therapy-related hypogammaglobulinemia (14). The most common B-cell malignancies associated with secondary hypogammaglobulinemia are CLL and MM, both of which predominantly affect adults (15). Conventional therapies that can result

in secondary hypogammaglobulinemia are commonly used to suppress B-cells in malignancies, such as corticosteroids, cyclophosphamide and other chemotherapies that nonspecifically kill fast growing cells (15). More recently, monoclonal antibodies and derivatives which directly target epitopes on B-cells – for example, rituximab (anti-CD20) and blinatumomab (anti-CD19) – have been used to treat hematologic malignancies and immune dysregulation disorders and can also cause secondary hypogammaglobulinemia (14-16). Additionally, chimeric antigen receptor T-cell (CAR-T) therapy and hematopoietic stem cell transplantation (HSCT) are associated with varying degrees of secondary hypogammaglobulinemia (17-20).

Unlike in PID, the role of IGRT for infection prevention in adults with secondary hypogammaglobulinemia is unclear due to limited evidence. A 2009 systematic review and meta-analysis of nine randomized controlled trials comparing prophylactic IVIG with a control (placebo, no treatment, another immunoglobulin preparation, or a different administration schedule or dose) in patients with CLL and MM did not show a benefit for routine IVIG prophylaxis (10). However, the study suggested that although IVIG does not decrease mortality, IVIG was associated with a significant decrease in clinically documented infections (10). This meta-analysis included patients treated in the 1980s and 1990s; since then, treatment protocols have dramatically changed for CLL and MM due to the introduction of monoclonal antibodies into upfront therapy. A 2019 consensus-based guideline for infection management in MM patients does not recommend routine IVIG use due to lack of current trials (21).

For pediatric oncology patients, the causes and prevalence of secondary hypogammaglobulinemia are less clear than for adults. While in adult CLL approximately 25-70% of patients have malignancy-associated hypogammaglobulinemia, the prevalence of hypogammaglobulinemia in children with B-cell malignancies is unknown as it is not routinely monitored (22-24). In children with B-ALL, hypogammaglobulinemia may be associated with the

intensity of chemotherapy and/or the duration of treatment (25). In a small study (n=20) of children, 25% of patients with pediatric leukemia had decreased levels of IgG 6 months after chemotherapy was completed (26). Survivors of pediatric leukemia have also been noted to have decreased levels of vaccine-specific IgG despite having overall normal IgG levels after cancer-directed treatment is complete (27).

The need for evidence to understand hypogammaglobulinemia in pediatric B-ALL patients is underscored by the need for effective methods to prevent infections in this vulnerable population. The burden of infections in children undergoing treatment for B-ALL is substantial. In a study of children with ALL treated on the Total XV study, more than 80% experienced at least one Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher infection during their treatment (1). Of these, sinopulmonary, bloodstream infections, and gastrointestinal infection are the most common and can be caused by bacterial, viral, or fungal pathogens (1). Infections contribute to morbidity including risk of end organ damage and exposure to antibiotics and hospitalization. Infections can also result in chemotherapy delays and modifications (1). Chemotherapy delays and interruptions can contribute to an increased risk of relapse (28, 29). Antibiotic prophylaxis has been recommended in select situations for B-ALL patients to reduce bacterial infections, but is not universally endorsed and does not obviate all the infectious risks (2). Similarly, prophylaxis with antifungals is not uniformly recommended for children with B-ALL due to weak evidence (3). Additionally, infection risk changes at different time points during treatment for pediatric B-ALL, with more infections occurring in the myelosuppressive treatment phase prior to maintenance than during the maintenance phase of chemotherapy (30, 31).

There is understandable interest in IVIG as an intervention for infection prevention, given the prevalence of infections in children with B-ALL, the few evidence-based infection

prophylaxis interventions available, and the underlying immune mechanisms of B-cell malignancy and secondary hypogammaglobulinemia. Similarly to the adult experience, however, the indications for treatment of secondary hypogammaglobulinemia in pediatric oncology patients are unclear due to limited studies (8, 9). Infants with ALL (age ≤1 year) have a worse prognosis than older children and therefore receive more intensive chemotherapy (32). Since infants experience significantly higher rates of early death during chemotherapy, IVIG supplementation is required for all patients with IgG ≤500mg/dL, though there have not been studies to evaluate its efficacy at infection prevention (32). For children age ≥1 year with B-ALL, there are no standard guidelines for IVIG supplementation. In a recent study of IVIG use in children with B-ALL, Van Winkle et al showed that patients who received double-delayed intensification chemotherapy and patients with an episode of bacteremia or fungemia before the maintenance phase of treatment were significantly more likely to receive IVIG supplementation (8). Another study suggested that IVIG given to children with B-ALL during the maintenance phase of treatment does not decrease the frequency of febrile illnesses (9). Despite the paucity of evidence, approximately 30% of children with B-ALL receive IVIG supplementation during modern cancer treatment approaches (8). IVIG administration is not a benign intervention, as adverse reactions of varying severity can occur in up to 25-40% of children (33-36). In addition, IVIG is a human plasma-derived product and therefore carries a theoretical risk of infection transmission from the product itself (37). IVIG is currently in short supply nationally due to increased demands and decreased supply (38). Therefore, it is of significant clinical importance to establish evidence for the appropriate use and potential benefits of IVIG in the pediatric B-ALL population.

METHODS

Hypotheses and Specific Aims

We hypothesized that IVIG receipt during treatment for pediatric B-ALL was associated with: 1) hypogammaglobulinemia and 2) previous history of severe infection. We also hypothesized that ED visits and hospitalization days decreased during IVIG supplementation. The first specific aim was to describe disease and demographic characteristics of pediatric B-ALL patients who received IVIG compared to those who did not. The second aim was to identify patient and disease characteristics associated with the initiation of IVIG in pediatric patients during treatment of B-ALL. The third aim is to compare outcomes during times of IVIG supplementation and times without IVIG supplementation among IVIG recipients during B-ALL treatment.

Study Design and Population Selection

We performed a retrospective cohort study through manual and automated chart review of the electronic medical record (EMR). Institutional Review Board approval was obtained through Children's Healthcare of Atlanta (CHOA). The cohort was identified through the Aflac Cancer and Blood Disorder's cancer registry. The Aflac Cancer and Blood Disorder's cancer registry gathers data on the demographics, pathology, primary tumor site, stage, treatment and outcomes for patients with reportable cancers. This data is directly submitted to the Georgia Center for Cancer Statistics which operates as part of the National Cancer Institute's Surveillance, Epidemiology and End Results Program. Only patients diagnosed at CHOA between January 1, 2010 and December 31, 2017 were included in the study. Patients from the two major campus hospitals of CHOA that provide oncology care – Scottish Rite and Egleston – were included. The cohort included children with de novo B-ALL who were between ages 1 and 21 years at time of diagnosis. Patients were excluded if they had a diagnosis of immunodeficiency

prior to B-ALL diagnosis, received IVIG prior to B-ALL diagnosis, had Down Syndrome, had infant B-ALL, or were initially treated at CHOA and moved to another hospital prior to the maintenance phase of treatment.

Data Collection and Definitions

Disease and demographic information were collected from a combination of querying the EMR and cancer registry, manual chart abstraction, and utilizing data previously abstracted from an institutional cohort of patients with ALL and acute myeloid leukemia. Data for each patient was collected from the date of diagnosis through the off treatment date. The off treatment date was defined by the date of whichever event occurred first – the last dose of chemotherapy, relapse, HSCT, death or December 31st, 2019 for those still undergoing treatment at the time of data collection. All patients were treated on or as per Children's Oncology Group (COG) chemotherapy study protocols.

Variables obtained from the EMR, cancer registry and the previous abstracted institutional cohort included age, sex, race/ethnicity, presence or absence of Philadelphia chromosome-positive (Ph+) B-ALL, presence or absence of hypodiploid B-ALL, COG protocol, dates of each cycle of chemotherapy, minimal residual disease (MRD) status at the end of the first phase of treatment (i.e. induction), absolute lymphocyte count (ALC) at time of diagnosis and at the start of the maintenance phase of treatment, National Cancer Institute (NCI) risk category at diagnosis, treating campus (Scottish Rite or Egleston), IgG nadir, IVIG receipt, number hospitalization days. The number and description of severe infections, number of ED visits, and number of episodes of febrile neutropenia were manually abstracted. Patient-reported race/ethnicity was categorized as Non-Hispanic White, Non-Hispanic Black, Hispanic or other. MRD at the end of induction chemotherapy was categorized as positive or negative, with positive being defined as the presence of ≥0.01% disease. MRD was unavailable for patients who

died before the end of induction chemotherapy. NCI risk category is defined as standard risk if a patient was age 1-9 years at the time of B-ALL diagnosis with an initial WBC count <50,000 cells/μL, or high risk if a patient was age ≥10 years at diagnosis or had an initial WBC ≥50,000 cells/μL (39). Only a patient's NCI risk category at B-ALL diagnosis was obtained. The first and last date of IVIG receipt and the number of doses each patient received were recorded. For patients who received IVIG, the IgG value just prior to the first IVIG dose was recorded, which was presumed to approximate the nadir. For patients who never received IVIG, all IgG levels were collected and the nadir was reported. Patients who had IVIG listed as an allergy in the medical chart were classified as having an adverse reaction to IVIG. These were not graded by severity. Hospitalization days were calculated from the date of admission to the date of discharge at CHOA. All hospitalization days were captured, independent of the reason for hospitalization. All ED visits at CHOA were recorded without regard to the chief complaint at time of visit. If an ED visit resulted in a hospitalization, this was counted as both an ED visit and as part of the hospitalization days.

Each patient chart underwent manual review by a single abstractor (H.E.) to document severe infections. Only severe infections were recorded. A severe infection was considered one that was grade 3 or higher. Infection definitions and grading were based on the Common Terminology Criteria for Adverse Events version 5 (**Supplemental Table A**) (40). For each infection, the following were recorded - date of onset, infection type, grade and pathogen identified, if applicable. To identify infections, admission and discharge summaries for each patient encounter were reviewed to determine if there was a description of an infection-related adverse event or a diagnosis code in the problem list related to infection. Clarification of infection information was ascertained through reading daily clinical progress notes and reviewing laboratory values and/or radiographic imaging. If two infections with overlapping

symptoms were present simultaneously, the infection which was more disseminated or more identifiable was selected as the infection type of record. For example, if a patient had fever and abdominal pain requiring hospital admission which would meet criteria for an abdominal infection, but also had a positive blood culture, this was recorded as sepsis. If two infections with unrelated symptoms occurred simultaneously, both were recorded as separate events if both were grade 3 or higher. If an infection was present at the time of initial leukemia diagnosis, but would otherwise be considered a grade 1 or 2 infection, it was not recorded. Any grade 3 or above infection that was present at the time of B-ALL diagnosis was recorded with the same date of onset as the date of B-ALL diagnosis, even if symptoms started prior to B-ALL diagnosis. If a patient was admitted to the hospital for scheduled chemotherapy and was noted to have an infection that would otherwise be a grade 2 or lower, it was not recorded.

Febrile neutropenia episodes were captured. Fever was defined as a single temperature of ≥38.3^{o}C (101^{o}F) or a sustained temperature of ≥ 38^{o}C (100.4^{o}F) for more than one hour. The fever could either be as reported by the patient or guardian as occurring prior to hospital arrival, or documented in the medical record. Neutropenia was defined as an absolute neutrophil count (ANC) of ≤500/mm^{3}. If a patient was admitted with fever and neutropenia, but the ANC was not ≤500/mm^{3} at the time of admission, subsequent daily progress notes were reviewed to see if a fever was ever present with an ANC ≤500/mm^{3} and if so, this was documented as a febrile neutropenia episode. If the patient was readmitted to the hospital <48 hours after admission for febrile neutropenia, this was considered part of the initial episode and was not recorded as an incident infection. If a patient was intermittently febrile during the same hospital admission with persistent neutropenia, this was considered to be part of a single episode of febrile neutropenia. Alternatively, if the patient had been afebrile for more than 72 hours during a hospitalization and then developed a new fever, this was considered a new episode of febrile neutropenia. If a

patient had an episode of febrile neutropenia recorded and concurrently had signs or symptoms of an infection, this was documented as both an episode of febrile neutropenia and as an infection as per the infection grading as described previously.

Statistical Analysis

Sample size and power calculations

As many patient charts were identified as possible that fit the definitions set by the inclusion criteria to maximize sample size. Using a post-hoc power analysis with a 0.05 significance level, we had 82% power to detect a difference in the number of patients with ≥2 severe infections per 1,000 treatment days between IVIG recipients and non-recipients (41).

Aim 1

All statistical analyses were done using SAS© version 9.4 (Cary, NC). Initial distribution analysis of continuous variables showed them to be non-parametric. Descriptive statistics of patient characteristics were obtained using medians and interquartile ranges for continuous variables and frequencies and proportions for categorical variables. Comparisons of patient characteristics were made between patients with an IgG level checked vs patients without an IgG level checked, using Mann-Whitney tests for continuous variables and Chi-square tests for categorical variables. Among patients with an IgG level checked, comparisons between IVIG recipients and non-recipients were made using the same methods for continuous and categorical variables as above. Odds ratios and 95% confidence intervals were obtained from univariate logistic regression with IgG level checked or IVIG receipt as the outcome. A p-value of <0.05 was considered statistically significant for all analyses. The frequency of infection types was reported for IVIG recipients and non-recipients.

Aim 2

Multivariable logistic regression modeling was used to examine associations between patient characteristics and IVIG receipt at any time during treatment, among patients with an IgG level checked. The primary outcome of interest was receipt of IVIG. To determine the independent variables for the multivariable logistic regression model, variables significant in the univariate logistic regression were put into forward, backward, and stepwise selection algorithms. Multiple models were then created that included significant variables from the selection algorithms in combination with variables determined to be clinically significant. The models were evaluated for interaction between all variables. Each interaction term was included in a version of the model, then kept in the model if the p value for the interaction term was <0.05. The Akaike information criterion (AIC) of these models were then compared and the model with the lowest AIC was selected. The final model was as follows:

$$log\frac{p(IVIG=1)}{1-p(IVIG=1)} = \beta_0 + \beta_1(\text{Race/eth}) + \beta_2(\text{MRD}) + \beta_3(\text{NCI Risk}) + \beta_4(\text{IgG}) + \beta_5(\text{inf}) + \beta_6(\text{NCI Risk * IgG})$$

This model assumes that severe infections is an independent variable, however this may be an invalid assumption if IVIG affects infection frequency. Additionally, the risk of infection may vary by phase of treatment. Therefore, a second multivariable logistic regression model was made to mitigate this. The outcome of the second multivariable model was IVIG receipt during the maintenance phase of chemotherapy. The same independent variables were used, with the exception that infections were redefined as infections occurring prior to the maintenance phase of chemotherapy.

Aim 3

To compare outcomes with and without IVIG supplementation, only IVIG recipients were included in the analysis. All treatment days were categorized as either an IVIG-supplemented day or a non-supplemented day. IVIG-supplemented days were defined as the days between the first dose of IVIG and 30 days after the last dose of IVIG, based on the estimated half-life of IVIG (42). Rates of severe infections, ED visits, hospitalization days, and febrile neutropenia episodes per 1,000 treatment days were recorded for IVIG-supplemented and non-supplemented days. Rate ratios and 95% confidence intervals were obtained using a general estimating equation model with a Poisson distribution to account for repeated outcomes at the level of the individual (43). Since the risk of outcomes may vary by phase of treatment, comparisons were reported for all IVIG recipients as well as the subgroup of patients who began IVIG during the maintenance phase of chemotherapy.

Sensitivity analysis

Patients who had unique characteristics of their disease or treatment course represented a sub-population of the cohort that could introduce bias into analysis. Therefore, all analyses described above were repeated after excluding patients who died, relapsed, underwent HSCT, had Ph+ B-ALL, or had hypodiploid B-ALL.

RESULTS

Cohort Characteristics

There were 443 patients with B-ALL initially identified in the study time period. Seventy patients were excluded due to: therapy-related B-ALL (n=1), previous IVIG receipt (n=2), a diagnosis of Down syndrome (n=10), misclassified as B-ALL but were actually B-lymphoblastic lymphoma (n=3), diagnosed at another institution (n=36), and moved care to another institution or electively stopped treatment prior to the maintenance phase of treatment (n=18). This resulted in 373 patients who met eligibility criteria for inclusion in the cohort (**Figure 2**). Baseline demographic information is summarized in **Table 1**. The median age at diagnosis was 5 years (IQR 3-10), 50.4% (n=188) were male and 49.3% (n=184) were Non-Hispanic White. Additional comparisons in patient characteristics by race/ethnicity are summarized in **Supplemental Tables B-D**.

Treatment information is summarized in **Supplemental Table E**. The high risk genotypic subtypes of B-ALL identified in the cohort were Ph+ B-ALL (n=12) and hypodiploidy (n=7). There were 14 patients who died prior to treatment completion, 12 patients who relapsed prior to treatment completion and 18 patients who underwent HSCT.

Aim 1

Of the 373 patients, 251 (67.3%) had at least one IgG level checked during their treatment. Comparisons between patients with and without an IgG level checked are summarized in **Table 2**. Compared to patients who never had an IgG level checked, patients who had at least one IgG level checked during treatment were younger at time of B-ALL diagnosis (median age 5 vs 6 years, p=0.01). Those that had an IgG level checked were more likely to have had a positive MRD (OR 2.49, 95% CI [1.38-4.52]) at the end of induction or be treated at the Scottish Rite campus (OR 4.01, 95% CI [2.54-6.33]). Non-Hispanic Black patients were 66% less

likely to have an IgG checked, with a 0.34 lower odds compared to Non-Hispanic White patients (95% CI [0.19-0.61]). Measurement of an IgG level was associated with a higher median number of severe infections per 1,000 days of treatment compared to those without an IgG checked (3.5 vs 1.7 infections, p<0.01).

Comparisons of disease and demographic characteristics for IVIG recipients vs. IVIG non-recipients among those with an IgG level checked, along with univariate logistic regression, is shown in **Table 3**. Among the 251 patients with a recorded IgG level, 113 (45.0%) patients received IVIG. There was one patient who received IVIG without an IgG level prior to beginning IVIG treatment. The median IgG nadir was lower for IVIG recipients (404 vs 675mg/dL, p<0.01).

IVIG recipients differed significantly from non-recipients by age, race, MRD status, IgG nadir and episodes of severe infection. Patients who received IVIG were younger compared to those who did not receive IVIG (median 4 vs 6 years, p<0.01). Non-Hispanic Black patients and Hispanic patients had a significantly lower odds of receiving IVIG compared to Non-Hispanic White patients (OR 0.17, 95% CI [0.07-0.44] and OR 0.45, 95%CI [0.24-0.84], respectively). During the entire treatment course, IVIG recipients sustained more severe infections per 1,000 treatment days (4.2 vs 2.5 infections, p<0.01). Infection information by IVIG receipt group is summarized in **Supplemental Table F**.

Aim 2

Of the 251 patients with an IgG level checked, 249 patients were included in the multivariable analysis to assess associations between IVIG receipt at any time during treatment and patient characteristics. Two patients were excluded due to unavailable MRD status. Forward, backward, and stepwise selection all suggested inclusion of race/ethnicity, IgG nadir, and severe infections per 1,000 treatment days in the model. Results of the Model 1 multivariable analysis are shown in **Table 4**. In this model, race/ethnicity and incident infections

were independently associated with IVIG receipt. Adjusting for covariates, the odds of IVIG receipt for Non-White patients were 0.43 times (95% CI 0.22 - 0.83) the odds of IVIG receipt for Non-Hispanic Whites. An interaction was noted between NCI risk status and IgG level. Among NCI HR patients, the odds of IVIG receipt for patients with an IgG nadir of <500mg/dL were 40.13 times (95% CI 11.29 – 142.65) the odds of IVIG receipt for patients with IgG ≥500mg/dL. Among NCI SR patients, the odds of IVIG receipt for patients with an IgG nadir of <500 mg/dL are 7.45 times (95% CI 3.54 – 15.70) the odds of IVIG receipt for patients with IgG ≥500 mg/dL. Among patients with an IgG ≥500 mg/dL, the odds of IVIG receipt for NCI HR patients are 0.28 times (95% CI 0.10 – 0.84) the odds of IVIG receipt for NCI SR patients. Among patients with an IgG <500 mg/dL, the odds of IVIG receipt were not significantly different by NCI risk category (adjusted OR (aOR) 1.53, 95% CI 0.57 – 4.10). Lastly, the odds of IVIG receipt for patients with > 2 severe infections per 1,000 treatment days were 2.57 times (95% CI 1.28 – 5.18) the odds of IVIG receipt for patients with ≤ 2 infections.

A second multivariable model (Model 2, shown in **Table 5**) was run to assess the association between IVIG receipt and patient characteristics restricted to the maintenance phase of treatment. The same variables were included in Model 2 as in Model 1, with the exception being severe infections per 1,000 treatment days were reclassified as severe infections prior to the maintenance phase of treatment. There was no statistical interaction in Model 2 between NCI risk and IgG nadir. Results of the multivariable analysis of Model 2 are shown in Table 5. Adjusting for covariates, the odds of IVIG receipt for Non-White patients were 0.51 times (95% CI 0.27 - 0.97) the odds of IVIG receipt for Non-Hispanic White patients. The odds of IVIG receipt for patients with an IgG nadir of <500 mg/dL are 7.37 times (95% CI 3.77 – 14.40) the odds of IVIG receipt for patients with IgG ≥500 mg/dL. The odds of IVIG receipt among patients with > 2 severe infections per 1,000 treatment days prior to maintenance did

not differ from the odds of IVIG receipt for patients with ≤ 2 infections (aOR 0.71, 95% CI 0.34 – 1.51).

Aim 3

Among IVIG recipients (n=114), the median time to initiation of IVIG was 403.5 days (IQR 240-543) from diagnosis. Patients received a median of 8 doses (IQR 4-14). There were 21 patients who only received 1 dose. Nineteen patients (16.7%) had an adverse reaction to IVIG infusion. Thirty-eight IVIG recipients (33.3%) started IVIG supplementation before the maintenance phase of treatment and 76 patients started during the maintenance phase of treatment.

Outcomes for IVIG-supplemented days (vs. non-supplemented days) are summarized in **Table 6**. Seven of the 114 total IVIG recipients were excluded since they had Ph+ B-ALL and had scheduled hospitalizations as part of the maintenance phase of treatment, which was not a standard part of treatment for rest of the included IVIG recipients (n=107). The rates of ED visits, hospitalizations days, episodes of febrile neutropenia and severe infections per 1,000 treatment days were all significantly lower for IVIG-supplemented days vs. non-supplemented days (Rate Ratio (RR) 0.52 95% CI [0.42-0.63]; RR 0.35 95%CI [0.26 – 0.46]; RR 0.29 95% CI [0.19 – 0.43]; and RR 0.37 95% CI [0.27 – 0.49], respectively).

Since the risk of the aforementioned outcomes can vary between patients during the treatment phase prior to maintenance, a sub-analysis was conducted to examine outcomes for IVIG recipients who began IVIG supplementation during maintenance (n=73). Results are shown in **Table 7**. The rates of ED visits, episodes of febrile neutropenia, and severe infections per 1,000 treatment days during maintenance were significantly lower for IVIG-supplemented days vs. non-supplemented days (RR 0.58 95% CI [0.42-0.80]; RR 0.37 95% CI [0.19 – 0.72]; and RR 0.52 95% CI [0.33 – 0.84], respectively). There was no difference in the rates of hospitalization

for IVIG-supplemented days vs non-supplemented days (RR 1.12 95% CI [0.76-1.65]) in the maintenance phase.

Sensitivity Analyses

The cohort characteristics after excluding special populations of patients (those who died, relapsed, underwent HSCT, had Ph+ B-ALL, or had hypodiploid B-ALL [N=54]) are summarized in **Table 8**. Similar to the full cohort, the median age at diagnosis was 5 years (IQR 3-9), 50.2% (N=160) were male and 50.5% (N=161) were Non-Hispanic White.

Comparisons between patients with and without an IgG level check are summarized in **Table 9**. Results of bivariate analyses were similar to those noted in the full cohort. Patients who had an IgG level checked during treatment were younger at time of B-ALL diagnosis (median 4 vs 6 years, p=0.01) and had more severe infections per 1,000 days of treatment (median 2.5 vs 1.6 infections, p<0.01). Patients with an IgG checked were more likely to have positive MRD (OR 2.53, 95%CI [1.28-4.98]), be treated at the Scottish Rite campus (OR 4.06, 95% CI [2.48-6.63]) and less likely to be Non-Hispanic Black as compared to Non-Hispanic White (OR 0.32 95% CI [0.17-0.79]).

Comparisons of disease and demographic characteristics for IVIG recipients vs IVIG non-recipients among those with an IgG level checked, along with univariate logistic regression, is shown in **Table 10**. Patients who received IVIG were younger than those who did not receive IVIG (median 4 vs 5 years, p<0.01). The majority of patients in both groups were Non-Hispanic White (68.3% IVIG recipients vs 43.1% IVIG non-recipients), though Non-Hispanic Black patients had a significantly lower odds of IVIG receipt compared to Non-Hispanic White patients (OR 0.15, 95% CI [0.05-0.42]). IVIG recipients had more severe infections per 1,000 treatment days (median 3.8 vs 2.3 infections, p<0.01). The median IgG nadir was lower for IVIG recipients (406 vs 675 mg/dL, p<0.01).

For multivariable model 1a, there were 210 patients included. Forward, backward, and stepwise selection suggested including IgG nadir, severe infections, and treating campus in the final model. There was no statistical interaction between IgG nadir and NCI risk group as observed in Model 1 of the full cohort. Therefore, the model used for Model 1a was:

$$log\frac{p(IVIG=1)}{1-p(IVIG=1)} = \beta_0 + \beta_1(\text{Race/eth}) + \beta_2(\text{MRD}) + \beta_3(\text{NCI Risk}) + \beta_4(\text{IgG}) + \beta_5(\text{inf}) + \beta_6(\text{Treatment Campus})$$

The multivariable analysis is shown in **Table 11**. There was a significant association between IgG nadir <500 mg/dL and IVIG receipt (aOR 12.08 95% CI [5.94 – 24.56]) as well as between > 2 severe infections per 1,000 treatment days and IVIG receipt (aOR 2.76 95% CI [1.32 – 5.75]).

For multivariable model 2a, there was statistical interaction between race/ethnicity and NCI risk group, which was not present in Model 2 of the full cohort. Therefore, the model used for Model 2a was:

$$log\frac{p(IVIG=1)}{1-p(IVIG=1)} = \beta_0 + \beta_1(\text{Race/eth}) + \beta_2(\text{MRD}) + \beta_3(\text{NCI Risk}) + \beta_4(\text{IgG}) + \beta_5(\text{inf}) + \beta_6(\text{Treatment Campus}) + \beta_7(\text{Race/eth*NCI Risk})$$

The multivariable analysis is shown in **Table 12**. Among NCI high risk patients, there was a significant association between Non-White race/ethnicity vs Non-Hispanic White race/ethnicity and IVIG receipt in maintenance (aOR 0.17 95%CI [0.04 – 0.75]). There was also an association between IgG nadir <500mg/dL and IVIG receipt (aOR 7.04 95% CI [3.43 – 14.42]). There was no association between severe infections per 1,000 treatment days prior to maintenance and IVIG receipt during maintenance.

For Aim 3 comparisons of outcomes among IVIG recipients, results are summarized in **Table 13** and **Table 14**. The rates of ED visits, hospitalizations days, episodes of febrile neutropenia and severe infections per 1,000 treatment days were all significantly lower for IVIG-supplemented days vs non-supplemented days (RR 0.49 95% CI [0.39-0.61]; RR 0.33 95% CI [0.25 – 0.44]; RR 0.26 95% CI [0.17 – 0.39]; and RR 0.35 95% CI[0.26 – 0.48], respectively). The rates of ED visits, episodes of febrile neutropenia, and severe infections per 1,000 treatment days during maintenance were lower for IVIG-supplemented days vs non-supplemented days (RR 0.56 95% CI [0.40-0.79]; RR 0.36 95% CI [0.18 – 0.71]; and RR 0.49 95% CI [0.31 – 0.79], respectively).

DISCUSSION

This study within a large single institution with a diverse population provides important descriptions of the current practices of IVIG supplementation in children with B-ALL in a contemporary treatment era. Despite the lack of national or institutional guidelines for routine monitoring of serum IgG levels in children with B-ALL, the majority of our cohort had an IgG level checked during treatment. This contrasts with the only other study in children with B-ALL that reports 46% of patients had an IgG checked during treatment (9). Since there are no established guidelines, measuring an IgG level remains a clinical decision. In our cohort, patients who had their IgG checked were younger, were more likely to have MRD positivity, had a higher frequency of severe infections, and were more likely to be Non-Hispanic White. While it is unclear which of these factors are influencing the clinical decision to check an IgG level since it is ultimately at the discretion of the medical provider, our data supports the idea that patient factors influenced the medical provider's decision.

Among those with an IgG level checked, our first hypothesis was partially supported by the multivariable analysis. Hypogammaglobulinemia was associated with IVIG receipt at any time during treatment, and during the maintenance phase of treatment based on Models 1 (**Table 4**) and 2 (**Table 5**). The hypothesized association between previous history of severe infection and IVIG receipt was less clear. In Model 1, severe infections were associated with IVIG receipt. However, when examining the association between severe infections prior to maintenance with IVIG receipt during maintenance (Model 2), there was not a significant association. Our second hypothesis that ED visits and hospitalization days decrease with IVIG supplementation was supported when considering the full treatment period. Among all IVIG recipients, the rates of ED visits and hospitalization days during IVIG-supplemented days were lower than the rates during non-supplemented days. However, the sub-analysis limited to those who received IVIG in

maintenance showed that ED visits rates were significantly lower during IVIG supplementation, but hospitalization days were not impacted.

Our study characteristics and conclusions differ considerably from the two published studies in literature examining IVIG supplementation in children with acute leukemia (**Supplemental Table G**). Our sample size of patients was larger and had more IVG recipients (n=373, n=114 respectively) compared to Holmes et al (n=136, n=38 respectively) and Van Winkle et al (n=118, n=36 respectively) and captures patients in a more contemporary treatment era. Unlike these studies, our cohort consisted exclusively of children with B-ALL and not those with T-ALL, as children with T-ALL undergo a different treatment regimen and have unique immunologic biology. Our study also reports rates of adverse reactions to IVIG by number of patients (16.7%) affected whereas Van Winkle et al and Holmes et al report an adverse reaction rate per number of IVIG doses (3.8%, 4.2%, respectively) (8, 9). Our per patient adverse reaction rate was lower than what is reported in children who receive IVIG for PID, and highlights the need for further studies about reaction severity and frequency specifically in children with B-ALL (33). We also did not limit analysis of IVIG associations or outcome comparisons during supplementation to the maintenance phase of treatment unlike these previous studies. By including data from the treatment phase prior to maintenance, we provide the first and only description of associations with IVIG supplementation and outcome comparisons of IVIG supplementation in children with B-ALL during this time period.

Van Winkle et al showed a significant association between IVIG receipt during maintenance and an episode of bacteremia or fungemia before maintenance treatment, but our analysis of associations with IVIG receipt during maintenance did not support a similar conclusion (8). This is likely due to difference in model selection and infection definitions. The model used by Van Winkle et al included only NCI risk category, double-delayed intensification chemotherapy and

episode of bacteremia or fungemia. Conversely, our model expanded upon these patient and disease-related variables to include race/ethnicity, and MRD at end of induction. For infections, we did not limit recorded infections to only bacteremia or fungemia but instead captured a broader range of infection types and incorporated infection severity by scoring episodes based on CTCAE grading guidelines.

Our infection definition also differed from that used by Holmes et al, which defined their infection outcome as a febrile episode (9). Holmes et al reports no difference in febrile episodes between IVIG supplemented days and non-supplemented days in patients with IgG monitoring, nor any differences in febrile episodes as compared to patients without IgG monitoring or IVIG supplementation (9). Based on these findings, the researchers propose there is no role for IgG monitoring or IVIG supplementation during the maintenance phase of treatment in children with ALL. Our contrasting findings in a larger and more ethnically diverse cohort do not support their conclusion and instead supports IVIG as an effective intervention for decreasing severe infections and infection-related outcomes.

These stark differences in our conclusions compared to those reached by Van Winkle et al and Holmes et al highlight an important limitation of how to assess benefit of IVIG as an infection prevention intervention (8, 9). Infection-related outcome definitions in literature evaluating IVIG efficacy are not consistent across studies or patient populations. In a 2010 systematic review and guideline statement about the use of IVIG in PID, the 19 included studies were noted to have variable and non-standardized definitions of infection outcomes (e.g. pneumonia, chronic infections, viral respiratory infections, bacterial respiratory infections, infections requiring hospitalization, etc.) (44). Similarly, in a meta-analysis of IVIG efficacy in patients with CLL or MM, the authors concluded that IVIG decreased clinically documented infections but noted variability in infection definitions in the included trials (10). Because of this

variability of infection definitions, the benefits of IVIG supplementation in children with B-ALL may be better reflected by examining its effect on ED visits, hospitalizations and interruptions in chemotherapy. Though we were unable to assess the effect of IVIG supplementation on interruptions to chemotherapy, our data did show that ED visits and hospitalizations were decreased with IVIG supplementation. This provides important justification for incorporating these outcomes into future prospective studies to evaluate IVIG efficacy instead of solely evaluating infection frequency.

The association observed between race/ethnicity and IVIG supplementation in our univariate and multivariable analyses was unexpected and has not previously been examined in the literature. There has been increasing recognition of how race/ethnicity affects not only patient outcomes and care, but also may be associated with differences in the immune microenvironment (45, 46). For example, it is already well established that individuals of African and Middle Eastern descent have lower neutrophil counts, termed benign ethnic neutropenia, which do not affect susceptibility to infection (47). In our univariate analysis, both having an IgG level checked and IVIG supplementation differed by race/ethnicity, although the frequency of hypogammaglobulinemia was lower in Black children when an IgG was checked (**Supplemental Table B**). When patient and disease characteristics were compared by race/ethnicity, Non-Hispanic Black patients had higher median IgG nadir, less incident severe infections, and less episodes of febrile neutropenia than Non-Hispanic White patients. Hispanic patients also had a higher median IgG nadir as compared to Non-Hispanic White patients. If clinicians are basing the decision to check an IgG level or give IVIG supplementation on factors such as hypogammaglobulinemia or frequency of severe infections, this could influence why Non-Hispanic Black patients or Hispanic patients are less frequently supplemented with IVIG than Non-Hispanic White patients. However, in Model 2, Non-White race/ethnicity remained an

independent risk for decreased odds of IVIG receipt. Recent data has suggested racial differences in immune function, specifically that Black patients have higher baseline IgG levels than White patients (12). The data from our study suggests that further inquiry is needed to understand what immune mechanisms, disease characteristics or socioeconomic factors may be influencing the differences in hypogammaglobulinemia and IVIG supplementation practices. Notably, differences in immune function during B-ALL treatment should be considered in context of the known disparities in disease-free survival and therapy adherence in Non-White children (28, 48, 49).

The immune mechanisms that result in hypogammaglobulinemia and pediatric B-ALL also played a role in the selection of our cohort and the observed associations. Patients with Down syndrome were excluded from the analysis due to the known association of this disease with immunologic function (50). We considered whether excluding patients with other unique genotypic characterizations of B-ALL – such as Ph+ or hypodiploidy – may be warranted, since the underlying immunologic mechanisms linking leukemic transformation, immune function and immunoglobulin production are incompletely understood. It is conceivable that these genotypic classifications could confound the associations between infection risk and hypogammaglobulinemia. However, there is no evidence to support a specific immunologic dysfunction in these two specific genotypic groups. In fact, there is evidence that pre-existing immune dysfunction is intimately associated with any leukemia development (51). We also considered the effect of keeping patients in our cohort who relapsed during treatment, died prior to treatment completion, or underwent HSCT. These patients had disease courses that may be suggestive of more severe underlying immunologic abnormalities. In conducting the sensitivity analysis without these special populations of children, the results of our univariate

and multivariable analyses on the IVIG effect comparisons were similar to the findings of our main analysis.

Strengths

The current analysis provides the largest and most diverse sample of children with B-ALL and IVIG supplementation for analysis. In contrast to prior literature, we also included information about MRD status in our analysis, which has become an important variable for disease classification and treatment intensity after the first 30 days of treatment and adds to the initial NCI risk classification. The patients in our cohort were treated according to contemporary chemotherapy protocols, meaning the immunosuppressive effects of chemotherapy that the cohort was exposed to closely mirror the chemotherapy regimens that patients are typically receiving. In contrast to prior analyses in children, we also were able to capture information about IVIG supplementation during all phases of treatment and not limit the analysis to only patients who received IVIG during the maintenance phase of treatment (8, 9). By analyzing IVIG supplementation both prior to and during the maintenance phase of treatment, we were able to show differences in associations with patient characteristics and outcomes depending on when IVIG is initiated.

Limitations

This study is limited by several factors. First, it is a single institution, retrospective cohort study and therefore conclusions cannot be made about causality and generalizability. Second, approximately one-third of patients did not have an IgG level checked at any time during treatment. In those who did have an IgG level checked, the time points of IgG levels were clinically driven and therefore not standardized. Since hypogammaglobulinemia may vary based on age, race, intensity of chemotherapy, and cumulative exposure to chemotherapy, the heterogeneity of IgG levels in our cohort is difficult to interpret. Third, since IVIG initiation is

ultimately at the provider's discretion, there may be other variables not considered in this analysis that influence clinical decisions beyond those captured and may be significant heterogeneity in practice. Clinicians may initiate IVIG due to minor sinopulmonary infections (i.e. < grade 3 CTCAE) or prolonged episodes of neutropenia that limit dose escalation of oral chemotherapy, both of which were not captured in this study. This likely lead to an under-representation of infections in the analysis. Finally, institutional antibiotic practices varied over the time period of the study, which may have influenced the frequency of observed infections.

Conclusions and Future Directions

The relationship between hypogammaglobulinemia, patient characteristics, and physician decision on IVIG supplementation in children with B-ALL remains complex. Medical providers make decisions regarding IVIG supplementation based on incompletely understood factors. Studies are needed to create and inform decision-modeling tools for clinicians. Though the models presented in our study are neither true casual models nor true predictive models, they are clinically useful to describe these associations and can inform variable selection for inclusion in clinical trials and guideline creation to inform decision models. It is anticipated that IVIG supplementation in children with B-ALL could become more complicated in the near future based on changes in supply and demand. IVIG has been on national shortage for years without a clear end in sight, and there are few evidence-based prioritization guidelines for medical providers to use for pediatric oncology patients (38). It will be necessary to consider the efficacy, cost and prioritization for specific patient groups. Additionally, the demand for IVIG products is increasing as more chemotherapy protocols incorporate targeted immunotherapy medications such as blinatumomab into upfront therapy for B-ALL treatment (52). These novel immunotherapies can cause long-term B-cell aplasia and hypogammaglobulinemia, potentially increasing the number of patients who may benefit from IVIG supplementation (53).

Furthermore, the advent of CAR-T approaches will also render a larger group of children with prolonged, potentially life-long, B-cell aplasia. We advocate for a standard institutional approach to evaluating for hypogammaglobulinemia at consistent time points in treatments. Prospective studies are needed to determine the prevalence of hypogammaglobulinemia in children with B-ALL undergoing treatment as well as its association with infection-related complications. Larger, multi-institutional trials to study the efficacy of IVIG supplementation for infection prevention in children with B-ALL with hypogammaglobulinemia could greatly impact clinical practice and improve patient outcomes.

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TABLES AND FIGURES

Figure 1. Concept diagram of association between hypogammaglobulinemia, infections and IVIG receipt, along with other factors in B-ALL treatment; IVIG – Intravenous immunoglobulin; PID – Primary immunodeficiency; ED – Emergency department

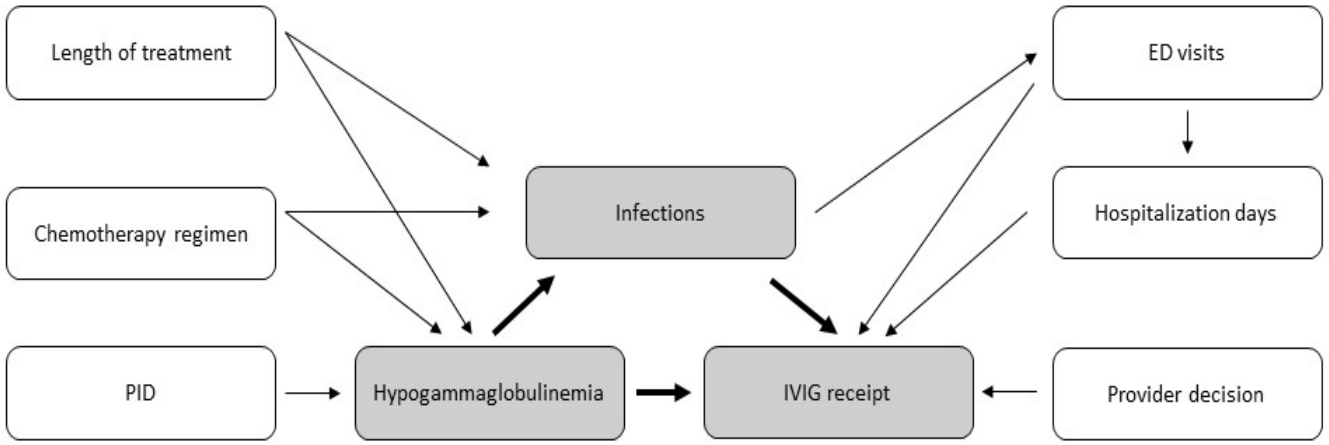

Figure 2. Flow diagram of patient inclusion and exclusion, along with categorization based on IgG level checked and IVIG receipt; B-ALL – B cell acute lymphoblastic leukemia; IVIG – Intravenous immunoglobulin; IgG – Immunoglobulin G; CHOA – Children's Healthcare of Atlanta

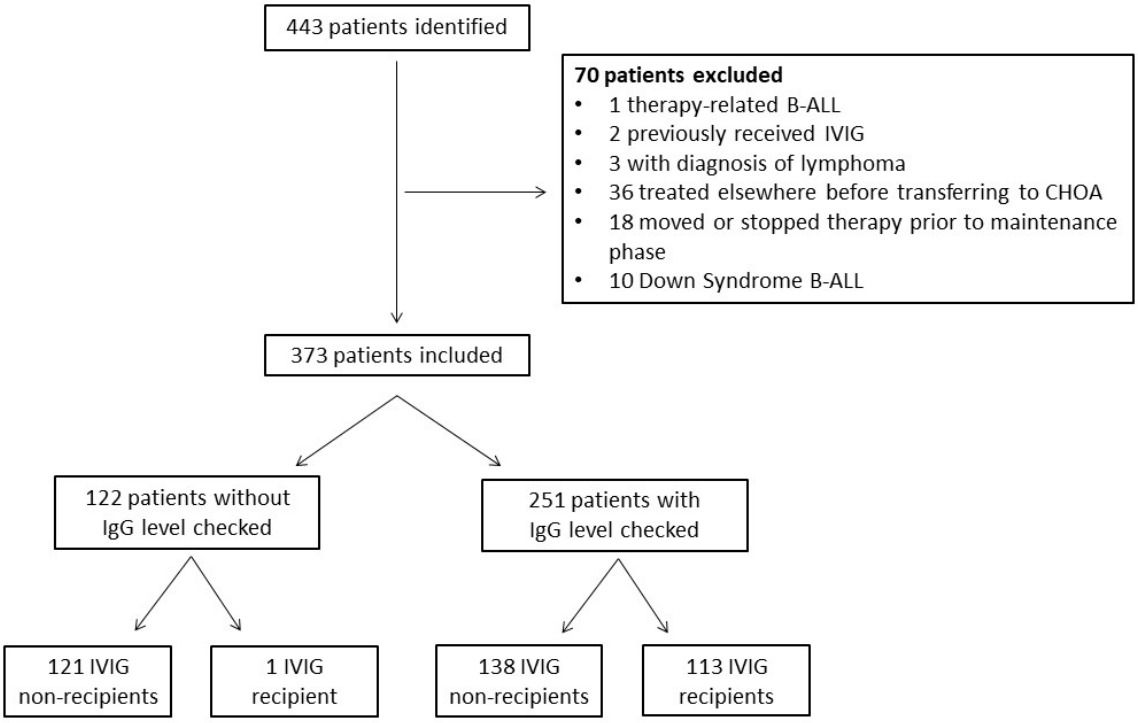

Table 1. Disease and demographic characteristics of children with B-ALL (N=373)

	N (%)*
Age at diagnosis, in years median (IQR)	5 (3-10)
Categorical age	
<10 years	274 (73.5)
≥10 years	99 (26.5)
Sex	
Male	188 (50.4)
Female	185 (49.6)
Race/ethnicity	
Non-Hispanic White	184 (49.3)
Hispanic	94 (25.2)
Non-Hispanic Black	69 (18.5)
Other†	26 (7.0)
Minimal residual disease	
Negative	281 (75.3)
Positive	86 (23.1)
Unavailable	6 (1.6)
WBC at diagnosis	
<50 $x10^9$/L	320 (85.8)
≥50 $x10^9$/L	53 (14.2)
Treating campus	
Scottish Rite	232 (62.2)
Egleston	141 (37.8)
NCI risk category	
Standard Risk	235 (63.0)
High Risk	138 (37.0)
Severe infections per 1,000 treatment days	
Median (IQR)	2.5 (1.1 – 5.0)

B-ALL – B cell acute lymphoblastic leukemia; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range

*Unless otherwise noted

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Table 2. Comparisons of patient characteristics by IgG level checked among children with B-ALL, using Mann-Whitney or univariable logistic regression analyses (N = 373)

Patient Characteristics	IgG Checked	IgG Never Checked	OR (95% CI)	P-value
	N (%)*	N (%)*		
	N=251 (67.3)	N=122 (32.7)		
Age at diagnosis in years, median (IQR)	5 (3-9)	6 (4-11)	--	0.01**
Categorical age				
<10 years	192 (76.5)	82 (67.2)	--	0.06
≥10 years	59 (23.5)	40 (32.8)	0.63 (0.39-1.02)	
Sex				
Male	125 (49.8)	63 (51.6)	--	0.74
Female	126 (50.2)	59 (48.4)	1.08 (0.70-1.66)	
Race/ethnicity				
Non-Hispanic White	134 (53.4)	50 (41.0)	--	
Non-Hispanic Black	33 (13.2)	36 (29.5)	0.34 (0.19-0.61)	<0.01
Hispanic	62 (24.7)	32 (26.2)	0.72 (0.42-1.24)	0.24
Other†	22 (8.8)	4 (3.3)	2.05 (0.67-6.25)	0.21
Minimal residual disease				
Negative	179 (71.3)	102 (83.6)	--	
Positive	70 (27.9)	16 (13.1)	2.49 (1.38-4.52)	<0.01
Unavailable	2 (0.8)	4 (3.3)	--	
WBC at diagnosis				
<50 x10^9/L	215 (85.6)	105 (86.1)	--	0.92
≥50 x10^9/L	36 (14.3)	17 (13.9)	1.03 (0.56-1.93)	
Treating campus				
Egleston	68 (27.1)	73 (59.8)	--	<0.01
Scottish Rite	183 (72.9)	49 (40.2)	4.01 (2.54-6.33)	
NCI risk category				
Standard Risk	160 (63.8)	75 (61.5)	--	0.67
High Risk	91 (36.2)	47 (38.5)	0.91 (0.58-1.42)	
Severe infections per 1,000 treatment days, median (IQR)	3.5 (1.6-5.7)	1.7 (0-3.5)	--	<0.01**

IgG – Immunoglobulin G; B-ALL – B cell acute lymphoblastic leukemia; OR – Odds ratio; CI – Confidence interval; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range

*Unless otherwise noted

**Mann-Whitney test

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Table 3. Comparisons of patient characteristics by IVIG receipt, among children with B-ALL with an IgG level checked using Mann-Whitney or univariable logistic regression analyses (N = 251)

Patient Characteristics	IVIG Recipients	IVIG Non-Recipients	OR (95% CI)	P-value
	N (%)*	N (%)*		
	N=113 (45.0)	N=138 (55.0)		
Age at diagnosis in years, median (IQR)	4 (3-7)	6 (3-10)	--	<0.01**
Categorical age				
<10 years	96 (85.0)	96 (69.6)	--	<0.01
≥10 years	17 (15.0)	42 (31.4)	0.41 (0.22 – 0.76)	
Sex				
Male	59 (52.2)	66 (47.8)	--	0.49
Female	54 (47.9)	72 (52.2)	0.84 (0.51 – 1.38)	
Race/ethnicity				
Non-Hispanic White	76 (67.3)	58 (42.0)	--	
Hispanic	23 (20.3)	39 (28.3)	0.45 (0.24 – 0.84)	0.01
Non-Hispanic Black	6 (5.3)	27 (19.6)	0.17 (0.07 – 0.44)	<0.01
Other†	8 (7.1)	14 (10.1)	0.44 (0.17 – 1.11)	0.08
Minimal residual disease			--	
Negative	80 (70.8)	99 (71.7)	1.10 (0.63 – 1.92)	0.73
Positive	33 (29.2)	37 (26.8)		
Unavailable	--	2 (1.5)		
WBC at diagnosis				
<50 x10^9/L	96 (85.0)	119 (86.2)	--	0.77
≥50 x10^9/L	17 (15.0)	19 (13.8)	1.11 (0.55 – 2.25)	
Treating campus				
Egleston	28 (24.8)	40 (29.0)	--	0.46
Scottish Rite	85 (75.2)	98 (71.0)	1.24 (0.71 – 2.18)	
NCI risk category				
Standard Risk	78 (69.0)	82 (59.4)	--	0.12
High Risk	35 (31.0)	56 (40.6)	0.66 (0.39 – 1.11)	
Severe infections per 1,000 treatment days, median (IQR)	4.2 (2.3-6.2)	2.5 (1.2-5.0)	--	<0.01**
Median IgG nadir, mg/dL (IQR)	404 (302-487)	675 (527-835)	--	<0.01**
IgG nadir				
<500 mg/dL	90 (79.7)	29 (21.0)	--	<0.01
≥500 mg/dL	23 (20.4)	109 (79.0)	0.07 (0.04-0.13)	

IVIG – Intravenous immunoglobulin; B-ALL – B cell acute lymphoblastic leukemia; IgG – Immunoglobulin G; OR – Odds ratio; CI – Confidence interval; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range

*Unless otherwise noted

**Mann-Whitney test

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Table 4. Multivariable Model 1 - Association of patient characteristics and IVIG receipt, among patients with an IgG level checked (n=249)

	Adjusted OR (95% CI)*
Race/ethnicity	
Non-Hispanic White	--
Non-White†	**0.43 (0.22 – 0.83)**
Minimal residual disease	
Negative	--
Positive	0.87 (0.43-1.78)
NCI High risk	
≥500 mg/dL	--
<500 mg/dL	**40.13 (11.29 – 142.65)**
NCI Standard risk	
≥500 mg/dL	--
<500 mg/dL	**7.45 (3.54 – 15.70)**
IgG nadir ≥500 mg/dL	
NCI Standard risk	--
NCI High risk	**0.28 (0.10 – 0.84)**
IgG nadir <500 mg/dL	
Standard risk	--
High risk	1.53 (0.57 – 4.10)
Severe infections	
≤2 infections per 1,000 treatment	--
>2 infections per 1,000 treatment	**2.57 (1.28 – 5.18)**

IVIG – Intravenous immunoglobulin; IgG – Immunoglobulin G; OR – Odds ratio; CI – Confidence interval; NCI – National Cancer Institute

*Adjusting for race/ethnicity, minimal residual disease, NCI risk category, IgG nadir and severe infections

†Includes Non-Hispanic Black patients, Hispanic patients, patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Bolded values statistically significant

Table 5. Multivariable Model 2 - Association of patient characteristics and IVIG receipt during the maintenance phase of treatment, among patients with an IgG level checked (n=249)

	Adjusted OR (95% CI)*
Race/ethnicity	
Non-Hispanic White	--
Non-White†	**0.51 (0.27 – 0.97)**
Minimal residual disease	
Negative	--
Positive	0.75 (0.38 – 1.51)
NCI Risk category	
Standard risk	--
High risk	0.73 (0.38 – 1.41)
IgG nadir	
≥500 mg/dL	--
<500 mg/dL	**7.37 (3.77 – 14.40)**
Severe infections prior to maintenance	
≤2 infections per 1,000 treatment days prior to maintenance	--
>2 infections per 1,000 treatment days prior to maintenance	0.71 (0.34 – 1.51)

IVIG – Intravenous immunoglobulin; IgG – Immunoglobulin G; OR – Odds ratio; CI – Confidence interval; NCI – National Cancer Institute

*Adjusting for race/ethnicity, minimal residual disease, NCI risk category, IgG nadir and severe infections

†Includes Non-Hispanic Black patients, Hispanic patients, patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Bolded values statistically significant

Table 6. Rate comparisons of infection-related outcomes during and without IVIG supplementation, among IVIG recipients (n=107)

	During IVIG Supplementation			**Without IVIG Supplementation**			**RR**	**95% CI**
	Number	Person Days*	Rate per 1,000 days	Number	Person Days*	Rate per 1,000 days		
ED visits	198	36432	5.44	714	67677	10.55	**0.52**	**0.42 - 0.63**
Hospitalization days	835	36432	22.92	4465	67677	65.98	**0.35**	**0.26 – 0.46**
Episodes of febrile neutropenia	40	36432	1.09	260	67677	3.84	**0.29**	**0.19 – 0.43**
Severe infections	70	36432	1.92	352	67677	5.20	**0.37**	**0.27 – 0.49**

IVIG – Intravenous immunoglobulin; RR – Rate ratio; CI – Confidence interval; ED – Emergency department
*Calculated as days between date of diagnosis and off treatment date
Bolded values statistically significant

Table 7. Rate comparisons of infection-related outcomes during and without IVIG supplementation, among IVIG recipients who began IVIG supplementation during the maintenance phase of treatment (n=73)

	During IVIG Supplementation			**Without IVIG Supplementation**			**RR**	**95% CI**
	Number†	Person Days*	Rate per 1,000 days	Number†	Person Days*	Rate per 1,000 days		
ED visits	114	22972	4.96	257	30105	8.54	**0.58**	**0.42 – 0.80**
Hospitalization days	296	22972	12.89	347	30105	11.53	1.12	0.76 – 1.65
Episodes of febrile neutropenia	16	22972	0.69	56	30105	1.86	**0.37**	**0.19 – 0.72**
Severe infections	36	22972	1.57	90	30105	2.99	**0.52**	**0.33 – 0.84**

IVIG – Intravenous immunoglobulin; RR – Rate ratio; CI – Confidence interval; ED – Emergency department
*Calculated as days between the date of start of maintenance treatment and off treatment date
†Only events occurring during the maintenance phase of treatment
Bolded values statistically significant

Table 8. Sensitivity analysis - disease and demographic characteristics of children with B-ALL, excluding special populations* (N=319)

	N (%)**
Age at diagnosis in years, median (IQR)	5 (3-9)
Categorical age	
<10 years	248 (77.7)
≥10 years	71 (22.3)
Sex	
Male	160 (50.2)
Female	159 (49.8)
Race/ethnicity	
Non-Hispanic White	161 (50.5)
Hispanic	72 (22.6)
Non-Hispanic Black	62 (19.4)
Other†	24 (7.5)
Minimal residual disease	
Negative	257 (80.6)
Positive	62 (19.4)
WBC at diagnosis	
<50 x10^9/L	279 (87.5)
≥50 x10^9/L	40 (12.5)
Treating campus	
Scottish Rite	203 (63.6)
Egleston	116 (36.4)
NCI Risk category	
Standard risk	216 (67.7)
High risk	103 (32.3)
Severe infections per 1,000 treatment days median (IQR)	2.4 (1.0-4.3)
IgG nadir mg/dL median (IQR)	499.5 (386-712)

B-ALL – B cell acute lymphoblastic leukemia; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range; IgG – Immunoglobulin G

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

**Unless otherwise noted

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Table 9. Sensitivity analysis - Comparisons of patient characteristics by IgG level checked among children with B-ALL, excluding special populations*, using Mann-Whitney or univariable logistic regression analyses (N=319)

Patient Characteristics	IgG Checked	IgG Never Checked	OR (95% CI)	P-value
	N (%)**	N (%)**		
	N=210 (65.8)	N=109 (34.2)		
Age at diagnosis in years median (IQR)	4 (3-8)	6 (4-10)	--	0.01††
Categorical age				
<10 years	172 (81.9)	76 (69.7)	--	0.01
≥10 years	38 (18.1)	33 (30.3)	0.51 (0.30-0.87)	
Sex				
Male	101 (48.1)	59 (54.1)	--	0.31
Female	109 (51.9)	50 (45.9)	1.27 (0.80-2.03)	
Race/ethnicity				
Non-Hispanic White	116 (55.2)	45 (41.3)	--	
Non-Hispanic Black	28 (13.3)	34 (31.2)	0.32 (0.17-0.79)	<0.01
Hispanic	46 (21.9)	26 (23.9)	0.69 (0.38-1.24)	0.21
Other†	20 (9.5)	4 (3.7)	1.94 (0.63-5.99)	0.25
Minimal residual disease				
Negative	160 (76.2)	97 (89.0)	--	<0.01
Positive	50 (23.8)	12 (11.0)	2.53 (1.28-4.98)	
WBC at diagnosis				
<50 x10^9/L	185 (88.1)	94 (86.2)	--	0.64
≥50 x10^9/L	25 (11.9)	15 (13.8)	0.85 (0.43-1.68)	
Treating campus				
Egleston	53 (25.2)	63 (57.8)	--	<0.01
Scottish Rite	157 (74.8)	46 (42.2)	4.06 (2.48-6.63)	
NCI Risk category				
Standard risk	146 (69.5)	70 (64.2)	--	0.34
High risk	64 (30.5)	39 (35.8)	0.79 (0.48-1.28)	
Severe infections per 1,000 treatment days median (IQR)	2.5 (1.3-5.0)	1.6 (0-2.8)	--	<0.01††

IgG – Immunoglobulin G; B-ALL – B cell acute lymphoblastic leukemia; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

**Unless otherwise noted

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

††Mann-Whitney test

Table 10. Sensitivity analysis – Comparisons of patient characteristics by IVIG receipt, among children with B-ALL with an IgG level checked, excluding special populations*, using Mann-Whitney or univariable logistic regression analyses (N = 210)

Patient Characteristics	IVIG Recipients	IVIG Non-Recipients	OR (95% CI)	P-value
	N (%)**	N (%)**		
	N=101 (48.1)	N=109 (51.9)		
Age at diagnosis in years, median (IQR)	4 (3-6)	5 (3-9)	--	<0.01††
Categorical age				
<10 years	89 (88.1)	83 (76.2)	--	0.03
≥10 years	12 (11.9)	26 (23.8)	0.43 (0.20 – 0.91)	
Sex				
Male	53 (52.5)	48 (44.0)	--	0.22
Female	48 (47.5)	61 (56.0)	0.71 (0.41 – 1.23)	
Race/ethnicity				
Non-Hispanic White	69 (68.3)	47 (43.1)	--	
Hispanic	20 (19.8)	26 (23.9)	0.52 (0.26 – 1.05)	0.07
Non-Hispanic Black	5 (5.0)	23 (21.1)	0.15 (0.05 – 0.42)	<0.01
Other†	7 (6.9)	13 (11.9)	0.37 (0.14 – 0.99)	0.05
Minimal residual disease				
Negative	75 (74.3)	85 (78.0)	--	
Positive	26 (25.7)	24 (22.0)	1.23 (0.65 – 2.32)	0.53
WBC at diagnosis				
<50 x10^9/L	87 (86.1)	98 (89.9)	--	0.40
≥50 x10^9/L	14 (13.9)	11 (10.1)	1.43 (0.62 – 3.32)	
Treating campus				
Egleston	21 (20.8)	32 (29.4)	--	0.16
Scottish Rite	80 (79.2)	77 (70.6)	1.58 (0.84 – 2.98)	
NCI Risk category				
Standard risk	73 (72.3)	73 (67.0)	--	0.40
High risk	28 (27.7)	36 (33.0)	0.78 (0.43 – 1.40)	
Severe infections per 1,000 treatment days, median (IQR)	3.8 (1.7-5.8)	2.3 (1.2-3.8)	--	<0.01††
Median IgG nadir, mg/dL (IQR)	406 (311-487)	675 (509-837)	--	<0.01††
IgG nadir				
<500 mg/dL	80 (79.2)	25 (22.9)	--	<0.01
≥500 mg/dL	21 (20.8)	84 (77.1)	0.08 (0.04-0.15)	

IVIG – Intravenous immunoglobulin; B-ALL – B cell acute lymphoblastic leukemia; IgG – Immunoglobulin G; OR – Odds ratio; CI – Confidence interval; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

**Unless otherwise noted

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

††Mann-Whitney test

Table 11. Sensitivity analysis – Multivariable Model 1a: Association of patient characteristics and IVIG initiation, among patients with IgG checked, excluding special populations* (n=210)

	Adjusted OR (95% CI)**
Race/ethnicity	
Non-Hispanic White	--
Non-White†	0.56 (0.27 – 1.16)
Minimal residual disease	
Negative	--
Positive	1.07 (0.47 – 2.42)
NCI Risk category	
Standard risk	--
High risk	0.85 (0.40 – 1.82)
IgG nadir	
≥500 mg/dL	--
<500 mg/dL	**12.08 (5.94 – 24.56)**
Treating campus	
Egleston	--
Scottish Rite	1.96 (0.86 – 4.46)
Severe infections	
≤2 infections per 1,000 treatment	--
>2 infections per 1,000 treatment	**2.76 (1.32 – 5.75)**

IVIG – Intravenous immunoglobulin; IgG – Immunoglobulin G; OR – Odds ratio; CI – Confidence interval; NCI – National Cancer Institute

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

**Adjusting for race/ethnicity, minimal residual disease, NCI risk category, IgG nadir, treating campus and severe infections

†Includes Non-Hispanic Black patients, Hispanic patients, patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Bolded values statistically significant

Table 12. Sensitivity analysis – Multivariable Model 2a: Association of patient characteristics and IVIG receipt during the maintenance phase of treatment, among patients with IgG checked, excluding special populations* (n=210)

	Adjusted OR (95% CI)**
Race/ethnicity – Non-Hispanic White	
NCI Standard Risk	--
NCI High Risk	1.85 (0.75 – 4.80)
Race/ethnicity – Non-White†	
NCI Standard Risk	--
NCI High Risk	0.31 (0.08 – 1.25)
NCI Standard risk	
Non-Hispanic White	--
Non-White†	1.06 (0.47 – 2.38)
NCI High risk	
Non-Hispanic White	--
Non-White†	**0.17 (0.04 – 0.75)**
Minimal residual disease	
Negative	--
Positive	1.36 (0.63 – 2.97)
IgG nadir	
≥500 mg/dL	--
<500 mg/dL	**7.04 (3.43 – 14.42)**
Treating campus	
Egleston	--
Scottish Rite	1.36 (0.62 – 3.02)
Severe infections prior to maintenance	
≤2 infections per 1,000 treatment days prior to maintenance	--
>2 infections per 1,000 treatment days prior to maintenance	0.64 (0.29 – 1.39)

IVIG – Intravenous immunoglobulin; IgG – Immunoglobulin G; OR – Odds ratio; CI – Confidence interval; NCI – National Cancer Institute

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

**Adjusting for race/ethnicity, minimal residual disease, NCI risk category, IgG nadir, treating campus and severe infections prior to maintenance

†Includes Non-Hispanic Black patients, Hispanic patients, patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Bolded values statistically significant

Table 13. Sensitivity analysis - Rate comparisons of infection-related outcomes during and without IVIG supplementation among IVIG recipients, excluding special populations* (n=102)

	During IVIG Supplementation			Without IVIG Supplementation			RR	95% CI
	Number	Person Days†	Rate per 1,000 days	Number	Person Days†	Rate per 1,000 days		
ED visits	181	35047	5.16	700	66631	10.51	**0.49**	**0.39 – 0.61**
Hospitalization days	744	35047	21.23	4253	66631	63.83	**0.33**	**0.25 – 0.44**
Episodes of febrile neutropenia	34	35047	0.97	252	66631	3.78	**0.26**	**0.17 – 0.39**
Severe infections	64	35047	1.83	344	66631	5.16	**0.35**	**0.26 – 0.48**

IVIG – Intravenous immunoglobulin; RR – Rate ratio; CI – Confidence interval; ED – Emergency department

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

†Calculated as days between date of diagnosis and off treatment date

Bolded values statistically significant

Table 14. Sensitivity analysis - Rate comparisons of infection-related outcomes during and without IVIG supplementation, among IVIG recipients who began IVIG supplementation during the maintenance phase of treatment excluding special populations* (n=72)

	During IVIG Supplementation			**Without IVIG Supplementation**			**RR**	**95% CI**
	Number††	Person Days†	Rate per 1,000 days	Number††	Person Days†	Rate per 1,000 days		
ED visits	107	22341	4.79	255	29937	8.52	**0.56**	**0.40 – 0.79**
Hospitalization days	282	22341	12.62	347	29937	11.59	1.09	0.73 – 1.62
Episodes of febrile neutropenia	15	22341	0.67	56	29937	1.87	**0.36**	**0.18 – 0.71**
Severe infections	33	22341	1.48	90	29937	3.01	**0.49**	**0.31 – 0.79**

IVIG – Intravenous immunoglobulin; RR – Rate ratio; CI – Confidence interval; ED – Emergency department

*Patients who died, relapsed, underwent hematopoietic stem cell transplant, had Philadelphia + B-ALL, or hypodiploid B-ALL

†Calculated as days between the date of start of maintenance treatment and off treatment date

†† Only events occurring during the maintenance phase of treatment

Bolded values statistically significant

APPENDIX

Supplemental Table A. Definitions of severe infection type and grade, based on Common Terminology Criteria for Adverse Events Version 5.0; ICU – Intensive care unit; PCR – polymerase chain reaction; IV - Intravenous

Infection Type	Definition of Grade 3	Definition of Grade 4	Additional Considerations
Lung infection	- Fever - Chest imaging consistent with pneumonia - Hospital admission	-Fever -Chest imaging consistent with pneumonia -ICU admission	-If chest imaging at an outside hospital showed pneumonia, but a repeat was done at Children's Healthcare of Atlanta within 24 hours and did NOT show pneumonia, this was not classified as a lung infection -If patient readmitted within 1 week of an episode and again met criteria, considered part of the first episode
Upper respiratory infection	-Fever - At least one of the following: cough, congestion, detectable virus on PCR testing -Hospital admission	-Fever - At least one of the following: cough, congestion, detectable virus on PCR testing -ICU admission	-If patient readmitted within 1 week of an episode and again met criteria, considered part of the first episode unless a new viral pathogen was identified
Skin infection (includes cellulitis, abscess, paronychia)	-Skin abnormality requiring hospital admission -IV treatment or surgical intervention (debridement, incision and drainage)	-Skin abnormality requiring hospital admission -Urgent IV treatment or surgical intervention (debridement, incision and drainage) indicated	
Sepsis	-Fever -Pathogen detected on blood culture	-Fever -Pathogen detected on blood culture -ICU admission	-If pathogens were detected on a blood culture within 7 days of the initial abnormal culture, considered part of the first episode unless a new pathogen was identified
Abdominal infection (includes enterocolitis)	-At least two of the following: fever, diarrhea, abdominal pain -Hospital admission	-At least two of the following: fever, diarrhea, abdominal pain -Hospital admission -Urgent surgical intervention or ICU admission	-Requires absence of other explanation for abdominal pain or diarrhea (i.e. pancreatitis, malabsorption)
Mucosal infection	-Fever -Signs or symptoms of mucosa-specific infection requiring antimicrobial treatment -Hospital admission	-Fever -Signs or symptoms of mucosa-specific infection requiring antimicrobial treatment -Urgent surgical intervention or ICU admission	

Supplemental Table B. Comparisons of disease and demographic characteristics in children with B-ALL by race/ethnicity (N=373)

Patient Characteristics	Non-Hispanic White	Non-Hispanic Black	Hispanic	Other†
	N (%)*	N (%)*	N (%)*	N (%)*
	184 (49.3)	69 (18.5)	94 (25.2)	26 (7.0)
Age at diagnosis, in years median (IQR)	5 (3-10)	5 (3-11)	6 (4-10)	4 (3-5)
Categorical age				
<10 years	137 (74.5)	45 (65.2)	70 (74.5)	22 (84.6)
≥10 years	47 (25.5)	24 (34.8)	24 (25.5)	4 (15.4)
Sex				
Male	92 (50.0)	35 (50.7)	53 (56.4)	9 (34.6)
Female	92 (50.0)	34 (49.3)	41 (42.6)	17 (65.4)
Minimal residual disease				
Negative	133 (72.3)	59 (85.5)	66 (70.2)	23 (88.5)
Positive	47 (25.5)	10 (14.5)	26 (27.7)	3 (11.5)
Unavailable	4 (2.2)	--	2 (2.1)	--
WBC at diagnosis				
<50 x10^9/L	157 (85.3)	57 (82.6)	83 (88.3)	23 (88.5)
≥50 x10^9/L	27 (14.7)	12 (17.4)	11 (11.7)	3 (11.5)
Treating campus				
Egleston	55 (29.9)	43 (62.3)	33 (35.1)	10 (38.5)
Scottish Rite	129 (70.1)	26 (37.7)	61 (64.9)	16 (61.5)
NCI Risk category				
Standard risk	114 (62.0)	39 (56.5)	64 (68.1)	18 (69.2)
High risk	70 (38.0)	30 (43.5)	30 (31.9)	8 (30.8)
Severe infections, Median (IQR)	2.5 (1.3 – 4.8)	1.3 (0 – 3.6)	3.8 (1.3 – 6.1)	2.5 (1.2 – 6.5)
IgG Checked				
No	50 (27.2)	36 (52.2)	32 (34.0)	4 (15.4)
Yes	134 (72.8)	33 (47.8)	62 (66.0)	22 (84.6)
Median IgG nadir, mg/dL (IQR)**	465 (342-594)	713 (527-830)	589.5 (460-821)	521.5 (430-792)
IgG nadir**				
<500 mg/dL	79 (59.0)	8 (24.2)	23 (37.1)	9 (40.9)
≥500 mg/dL	55 (41.0)	25 (75.8)	39 (62.9)	13 (59.1)

B-ALL – B cell acute lymphoblastic leukemia; WBC – White blood cell; NCI – National Cancer Institute; IQR – Interquartile range; IgG – Immunoglobulin G

*Unless otherwise noted

**Among N=251 patient with an IgG level checked

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

Supplemental Table C. Multinomial logistic regression crude odds ratios of patient characteristics by race/ethnicity compared to Non-Hispanic White patients (N=373)

Patient Characteristics	Hispanic (N=94) vs Non-Hispanic White (N=184)	Non-Hispanic Black (N=69) vs Non-Hispanic White (N=184)	Other† (N=26) vs. Non-Hispanic White (N=184)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Categorical age (≥10 vs <10 years)	1.00 (0.57 – 1.77)	1.56 (0.86 – 2.82)	0.53 (0.17 – 1.62)
Sex (Female vs Male)	0.77 (0.47 – 1.28)	1.03 (0.59 – 1.79)	1.89 (0.80 – 4.46)
Minimal residual disease (Positive vs Negative)	1.12 (0.64 – 1.96)	0.48 (0.23 – 1.01)	0.37 (0.11 – 1.29)
WBC at diagnosis (≥50 vs <50 x10^9/L)	0.77 (0.36 – 1.63)	1.22 (0.58 – 2.58)	0.76 (0.21 – 2.70)
Treating campus (Scottish Rite vs Egleston)	0.79 (0.47 – 1.34)	**0.26 (0.14 – 0.46)**	0.68 (0.29 – 1.60)
NCI Risk Category (High vs Standard Risk)	0.76 (0.45 – 1.29)	1.25 (0.72 – 2.20)	0.72 (0.30 – 1.75)
IgG Checked (Yes vs No)	0.72 (0.42 – 1.24)	**0.34 (0.19 – 0.61)**	2.05 (0.67 – 6.25)
IgG nadir* (≥500 vs <500 mg/dL)	**2.44 (1.31 – 4.53)**	**4.49 (1.89 – 10.69)**	2.08 (0.83 – 5.19)

OR – Odds ratio; CI – Confidence interval; WBC – White blood cell; NCI – National Cancer Institute; IgG – Immunoglobulin G

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

*Among N=251 patients with an IgG level checked

Bolded values statistically significant

Supplemental Table D. Multiple comparison analysis (Dwass, Steel, Critchlow-Fligner Method) P values of patient characteristics by race/ethnicity compared to Non-Hispanic White patients (N=373)

Patient Characteristics	Hispanic (N=94) vs Non-Hispanic White (N=184)	Non-Hispanic Black (N=69) vs Non-Hispanic White (N=184)	Other† (N=26) vs Non-Hispanic White (N=184)
Age at diagnosis	0.53	0.99	0.42
ED visits	0.10	0.90	0.34
Hospitalization days	0.31	0.38	0.99
Severe infections	0.18	**<0.01**	0.97
Febrile neutropenia episodes	0.40	**0.01**	0.53
Median IgG nadir*	**<0.01**	**<0.01**	0.11

ED – Emergency department; IgG – Immunoglobulin G

†Includes patients without a race/ethnicity documented, patients who were multiracial, or patients with a race/ethnicity documented other than Non-Hispanic White, Non-Hispanic Black, or Hispanic

*Among N=251 patients with an IgG level checked

Bolded values statistically significant

Supplemental Table E. Induction and post-induction chemotherapy treatment regimens followed for the treatment of B-ALL in cohort patients (N=373)

Induction treatment	N (%)
AALL0932	205 (55.0)
AALL1131	96 (25.7)
AALL0232	34 (9.1)
AALL0331	27 (7.2)
AALL08P1	5 (1.3)
AALL0031	2 (0.5)
AALL1122	2 (0.5)
AALL0622	1 (0.3)
Non-standardized regimen	1 (0.3)
Post-induction treatment*	
AALL1131	138 (37.0)
AALL0932	133 (35.7)
AALL0232	49 (13.1)
AALL0331	21 (5.6)
AALL0031	9 (2.4)
AALL0622	5 (1.3)
AALL08P1	4 (1.1)
AALL1122	2 (0.5)
AALL1521	2 (0.5)
Non-standardized regimen	1 (0.3)

*Patients reclassified after induction chemotherapy based on minimal residual disease and cytogenetic results

Supplemental Table F. Comparison of severe infections during treatment of B-ALL in children with an IgG level checked, according to IVIG receipt (N=251)

Infection Type	IVIG Recipients N=113	IVIG Non-Recipients N=138
	N (%)	N (%)
Total infections	474	346
Upper respiratory	169 (35.7)	122 (32.4)
Lung	72 (15.2)	41 (11.8)
Abdominal	73 (15.4)	45 (13.0)
Sepsis	66 (13.9)	56 (16.2)
Skin	39 (8.2)	41 (11.8)
Mucosal	22 (4.6)	19 (5.5)
Other†	33 (7.0)	22 (6.4)

B-ALL – B cell acute lymphoblastic leukemia; IgG – Immunoglobulin G; IVIG – Intravenous immunoglobulin
†Includes kidney/urinary tract infection, otitis media, bone infection, sinusitis, tooth infection, lymphadenitis, vaginal infection, meningitis/encephalitis, joint infection, pharyngitis, and soft tissue infection

Supplemental Table G. Characteristics of studies evaluating IVIG supplementation in children with acute leukemia

	Van Winkle et al (8)	**Holmes et al (9)**	**Edington et al**
Data source	Single health maintenance organization, multicenter	Single institution, single campus	Single institution, multicenter
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort
Years	2008-2014	2006-2011	2010-2017
Age	9 month – 19 years	Unspecified	1-21 years
Disease	B-ALL, T-ALL	B-ALL, T-ALL	B-ALL
Total N	T-ALL – 12 B-ALL – 106 Total - 118	T-ALL – 19 B-ALL – 117 Total – 136	T-ALL - 0 B-ALL – 373 Total - 373
IVIG recipients (N)	36	38	114
Objective	Evaluate IVIG prevalence and safety	Evaluate if monitoring IgG and IVIG supplementation reduces rate of febrile illnesses	(1) Evaluate association between infections and hypogammaglobulinemia with IVIG receipt (2) Evaluate IVIG effect on rate of ED visits and hospitalizations
Race and ethnicity	<u>Race/ethnicity</u> 60% Hispanic 25% White 7% Asian 5% African American 3% Other	<u>Race</u> 82% White 14% Black 4% Other <u>Ethnicity</u> 8% Hispanic 74% Non-Hispanic 18% Other	<u>Race/ethnicity</u> 49% Non-Hispanic White 25% Hispanic 19% Non-Hispanic Black 7% Other
Phase of treatment	Maintenance only	Maintenance only	Prior to maintenance and during maintenance
Statistical analyses	Multivariable logistic regression	Generalized mixed effect Poisson model	Multivariable logistic regression, General estimating equation with Poisson distribution

IVIG – Intravenous immunoglobulin; B-ALL – B cell acute lymphoblastic leukemia; T-ALL – T cell acute lymphoblastic leukemia; IgG – Immunoglobulin G; ED – emergency department