



Improving Medication Adherence: Pediatric Acute Lymphoblastic Leukemia

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Abstract

Medication adherence in pediatric acute lymphoblastic leukemia (ALL) is critical for achieving remission. In spite of this, adherence rates to oral chemotherapy remain suboptimal. The following review of literature synthesizes existing information concerning the importance of medication adherence with regard to ALL. The review addresses the importance of adherence in prevention of disease progression, as well as the most prominent barriers found to be associated with inadequate adherence. Such barriers have been categorized as either patient, clinician, treatment, or socioeconomic related barriers for the purpose of recognizing corresponding interventions. Several interventions that have been recommended for use in clinical settings are explored as well, based on existing intervention studies and on interviews with pediatric oncologists. The current literature review explores the most prevalent barriers identified by patients/parents as well as corresponding interventions that may be applied to such barriers. Due to the current inadequate literature pertaining specifically to adherence interventions with regard to pediatric ALL, this study aims to correlate generalized adherence barriers and interventions and extend them to the pediatric ALL population. Findings indicate that the vast majority of patients report experiencing at least one adherence barrier.

Keywords: acute lymphoblastic leukemia (ALL), medication adherence, adherence barriers, interventions

I. Introduction

Leukemia is the term encompassing a disease where leukocytes become irregularly shaped and perform abnormally (Hammar, 2021). In appreciating the importance of treatment adherence, it is critical to develop a basic comprehension of the disease itself, to act as building blocks for understanding how nonadherence affects the progression of the disease. Leukocytes (white blood cells), typically follow a pattern in which they go from stem cells, to immature lymphoblasts, to B and T cells. However, due to a mutation, leukemia cells stop at the lymphoblast stage and rapidly reproduce at this immature stage (Bamme, 2024). This concept was further explored in an interview with Dr. Yoram Unguru MD, a pediatric hematologist/oncologist at Sinai Hospital of Baltimore Maryland, where the author completed a year long practicum. He stated, “If your bone marrow is your garden...ALL is simply when your garden gets overrun by one weed” (Unguru 2024).

Due in large part to the revolutionary advances of treatment regimens for ALL, the 5-year event-free survival rate for pediatric ALL has experienced an incredible increase over the past few decades alone, from 63% in the 1990s to 93% for

standard-risk patients (Pieters et al. 2016), indicating that survival rates are continually increasing. These remarkable increases in survival rates can be primarily attributed to the extended period of time in which a patient receives maintenance therapy (prolonged chemotherapy at lower doses), as proven from extensive clinical trials (Pieters et al. 2016). Such an increase in survival rates is indicative of the effectiveness of various forms of chemotherapy and suggests that adherence to the medication regimen is a critical component of relapse free remission.

Proper medication adherence is critical to the survival and relapse free remission of all pediatric ALL patients. In an interview with Dr. Yevgeniya Bamme, a Pediatric Hematologist/Oncologist at Sinai Hospital, the nature of medication adherence in the maintenance phase of treatment is addressed.

“When we do leukemia treatment, the first 6-9 months are pretty intense... in theory we would wipe out all of the leukemia cells at that point. But we can’t guarantee it because our technology is only so good, and we can only detect cells to a certain level...there might be one or two ‘bad clones’ still living in the bone marrow, and we just don’t want to give them a chance to replicate...it’s been proven that if patients don’t have good compliance with their oral medication during maintenance, it does increase the risk of relapse.”

Dr. Bamme’s remarks highlight the critical importance of adhering to oral chemotherapy to prevent relapse of pediatric ALL. In spite of this, there is limited research pertaining specifically to adherence barriers and solutions in pediatric ALL. We therefore look first to general pediatric medical adherence studies to identify barriers that have been found to be associated with pediatric medication adherence in general, and aim to apply them in the context of ALL to answer the question of how barriers to adherence can be eliminated. Findings could additionally be relevant for barriers to adherence in other pediatric cancers.

1.1 Importance of Medication Adherence

Nonadherence can greatly worsen a patient’s prognosis, as the patient becomes increasingly susceptible to rapid cell reproduction of the immature lymphoblasts, as they are not being eradicated by chemotherapy. This prevents other cells from performing their designated functions, as they are crowded out by the blasts. Further, the lymphoblasts can build up an immunity to the chemotherapy, if it is not administered consistently. These cells will be more adept at fighting the medication when it is reintroduced, so each and every dose at the proper dosage is necessary to overwhelm the cells and eradicate them (Unguru, 2024). In an interview with Dr. Unguru, the process of the leukemia cells’ ability to build up an immunity to the chemotherapy was further addressed.

“...built in to any cancer cell is mechanisms by which the cell is able to evade, get by the body’s normal defenses...The moment you take your foot off the accelerator, and if you’re not taking those medicines regularly, those cells are like ‘I got a break, now I can figure out how to get by.’...by stopping to take the medicine regularly, by skipping doses, by giving lower doses than what is prescribed, the cancer cells have a way to evade and develop resistance.” (Unguru 2024)

The phase 3 RESONATE trial, a randomized, open-label study comparing the efficacy and safety of two drugs used to treat leukemia, demonstrated that leukemia patients who were not adherent to the treatment protocol were two times more likely to be hospitalized as opposed to patients who were adherent (Gentry, 2019). Conversely, medication adherence has strongly proven to result in better treatment outcomes, including a significantly lower risk of relapse along with improved mood and quality of life (Gentry, 2019). It is evident that medication adherence is critical for all pediatric patients with ALL; however, there may be multiple patient, clinician, treatment, and socioeconomic barriers to adherence, and a

combination of approaches may be necessary to eliminate such barriers. This study sought to link identified barriers with potential interventions.

II. Methods

The major goal of this study was to match identified medication adherence barriers with potential interventions to reduce those barriers. A literature review was conducted to identify significant medication adherence barriers for pediatric patients, as well as appropriate corresponding solutions. In regard to the studies conducted on barriers to medication adherence (Müller et al. 2015; Chan et al. 2020), both utilized a questionnaire, from which several barriers were identified. The findings from these studies concerning adherence barriers can be referenced in Figure 1. A barrier was classified as significant if identified by multiple studies (Figure 2).

The latter studies conducted by Bussell et al (2017) and Aremu et al (2022), discussing possible interventions to nonadherence, have been recommended for use in the clinical setting; such solutions may be found in Figure 3. This study hypothesized the probable reason for effectiveness of various interventions identified in Figure 3. Such barriers and solutions identified via the aforementioned studies were analyzed inductively resulting in specific solutions assigned to each barrier. Additionally, interventions were identified for those barriers based on past research findings (Figure 4). These data were analyzed inductively, that is, they originated from an observation: pediatric ALL patients experience medication nonadherence due to several barriers, and this observation resulted in exploration of solutions to such barriers.

This literature review used several scholarly studies, each respectively from the National Institutes of Health (NIH), derived from a search through Google Scholar as well as through an analysis of relevant sources cited in previously reviewed studies. In the process of evaluating the several studies used in this literature review, each chosen study served a distinct purpose, and several inclusion criteria were used. Specifically, sources were evaluated on the various statistical analyses they included, such as the inclusion of a numerical value assigned to a wide range of adherence barriers, indicating their prevalence (Müller et al., 2015).

III. Data

Table 1: Barriers identified in regard to medication adherence

Study	Patient Related Barriers	Clinician Related Barriers	Treatment Related Barriers	Socioeconomic Related Barriers
Müller et al., 2015 <i>Focused on medication adherence in patients with atrial fibrillation. Specifically, this study focuses on adherence to long-term oral anticoagulation therapy.</i>	<ul style="list-style-type: none"> - Knowledge of disease and importance of treatment regimen - Knowledge in regard to prescribed medication - Perceived unattainable level of compliance - Habitual aspects (medication taken at same time everyday) - Ideology concerning the medication (medications are 	<ul style="list-style-type: none"> - Ensuring patient knowledge of disease and specific prescribed medication regimen - Doctor-patient relationship - Presence of (SDM) model - Unclear instructions 	<ul style="list-style-type: none"> - Complexity of treatment regimen - Problems taking the medication - Issues with compliance in regard to corequisites for taking the medication - Undesirable side effects 	<ul style="list-style-type: none"> - Copayments associated with the medication - Assorted healthcare obstacles - Need for additional help/support on a daily basis due to difficulties taking the medications

	<p>poisonous, perhaps, and should be avoided)</p> <ul style="list-style-type: none"> - Questioning necessity of adherence due to health status - Forgetfulness - State of mental health - Problems taking the medication - Issues in regard to corequisites for taking the medication 			
<p>Chan et al., 2020</p> <p><i>Focused on medication adherence in various chronic diseases such as diabetes and respiratory conditions.</i></p>	<ul style="list-style-type: none"> - Swallowing difficulties - Forgetfulness - Busy schedule - Difficulty maintaining a medication routine (habitual) - Knowledge in regard to prescribed medication - Unable to understand doctor’s instructions - Dose calculations - Knowledge of disease and importance of treatment regimen 	<ul style="list-style-type: none"> - Unclear instructions - Knowledge of specific prescribed medication and ensuring patient/parent understanding of treatment regimen - Inadequate drug monitoring system - Doctor-patient relationship 	<ul style="list-style-type: none"> - Taste of tablets - Shape of tablets - Size of tablets - Dosing frequency - Polypharmacy - Storage of medications - Issues with compliance in regard to corequisites for taking the medication - Variable dose pattern - Undesirable side effects - Drug monitoring requirements - Complexity of treatment regimen - Difficulty maintaining a medication routine - Medication handling - Complex dose calculations - Pills that require cutting 	<ul style="list-style-type: none"> - Copayments associated with medications - Assorted healthcare obstacles - Financial strain - Lacking supply of the medications - Transportation is unavailable to obtain medication from pharmacy - Social influences such as hesitance to administer medication in public - Stigma associated with the medication - Need for additional help/support on a daily basis due to difficulties taking the medications

Table 2: Most prevalent barriers identified across both studies and percentage* of patients who report the barrier

Patient Related Barriers	Clinician Related Barriers	Treatment Related Barriers	Socioeconomic Related Barriers
- Knowledge of disease and importance of treatment regimen (9.0%) - Knowledge in regard to prescribed medication (43.3%) - Difficulty maintaining a medication routine (habitual) (4.2%) - Forgetfulness (34.7%) - Problems taking the medication (swallowing difficulties) (15.5%)	- Ensuring patient/parent knowledge of disease and specific prescribed medications (9.0%) - Unclear instructions (9.0%) - Doctor-patient relationship (2.1%)	- Complexity of treatment regimen (including polypharmacy) (4.2%) - Issues with compliance in regard to corequisites for taking the medication (15.5%) - Undesirable side effects (19.4-21.1%)	- Copayments associated with the medication (54.6%) - Assorted healthcare obstacles (29.6%) - Need for additional help/support on a daily basis due to difficulties taking the medications (12.5%)

*(Müller et al. 2015)

Studies conducted by Bussell et al., 2017, as well as Aremu et al., 2022 looked to identify potential solutions to medication adherence barriers. In Figure 3, we highlight those interventions that we feel are most relevant for the barriers indicated by Mueller (2015) and Chan (2020).

Table 3: Possible implementable interventions to address medication nonadherence

Study	Intervention/Solution
Bussell et al., 2017	Strengthen the relationship/partnership with patients. <ul style="list-style-type: none"> ● Build trust ● Increase provider monitoring of adherence.
	Increase health literacy <ul style="list-style-type: none"> ● Help patient understand why each medication is necessary, as well as how to administer them ● Have patient repeat back the instructions ● Address concerns about side effects
	Simplify the medication regimen <ul style="list-style-type: none"> ● Streamline medication dosing schedule ● Reduce polypharmacy ● Once daily dosing ● Combination pills ● Use of a pillbox
	Understand the importance of cost <ul style="list-style-type: none"> ● Address concerns about finances non-judgmentally ● Provider awareness of medication costs ● Alternative medications ● Local discount drug programs

	<p>Increase self-efficacy</p> <ul style="list-style-type: none"> ● Promote parent involvement ● Motivational interviewing ● Electronic web/smart phone portals for questions <p>Continual reassessment</p> <ul style="list-style-type: none"> ● Monitor patient’s prescription refill rate ● Pill counts
<p>Aremu et al., 2022</p>	<p>Provider education</p> <ul style="list-style-type: none"> ● Provider knowledge of available drugs ● Provider knowledge of price and brand of drug ● Provider knowledge of patient and an optimal dosing schedule <p>Increased patient-provider communication</p> <ul style="list-style-type: none"> ● Provider communication and interpersonal skills ● Build patient-provider trust ● Send reminder text messages, emails, letters, and calls to the patient <p>Increasing patient education</p> <ul style="list-style-type: none"> ● Patient knowledge of consequences of noncompliance ● Patient knowledge of the importance of follow ups <p>One-on-one interaction with the healthcare providers</p> <ul style="list-style-type: none"> ● Word-of-mouth messages and handouts provided by healthcare professionals <p>Communication using social and digital media</p> <ul style="list-style-type: none"> ● Patient education through reputable online resources ● Reinforce the importance of compliance ● Support in managing side effects <p>Community/faith based organizations</p> <ul style="list-style-type: none"> ● Trusted leaders can encourage adherence to healthcare recommendations <p>Advocacy concerning medication expenses</p> <ul style="list-style-type: none"> ● Increase medication affordability ● Reduce the practice of rationing doses ● Speak out against rising healthcare costs <p>Adaptations of medications</p> <ul style="list-style-type: none"> ● Alter the composition of medicines (solid or liquid forms) ● Alter strength of medication ● Slow release capsules

Table 4: Prevalent adherence barriers with corresponding interventions across all studies

Adherence Barrier	Intervention
Knowledge of disease and importance of treatment regimen	<ul style="list-style-type: none"> ● Strengthen the relationship/partnership with patients ● Help the patient/parent to understand why each prescribed medication is necessary, as well as how to administer them ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Increasing patient's education ● Provider's education ● Increased communication between patient and treatment team ● One-on-one interaction with the healthcare providers ● Mass communication using social and digital media
Knowledge in regard to prescribed medication	<ul style="list-style-type: none"> ● Strengthen the relationship/partnership with patients ● Help the patient to understand why each prescribed medication is necessary, as well as how to administer them ● Increasing patient's education ● Provider's education ● Increased communication between patient/parent and treatment team ● One-on-one interaction with the healthcare providers ● Mass communication using social and digital media
Difficulty maintaining a medication routine (habitual)	<ul style="list-style-type: none"> ● Simplify the medication regimen ● Adaptations of medications
Forgetfulness	<ul style="list-style-type: none"> ● Simplify the medication regimen ● Continual reassessment ● Increased communication between patient/parent and treatment team
Problems taking the medication (swallowing difficulties)	<ul style="list-style-type: none"> ● Adaptations of medications ● One-on-one interaction with the healthcare providers ● Increased communication between patient/parent and treatment team
Unclear instructions	<ul style="list-style-type: none"> ● Strengthen the relationship/partnership with patients ● Help the patient/parent to understand why each prescribed medication is necessary, as well as how to administer them ● Simplify the medication regimen ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Provider's education ● Increased communication between patient and treatment team ● Increasing patient's education ● One-on-one interaction with the healthcare providers
Doctor-patient relationship	<ul style="list-style-type: none"> ● Strengthen the relationship/partnership with patients ● [Provider] understands the importance of cost

	<ul style="list-style-type: none"> ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Increased communication between patient and treatment team ● One-on-one interaction with the healthcare providers
Complexity of treatment regimen (including polypharmacy)	<ul style="list-style-type: none"> ● Simplify the medication regimen ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Increased communication between patient and treatment team ● Adaption of medications
Issues with compliance in regard to corequisites for taking the medication	<ul style="list-style-type: none"> ● Help the patient to understand why each prescribed medication is necessary, as well as how to administer them ● Simplify the medication regimen ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Adaption of medication ● Community/faith based organizations
Undesirable side effects	<ul style="list-style-type: none"> ● Help the patient to understand why each prescribed medication is necessary, as well as how to administer them ● Simplify the medication regimen ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Continual reassessment ● Provider’s education ● Increased communication between patient/caregiver and treatment team ● Increasing patient’s education ● One-on-one interaction with the healthcare providers ● Mass communication using social and digital media
Copayments associated with the medication	<ul style="list-style-type: none"> ● Simplify the medication regimen ● [Provider] understands the importance of cost ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Provider’s education ● Increased communication between patient and treatment team ● One-on-one interaction with the healthcare providers ● Advocacy concerning medication expenses
Assorted healthcare obstacles	<ul style="list-style-type: none"> ● All interventions may apply depending on the specific obstacle
Need for additional help/support on a daily basis due to difficulties taking the medications	<ul style="list-style-type: none"> ● Adaption of medications ● Use of various tools to aid patients in feeling more capable of meeting their medication requirements (increasing self-efficacy) ● Continual reassessment ● Increased communication between patient and treatment team ● One-on-one interaction with the healthcare providers

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| | <ul style="list-style-type: none"> ● Mass communication using social and digital media ● Community/faith based organizations |
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IV. Results

The main objective of this study was to explore the most prevalent barriers that patients experience in regard to medication adherence, and provide easily implementable solutions that will increase adherence. This is of major importance, as medication adherence is critical for patient survival and maintaining remission. Although the percentage of patients experiencing a given barrier may not appear substantial, when put together, these barriers can amount to many lives, so it is of critical importance to address all adherence barriers with easily implementable interventions. In a study conducted by Heneghan et al., 90% of pediatric ALL patients endorsed at least one adherence barrier, namely, inadequate education regarding their medications and their functions. This data was confirmed in a study conducted by Müller et al. (2015), in which 85.9% of patients reported experiencing at least one barrier. In order to enhance adherence, maximal reduction in barriers will require reliable solutions. All interventions explored in this study are intended to target adherence barriers and increase overall medication adherence in pediatric ALL.

Patients' barriers to medication adherence can be difficult for healthcare providers to address, perhaps due to the time constraints of their jobs, increasing the necessity for easily implementable interventions. Many of the barriers presented here are patient related, which increases the burden placed on patients and their families to overcome such barriers. However, this literature review points to practical interventions for each of the most prevalent barriers endorsed by patients.

With regard to patient related barriers in particular, through correlation of barriers with practical intervention, it was discovered that increasing communication between the patient and their treatment team can result in improved adherence. Specifically, per Müller et al. (2015) many patient-related barriers can be resolved by increasing communications with healthcare providers. For instance, knowledge of disease and importance of treatment regimen, knowledge in regard to prescribed medication, and problems taking medication, such as difficulty swallowing pills, may all be improved or resolved by increasing communication between patient and treatment teams. Patients who are in constant communication with their treatment team are more apt to have their barriers resolved more efficiently, increasing adherence. Communication can be increased by updating and checking patient portals on a regular basis and scheduling regular follow up visits, either in person or through virtual platforms.

Regarding clinician related barriers, several prevalent barriers identified in the studies conducted by Müller et al. 2015 and Chan et al. 2020 may be diminished or resolved through strengthening the relationship with the patient/family, as confirmed by Bussell et al. (2017). This can be achieved through increased one-on-one interaction with the patient/family, which allows the opportunity to ask questions that they may have regarding their leukemia, as well as give the clinician the chance to better understand the patient's condition so as to develop a better treatment plan. A stronger relationship with the patient and family helps to build a sense of trust, thus increasing the likelihood that a patient remains adherent to the prescribed medication regimen. Respectively, each clinician-related barrier identified in this study (e.g., unclear instructions and ineffective doctor-patient relationship), can be improved by a strengthened doctor-patient relationship. As physicians' schedules tend to be limited in the current healthcare environment, increased access to online patient portals could increase access to providers.

Medication related barriers are arguably one of the most prominent subcategories of barriers to adherence. Medication-specific barriers addressed by Müller et al. 2015 and Chan et al. 2020 may be largely resolved by the adaptation or alteration of the medication's composition (i.e., tablet, liquid, dosing) and simplifying the regimen when possible. This solution was proposed by Aremu et al (2022). These strategies can greatly reduce intolerable side effects, simplify the complexity of the treatment regimen, as well as reduce issues with compliance in regard to corequisites for taking the medication. Simplifying the medication regimen may be achieved through the adaptation of the medication to reduce the frequency that the medication must be administered, thus becoming less intrusive on the patient's life. Further, if a patient experiences fewer side effects, they are more likely to adhere to their medication regimen. Side effects have been correlated with decreased adherence rates (DiBonaventura et al., 2012).

Decreasing the many socioeconomic barriers that patients face is perhaps the most challenging, as these issues must be largely resolved by the healthcare system itself. However, both Müller et al. 2015 and Chan et al. 2020 note that it is critical that the clinician understands the importance of the cost of outpatient chemotherapy, which, in the US, can range from \$50,000, to over \$160,000 over the course of treatment (Cutler et al., 2022). In doing so, they may aid the patient in reducing the financial strain placed upon them by recommending several medical aid programs discussed previously in Figure 3 and identified by Aremu et al. (2022). Further, they may recommend alternative or generic medications that serve the same purpose. However, larger scale changes must be made over time through continued advocacy concerning medication expenses.

After completing a comprehensive search of studies relating to pediatric ALL it was concluded that an adequate quantity of studies to satisfy the requirements for this literature review were not yet in existence, therefore, a more generalized analysis of medication adherence was conducted.

V. Discussion

This literature review identified several barriers to adherence, and proposed related solutions. At this time, very few studies exist concerning solutions for medication adherence related barriers pertaining specifically to pediatric ALL, or even ALL in general. Although existing studies, including the studies reviewed in the current literature review, have a more generalized analysis of barriers and interventions for medication adherence, and relate them to ALL, more research is necessary to further understand specific ALL barriers and effective solutions, as this will increase medication adherence in ALL on a very large scale, thus improving overall survival and remission rates.

With regard to generalized interventions, oncology nurse navigators (ONN), who are tasked with educating the patient on the importance of their medication, as well as serving as the point of communication between the patient and treatment team provide substantial support for the patient and their family (Gentry, 2019). Further, patient and family involvement in care, such as the implementation of the shared decision making model (SDM) has proven to be effective (Fiorillo et al. 2020)

Although several studies have been conducted previously pertaining to medication adherence barriers and interventions in the adult population, very few studies exist concerning the pediatric population. More extensive age-focused studies should be conducted in regard to medication adherence barriers in the pediatric population, as these would uniquely include parents and caregivers.

VI. Conclusion

Medication adherence is critically important for all pediatric ALL patients. Studies exploring barriers to chemotherapy

adherence are of utmost importance to increasing survival rates, as these will direct solutions that can be applied to such barriers. Patients who adhere to their medication regimen are proven to have a higher survival rate (Pritchard et al., 2006), as adherence to chemotherapy prevents the cancer cells from developing immunity to the treatment.

As explored in the current literature review, there are several barriers that inhibit a patient's ability to maintain compliance with their medication regimen. These barriers can be generally categorized as patient, clinician, treatment, and socioeconomic barriers. Several solutions that have been developed to counteract barriers have been explored in the current literature review. These include the use of oncology nurse navigators (ONNs), as well as the implementation of the shared decision making model (Fiorillo et al. 2020).

Although tremendous advancements have been made in treatment of pediatric ALL, inadequate medication adherence can negatively affect prognosis. Continued research is necessary for the discovery of more comprehensive strategies to increase medication adherence, which will ultimately result in increased survival rates.

VII. Limitations

In regard to limitations of the studies reviewed, patient self-report via questionnaires could mean that there may not be a completely accurate portrayal of the true degree to which a given barrier is an issue. Further, these studies were not conducted specifically on ALL, and there may be some differences when specifically addressing treatment barriers for ALL. However, all participants were taking one or more prescription medications for a medical condition. A review of literature was the most appropriate method of analysis, as this allows the researcher to derive new insights and correlations between preexisting barriers and solutions to medication adherence.

Further studies may be conducted which implement the solutions explored in the current literature review to evaluate the effectiveness of each intervention. These interventions may then be more broadly implemented in the hematology/oncology clinical setting to increase pediatric ALL survival rates. The current results serve as an excellent starting point for future research regarding effective interventions pertaining to barriers experienced by pediatric ALL patients. The current literature review, coupled with additional pre-existing studies as well as the recommended future research will ultimately increase medication adherence in pediatric ALL patients, thus increasing both survival and remission rates worldwide.

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