**COVID-19 Infection in Children with Acute Lymphoblastic Leukemia Receiving Maintenance Therapy: Don’t Discount the Risk**

Running Head: COVID-19 and Childhood ALL in Maintenance

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**Key points**:

* Children with acute lymphoblastic leukemia in maintenance therapy are at risk of morbidity from COVID-19 infection.
* Risks include hospitalization, ICU admission, and delays in chemotherapy.

**Abstract**

Background: Unlike other pediatric cancers, acute lymphoblastic leukemia (ALL) treatment includes a prolonged maintenance phase during which children typically resume regular activities. As COVID-19 transmission persists despite the end of the public health emergency declaration, physicians need data regarding the impact of COVID-19 in this population to guide families in managing risk.

Procedure: The Pediatric Oncology COVID-19 Case Report (POCC) collected de-identified clinical and sociodemographic data on children with cancer and COVID-19. This subset analysis compares 481 children (≤21yo at COVID-19 infection) with ALL in maintenance (ALL-MTN) to other children with cancer and COVID-19 (n=1,190).

Results: Children in ALL-MTN had fewer hospitalizations, (23% vs 29%, p=0.01), intensive care unit admissions (ICU: 3% vs 5%, p=0.01), and were less likely to die (0% vs 2%, p=<0.01). However, they more often had cancer therapy changed (50% vs 33%, p=<0.01). Lower odds of hospitalization and ICU admission persisted in multivariable analyses adjusting for age, race/ethnicity, insurance, ANC, and comorbidities. There were independent associations among children in ALL-MTN with sociodemographic factors (Hispanic ethnicity, public insurance) and clinical characteristics (comorbid conditions, neutropenia) and both hospitalization and ICU admission. Vaccination decreased odds of hospitalization.

Conclusions: Children in ALL-MTN continue to have significant COVID-19 risks, with less hospitalization and ICU admission but more therapy changes than other children with cancer. These risks should be addressed when discussing participation in activities (school, camp, sports, etc.), prevention (COVID-19 vaccination) and mitigation (masking) strategies. The high level of therapy modifications could have long-term consequences and should continue to be followed.

**INTRODUCTION**

Acute lymphoblastic leukemia (ALL) is the most common cancer in children, comprising approximately 20% of new diagnoses in patients <20 years old. Over 3,000 new cases are diagnosed each year in the United States.1 Treatment for pediatric ALL involves 6-8 months of intensive therapy followed by 1-2 years of less intensive maintenance therapy. Children with cancer tend to be kept fairly isolated during treatment due to their high risk of infection. For instance, children undergoing treatment for cancer frequently do not attend in-person school and are advised to limit in-person social interactions. However, during maintenance therapy, children with ALL usually return to in-person school and participate in normal childhood activities; they even potentially return to their general pediatrician for non-cancer-related problems.2

Children with cancer and COVID-19 are at risk of severe disease.3 Among 917 children with cancer and COVID-19 infection across 94 centers, 31% were hospitalized, 9% admitted to the intensive care unit (ICU), 2% developed MIS-C, and 2% died due to COVID-19.3 Compared with the US population of children with cancer (SEER), children with hematologic malignancies were over-represented in the COVID-19 cohort, comprising two-thirds of the cohort.4 Furthermore, compared with children with solid tumors, children with hematologic malignancies were more likely to be symptomatic, hospitalized, require respiratory support, and have changes in their cancer-directed therapy.3 However, the specific risks for severe infection among children with ALL in maintenance therapy (ALL-MTN) remain unknown.

In March 2020, Wuhan Children’s Hospital was the first to describe a COVID-19 infection in a pediatric patient in ALL-MTN, who required ICU admission and intubation.5 Subsequent early regional small case series reported a relatively benign clinical course in children with ALL-MTN and COVID-19 infections in contrast to significant morbidity in the overall childhood cancer population.6–8 However, to truly understand the burden of COVID-19-related complications in this population requires a larger cohort identified over a longer period of time.

Policies and practices related to public health mitigation strategies (masking, social distancing) and vaccinations have changed over time and vary across regions. As schools, camps, and other activities are now primarily in-person and the public health emergency declaration has ended, it is imperative to specifically understand how children with ALL-MTN fare when they are infected with COVID-19. Unlike other children with cancer, they and their parents are likely to be contemplating whether they can participate in “normal” childhood activities as they would have in a pre-COVID world. Pediatric oncology clinicians also require guidance to understand the health risks to these patients if they develop COVID-19. To this end, we leveraged the Pediatric Oncology COVID-19 Case Report (POCC) data to assess the clinical course of a COVID-19 infection in patients with ALL-MTN and to compare their risks to the general pediatric oncology population. The goal is to help guide patients, families, and health care providers as they consider mitigation strategies and participation in activities in this population as external protections recede.

**METHODS**

**Data Source**

The POCC Report is an ongoing observational study of children, adolescents, and young adults with cancer and COVID-19.9 Since April 2020, POCC has provided pediatric oncologists with real-time information about the clinical course of COVID-19 in children with cancer. Patients are eligible if they are 0-39 years at the time of COVID-19 infection, and they are actively receiving cancer-directed therapy or received therapy ≤12 months prior to infection. Institutions regularly enter de-identified data (prospectively and retrospectively) for each child with cancer and COVID-19 regarding the first 12 weeks of their clinical course following infection. The study was approved by the Institutional Review Board (IRB) at the University of Alabama at Birmingham. All participating institutions adhered to local IRB policies and procedures. To facilitate rapid review by local IRBs during the pandemic, no personal health information was collected.

**Study Design and Population**

Analyses presented here include patients ≤21 years at time of COVID-19 infection (between 04/29/2020 – 05/18/2022), with a focus on those receiving maintenance therapy for ALL. Patients were defined as being in maintenance phase if “maintenance” was listed as the phase of therapy or via direct communication with the site (as necessary). Children with ALL-MTN were compared to all other children (≤21 years) in POCC.

**Independent Variables**

Independent variables included sociodemographic (age at COVID-19 infection, sex, race/ethnicity, and health insurance) and clinical (immunophenotype [T- or B-cell], absolute neutrophil count [ANC: <500 cell/µL vs. ≥500 cells/µL] at time of infection, history and type of blood or marrow transplantation [BMT], disease status [relapse vs. first complete remission], comorbidities) factors. T- or B-cell leukemia was confirmed via direct communication with the site when not clear from treatment regimen.

**Dependent Variables**

Dependent variables included symptoms related to COVID-19 infection (including MIS-C and death), duration of symptoms, level of support required for COVID-19 infection (hospitalization, ICU admission, respiratory support, other support [vasopressors, ECMO, dialysis], COVID-19-directed therapy, and changes in cancer-directed therapy [overall and related to cytopenias]).

**Statistical Analysis**

In order to compare children in ALL-MTN to all other children in POCC, descriptive statistics were used (chi-square for categorical, Wilcoxon rank sum for continuous). Multivariable logistic regression were used to model factors associated with hospitalization, ICU admission, and changes in cancer-directed therapy. Models were constructed using a combination of a priori-selected univariate associations as well as backward selection (sls=0.2). **[Supplemental Tables 1-2]** Patients with missing data were excluded from each analysis using listwise deletion except patients with missing ANC as they could have been clinically distinct from those without missing laboratory data. All analyses were conducted using SAS version 9.4 (SAS, Cary, NC). A p-value of <0.05 was considered significant.

**Data Sharing Statement**

For original data, please contact POCCReport@uabmc.edu.

**RESULTS**

**Study Population**

*ALL-MTN:* Among the POCC cohort, 481 children (29%), were identified as having ALL and being on maintenance therapy. **[Table 1]** Among children in ALL-MTN, the mean age at COVID-19 infection was 9.5 years (SD=5.5). B-cell leukemia was the primary cancer diagnosis (85%). At the time of COVID-19 infection, 12% had an ANC <500 cells/uL. Twenty five percent had at least one comorbidity, with the most common being obesity (8%), trisomy 21 (4%), diabetes mellitus (4%), asthma (4%), and hypertension (3%). **[Supplemental Table 3]**

*Comparison to POCC Cohort:* Compared with other children in POCC, those with ALL-MTN were of similar age (mean 9.5 years vs 9.6 years, p=0.78) and had similar rates of private insurance (45% vs. 41%, p=0.08). **[Table 1]** Complete 12-week follow-up data were entered for 97% of all children in POCC (ALL-MTN: 98%; all others: 97%; p=0.28).

**Symptoms**

In the setting of their COVID-19 infections, 78% of children in ALL-MTN were symptomatic. **[Table 2]** The most common symptoms in this population were fever (51%), cough (41%), rhinorrhea (33%), fatigue (12%), and headache (12%), while 1% developed MIS-C. Among those with symptoms, the median duration of symptoms was 3 days (range 1-51 days). When compared with the remainder of the POCC cohort, children in ALL-MTN were more often symptomatic (78% vs 67%, p=<0.01), and more often had general systemic symptoms such as fever (p<0.01) and respiratory symptoms (p<0.01). No children in ALL-MTN died, compared with 2% of the rest of the cohort (with 1% dying due to COVID-19) (p=<0.01).

**Maximum Level of Medical Support**

Among children in ALL-MTN, 23% were hospitalized and 3% admitted to the ICU. **[Table 2]** Children in ALL-MTN were hospitalized at lower rates compared to the rest of the cohort (23% vs 29%, p=0.01) and they had lower rates of ICU admission (3% vs 5%, p=0.01). When compared with the remainder of the POCC cohort in multivariable analysis, children in ALL-MTN continued to have a lower odds of admission to the hospital (OR=0.7, 95% CI=0.6-0.9, Reference=non ALL-MTN), and a lower odds of admission to the ICU (OR=0.5, 95% CI=0.2-0.8, Reference=non ALL-MTN). (Full models are presented in **Supplemental Table 1**.) Demographic factors affecting rates of hospitalization in multivariable analysis included Hispanic ethnicity (OR=1.54, 95% CI=1.2-2.0, reference=non-Hispanic White) and public or no insurance (OR=1.49, 95% CI=1.2-1.9, reference=private insurance). ANC<500 was associated with hospitalization (OR=3.5 95% CI 2.6-4.6, reference=ANC>500) but not ICU admission. Co-morbid conditions were associated with both increased hospitalization (OR=1.7, 95% CI=1.4-2.2, reference=no comorbidities) and ICU admission (OR=3.5, 95% CI=2.2-5.6, reference=no comorbidities). Vaccination was associated with a significant decrease in hospitalization (OR=0.7, 95% CI=0.5-0.9, reference=no vaccination)

**Changes in Leukemia-Directed Therapy**

More children in ALL-MTN had their leukemia-directed therapy changed than did the remainder of the cohort (50% vs. 33%, p<0.01). The most common changes were delays in chemotherapy, with 15% of patients delayed due to cytopenias and 33% delayed for other reasons (e.g. provider discretion). **[Table 2]** Among those with delays, 36% were delayed for a period of greater than two weeks. In multivariable analyses adjusting for age, race/ethnicity, insurance, ANC and comorbidities, children in ALL-MTN continued to have an increased odds of changes to leukemia-directed therapywhen compared with the remainder of the POCC cohort (OR=2, 95%CI=1.6-2.5, reference=non ALL-MTN).Hispanic ethnicity (OR=1.8, 95% CI=1.4-2.2, reference=Non-Hispanic White) and comorbid conditions (OR=1.4, 95% CI=1.1-1.7, reference=comofrbitdities) were both associated with changes to leukemia-directed therapy **[Supplemental Table 1].**

**COVID-19 Directed Therapy**

Sixteen percent of children in ALL-MTN received COVID-19-directed therapy; these included Remdesivir (8%), monoclonal antibody (8%), corticosteroids (4%), intravenous immunoglobulin [IVIG] (2%), and convalescent plasma (2%). **[Table 2]** The rate of children in ALL-MTN receiving COVID-directed therapy was not different (p=0.96) from the remainder of the cohort.

**DISCUSSION**

Leveraging national POCC Report registry data, we found that children in ALL-MTN experienced lower rates of hospitalization and ICU admission in the setting of COVID-19 infections when compared with children who have different cancers and in other phases of ALL therapy. Nevertheless, a COVID-19 infection led to a modification of leukemia-directed therapy in more than half of children in ALL-MTN, a practice which could have long-term implications for disease free survival.

While there were no COVID-19-related deaths among children in ALL-MTN in the POCC registry, 23% required hospitalization and 3% required ICU admission due to COVID-19. While lower than other children with cancer, compared with the general US pediatric population, these rates of hospitalization (3%) and ICU admission (1%) are both higher.10 Just as in the full POCC cohort, among children in ALL-MTN there were independent associations between sociodemographic factors (Hispanic ethnicity, public insurance) and clinical characteristics (comorbid conditions, neutropenia) and hospitalization/ICU admission.3 **[Supplemental Table 1]** Based on these outcome measures, the clinical management and prevention of COVID-19 should be approached similarly for both children in ALL-MTN and children with other cancers (and in other phases of therapy) in the context of the risks of this infection.

Despite a similar clinical course, more than half of children in ALL-MTN had their leukemia-directed therapy modified in some way. In fact, children in ALL-MTN experienced more chemotherapy delays than the general oncology population who are receiving more intensive therapies. At first glance, this might be assumed to be secondary to the hematologic guidelines on increasing, decreasing or holding chemotherapy throughout ALL maintenance therapy. However, while some chemotherapy delays were due to cytopenias, the majority were for other reasons. There are a number of conceivable circumstances that may have contributed to these delays, including: (i) clinicians had concerns regarding the potential for infection-associated marrow suppression; (ii) sedation for a lumbar puncture was considered unsafe or logistically not feasible while patients were infected thus delaying intrathecal chemotherapy; (iii) logistical difficulties with CBC monitoring were encountered while patients were considered contagious; (iv) family members were also infected with COVID-19 and were unable to bring patient to clinic.

Nevertheless, chemotherapy delays during ALL maintenance therapy are particularly concerning as consistent 6MP exposure plays a key role in sustaining remission in ALL. Specifically, ALL patients with mean 6MP adherence rates <95% during maintenance face nearly three times the risk of relapse, even among adherent patients; furthermore, variability in 6MP metabolites contributes to increased relapse risk with drug interruptions playing a significant role.11,12 There is a concern that the drug interruptions of maintenance medications, described here may increase patients’ risk of relapse. Therefore, the full impact of COVID-19 infection-related chemotherapy interruptions will only become known with dedicated long-term follow-up.

In patients who are not neutropenic, our data suggests interruptions should be avoided if possible and chemotherapy should be resumed as soon as safe. Chemotherapy delays due to COVID-19 infection may also serve to exacerbate pre-existing disparities. Our data showed that Hispanic children had increased rates of chemotherapy delays. This is particularly notable as Hispanic children with ALL already have poorer overall survival compared to white children, an effect which has persisted over decades.13,14 Disparities in chemotherapy delays resulting from COVID-19 infection may only serve to exacerbate these differences in survival.

Children with comorbidities had increased risks of hospitalization, ICU admission and changes in leukemia-directed therapy, suggesting that these clinicians and families may consider additional precautions in this population compared to other children in maintenance therapy. Conversely, vaccination is a modifiable risk factor which decreases the risk of hospitalization.

There are limitations to the use of registry data in describing the clinical course of COVID-19 infection in ALL patients during maintenance therapy. There may be differences between sites that did and did not participate in this registry. However, the registry does include large and small centers from all regions of the country and represents over half of the pediatric oncology sites in the US. Comprehensive reasons for each hospitalization were not captured, thus it is plausible that some patients were hospitalized out of an abundance of caution on the part of clinicians treating a new disease entity, rather than true need for hospitalization. Regardless of the reason, hospitalization is still disruptive for patients and their families and places them at risk for iatrogenic complications such as nosocomial infection. Due to the lack of PHI, outcomes could not be trended over time and as variants emerged. It is also possible that given the size of this sub-cohort, analyses may be underpowered to detect additional differences in this patient population. In the future, as vaccines are now approved in all age groups, it will be useful to also look for further emerging differences between immunized and non-immunized patients in this population.

In summary, in the setting of COVID-19, children in ALL-MTN have high rates of hospital admission, ICU admission, and changes in their leukemia therapy, but odds of hospitalization, ICU admission and death are lower than other children with cancer. Nevertheless, they face high morbidity in the setting of COVID-19 relative to the general pediatric population. Furthermore, COVID-19 infections in these patients are associated with chemotherapy delays that have the potential to affect their leukemia outcome. These findings can inform physicians and families as they contemplate precautions and interventions to prevent and mitigate the effects of COVID-19 in the setting of the CDC’s retraction of the public health emergency declaration and the updated CDC guidelines that incorporate individual-level risk factors*.*15 This may include decision-making regarding participation in and precautions during in-person events that may increase the risk of COVID-19 infection, such as schools, camps, schools and other activities. This may also include discussion of prevention strategies such as masking and vaccination and treatment with anti-viral agents in order to decrease risks of hospitalization and chemotherapy holds that may affect cancer prognosis.

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**FIGURE LEGENDS**

**Figure 1.** Odds of Hospitalization, ICU Admission and Changes to Leukemia-Directed Therapy: Children with ALL in Maintenance vs. Remainder of POCC Cohort