Clinical Practice Guideline for the Diagnosis and Management of Acute Lymphoblastic Leukemia

Southern Philippines Medical Center

2021

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2 EXECUTIVE SUMMARY

2.1 BACKGROUND

Acute lymphoblastic leukemia (ALL) is one of the most common childhood cancers. Based on the DOH 2010 statistics, leukemia was among the top ten leading causes of mortality for children aged 1-14. Survival rates in high income countries reach up to > 80% while developing low to middle income countries (LMIC) achieve much lower rates. Developing LMIC suffer from economic difficulties, fragmented health systems, advanced disease at presentation and limited health resources that prevent achieving and providing better cure rates compared to developed high income countries (HIC). While there are international guidelines available, the local context and availability of resources differ hence the need to develop a country-specific guideline. These standardized recommendations that can be implemented in various settings across the country will guide those who care for children with ALL and also guide policy makers to direct investments on diagnostics and treatment that can improve survival and quality of life for these patients and their families.

The SPMC-CCI ALL Guideline Development group followed the guidelines set forth by the Department of Health based on DOH Administrative Order No. 2021-0020 entitled Revised Guidelines on National Practice Guideline Development, Adoption and Dissemination and the modified Grading of Recommendations, Assessment, Development and Evaluation or the GRADE approach. Briefly the following steps were done which will be elaborated in greater detail in the methodology section; 1) Formation of the Technical Working Group, 2) Consultation with Care Providers, Patients and Families and Formulation of Key Questions, 3) Searching, Selection and Assessment of the Evidence, 4) Formulation and Grading of Recommendations, and 5) External Review and Updating.

2.2 SUMMARY OF RECOMMENDATIONS

Prevention

Recommendation 1 - We advise expectant mothers to breastfeed for 6 months or more and fathers to avoid smoking during maternal preconception and pregnancy to decrease risk of childhood ALL. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 2 - Offer parental and carer education on childhood leukemia diagnosis and management using different strategies to improve quality of life and outcomes. (Low-Moderate Quality Evidence, Strong Recommendation)

Assessment and Diagnosis

Recommendation 3 - A clinical impression of ALL should be considered among pediatric patients presenting with any combination of the following: fever, pallor, hepatomegaly, splenomegaly and lymphadenopathy, bone pain, ecchymoses, fatigue and anorexia. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 4 - Among pediatric patients considered to have ALL, the physician should perform Bone Marrow Aspiration. (High Quality Evidence, Strong Recommendation)

Recommendation 5 - We recommend Bone Marrow Trephine in cases of “dry tap” or difficulty in aspirating for specimen. (High Quality Evidence, Strong Recommendation)

Recommendation 6 - We recommend bone marrow flow cytometry, if available, in the diagnosis of acute leukemia. (Moderate Quality Evidence. Strong Recommendation)

Risk Stratification

Recommendation 7 - We advise determination of risk stratification for newly diagnosed children with ALL using factors on NCI criteria such as age, WBC count, and presence of extra-medullary disease. (High Quality Evidence, Strong Recommendation)

Recommendation 8 - We suggest the use of the following prognostic factors to stratify as Standard Risk among children with ALL: age 1-10 years old, WBC < 50,000, female gender, B-cell immunophenotype, CNS1 or CNS 2, no testicular disease in males at diagnosis and if available, DNA index and good cytogenetic markers. (High Quality Evidence, Strong Recommendation)

Recommendation 9 - We suggest the use of the following prognostic factors to stratify High Risk ALL among children with ALL: age <1 and > 10 years old, WBC count > 50,000/ul, male gender, T-cell immunophenotype, CNS3, traumatic tap with blasts and with testicular disease in males at diagnosis and if available, poor cytogenetic factors and DNA index. (High Quality Evidence, Strong Recommendation)

Treatment

Recommendation 10 - We advise that treatment regimen be based on the risk stratification of the child at diagnosis for newly diagnosed childhood ALL. (High Quality Evidence, Strong Recommendation)

Recommendation 11 - We advise the less toxic regimens using a 3 drug induction protocol without an intensive consolidation for the treatment of standard-risk childhood ALL with favorable features. We advise addition of a delayed intensification phase to improve event free survival (EFS). (High Quality Evidence, Strong Recommendation).

Recommendation 12 - We recommend more intensive therapy for children diagnosed with high-risk ALL with poor cytogenetic factors, overt CNS involvement and poor early steroid response. We recommend additional intensive consolidation and delayed intensification during the continuation phases of chemotherapy to improve overall survival. (High Quality Evidence, Strong Recommendation)

Recommendation 13 - We advise delayed first intrathecal chemotherapy over cranial irradiation for CNS prophylaxis in children with standard risk ALL and after risk adjusted chemotherapy. (High Quality Evidence, Strong Recommendation).

Recommendation 14 - We advise cranial irradiation as a therapeutic option following standard ALL protocol in addition to intrathecal chemotherapy and risk-adjusted systemic treatment for CNS-directed therapy of children with high risk ALL and CNS3 or overt CNS involvement. (High Quality Evidence, Strong Recommendation).

Monitoring of Treatment

Recommendation 15 - We advise adequate monitoring of acute side effects or toxicities from combination of multi-agent chemotherapy in the treatment of childhood ALL. (High Quality Evidence, Strong Recommendation).

Recommendation 16 - We suggest Minimal Residual Disease (MRD) to monitor response to treatment of children with ALL undergoing therapy. (High Quality Evidence, Strong Recommendation).

Recommendation 17 - We advise to monitor WBC count and peripheral blast count after 1 week of prednisone pre-phase as well as bone marrow blast count and platelet count at day 28 to determine treatment response of childhood ALL when MRD is not available. (High Quality Evidence, Strong Recommendation)

Recommendation 18 - We recommend addressing the following when feasible: financial constraints, false perception of cure, experience of severe side effects, dissatisfaction with healthcare providers, poor general condition of the child, no clinical improvement in the child and health systems access issues to improve treatment adherence. (High Quality Evidence, Strong Recommendation)

Recommendation 19 - We advise reinforcement of health education on treatment compliance or adherence especially during the induction and maintenance phases of chemotherapy to lessen treatment abandonment. (High Quality Evidence, Strong Recommendation)

Prognosis

Recommendation 20 - We recommend that patient characteristics at diagnosis such as age, gender, WBC count and CNS status be used in assessing prognosis of childhood ALL. Absolute Lymphocyte Count (ALC) recovery is a good prognostic tool in a setting where Minimal Residual Disease (MRD) is not available. (High Quality Evidence, Strong Recommendation)

Side Effects and Complications

Recommendation 21 - We recommend monitoring of long-term side effects of chemotherapy in the treatment of childhood ALL such as neuromuscular impairment, limitation of physical performance, diabetes mellitus and cardiotoxicity. (High Quality Evidence, Strong recommendation)

Recommendation 22 - We recommend the use of broad-spectrum antibiotics in childhood ALL with febrile neutropenia. The addition of GCSF to the antibiotic regimen may reduce number of hospitalization days, promote faster recovery and reduce duration of antibiotic use. (High Quality Evidence, Strong Recommendation).

Recommendation 23 - We recommend prompt use of antibiotics to help manage frequency of neutropenia attacks and control treatment-related infections such as mucositis leading to invasive fungal disease, neutropenic enterocolitis, respiratory and bloodstream infections. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 24 - We recommend that during sepsis work-up, blood cultures and C-Reactive Protein should be performed immediately to identify the infectious microorganisms and appropriate antibiogram. (Moderate Quality Evidence, Strong recommendation)

Recommendation 25 - We recommend prompt use of antibiotic prophylaxis for ALL pediatric patients with ongoing chemotherapy. (Moderate Quality Evidence, Strong Recommendation)

Supportive and Palliative Care

Recommendation 26 - We advise evaluation of quality of life outcomes of patients and their families with high psychosocial risk through a psychosocial screening during diagnosis, treatment and final outcome. A validated measure should be used to identify those in need of psychosocial support. (High Quality Evidence, Strong Recommendation)

Recommendation 27- We recommend nutritional supplementation in ALL children like peanut based ready-to-use food, high quality protein blend formula given during chemotherapy to improve their nutritional status, reduce incidence of complications and decrease the costs of hospitalization. (Moderate Quality Evidence, Strong Recommendation).

Recommendation 28 - We advise assessment of activities of daily living (ADL) and identification of patients who require assistance among children with ALL to enhance patient care and promote better quality of life and safe living conditions. (High Quality Evidence, Strong Recommendation)

Recommendation 29 - We advise observance of proper oral care in children with ALL to prevent and manage oral complications during chemotherapy (Moderate Quality Evidence, Strong Recommendation)

Recommendation 30 - We advise referral to palliative care at any point in the course of illness of newly diagnosed children with ALL to address psychosocial concerns, symptom management and end-of-life care. (High Quality Evidence, Strong recommendation)

Recommendation 31 - We recommend use of the WHO analgesic ladder in the management of pain in children with ALL. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 32 - We recommend low-dose oral ketamine for procedural analgesia in pediatric cancer patients undergoing lumbar puncture in a resource limited hospital setting. (High Quality Evidence, Strong Recommendation)

Health System Support

Recommendation 33 - We recommend provision of health systems support interventions such as twinning programs, adoption of treatment protocols, financial support for patient and family needs, health insurance, access to medicines and creation of dedicated pediatric oncology units to improve survival outcomes in children with ALL. (Low Quality Evidence, Strong recommendation)

3 BACKGROUND

Acute Lymphoblastic Leukemia (ALL) is the most common cancer in children. Approximately 30% of the malignant tumors in children are acute leukemia, and 75% of them have ALL. There were a total of 53,808 cases of ALL in the Disease Registry Program of the Philippine Pediatric Society (PPS) from January, 2016 until October, 2021 comprising 1.1% of the total cases reported by PPS-Hospital Accreditation Board approved hospitals nationwide. Leukemia was one of the top ten leading causes of child mortality by age (1-14 years old) and sex with a rate of 2.7/100,000 population as reported in the Census of the Department of Health in 2010. The Southern Philippines Medical Center Children's Cancer Institute (SPMC-CCI), a public hospital that serves as an end referral center for pediatric cancer in Mindanao diagnosed a total of 545 cases of ALL for a period of 11 years (2010-2021). There was slight male preponderance of (58%) and common age of occurrence in the preschool age group, 1-5 years old (47.7%). The adolescent age group between 11-18 years old comprised 27% of the patients. Among those who had immunophenotyping results, majority had precursor B cell ALL (15.5%). Seventeen percent, 93 cases did not have flow cytometry results. The 11- year Event Free Survival was 46.7% while mortality rate was 28.9% arising from treatment-related infections, CNS and/or bone marrow relapses. The 11-year ALL retrospective review encompasses different time periods including changes in infrastructure from a 10-bed space for pediatric cancer patients, a 25-bed capacity Children's Cancer and Blood Diseases Unit (2012), the CCI (2017) as well as progressive changes in the multidisciplinary team.

ALL is characterized by high cure rates and good treatment outcomes of > 80% in high-income countries (HIC), yet few studies are conducted regarding treatment outcomes and relapse rates in low to middle income countries (LIC/MIC). Developing LMIC suffer from economic difficulties, fragmented health systems, advanced disease at presentation and limited health workforce/infrastructure resources that prevent achieving and providing better cure rates compared to developed high income countries (HIC).

The main aim of the SPMC- CCI ALL Technical Working Group is to promote cure, reduce mortality and improve early diagnosis and treatment of children and adolescents <19 years old by developing Clinical Practice Guidelines (CPG) for newly diagnosed acute lymphoblastic leukemia. The ALL CPG shall provide recommendations regarding early detection, diagnosis, treatment, monitoring and supportive care among these patients. The risk factors and early detection sections shall apply to all levels of the healthcare system encompassing medical specialists, family and palliative care physicians, nurses and other allied healthcare professionals. Clinical aspects of diagnosis, treatment, monitoring of adverse events, prognosis and supportive/palliative shall address care at the level of centers capable of high diagnosis and treatment complexity, pediatric hematology and oncology units, and specialized medical and infrastructure for specialized pediatric cancer care. The recent enactment into law of RA 11215 (National Integrated Cancer Control Act) on February 14, 2019, is expected to bring better comprehensive cancer care for adults and children that ultimately will result to better cures.

4 SCOPE AND PURPOSE

4.1 TARGET POPULATION

This guideline is intended to be applicable to children and adolescents < 19 years old with newly diagnosed Acute Lymphoblastic Leukemia (ALL) using risk group stratification in countries with limited resources. Patients who have abandoned treatment, with relapsed or refractory ALL and patients for hematopoietic stem cell transplantation or on novel agent therapy are not covered in this recommendation.

4.2 TARGET USERS

This guideline is intended for use by a multidisciplinary care team of specialist physicians, nurses, allied medical professionals, and support staff who care for children with newly diagnosed Acute Lymphoblastic Leukemia working in a tertiary care setting in countries with limited resources. The recommendations will be intended to provide informed clinical decisions for these carers. The recommendations are also intended for policy makers who develop standards of care for quality improvement. This is also intended for social insurance, private insurance or other third-party payer of health care for policy decisions on health financing.

5 OBJECTIVES

5.1 GENERAL AND SPECIFIC OBJECTIVES

The overall objective of the guideline is to provide evidence-based recommendations on clinical decisions for the diagnosis, management and supportive care of children and adolescents < 19 years old with newly diagnosed ALL. The guideline aims to provide critically appraised and peer reviewed evidence-based recommendations that answer critical questions encountered in the areas of:

- Screening and Prevention
- Assessment and Diagnosis
- Pharmacologic Intervention
- Complications and Prognosis
- Supportive and Palliative Care
- Health System Support

5.2 CLINICAL QUESTIONS ADDRESSED BY THE RECOMMENDATIONS

The general clinical questions to be addressed with recommendations are generally grouped into the following:

- What are the screening and prevention strategies that can be done for ALL in children?
- What are the clinical assessment strategies and diagnostic test that can be done to confirm ALL in children?
- Among children with conformed ALL, what are the effective pharmacologic intervention?
- What are the prognostic factors and complications during treatment?
- What are the supportive and palliative care to be given?
- What are the health system support that can be given to children with ALL and their family?

6 METHODS OF DEVELOPMENT

6.1 TECHNICAL WORKING GROUP AND CONSENSUS PANEL

The guideline development for children with ALL was an activity funded by the Department of Health. A Steering Committee was formed from the Department of Pediatrics assisted by the SPMC training office. The committee led in the formation of the Technical Working Group to develop the guideline. The technical working group included general pediatricians, pediatric oncologists, clinical pathologists, palliative care specialists, family physicians, nurses, medical technologists and other allied health professions. All members are active health practitioners affiliated with SPMC. The team also hired an external consultant who is an experienced clinical epidemiologist and guideline developer. The consultant guided the development process from start to finalization. The consultant also provided the team orientation and training on guideline development including question formulation, literature search, selecting, appraising and abstracting the evidence and the tools to be used such as GRADEPro and AGREE. The GRADEPro was the tool used for summarizing and assessing the quality of the evidence, while the AGREE was the standard used in writing the final guideline. The members of the TWG were not employed by companies with interest in pharmaceuticals, medical devices and diagnostics.

A Consensus Panel (CP) was also formed by the SC. The members were also selected from a list of pediatric cancer experts, other health workers, administrators and representative of patient groups who are potential users and implementors of the guideline. Selection priority was given to those who are practicing outside of SPMC. None of the members of the CP are employed by companies with interest in pharmaceuticals, medical devices and diagnostics.

6.2 CONSULTATION WITH CARE PROVIDERS, PATIENTS AND FAMILIES

The technical working group consulted in a meeting and established the target users of the guideline. The meeting included relevant decisions to be made by the health care provider to pediatric patients with ALL. Consultations were also done with patients and families of children with ALL. A total of 39 respondents were recruited for the Acute Lymphoblastic Leukemia (ALL) survey. These included doctors (25.6%) and caretakers of patients diagnosed with ALL (74.4%). They were asked to answer a survey composed of 3 questions on which topics they would like to know more in terms of:

- Knowledge on the disease.
- Medications
- Opportunities for improvement in care for newly diagnosed children with ALL.

The respondents would like to know more about disease prevention (92.3%), complications (89.7%), supportive treatment (87.2%), medications and novel drugs (84.6%) on disease knowledge. The respondents wanted to learn more about the drug's efficacy (82%), side effects (61.5%), PhilHealth or insurance coverage (43.6), cost and availability of drugs (41%) in terms of medications. Opportunities for

improvement in care included diagnostic tests (71.8%), treatment options (59%), prognosis disclosure (59%), diagnosis disclosure (51.3%) and recognition of complications (46.1%) of ALL in children and adolescents less than 19 years old. The results of these consultations are summarized in Appendix A and B.

The technical working group formulated key search questions for evidence to provide answers in addressing the concerns and clinical questions raised during the initial consultation. In developing the questions, the team initially followed the standard patient-intervention-comparator-outcome (PICO) format. This was done for the treatment and intervention questions. For other questions like those related to clinical assessment of patients, palliative care and health systems related question, the team also adopted a more general approach i.e., patient-exposure-outcome (PEO), patient-test-outcome (PTO). Since the guideline is for children with ALL, the questions as shown in Box 2 was stated in general term. These initial questions were further refined as the search strategy, retrieval and appraisal of the evidence were being conducted.

Box 2. Key Questions Addressed by the Guideline

- Screening and Prevention
  - What are the modifiable factors that increase risk for developing childhood ALL?
  - Would health education strategies prevent poorer outcomes and improve quality of life of children with ALL and their families?
- Assessment and Diagnosis
  - What is the clinical presentation of children and adolescents with Acute Lymphoblastic Leukemia?
  - What are the diagnostic tests for pediatric ALL?
  - What is the risk stratification used for pediatric ALL?
- Pharmacologic Intervention
  - What are the therapeutic options for newly diagnosed pediatric ALL in countries with limited resources?
- Monitoring of Treatment
  - How is treatment response monitored for pediatric ALL in countries with limited resources?
  - What factors affect compliance or adherence to treatment for pediatric ALL in countries with limited resources?
- Prognosis
  - What is the prognostic factors that affect survival or effectiveness of treatment to pediatric ALL?
- Side Effects and Complications
  - What are the long-term side effects of ALL treatment?
  - What is the management of chemotherapy induced neutropenia in children with cancer?
  - What are the treatment related infections following chemotherapy for Pediatric ALL?
  - What is the role of antibiotic prophylaxis for pediatric patients with ALL with ongoing chemotherapy?
- Supportive and Palliative Care
  - What psychosocial support can be offered to pediatric acute lymphoblastic patients and their families to improve their quality of life?

- What are the recommendations for the nutritional intake and diet of pediatric patients diagnosed with ALL?
- How will treatment for childhood ALL affect a patient's activities of daily living? Will they be able to attend school?
- What are the recommended oral care guidelines for patients diagnosed with pediatric acute lymphoblastic leukemia?
- What are the indications for referral to palliative care among newly diagnosed patients with pediatric acute lymphoblastic leukemia?
- How do we manage pain among newly diagnosed pediatric acute lymphoblastic leukemia?

- Health System Support
  - Among pediatric patients with ALL, what referral and health system support services lead to improved outcomes?

6.3 Searching, Selection and Assessment of the Evidence

The team agreed on the scope on children with newly diagnosed ALL. The team divided their review assignments based on the grouping of the clinical questions. Assignments were based on the capacity and expertise of the team member. There were 3-4 team members assigned per clinical review question. The members independently reviewed relevant publications. The key terms used for literature search were based on the agreed search questions. The most common search terms used were "acute lymphoblastic leukemia", and "children". Additional terms such as "clinical manifestation", "diagnosis", "risk factors", "treatment", and "prognosis" were added. The main databases searched were PubMed, NCCN and Google Scholar for the grey literature. The team also consulted library search for other databases with library science students from the College of Information and Computing at the University of Southeastern Philippines. This will allow search for other databases that were not available in internet. Searched articles were limited to clinical trials, systematic reviews, meta-analysis, randomized controlled trials and guidelines.

The titles and abstracts were independently reviewed. Studies involving <19 years old and newly diagnosed children with ALL were included. Studies that addressed the clinical questions were considered. An inclusive approach i.e., to include as many relevant articles was applied. The team created a list of relevant studies and developed a consensus on articles to include. The full-text articles of included titles and abstracts were retrieved.

The quality of the full text articles was evaluated using GRADEPro. The tool used the parameters that include study design, limitations, inconsistency, indirectness, imprecision, publication bias and additional considerations for quality assessment. Sometimes the available evidence after a thorough search may not provide answer to the question because of these parameters being present. In such cases, the level of evidence was downgraded. The GRADEPro gives a higher quality score for randomized control trial designs over observational studies. Clinical questions on clinical risk, manifestations, prognosis and diagnosis are usually observational studies. The TWG modified GRADEPro approach to

assess the certainty of evidence in observational studies. Using the same evaluation parameters for both GRADEPro for intervention questions and the modified GRADEPro for non-intervention questions, the TWG classified the quality of evidence as high, moderate, low and very low quality. The chosen articles were extracted by the individual team members using a standardized data extraction form. The extracted data were verified by the other team members and logged in the GRADEPro software to generate the evidence table.

Before using the GRADEPro, the TWG in a consensus meeting, prioritized the clinically important outcomes that should be considered when developing the recommendations. The team developed the prioritization also considering initial consultation with the patients and their experience and expertise as carers for children with ALL. Prioritization was qualitative and arrived at based on TWG discussion and consensus. For questions related to treatment or intervention i.e., chemotherapy, radiotherapy, supportive and palliative care, the prioritized outcomes were overall survival, event-free survival, quality of life and relief of symptoms. The TWG also balanced these benefits with the side effects and other adverse events associated with treatment or intervention. For questions related to diagnosis and clinical assessment, the outcomes prioritized was the accuracy of the test and the predictive accuracy of clinical symptoms, risk or prognostic factors. For the questions related to health system the prioritized outcomes were cost-effectiveness. GRADEPro tables were developed for each clinical question.

6.4 Formulation and Grading of Recommendations

A narrative description and interpretation of the results in the GRADEPro tables were developed by each of the team in the TWG. Group discussions on the results were done and a consensus was arrived at for the summary interpretation. The summary interpretation was the basis for developing unambiguous recommendations. Recommendations were made on the following: prevention, assessment and diagnosis, risk stratification, treatment, monitoring of treatment, prognosis, supportive and palliative care and health system recommendations. The recommendations were stated considering patient involvement in the decision making. The recommendations for each section were initially developed by the team and was presented to the TWG for discussion and consensus. This process was qualitative, and consensus was assumed when there were no objections to the recommendation after discussion.

The grading for the quality of the evidence of the recommendation was based on the GRADEPro classification i.e., high, moderate, low and very low. For the clinical question on treatment or intervention, a randomized controlled trial was considered as the high-quality design. This was further evaluated if there was limitation or bias, inconsistency, indirectness, imprecision and other considerations. The quality was downgraded accordingly if these were present. For clinical question on clinical assessment and diagnosis, a cross-sectional study design was considered high quality and for risk and prognosis, a cohort or case-control study design was considered as high quality. They were also evaluated if there was limitation or bias, inconsistency, indirectness, imprecision and other considerations and the quality downgraded if these were present.

The formulated recommendations with the quality of evidence were then presented to the consensus panel for voting if the recommendation should be adopted or not. The written recommendations were given to the panel at least a week prior to the panel voting. Orientation was given to the consensus panel on the process and the framework for evidence to decision as the basis for voting. The framework includes issues to consider prior to voting for or against the recommendation i.e., addressing an important problem, balance of benefit and harm, priority outcome, quality of evidence, cost and resources to be used, equity, equality, fairness and respect for patient's rights, acceptability and feasibility and health system consideration. Prior to the formal consensus meeting, a written vote for each of the recommendation was obtained from all the panel members and kept for documentation.

The CP voting session was a series of two-hour sessions (4 sessions total) where each of the recommendations were discussed. The TWG presented the summary of evidence and the recommendations. The CP was allowed to ask questions and give suggestions on the recommendation. The initial vote based on the evidence to decision framework was also presented. A final vote from each member of the CP was then obtained. Each recommendation was graded as "strong" if all the CP members agreed, "moderate" if 80% agreed and "weak" if only the majority agreed. This was used as the grade of the consensus panel.

The final grade of the recommendation was a combination of the quality of the evidence and the consensus panel grade i.e., high quality evidence; strong recommendation or low-quality evidence; strong recommendation. In most cases, recommendations based on high quality evidence will also get strong recommendations from panel vote. But there are also recommendations based on low-moderate quality evidence but may also be strongly recommended by the consensus panel because the recommendation addressed social equity issue. A good example is a financing and health system intervention that is not usually subjected to randomized trial and therefore will only be graded as low-moderate quality evidence but will be voted strongly by the consensus panel because it will address social and equity issue especially for children with ALL.

6.5 External Review and Updating

The initial draft of the guideline was shared to other experts and potential users of the guideline for comments and review. External reviewers were experts from the Hematology and Oncology of the Philippine General Hospital, the Cancer and Hematology Center of the Philippine Children's Medical Center, the Philippine Society of Pediatric Oncology and Philippine Society of Pediatric Hematology. The TWG recommended the AGREE Method for the review, but the TWG also allowed the reviewer to use what they think is more appropriate. The guideline was finalized and published based on their comments and feedback. This guideline will be updated after 3 years at the earliest or 5 years at the latest. The TWG considered this period as appropriate based on the expected duration of new cancer trials and other studies from conception, implementation, analysis to final result. The priority question and methods of review may be similar or modified as appropriate at the time of update.

7 RECOMMENDATIONS AND EVIDENCE TO RECOMMENDATION

7.1 PREVENTION

Recommendation 1 - We advise expectant mothers to breastfeed for 6 months or more and fathers to avoid smoking during maternal preconception and pregnancy to decrease risk of childhood ALL. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 2 - Offer parental and carer education on childhood leukemia diagnosis and management using different strategies to improve quality of life and outcomes. (Low-Moderate Quality Evidence, Strong Recommendation)

Evidence to Recommendation for Prevention

Modification of lifestyle risk factors and environmental exposures and screening has been long established for adult cancers. This has not been the case for many childhood cancers. In recent years though, there are environmental and lifestyle factors of parents that have been implicated as risk and protective factors particularly in relation with childhood acute lymphoblastic leukemia. **(Whitehead et al, 2016**)

We searched PUBMED in July 2021 using keywords: "Prevention" AND "Childhood" AND "Leukemia" in order to answer this question. We limited our search to meta-analysis and limited to participants belonging in the 0-18 age groups. A total of 25 articles were found. We did a quick review of the titles and availability of full text articles and concentrated on meta-analysis and found 3 relevant articles for inclusion. Additional relevant titles were retrieved using a google scholar web search.

A total of 3 meta-analysis of observational studies of moderate quality evidence with a total of 20 individual studies were included. A meta-analysis study **(Kwan, 2004)** included 14 case control studies with 6470 cases; the combined odds ratio for developing ALL among children who were breastfed for 6 months or more compared to those who breastfed for less than this period or were never breastfed was 0.75 (95% CI 0.67, 0.85) adjusted for socioeconomic status. This means that the combined case control studies support the potential beneficial effects of breastfeeding in the prevention of childhood ALL. Another meta-analysis **(Martin et al, 2005)** which reviewed 26 studies but included 13 studies focusing on ALL supported a similar conclusion with a combined odds ratio of 0.81 (0.72, 0.91) of developing childhood ALL among those breastfed for 6 months or longer compared to those breastfed less than 6 months or never breastfed. Again, this supports the protective effect of breastfeeding. It is of note however, that the 2 meta-analyses included 9 similar studies. The most recent meta-analysis that initially included 17 studies but later focused on 8 higher quality studies with 6690 cases and 13723 controls, also showed benefit of breastfeeding for > 6months with OR 0.86 (95% CI 0.78, 0.95). **(Amitay and Keinan-Boker, 2015)** The study of Rudant et al, 2010 and MacArthur et al, 2008 out of the 8 studies was unique in this meta-analysis as the other 6 studies were mentioned in the 2 earlier meta-analysis studies. It is notable that although the point estimate of Odd's from two studies are 0.78 and 0.89

respectively, both confidence intervals cross 1.0. In general, the 3 meta-analysis offers moderate evidence of the protective effect of breastfeeding for 6 months or longer compared to breastfeeding for less than 6 months or never breastfeeding in the development of childhood ALL.

We also looked at the effect of smoking as a risk for development of childhood ALL. The 3 meta-analyses included a combined total of 22 studies since there were studies that were included in all 3 or at least 2 of the meta-analysis. A case-control study with a meta-analysis **(Milne, 2012)** that looked at paternal ever smoking at time of conception compared to never with 10 studies with 9,323 cases and found an increased risk of developing childhood ALL with OR of 1.15 (95% CI 1.06, 1.24). In the same study a total of 8 studies with 2,118 cases were combined to look at >20 cigars per day smoking compared to less or never smoking and found a greater increase in developing childhood ALL with OR of 1.44 (95% CI 1.24, 1.68). Another meta-analysis **(Chunxia et al, 2019)** included 8 studies for paternal smoking before conception and during pregnancy with increased risk in ALL and the following OR of 1.146 (1.009 to 1.302) and OR 1.23 (0.989 to 1.530). Although point estimates of odds for both preconception and during pregnancy showed risk, the confidence interval of the latter unlike in the *Milne et al, 2012* meta-analysis crossed 1. Similar to the earlier meta-analysis there was a higher risk for developing childhood ALL for those whose fathers smoked > 20 cigars per day with OR 1.3 (1.072 to 1.586). Paternal smoking before conception and during pregnancy and the risk for childhood ALL was reviewed in a meta-analysis **(Cao, 2020).** Due to publication bias seen by the authors despite the dose-response gradient in terms of the higher number of pack years the more the risk, the evidence was low quality. But this meta-analysis showed increased risk for smoking both in those exposed pre-conception and during pregnancy with OR of 1.15 (95% CI 1.04,1.27) and 1.20 (95% CI 1.12, 1.28) respectively. The evidence supports that paternal smoking pre-conception and during pregnancy increases risk of childhood ALL with risk increasing if paternal cigarette consumption is 20 cigarettes per day or more.

In summary, based on moderate quality meta-analysis breastfeeding of 6 months or more was protective, while paternal smoking increased risk of developing childhood ALL. Notable however are the overlaps in the studies included in the different meta-analysis of the risk and protective factors. Still, it would be prudent to advise expectant parents on the aforementioned risks and protective factors.

Usual care for children and families dealing with acute lymphoblastic leukemia is the doctor or health workers advise. In recent years, with emphasis on increasing health literacy to empower patients and their families; various educational support strategies to help increase involvement and improve outcomes have been espoused. We searched PubMed until October 6, 2021, using the search terms “educational intervention” AND “childhood leukemia” AND “improved outcomes'' which yielded 36 results but upon review of abstracts, 2 articles were included that could answer our question. Two additional articles were also retrieved from web search. Evidence ranged from low to moderate quality.

A low quality before and after study that looked into structured parental education involving a video presentation and open forum and support for free chemotherapy given by a foundation yielded over-all benefits in terms of decreased treatment refusal (11% vs 3%, p value of .01) and decreased progressive or relapsed leukemia (18% vs. 7%, p value of 0.017). However, in terms of event free survival, the benefits were only present for those families classified as poor (13% vs. 29%, p value of 0.004). Note also the overall effects for treatment related death was greater after intervention (36% vs. 23%, p value of 0.017) attributed to the more severe admissions after intervention and stronger

chemotherapeutic agents and in the prosperous families there were more treatment abandonments (13% vs. 0%, p value of 0.037) after the intervention. **(Mostert et al, 2010)**

An RCT of moderate quality compared structured parental education with structured parental education + a medication diary book and looked at event free survival. The study only showed that the addition of a medication diary book improved event free survival for those patients whose mother's had a high level of education for them EFS was at 62% compared to the 29% of those that only received structured parental education. **(Sitaresmi, 2013)**

A before and after study of low quality looked into the additional benefits of a DVD that included the knowledge needs of patients in addition to verbal advise was done which showed that patient satisfaction to verbal explanation alone and verbal explanation with DVD was similar. However, after watching the DVD there were more who had their anxiety relieved and the difference was significant (percent reporting anxiety before 33.3% vs. after at 8.3%, p value 0.003). **(Di Giuseppe, 2020)** An RCT of moderate quality looking into the effectiveness of educational sessions of 45-60 minutes coupled with educational posters in Iran for low literacy parents tailored to their comprehension found that QOL scores of intervention and control groups were similar at baseline. After intervention all QOL scores were higher in the treatment group. At baseline, the treatment group overall QOL was 224.9 ± 24.1 while baseline overall QOL post intervention was 338.2 ± 7.8. The overall QOL of the control group at baseline was 225.7 ± 24.3 while post intervention was 226.7 ± 23.8; post intervention, the QOL of the control group was lower than the treatment group. **(Ghodsbin et al, 2012)**

Based on the 4 low-moderate quality evidence, tailored education using various strategies improve outcomes in different groups. For those parents with low income, structured education with video, open forum and medicine support improved EFS. A medication diary book however seems to be a good add on for those parents with high literacy as this improves EFS. Quality of life measures and reduction of anxiety however was seen among parents/caregivers given educational face to face sessions with posters or additions of take-home videos. It is therefore recommended that a variety of educational strategies form part and parcel of support provided to parents/caregivers of children with ALL.

7.2 Assessment and Diagnosis

Recommendation 3 - A clinical impression of ALL should be considered among pediatric patients presenting with any combination of the following: fever, pallor, hepatomegaly, splenomegaly and lymphadenopathy, bone pain, ecchymoses, fatigue and anorexia. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 4 - Among pediatric patients considered to have ALL, the physician should perform Bone Marrow Aspiration. (High Quality Evidence, Strong Recommendation)

Recommendation 5 - We recommend Bone Marrow Trephine in cases of "dry tap" or difficulty in aspirating for specimen. (High Quality Evidence, Strong Recommendation)

Recommendation 6 - We recommend bone marrow flow cytometry, if available, in the diagnosis of acute leukemia. (Moderate Quality Evidence. Strong Recommendation)

Evidence to Recommendation for Assessment

Acute Lymphoblastic Leukemia is the most common cancer of childhood. Clinical Assessment of childhood ALL include a thorough history and physical examination. In order to assist clinicians in its early detection, we reviewed existing data on signs and symptoms of this disease. We used PubMed and Google scholar as our search strategies. The search terms used during documentation were “Children”, “Acute lymphoblastic leukemia and clinical manifestation”, AND “diagnosis of acute lymphoblastic leukemia in children”. We initially reviewed 12 studies but we only included 1 study with high quality of evidence and 6 moderate quality studies due to insufficient data.

The high-quality evidence study is a meta-analysis that screened 12,303 abstracts and included 33 studies with a total of 3084 participants. All are cohort studies with control groups. The 5 most common features present in more than 50 % of the participants are hepatomegaly (64%), splenomegaly (61 %), pallor (54%), fever (53%), and bruising (53%) **(Clarke, 2016)**. The moderate quality evidence studies are composed of cohort, cross-sectional, and control studies. A total of 462 participants were included in the studies. The most common manifestations are pallor (61.1 to 100%), fever (60 to 100%), joint pains (39 to 81.6%), hepatomegaly (56.5 to 78%), lymphadenopathy (50 to 100%), bone pain (67.7%), splenomegaly (30.6 to 66.6%). Less common manifestations are fatigue (62%), ecchymoses (53.3%) and anorexia 24.5% **(Lovigne 2020, Jaime-Perez 2019, Zahid 1996, Hassan 1992, Biswas 2009, Brix 2020)**

Overall, we have moderate to high-quality evidence suggesting the most common clinical manifestations of ALL. The symptoms are: 1) fever (55.4 to 100%), 2) pallor 61.1 to 100%), 3) hepatomegaly (46.6 to 78%), 4) splenomegaly 30.6 to 63%), and 5) lymphadenopathy 36.8 to 57.1%).

Evidence to Recommendation for Diagnosis

Accurate Diagnosis is imperative in children and adolescents with Acute Lymphoblastic Leukemia for the appropriateness of treatment. Diagnostic exams include complete blood count (CBC), Peripheral Blood Smears (PBS), Bone Marrow Aspiration (BMA), Flow cytometry, Immunophenotyping, Fluorescent In Situ Hybridization (FISH), and cytogenetics. We used PubMed and Google scholar as our search engines. The search terms used are: "children" AND "acute lymphoblastic leukemia" (initial diagnostics), “Initial diagnostic test for acute lymphoblastic leukemia in children and children" or "pediatric" diagnosis" AND "children" AND "acute lymphoblastic leukemia”.

We reviewed a total of 13 observation studies, 10 studies with high quality evidence and 3 studies with moderate quality evidence. The high-quality evidence studies included 7 cohort studies, 2 cross-sectional studies and 1 expert opinion. The moderate quality evidence studies included 2 cross-sectional studies and 1 case control study.

Our review showed that the most common initial CBC with differential findings were: neutropenia (65.4 %), anemia (61.5%), thrombocytopenia (34.5%), and leukocytosis (31.6%) **(Lovigne, 2020;Brix, 2020**). In a cohort study with 203 participants, a combination of cbc with differential findings are more reliable: anemia and leucocytosis and thrombocytopenia (27.1%), anemia and leukopenia and thrombocytopenia (26.6%), anemia and thrombocytopenia (17.2%), anemia and leukopenia (5.4%), leukocytosis and thrombocytopenia (5.4%) compared to anemia (4.4%), thrombocytopenia (3.9%), leukocytosis (1.5%), leukopenia (1%), and no findings (1%) **(Jaime – Perez, 2019)**. Four moderate quality studies discussed Bone Marrow Aspiration and Bone Marrow Trephine with a total of 1,170 participants. Bone marrow aspirate and bone marrow trephine is an indispensable diagnostic tool for the evaluation of hematologic and non-hematologic disorders. The sensitivity of BMA was 82.2-100%, specificity of 90-100%, and accuracy of 82.5–100%. On the other hand, Bone Marrow Trephine's sensitivity was 84 to 100%, specificity of 90-100 %, and accuracy of 98.5-100% (**Tilak, 2014; Manju, 2016; Goyal, 2014; Chauchan, 2017)**. Bone Marrow Imprint has a sensitivity of 84 to 100%, specificity of 100 % and accuracy of 100% **(Pant,2020; Chandra, 2011; Aboul-Nasr, 1999).**

Bone marrow imprint is prepared by gentle touch and rolling of core biopsy over glass slides so that cell impression was made by all aspects of core biopsy This procedure will enhance the detection of focal involvement of marrow **(Tilak, 2014).** Touch imprints were useful for studying cell morphology, where aspiration yielded dry tap. Appropriately prepared imprint cytology smears not only provide cellular composition of marrow but also define the topographical architecture of marrow **(Pant, 2020).** Bone Marrow Aspiration, Bone Marrow Imprint and Bone Marrow Biopsy complement each other for evaluation **(Chandra, 2011).**

Bone Marrow Imprint has high specificity, sensitivity, and accuracy compared to that of bone marrow aspiration. It should be standard practice and be considered as an early and reliable diagnostic tool for diagnosing Acute Lymphoblastic Leukemia. Bone marrow aspiration is a simple, reliable, and rapid method of marrow evaluation while Bone Marrow Trephine provides more comprehensive information regarding the marrow cellularity, architectural patterns, and overall hematopoiesis. It is the diagnostic investigation in "dry tap" aspiration. However, Bone Marrow Trephine is a painful procedure and requires more skills **(Manju, 2016).** Touch imprints were useful for studying cell morphology, where aspiration yielded dry tap. Appropriately prepared imprint cytology smears not only provide cellular composition of marrow but also define the topographical architecture of marrow **(Pant, 2020).** Bone Marrow Aspiration, Bone Marrow Imprint and Bone Marrow Biopsy complement each other for evaluation **(Chandra, 2011).**

Flow cytometry is a technology that provides rapid multi-parametric analysis of single cells in solution. The distinction between lymphoid and myeloid leukemias is often made by flow cytometry. Several advances in flow cytometry have dramatically improved the utility of flow cytometry in the diagnosis and classification of leukemia. Bone marrow flow cytometry (BMFC) has been the standard for the immunophenotypic characterization of acute leukemia. Peripheral blood flow cytometry (PBFC) represents a less invasive approach to the immunophenotyping of the leukemic clone which can facilitate a quicker diagnosis. In B - ALL, the sensitivity of peripheral flow cytometry is 100 % while bone marrow flow cytometry is 100%. The specificity and accuracy for both peripheral flow cytometry and bone marrow flow cytometry is 100%. In T- ALL, sensitivity and specificity of peripheral flow cytometry is 98.2 % while in bone marrow flow cytometry is 100%. While the accuracy for both peripheral flow cytometry and bone marrow flow cytometry is 100%, there are, however, notable exceptions in which

PBFC has the potential to provide a misdiagnosis of ETP-ALL, MPAL T/M, or AMKL. When these entities are suspected by PBFC, BM evaluation is indicated for obtaining a definitive diagnosis. (**Cheng, 2018)**

Flow cytometric immunophenotyping can be used to assist in acute leukemia diagnosis. The test is more objective and definitive in confirming both the presence of expanded hematopoietic progenitors and demonstrating immunophenotypic abnormality. The demonstration of immunophenotypic abnormality provides specificity for the diagnosis of acute leukemia. To evaluate the usefulness of flow cytometric detection of intracellular antigens (Ags) in establishing proper lineage affiliation and its contribution to the diagnosis of acute leukemia, a moderate evidence cohort study was done involving 74 participants. The presence of CD79 has a sensitivity of 100%, specificity of 87.8%, and accuracy of 100%. CD 22 has a sensitivity of 97.3%, specificity of 87.8%, and accuracy of 100%, CD3 has a sensitivity of 100%, sensitivity of 97.3%, and accuracy of 100%. MPO has a sensitivity of 100%, specificity of 98.6%, and accuracy of 100% **(Paredes - Aguilar, 2001)**. In B cell ALL, the most important markers for diagnosis and subclassification are CD 19, CD20, CD22, CD24, AND CD79a. In T cell ALL, CD1a, CD2, CD3, CD4, CD5, CD7, AND CD8 are important. Distinction from B cell and T cell ALL is vital because the former has a favorable prognosis while the latter has a poor prognosis.

A low-quality evidence study was done with an expert opinion involving 197 participants on evaluation of testing of Acute Leukemia Samples. These results are: Bone marrow morphologic assessment (97%), flow cytometry (97%), cytogenetics (95.4%), FISH (94.9%), PBS morphology (92.4%), Molecular genetics (91.4%) and CBC with differentials (88.3%). CBC with differentials with accurate history and physical examination is recommended as an initial diagnostic tool in the decision for patient referral to a specialist for further evaluation. Pancytopenia in CBC is an important criterion to perform Peripheral Blood Smear. The presence of lymphoblasts in PBS warrants Bone Marrow Aspiration for the diagnosis and further classification of ALL. French- American-British (FAB) classification defined ALL types purely by blast cell morphology with three types, termed L1, L2, and L3. L1 lymphoblasts are usually smaller, with scant cytoplasm and inconspicuous nucleoli. Cells of the L2 variety are larger, and demonstrate considerable heterogeneity in size, prominent nucleoli, and more abundant cytoplasm. Lymphoblasts of the L3 type, notable for their deep cytoplasmic basophilia, are large, frequently display prominent cytoplasmic vacuolation, and are morphologically identical to Burkitt's lymphoma cells. The application of ancillary techniques such as flow cytometry and Immunohistochemistry proved to be an additional advantage in ALL diagnosis. **(George et al, 2017)**

Overall, we found moderate to high quality evidence suggesting that bone marrow aspiration and bone marrow trephine biopsy are equally accurate in the diagnosis of ALL. Bone marrow aspiration remains the gold standard in ALL diagnosis. Bone marrow touch imprint smears may serve as an invaluable adjunct to optimize diagnostic utility of bone marrow cytomorphology. Both procedures are complementary and can be performed together for better evaluation of bone marrow diagnostics. Bone marrow flow cytometry is used when there is a need for immunophenotypic assessment.

7.3 RISK STRATIFICATION

Recommendation 7 - We advise determination of risk stratification for newly diagnosed children with ALL using factors on NCI criteria such as age, WBC count, and presence of extra-medullary disease. (High Quality Evidence, Strong Recommendation)

Recommendation 8 - We suggest the use of the following prognostic factors to stratify as Standard Risk among children with ALL: age 1-10 years old, WBC < 50,000, female gender, B-cell immunophenotype, CNS1 or CNS 2, no testicular disease in males at diagnosis and if available, DNA index and good cytogenetic markers. (High Quality Evidence, Strong Recommendation)

Recommendation 9 - We suggest the use of the following prognostic factors to stratify High Risk ALL among children with ALL: age <1 and > 10 years old, WBC count > 50,000/ul, male gender, T-cell immunophenotype, CNS3, traumatic tap with blasts and with testicular disease in males at diagnosis and if available, poor cytogenetic factors and DNA index. (High Quality Evidence, Strong Recommendation)

Evidence to Recommendation for Risk Stratification

Risk Stratifications affect the treatment and prognosis of children with ALL. Reliance on risk-based treatment is one of the hallmarks of childhood ALL. It is therefore paramount to identify those features shown to consistently affect prognosis and influence treatment. Those with favorable features can be treated with less toxic regimens while those with more high-risk disease require more aggressive regimens. In 1993, the National Cancer Institute (NCI) published a common set of risk criteria for childhood ALL. This was based on factors that had international acceptance such as age, initial white blood cell (WBC) count, and the presence of extramedullary disease at diagnosis. We used PubMed and Google Scholar as our research strategy. The search terms used for documentation were: “risk stratification” AND “childhood acute lymphoblastic leukemia”, “risk stratification of pediatric acute lymphoblastic leukemia”. We included 4 high quality evidence studies and 1 moderate evidence study out of the 9 initial studies.

In general, the following conditions affect the 5-year survival rate of patients: age, sex, race, ethnicity, Immunophenotype and NCI risk group. For the age group: Less than 1 year old, EFS 29 – 70%; 1 to less than 10 years old, EFS 82 – 94.5%; more than 10 years old, EFS 74.9 – 82.6%; 10 to less than 15 years old 84.7 – 96.2% and for more than 15 years old EFS 75.9 to 78.5 %. For gender, males have EFS of 49 to 100% while females EFS of 81 to 91.6%. For race, whites have EFS of 79.3 – 91.6% while blacks have EFS of 85.5 to 89.8%. For Ethnicity, the Hispanic has an EFS of 87.6 – 88.8%, while the non-Hispanics have an EFS of 91.4 – 91.9%, and the unknown has EFS 83.8 – 86%. For the immunophenotype, B – cell has an EFS of 79 – 91.6% while T-cell has an EFS of 71.9 – 83.8%. For the NCI risk stratification on diagnosis, standard risk has EFS of 87.3 – 95.4% while high risk has EFS of 76.7 – 84%. While on Dana Farber Cancer Institute (DCFI) standard risk EFS of 80 – 84% while high risk EFS of 74 – 78%. For the initial white blood count (WBC) on diagnosis: WBC less than 20 x 10^9 /L EFS of 85 – 89%; WBC 20 t0 49 x 10^9 /L 66 to 82.7%; WBC 50 to 100 x 10^9 /L 73 – 85% and for WBC more than 100 x 10^9 /L

EFS of 59 – 73%. For the initial CNS findings on diagnosis, CNS1 EFS of 75 – 85%; CNS 2 EFS of 65- 80.6%; CNS 3 62 – 88% and traumatic tap has EFS of 57 – 82.4%. The most common congenital anomaly associated with ALL is Down Syndrome (DS). ALL patients with DS have EFS of 59 – 83% while those with no DS has EFS of 80 – 84%, hyper-diploid of more than 50 has EFS of 82 - 90%, hyper-diploid less than 50 has EFS of 64 – 82%, diploid has EFS of 84%, Pseudodiploid has EFS of 65 – 77%, and hypodiploid had EFS of 61 – 85%. Those with DNA index of 1.6 has EFS of 91.2% while those who has DNA index of < 1.6 has EFS of 78.5%. Cytogenetics also affects the prognosis of ALL. Patients with positive BCR-ABL has EFS of 28.6% while those who are negative EFS is 82.3%, E2A-PBX1 positive patients have EFS 80% while those who are negative has EFS of 81%. TEL -AML positive patients have EFS of 84.5% while those who are negative have EFS 78.8% **(Hunger,2012; Mograbi,2007; Pui, 2004).**

A high evidence study compared the analysis of the Pediatric Oncology group (POG) and Children's Cancer Group (CCG). For the sex, both groups analyzed that female have greater EFS of 67 – 69% compared to males with EFS of 54 – 68.5%. For the race, other race has the highest EFS of 61.9 – 70.7%, followed by Hispanic race with EFS of 54.3 – 67.7%, the African American has the lowest EFS of 53.1 – 56.9%. For the age, those with less than 15 years of age has a higher EFS of 60.9 – 71% while those with more than 15 years of age has lower EFS of 51.1 – 59%. For the initial WBC count on diagnosis: WBC of 200 x 10^9 /L has EFS of 61.6 – 70% while wbc of more than 200 x 10^9 /L has lower EFS of 51.1 – 59%. For the Initial CNS status on diagnosis, patients on standard risk with CNS 1 has EFS of 79.9 – 81.2%, while standard risk with CNS2 EFS 70.1 – 68.2 and standard risk with CNS 3 EFS of 71.8 – 75%. On the other hand, for high risk with CNS 1 EFS 64 – 72.2%, while High risk with CNS2 EFS of 59 – 65%, and High risk with CNS 3 EFS of 58.7 – 76.9%. Lastly, for patients with testicular disease on diagnosis EFS is 62.5 – 90% while those without testicular disease the EFS is 62.5 -90% (**Schultz, 2017).**

We included one moderate quality evidence study of retrospective study design. For the initial DCFCI risk group: standard risk has EFS of 84 – 94% while high risk has EFS of 71 – 82%. For the age at diagnosis: less than 10 years old has EFS of 86 – 91%, more than 10 years old EFS of 71 – 85%, 10 to 15 years old EFS of 76 – 91% and more than 15 years old has EFS of 51 – 78%. For the WBC at diagnosis: more than 50 x 10^9 /L EFS 87 – 92%, while WBC less than 50 x 10^9 /L 60 – 78%. For the gender: males have EFS 82 – 89%, while females have EFS 83 – 91%. For the CNS status at diagnosis: CNS 1 has EFS of 84-90%, CNS2 has EFS of 77-92%, CNS 3 EFS 88%. Traumatic tap with blasts has EFS of 53 – 88% while traumatic tap without blasts has EFS of 62-97%. Patients with Down Sydrome has EFS of 84 – 93%. For cytogenetics: Hyperdilploidy has EFS of 84-93%,Hypodiploidy has EFS of 41-95%, Trisomy 4 and 10 has EFS of 86-96%, no double trisomy has EFS of 74-91%, ETV – RUNX1 has EFS of 90-98%, Rearranged KMT2A has EFS 27-80%, iAMP21 has EFS 33-86%, TCF3-PBX1 EFS of 59-93% while normal karyotype has EFS of 79-92% (**Vrooman, 2018).**

Overall, the following criteria for good risk stratification are as follows: 1)Age of more than or equal to 1 year old but not less than 10 years old, 2) female gender, 3) white race, 4) non - Hispanic ethnicity, 5) B – Cell Immunophenotype, 6) NCI standard risk classification, 7) Initial WBC count of less than 20 x 10^9 /L, 8) CNS1 on diagnosis, 9) Hyper-diploidy, 10) BCR – ABL negative, 11) TEL AML positive, and 12) No testicular disease on diagnosis.

7.4 TREATMENT

Recommendation 10 - We advise that treatment regimen be based on the risk stratification of the child at diagnosis for newly diagnosed childhood ALL. (High Quality Evidence, Strong Recommendation)

Recommendation 11 - We advise the less toxic regimens using a 3-drug induction protocol without an intensive consolidation for the treatment of standard-risk childhood ALL with favorable features. We advise addition of a delayed intensification phase to improve event free survival (EFS). (High Quality Evidence, Strong Recommendation).

Recommendation 12 - We recommend more intensive therapy for children diagnosed with high-risk ALL with poor cytogenetic factors, overt CNS involvement and poor early steroid response. We recommend additional intensive consolidation and delayed intensification during the continuation phases of chemotherapy to improve overall survival. (High Quality Evidence, Strong Recommendation)

Recommendation 13 - We advise delayed first intrathecal chemotherapy over cranial irradiation for CNS prophylaxis in children with standard risk ALL and after risk adjusted chemotherapy. (High Quality Evidence, Strong Recommendation).

Recommendation 14 - We advise cranial irradiation as a therapeutic option following standard ALL protocol in addition to intrathecal chemotherapy and risk-adjusted systemic treatment for CNS-directed therapy of children with high risk ALL and CNS3 or overt CNS involvement. (High Quality Evidence, Strong Recommendation).

Evidence to Recommendation for Treatment

The treatment of childhood ALL varies according to the risk stratification of the child at diagnosis. It can be divided into 4 phases of chemotherapy: Remission-Induction, Consolidation/Intensification, Maintenance and CNS Prophylaxis. Graduated intensity of chemotherapy has added Intensification to some subgroup of children with high-risk stratification. Contemporary treatment consists of complex combination chemotherapy regimens that last 2.5-3 years with six to eight months of relatively intensive therapy, followed by 1.5-2 years of low intensity maintenance therapy.

We searched using PubMed and Google Scholar using the terms “pediatrics” OR “childhood acute lymphoblastic leukemia” AND “therapy or treatment or chemotherapy, phases of chemotherapy or management” AND “induction or consolidation or intensification or maintenance or CNS prophylaxis” AND “risk stratification” OR “standard risk” OR “high risk” AND “Meta-analysis” OR “RCT” OR “Clinical Trials” OR “Cohort”.

We reviewed a total of 6 studies with high quality evidence. One was a meta-analysis consisting of 8 collaborative studies and 6 additional randomized clinical trials. Treatment regimens were based on

Risk Stratification Criteria that divides patients to either Standard Risk or High Risk based primarily on factors readily available in all centers: age, initial white blood cell count (WBC), central nervous system (CNS) status, blast cell immunophenotype, cytogenetics and early response.

Standard Risk includes B-precursor ALL with age 1-10 years old, WBC <50,000/ul, good prednisone response, CNS 1 or CNS 2 and Day 15 M1/M2 marrow and D29 M1 marrow, DNA index of 1.116, translocation T (12,21)(ETV6-RUNX1). High Risk includes B-cell precursor ALL with age <1 and >10 years old, WBC count >50,000/ul, poor prednisone response, CNS3 or T-cell ALL, Day 15 M3 marrow or Day 29 M2/M3 marrow, t (9,22)(BCR-ABL1), level of MRD of 1 % after completion of induction therapy**.(Hunger & Howard,2009 & Pui, 2009)**

Our review showed that the 16 year event-free survival was higher in children given prednisone pre-phase of 60 mg/m2 at 73% compared with prednisone tapering to 40 mg/m2 at 59% along the course of Induction with 3-drug induction regimen consisting of vincristine at 1.5 mg/m2 , prednisone at 40 mg/m2, and L-asparaginase 6,000 IU/m2 given for a duration of 4 weeks. The higher EFS was associated with added intensive consolidation using vincristine 1.5 mg/m2, 6-mercaptopurine 50-75 mg/m2 and intrathecal methotrexate with dose range of 10-15 mg/dose depending on the age or a 2 month delayed intensification phase using dexamethasone at 6 mg/m2, vincristine at 1.5 mg/m2, doxorubicin 25 mg/m2 , L-asparaginase at 6,000 IU/m2, cyclophosphamide at 1000 mg/m2, cytarabine 75 mg/m2, 6-Mercaptopurine at 60 mg/m2 and intrathecal methotrexate with dose range of 10-15 mg depending on the age. **(Hunger & Howard,2009)**

Over-all remission-induction rate was 98% for induction protocol using prednisone 40 mg/m2 pre-phase and 4-drug induction (vincristine 1.5 mg/m2, prednisone at 40 mg/m2, doxorubicin at 25 mg/m2,L-asparaginase at 6000 IU/m2) for standard risk ALL children and 96% using L-asparaginase pre-phase at 6,000 IU/m2 x 5 days, 4-drug induction with added high dose methotrexate at 5 mg/m2 and cytarabine at 75 mg/m2 for high risk children. Absence of toxic deaths are higher in treatment regimens utilizing prednisone pre-phase with 3 drug induction without intensive consolidation or delayed intensification for standard risk children at 60% compared to treatment regimens using 4 drug induction with addition of anthracycline at 40% (Hunger & Howard,2009). The 10-year event-free survival of children with Standard Risk ALL (84.3%) and High Risk ALL (78.9%) utilizing prednisone pre-phase plus a total of 30 weeks of L-asparaginase during intensification and continuation phases of treatment were higher compared to utilizing L-asparaginase pre-phase plus a total of 20 weeks L-asparaginase in the intensification and continuation phases of treatment of both standard risk (77.4%) and high risk children (72.2%). However, induction death from toxicity was higher (2.2%) among children given L-Asparaginase prephase (**Silverman,2009**). Children with ALL given Individualized Dose L-asparaginase has higher EFS (90%) and overall survival (OS)(96%) compared to children given fixed Dose L-Asparaginase (EFS 82% and OS 93%). Fixed-Dose L-Asparaginase has higher incidence of the following compared to individualized dose L-Asparaginase; osteonecrosis (29% vs 10%,p=0.06), pancreatitis (5.1% vs 3.2%,p=0.06) and thrombosis (8.2% vs 3.7%,p=0.06). (**Vrooman,2013**).

The 6-year event-free survival among children in the dexamethasone (6 mg/m2) arm post-induction was higher at 85% compared to the Prednisone (40 mg/m2) arm post-induction at 77% in delayed intensification (DI) phase and interim maintenance therapy using 6MP, weekly oral methotrexate, monthly Vincristine/steroid pulses for 2.5 years or 30 months **(Hunger & Howard,2009).** Using the COG clinical trials, the 10-year OS was higher among children given

dexamethasone and additional doses of triple intrathecal chemotherapy during induction phase for both standard risk and high-risk children at 90.4% compared to children given prednisone at 82% **(Hunger,2012).** Both 5-year EFS and 5 year OS were higher among children given dexamethasone (90% and 95% respectively, p=<0.01) over prednisone (81% and 94% respectively, p=0.31) in the remission induction and continuation phases of chemotherapy **(Vrooman,2013)**. However, toxicities including death during induction (1.7%), neuropsychiatric events (3.6%), osteonecrosis (3.9%) including osteonecrosis with 5-yr cumulative fractures (23% vs.5%, p=<0.01) were higher among children given dexamethasone. **(Vrooman,2013 & Teuffel,2011)**

The 7-year event-free survival was 80-85% among children with standard risk ALL given an additional delayed intensification phase and 63% among children with a BFM style consolidation using cyclophosphamide 1,000 mg/m2, cytarabine 75 mg/m2, 6-mercaptopurine at 75 mg/m2 and intrathecal methotrexate **(Hunger & Howard,2009)**. High dose methotrexate of 5 g/m2 was associated with a higher 5-year treatment-related death prior to relapse (2.04%) compared to methotrexate of 2-3 g/m2 (1.57%) when given during reinduction and reconsolidation phases of treatment. **(Hunger,2012)**

The 10-year EFS (77.6 +/- 2.9%) and OS (83.7 +/- 2.5%) were both higher among children with ALL given SJCRH total therapies 13B due to addition of intensified systemic treatment with additional doses of L-asparaginase during reinduction and intensification phases. Early intensive intrathecal treatment during remission-induction and continuation treatment as well as the use of dexamethasone in the SJCRH Total Therapy 13A resulted in a lower CNS Relapse (1.2%) despite the reduced dose of craniospinal irradiation. However, use of high dose methotrexate at 5 g/m2 resulted in a higher 10 year cumulative risk of death and infectious death during remission-induction phase (4%). This resulted to a higher rate of abandonment in treatment. Risk of hematologic and testicular relapses were low (0.41%) but there was no difference in the incidence of secondary cancer (5.6%). **(Pui,2009)**

Overall, treatment regimens were based primarily on risk stratification of childhood ALL at diagnosis. Remission-induction utilized 3-drug induction for Standard Risk children with a therapeutic option to utilize a 4-drug induction for high-risk children with poor cytogenetic factors, CNS status and poor responders. Intensive systemic disease control with the use of Dexamethasone over Prednisone, additional delayed intensification or intensive consolidation during the continuation phases of chemotherapy give a higher EFS and OS with lower CNS relapses but with higher incidence of treatment-related toxicities.

Evidence to Recommendation for CNS Treatment

Central nervous system directed therapy in childhood ALL depends on the CNS status of the patient at diagnosis or during chemotherapy. Therapeutic options include prophylactic intrathecal chemotherapy and/or craniospinal irradiation for overt CNS Involvement. We searched using Pubmed and Google Scholar using the terms “pediatrics” OR “childhood acute lymphoblastic leukemia” AND “therapy or treatment or chemotherapy or management” AND “risk stratification” OR “low risk or standard risk” OR “high risk” AND “Randomized Controlled Trial” OR “Clinical Trial” OR “Cohort”. We reviewed a total of 5 high quality evidence researches. One was a meta-analysis consisting of 10 collaborative groups and 4 additional randomized controlled trials.

Risk stratification in the studies used low risk or standard risk which included B-cell precursor ALL, age between 1-10 years old, WBC count <50,000, DNA index of 1.16, translocation T (12,21) (ETV6-RUNX1), with minimal residual disease of 1% or more in the BMA on D19 remission induction or 0.10 to 0.99% MRD after completion of 6 weeks of induction therapy. High risk included children and adolescents <1 and >10 years of age, t(9;22)(BCR-ABL1), level of MRD 1% or more after completion of induction therapy **(Pui,2009**). Subgroup analysis of patients in the 10 collaborative trials who used craniospinal irradiation include overt CNS Disease or CNS3 at diagnosis, T-cell immunophenotype, high initial WBC > 100,000, slow early response defined as either persistent circulating blasts > 1 x 10*9/L after 7 days of single agent prednisolone or > 25% blasts in the bone marrow after 7-14 days of induction chemotherapy (**Vora,2011**).

Our review showed no significant differences between delayed first intrathecal chemotherapy without CrRT and intrathecal chemotherapy with CrRT in the rates of EFS (72.1% +/- 2.4% vs 75.7 +/- 1.4% p = 0.260); rates of OS (79.4% +/-2.1% vs 83% +/-1.3% p=0.069), cumulative risk of isolated CNS relapse (4.1%+/-1.0% vs 4.0%+/-0.7%p=0.960), and even with non CNS-1 EFS (62.9%+/-9.4% vs 52.3%+/-5.8%p=0.199) (**Yeh,2008**). The CNS control rate of extended intrathecal chemotherapy without intensive induction or consolidation or delayed intensification as CNS prophylaxis for standard risk ALL was 80% while cranial irradiation using 1800 cGy for those CNS3 as CNS Prophylaxis for high risk ALL was 90**%. (Hunger & Howard,2009).** Among children with ALL given additional doses of intrathecal chemotherapy for standard/low risk stratification, isolated CNS relapse was less at 1.5% compared to those given CrRT alone at 4%. **(Sima Jeha, 2019)**

The impact of CrRT on clinical outcomes among patients treated in the 10 major collaborative trials with substantial differences in the proportions of patients receiving CrRT, which ranged from 4-33%. The meta-analysis identified patients with CNS3 at diagnosis as the only subgroup with a reduction in the rate of any or isolated CNS relapses after CrRT vs without CrRT(4.3% vs 16.7% p=0.02), but there was no significant differences in the cumulative risk of any adverse events(32.2% for CrRT vs 34.4% without CrRT) or in survival between patients with CNS3 status treated with or without CrRT **(Vora,2011).**

Overall, modified CNS-directed therapy with delayed administration of the first triple intrathecal chemotherapy using methotrexate, hydrocortisone, cytarabine and total omission of craniospinal irradiation (CrRT) did not compromise the overall survival and adverse events for childhood ALL. But CrRT may reduce CNS relapse in subgroup of patients with CNS3 at diagnosis.

Treatment Protocols Used in the Clinical Trials used for Evidence to Recommendation

Dana-Farber Cancer Institute ALL PROTOCOL (96-01)

INDUCTION (4 weeks)
Vincristine 1.5 mg/m2 weekly x 4 weeks (maximum 2 mg)
Prednisone 40 mg/m2 Days 0-28
Doxorubicin 30 mg/m2 /days 0 and 1
Methotrexate 4 gm/m2 x1 dose (Day 2)
L-asparaginase E. coli or Erwinia ASP 25,000 IU/m2 x 1 dose (Day 4)
IT Cytarabine x 1 dose (Day 0), IT chemotherapy Day 14

CNS THERAPY (3 weeks)
Vincristine 2.0 mg/m2 Day 1 (maximum 2 mg)
6 Mercaptopurine 50 mg/m2 oral Days 1-15
HR only: Doxorubicin 30 mg/m2 Day 1
IT chemotherapy twice weekly x 4 doses
Cranial Irradiation:
SR – randomized to no CrRT vs 18 Gy
HR – 18Gy

INTENSIFICATION (20-30 weeks)
Every 3 week cycles

Standard Risk:
Vincristine 2.0 mg/m2 (max 2 mg)
Prednisone 40 mg/m2 orally x 5 days
Methotrexate 30 mg/m2 IV or IM Days 1,8,15
6 MP 50 mg/m2 Days 1-15
L-asparaginase E. coli or Erwinia ASP 25,000 IU/m2 weekly

High Risk: same as SR except Prednisone higher at 120 mg/m2 x 5 days
No Methotrexate
Doxorubicin 30 mg/m2 Day 1
Doxorubicin +/- Dexrazoxane 300 mg/m2

CONTINUATION (UNTIL 24 MONTHS CCR)
Every 3 week cycle
SR – same as intensification, except no L-Asparaginase
HR – same as SR patients
IT Chemotherapy per test

CHILDREN'S ONCOLOGY GROUP (COG) CLINICAL TRIAL (Study of Hunger and Howard)
STANDARD RISK
REGIMEN 1

INDUCTION (4 weeks)
Prednisone prephase 60 mg/m2 Days 1-7
Prednisone 40 mg/m2 Days 8-29
Vincristine 1.5 mg/m2 Days 8,15,22,29
L-asparaginase 6000 IU/m2 3x a week MWF starting Day 8
Intrathecal Methotrexate Days 1,8,29
Extra IT Methotrexate on Days 15,22 if CNS 3

CONSOLIDATION (4 weeks)
Vincristine 1.5 mg/m2 Day 1
6-Mercaptopurine 75 mg/m2 Days 1-28
Intrathecal Methotrexate Days 1,8,15

MAINTENANCE (84 day cycles until 30 months from start of therapy)
Dexamethasone 6 mg/m2/day Days 1-5,29-33,57-61
Vincristine 1.5 mg/m2 Days 1,29,57
6-Mercaptopurine (75 mg/m2) Days 1-84
Oral Methotrexate (20 mg/m2) weekly starting Day 1
Intrathecal Methotrexate Day 1
(omit oral MTX when IT MTX given)

REGIMEN 1 with Cranial Irradiation
Same Induction/Consolidation/Maintenance
-add Cranial Irradiation (1260 cGy for CNS1 & CNS2 & 1800 cGy for CNS3 at the start of the 1st cycle

REGIMEN 2
INDUCTION (4 weeks)
Prednisone (60 mg/m22/day) Days 1-29
Vincristine 1.5 mg/m2 Days 8,15,22,29
L-asparaginase 6000 IU/m2 3x a week x 3 weeks starting Day 8
IT MTX Days 1,8,29
Extra IT Mtx on Days 15,22 if CNS 3

CONSOLIDATION(4 weeks)
Vincristine 1.5 mg/m2 Day 1
6-Mercaptopurine 75 mg/m2 Day 1-28
IT MTX Days 1,8,15

INTERIM MAINTENANCE (8 weeks)
Dexamethasone 6 mg/m2 Days 1-5,29-33
Vincristine 1.5 mg/m2 Days 1,29
6-Mercaptopurine 75 mg/m2 Days 1-50
MTX 20 mg/m2 weekly Days 1,8,15,22,29,26,43,50
IT Mtx Day 29

DELAYED INTENSIFICATION (8 weeks)
Dexamethasone 10 mg/m2/day Days 1-7,15-21
Vincristine 1.5.m2 Days 1,18,15
Doxorubicin 25 mg/m2 Days 1,8,15
L-asparaginase 6000 IU/m2 3x a week x 2 weeks starting Day 3
Cyclophosphamide 1000 mg/m2 Day 29
Cytarabine 75 mg/m2 Days 29-32, 36-39
6-Mercaptopurine 60 mg/m2 Days 29-43
IT MTX Days 1,29,36
Must have blood counts before starting Day 29 therapy

MAINTENANCE (84 cycles until 30 months from start of therapy)
Dexamethasone 6 mg/m2/day Days 1-5,29-33,57-61
Vincristine 1.5 mg/m2 Days 1,29,57
6-Mercaptopurine 75 mg/m2 Days 1-84
Oral Methotrexate 20 mg/m2 starting Day 1
IT MTX Day 1,29 for first 4 cycles then Day 1 only
(omit oral MTX when IT Mtx given

REGIMEN 2 with CrRT – same as Regimen 2 but add
-Cranial Irradiation 1260 cGy for CNS1 & CNS2 and 1800 cGy for CNS3
At start of 1st cycle (omit oral MTX on Day 1 of cycle # 1 and when IT MTX given)

High Risk ALL with BFM type Consolidation

REGIMEN 3

INDUCTION (4 weeks)
Prednisone (60 mg/m22/day) Days 1-29
Vincristine 1.5 mg/m2 Days 8,15,22,29
L-asparaginase 6000 IU/m2 3x a week x 3 weeks starting Day 8
IT MTX Days 1,8,29
Extra IT Mtx on Days 15,22 if CNS 3

CONSOLIDATION (4 weeks)
Cyclophosphamide 1000 mg/m2 Days 1,15
Cytarabine 75 mg/m2 Days 1-4,8-11,15-18,22-25
6-Mercaptopurine 60 mg/m2 Days 1-28
IT MTX Days 1,8,15,22
Must have blood count recovery before starting Day 15 therapy

INTERIM MAINTENANCE (8 weeks)
Dexamethasone 6 mg/m2 Days 1-5,29-33
Vincristine 1.5 mg/m2 Days 1,29
6-Mercaptopurine 75 mg/m2 Days 1-50
MTX 20 mg/m2 weekly Days 1,8,15,22,29,26,43,50
IT Mtx Day 29

DELAYED INTENSIFICATION (8 weeks)
Dexamethasone 10 mg/m2/day Days 1-7,15-21
Vincristine 1.5.m2 Days 1,18,15
Doxorubicin 25 mg/m2 Days 1,8,15
L-asparaginase 6000 IU/m2 3x a week x 2 weeks starting Day 3
Cyclophosphamide 1000 mg/m2 Day 29
Cytarabine 75 mg/m2 Days 29-32, 36-39
6-Mercaptopurine 60 mg/m2 Days 29-43
IT MTX Days 1,29,36

MAINTENANCE (84 cycles until 30 months from start of therapy)
Dexamethasone 6 mg/m2/day Days 1-5,29-33,57-61
Vincristine 1.5 mg/m2 Days 1,29,57
6-Mercaptopurine 75 mg/m2 Days 1-84
Oral Methotrexate 20 mg/m2 starting Day 1
IT MTX Day 1,29 for first 4 cycles then Day 1 only
(omit oral MTX when IT Mtx given)

REGIMEN 4 – same as Regimen 3 but add
Cranial irradiation (1200 cGy for CNS 1 & CNS 2 & 1800 cGy for CNS 3)
At start of 1st cycle (omit oral MTX on Day 1 of cycle # 1 and when IT MTX given)

Protocol from Hunger Study (ALL9)
For STANDARD RISK ALL
INDUCTION:
Vincristine 1.5 mg/m2 weekly x 4 weekks
Dexamethasone 6 mg/m2 D0-28
L-asparaginase 6000 IU/m2 3x a week x 9 doses
Triple Intrathecal chemotherapy using Methotrexate/Hydrocortisone/Cytarabine 2x

CNS PROPHYLAXIS
Intermediate dose Methotrexate 2 g/m2
Triple Intrathecal chemotherapy 2x

MAINTENANCE
Vincristine 1.5 mg/m2
Dexamethasone 6 mg/m2
Methotrexate 75 mg/m2
Triple Intrathecal chemotherapy 3x

FOR HIGH RISK ALL
INDUCTION:
Vincristine 1.5 mg/m2 weekly x 4 weeks
Daunorubicin 30 mg/m2
Dexamethasone 6 mg/m2
L-asparaginase 6,000 IU/m2 3x a week x 9 doses
Triple Intrathecal chemotherapy x 2-4x
CNS PROPHYLAXIS:
HD Methotrexate 3 g/m2
6-Mercaptopurine 60 mg/m2
Triple Intrathecal Chemotherapy 4x

REINDUCTION:
Vincristine 1.5 mg/m2
Daunorubicin 30 mg/m2
6-MP 75 mg/m2
L-asparaginase 6,000 IU/m2
Triple Intrathecal chemotherapy x 1

SUPERCONSOLIDATION
Cyclophosphamide 1,000 mg/m2
Cytarabine 75 mg/m2
(4 day courses x 6x)

MAINTENANCE
Vincristine 1.5 mg/m2
Dexamethasone 6 mg/m2
6-Mercaptopurine 75 mg/m2
Methotrexate 10-20 mg/m2 oral
Triple Intrathecal chemotherapy 8x

ST. JUDE CHILDREN'S RESEARCH HOSPITAL (SJCRH) Total Therapy Study 13A (Study of Hunger)

For STANDARD RISK ALL

REMISSION/INDUCTION:
IV Methotrexate 30 mg/m2
Etoposide 100 mg/m2
2 additional weekly Intrathecal Methotrexate

CONSOLIDATION:
HD methotrexate 2 gm/m2
6-MP 75 mg/m2
Vincristine 1.5 mg/m2
Prednisone 40 mg/m2

REINDUCTION:
Vincristine 1.5 mg/m2
Prednisone 40 mg/m2
L-asparaginase 6000 IU/m2
Intrathecal Methotrexate total of 15 doses
Craniospinal Irradiation for T-cell ALL

CONTINUATION THERAPY:
Dexamethasone 6 mg/m2
Vincristine 1.5 mg/m2
6-Mercaptopurine 75 mg/m2
Methotrexate oral 10-20 mg/m2

FOR HIGH RISK ALL
INDUCTION – IV Methotrexate is 1 g/m2 instead of 30 mg/m2
Etoposide 100 mg/m2/Intrathecal Methotrexate

CONSOLIDATION – add L-asparaginase 6000 IU/m2
HD Mtx 2 g/m2
6MP 75 mg/m2
Vincristine 1.5 mg/m2
Prednisone 40 mg/m2

REINDUCTION
Same above SR but Intrathecal Methotrexate is 22-26 doses
Craniospinal Irradiation for WBC >100,000 and T-cell ALL

CONTINUATION THERAPY
Same as SR

SIDE EFFECTS/ TOXICITIES OF CHEMOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA

Anthracyclines	
Daunorubicin	Cardiac dysfunction
Doxorubicin	Vomiting, Nausea
Mitoxantrone	Secondary cancers
	Enhances radiation effects
	Marrow Suppression
Alkylating Agents	
Cyclophosphamide	Marrow suppression
Ifosfamide	Scarring, Hemorrhagic cystitis
	Infertility, Gonadal Dysfunction
	Pulmonary scarring, kidney dysfunction
	Secondary cancers
Topoisomerase II Inhibitors	
Etoposide	Nausea, vomiting,
	Marrow suppression
	Secondary Cancers
	Gonadal Dysfunction
Anti-metabolites	
Methotrexate	Hepatic fibrosis
Cytarabine	Neurocognitive changes
6-Mercaptopurine	Marrow suppression
6-Thioguanine	
Vinca Alkaloids	
Vincristine	peripheral neuropathy
	Weakness, sensory deficits
Steroids	
Prednisone	Avascular Necrosis/Osteonecrosis
Dexamethasone	weight gain
	Risk for Metabolic Syndrome
	Cushingoid facies, hirsutism
Enzyme	
L-asparaginase	Hypersensitivity/Anaphylaxis
	Pancreatitis, Thrombosis

7.5 MONITORING OF TREATMENT

Recommendation 15 - We advise adequate monitoring of acute side effects or toxicities from combination of multi-agent chemotherapy in the treatment of childhood ALL. (High Quality Evidence, Strong Recommendation).

Recommendation 16 - We suggest Minimal Residual Disease (MRD) to monitor response to treatment of children with ALL undergoing therapy. (High Quality Evidence, Strong Recommendation).

Recommendation 17 - We advise to monitor WBC count and peripheral blast count after 1 week of prednisone pre-phase as well as bone marrow blast count and platelet count at day 28 to determine treatment response of childhood ALL when MRD is not available. (High Quality Evidence, Strong Recommendation)

Recommendation 18 - We recommend addressing the following when feasible: financial constraints, false perception of cure, experience of severe side effects, dissatisfaction with healthcare providers, poor general condition of the child, no clinical improvement in the child and health systems access issues to improve treatment adherence. (High Quality Evidence, Strong Recommendation)

Recommendation 19 - We advise reinforcement of health education on treatment compliance or adherence especially during the induction and maintenance phases of chemotherapy to lessen treatment abandonment. (High Quality Evidence, Strong Recommendation)

Evidence to Recommendation for Monitoring of Treatment

MRD compared to conventional prognostic factors used in NCI risk criteria such as age, WBC count at diagnosis, genetic abnormalities and prednisone has been demonstrated to be highly predictive of outcome and risk of relapse among children with ALL undergoing chemotherapy. The search terms used during documentation of Search Strategy using PubMed and Google Scholar were “pediatrics” OR “childhood acute lymphoblastic leukemia” AND “monitoring treatment response” AND “clinical trial” OR “systematic review” OR “cohort”. A total of 15 abstracts were reviewed and 3 observational studies of prospective cohort study design of high-quality evidence were included.

One high quality study stratified children with acute lymphoblastic leukemia based on minimal residual disease (MRD) level by PCR on day 33 and 78. Patients with MRD Standard Risk (<0.01%) had a higher 5-year EFS 92.3% compared to MRD intermediate risk (0.1 to <1%) and MRD high risk (>1%) with 5-year EFS of 77.6% and 50.1% respectively. Subgroups classified based on NCI as standard risk and high risk had no difference in their 5-year EFS if grouped under the same MRD risk stratification. The Cumulative incidence of relapse also significantly increases with MRD risk stratification with 6%, 21%, 34.9% for MRD-SR, MRD-IR and MRD-HR respectively. **(Conteri et al, 2010)**

Another high-quality study used conventional prognostic factors such as WBC count at day 7 and bone marrow blast count at day 28 to predict 5-year EFS and compared it with MRD. A WBC > 5000 after 1 week (78.8 %) induction chemotherapy had significantly higher 5-year EFS (p-value 0.014) compared to <5000 (46.2%) while a blast count >5% on day 28 of chemotherapy (33.3 %) had a lower 5-year EFS compared to <5% (80.2 %). MRD positive at day 28 of treatment had no significant difference in 5-year EFS regardless of NCI risk stratification (ALL-SR 33% vs ALL-HR 21.4%). **(Scrideli et al, 2006)**

A more recent high-quality study included peripheral blast count on day 8 and platelet count on day 33 of treatment as well as MRD level. The combination of high blast count (≥0.1 x 10^9/L) and low platelet count (<100 x 10^9/L) yielded a poorer outcome (3-year EFS 53.8%, 3-year OS 61.5%) compared to low blast count (<0.1 x 10^9/L) and high platelet count (≥100 x 10^9/L) (3-year EFS 86.3%, 3-year OS 90.1%). This combination of peripheral blast and platelet count with MRD-based risk stratification can be correlated. **(Dai et al, 2021)**

Overall, we found high quality evidence suggesting treatment response based on MRD level to be a more superior prognostic factor in childhood ALL with a significantly better EFS for MRD Standard Risk (92.3%) compared to MRD High Risk (50.1%) and no significant difference regardless of NCI criteria belonging to the same MRD risk stratification. Simplified methods for the evaluation of an early response, such peripheral and bone marrow blast count, WBC count and platelet count also proved to be a good predictor of EFS for the course of children with ALL when MRD is not available.

Evidence to Recommendation for Adherence to Treatment

Poor adherence to treatment is a known problem in pediatric ALL management. Several factors could lead to refusal (non-initiation) and abandonment (non-completion) of treatment resulting in poor treatment outcomes. The search terms used during documentation of Search Strategy using Pubmed were “pediatric acute lymphoblastic leukemia” OR “childhood acute lymphoblastic AND “compliance” AND “treatment protocol” OR “chemotherapy schedule” OR “therapy schedule” AND “systematic review” OR “Meta-analysis” OR “cohort”. Using Google Scholar, search terms used were “acute lymphoblastic leukemia” “children” “compliance” “chemotherapy”. A total of 13 abstracts were reviewed. Three observational studies of prospective cohort study design of high-quality evidence and 2 moderate to high quality evidence studies were included.

A retrospective study of high-quality evidence identified the prevalence and reasons behind treatment refusal and abandonment in childhood ALL. A total of 96 out of 572 (16.8%) patients refused treatment. Refusal of care was statistically higher for infants ($p = 0.004$), girls ($p = 0.04$), those of lower socioeconomic status ($p < 0.001$), living in rural areas ($p = 0.05$) and children of parents with poor literacy ($p < 0.001$). Main causes of treatment refusal were financial constraints (59.4%) and a misplaced belief about the incurability of cancer (22.9%). A total of 139 out of 476 (29.2%) children abandoned chemotherapy with the majority (41%) during induction, followed by maintenance (17.9%) phase. Major reasons for abandonment were financial constraints (34.5%), false perception of cure (20%), poor general condition of the child (15%), no improvement in the child (13%) and blood donation refusal (3%). The reasons cited were different in various treatment phases. Abandonment was significantly higher in children from lower socioeconomic status ($p < 0.001$), living in rural areas ($p < 0.001$) and in those with fathers having a lower literacy status ($p < 0.001$) **(Alam 2018).**

Another study of high-quality evidence included 40 out of 159 (25%) pediatric patients diagnosed with ALL who refused or abandoned therapy, of which 37 (93%) were home-visited and interviewed. There was no significant difference in the age, sex, risk classification, parent’s educational level and travel time to the hospital. The main reasons for abandonment included financial difficulties (60%) and belief of disease incurability (60%), followed by experience of severe side effects (35%), dissatisfaction with healthcare providers (22%), transportation difficulties (22%), no room availability

(5%) and child looked healthy (5%). Most patients abandoned treatment during the remission-induction phase (48%) followed by maintenance phase (25%) **(Sitaresmi 2010)**.

One high quality evidence study assessed the rate of adherence to 6-MP medication using two methods and identified factors that could influence adherence. A total of 52 children and their caregiver were included. The first method objectively measured 6-MP metabolites yielding an adherence rate of 84.6% while the second method was subjective using parent and child self-report via the Medication Adherence Report Scale (MARS) with a rate of 94.2% to 100% as perceived by the caregiver and patient, respectively. However, factors studied such as child age, parent age, child gender, parent gender, parent educational level, duration of ALL treatment, number of medications, and the presence of side effects were not found to significantly affect adherence ($p>0.05$)**. (Alsous 2017).**

One moderate to high quality evidence determined the overall non-adherence rate to oral 6MP as maintenance chemotherapy to be 55.81%. Forgetfulness of the caregiver or parent was the main cause of non-adherence at 47%, followed by refusal of the child to take the medication (25%), drug unavailability (13%), negligence (11%) and medical staff error (4%). Serum levels of 6MP was another way of evaluating adherence to treatment. Serum level of 6MP <9.3 ng was assessed to be non-adherent and was noted in 50% of children with ALL. Non-adherence was significantly associated with low socioeconomic status by questionnaire (82.9%) and serum 6MP levels (85.4%), non-educated caregiver or parent by questionnaire (70.6%) and serum 6MP levels (56.9%), low educational level of primary caregiver by questionnaire (74.4%) and serum 6MP levels (72.1%) ($p=0.001$). Large families with 5 or more members showed a significant association with non-adherence by both questionnaire (70.7%) and serum 6MP levels (63.4%) with a p value of $p=0.02$ and $p=0.04$ respectively. Significant association with non-adherence was observed among those who needed more money to come for follow-up visits by questionnaire (64.1%) but no serum 6MP levels (56.2%) ($p=0.03$ and $p=0.09$ respectively)**. (Kamal et al, 2015).**

Another moderate to high quality study about treatment delays and the risk of relapse in childhood ALL showed that the risk of relapse did not differ between patients with longer or shorter delays either cumulatively or in the intensive phase of chemotherapy ($p=0.68$ and $p=0.65$ respectively). There was a tendency for a reduced risk of relapse in the group with longer delays during the maintenance phase of treatment ($p=0.07$). When median lengths of delay were divided into quartiles, the risk of relapse did not differ between the lowest and the highest quartiles in the cumulative and intensive phases of chemotherapy ($p=0.23$ and $p=0.94$ respectively). In the maintenance phase, the difference was significant with fewer relapses among patients in the highest quartile for treatment delays ($p=0.04$). This is a moderate evidence study in terms of observed causes of treatment delays in relation to the intensive and maintenance phases of chemotherapy. The observed frequencies for the most common causes for delay were similar for both intensive and maintenance phases which were: low blood counts (33.3% and 44.7% respectively), severe infections (19.9% and 11.3% respectively), and febrile neutropenia (19.1% and 5.7% respectively). **(Yeoh et al, 2017)**

Overall, the moderate to high quality evidence studies identified factors that affect adherence or compliance. The most common factors cited were financial constraints (34.5%-60%), false perception of cure (20-60%), experience of severe side effects (35%), dissatisfaction with healthcare providers (22%), transportation difficulties (22%), poor general condition of the child (15%), no improvement in

the child (13%), no room availability (5%) and child looked healthy (5%) and blood donation refusal (3%). Most patients abandon treatment during induction and maintenance phases of chemotherapy.

7.6 PROGNOSIS

Recommendation 20 - We recommend that patient characteristics at diagnosis such as age, gender, WBC count and CNS status be used in assessing prognosis of childhood ALL. Absolute Lymphocyte Count (ALC) recovery is a good prognostic tool in a setting where Minimal Residual Disease (MRD) is not available. (High Quality Evidence, Strong Recommendation)

Evidence to Recommendation for Prognosis

Several prognostic factors including patient characteristics and laboratory parameters affect overall survival of Childhood ALL. We searched Pubmed using the search terms "prognosis or prognostic factors" AND "pediatric ALL" OR "childhood ALL". We reviewed a total of 4 high quality evidence, observational studies. There were 2 studies on absolute lymphocyte count recovery involving 212 and 171 patients respectively. There was one study on patient characteristics associated with high failure rate of treatment. One study on CSF pleocytosis upon diagnosis with a study population of 8,379 subjects.

Our review showed that age <1 year old (78%, p=0.001), male sex (51%, p=0.0003), WBC > 50,000/cumm (56%, p=0.01) at diagnosis were associated with high failure rate of treatment. **(S.M. Ng et al)** ALC recovery was a good prognostic tool in the management of childhood ALL. ALC of > 500 on Day 15 of induction chemotherapy showed an Overall Survival (OS), Relapse Free Survival (RFS) and Event Free Survival (EFS) of 84%, 79.2% and 72% respectively. ALC of >1000 on Day 29 of induction chemotherapy showed an OS, RFS, and EFS of 88.1%, 88.5%, and 77.8% respectively. **(Gupta)** A similar study presented a univariate analysis of ALL patients with ALC of <1500 on Day 29 of chemotherapy showing RFS and OS (p=0.018 and 0.001 respectively). **(Rabin et al).** CNS Pleocytosis (CNS 2 or CNS 3) on baseline CSF analysis was also significant in predicting EFS, OS, combined and isolated CNS Relapse (p=0.001). However, it did not predict the occurrence of bone marrow relapse(p=0.08). **(Winick)**.

Overall, we found high quality evidence that age < 1 year old, male gender and initial WBC >50,000/cumm are poor prognostic factors. We also found high quality evidence that ALC recovery is a good prognostic tool in a setting where MRD is not available. CNS pleocytosis was predictive of EFS<OS, combined and isolated CNS relapse but not of bone marrow relapse.

7.7 SIDE EFFECTS AND COMPLICATIONS

Recommendation 21 - We recommend monitoring of long-term side effects of chemotherapy in the treatment of childhood ALL such as neuromuscular impairment, limitation of physical performance, diabetes mellitus and cardiotoxicity. (High Quality Evidence, Strong recommendation)

Recommendation 22 - We recommend the use of broad-spectrum antibiotics in childhood ALL with febrile neutropenia. The addition of GCSF to the antibiotic regimen may reduce number of hospitalization days, promote faster recovery and reduce duration of antibiotic use. (High Quality Evidence, Strong Recommendation).

Recommendation 23 - We recommend prompt use of antibiotics to help manage frequency of neutropenia attacks and control treatment-related infections such as mucositis leading to invasive fungal disease, neutropenic enterocolitis, respiratory and bloodstream infections. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 24 - We recommend that during sepsis work-up, blood cultures and C-Reactive Protein should be performed immediately to identify the infectious microorganisms and appropriate antibiogram. (Moderate Quality Evidence, Strong recommendation)

Recommendation 25 - We recommend prompt use of antibiotic prophylaxis for ALL pediatric patients with ongoing chemotherapy. (Moderate Quality Evidence, Strong Recommendation)

Evidence to Recommendation for Complications

Chemotherapy is associated with treatment related long-term complications. We searched using Pubmed using the terms “long term” and “side effects of chemotherapy” and “children” and “acute lymphoblastic leukemia”. We reviewed a total of 3 cohort studies with high quality evidence. One study comprehensively assessed the frequency of neuromuscular impairments and physical performance limitations. Another study assessed the cardiac status of 115 children treated with anthracycline and another study evaluated contributions of treatment-related risk factors for diabetes.

Our review showed that survivors who received total vincristine doses of 39-220 mg/m^2 were 1.5 (95% CI 1.0–2.5) times more likely to have impaired active dorsiflexion ROM than those who received a dose less than 39 mg/m^2. Limited walking efficiency was also associated with vincristine doses of 39-220 mg/m^2 (OR 1.3, 95% CI 0.9-2.1). Survivors who received IT methotrexate doses within 215-694mg/m2, were also 3.4 times (95% CI 1.2–9.8) more likely to have impaired active dorsiflexion ROM than those who did not. Intrathecal methotrexate doses were also associated with limited walking distance at doses of 47-214mg/m2 (OR 4.0, 95% CI 1.5–10.7) and at doses of 215–694 mg/m^2 (OR 5.8, 95% CI 2.2–15.4) than without IT Methotrexate, and with reduced knee extension strength at doses of 47–214 mg/m^2 (OR 3.7, 95% CI 1.2–11.2) and 215–694 mg/m^2 (OR 4.1, 95% CI 1.3–13.2) than without IT Methotrexate. **(Ness et al,2012)**

Outcome of the following drugs (L-asparaginase, prednisone and dexamethasone) may be associated with diabetes mellitus for ALL survivors which were dependent on their cumulative doses. Acute lymphoblastic leukemia survivors ≥15 years of age at diagnosis with every 1000units/m2 (OR 1.12, 95% CI 1.02 – 1.23) increase with l-asparaginase dose, while those ≤15 years of age at diagnosis with every 1000mg/m2 (OR 1.58, 95% CI 1.05 – 2.37) dexamethasone exposure, increased the odds of developing drug-induced diabetes mellitus. **(Williams et al,2020)**

Survivors who received doxorubicin exhibited complications of cardiotoxicity in a dose related manner. Out of 97 ALL survivors who have received cumulative doses of doxorubicin, ranging from 228-550 mg/m2, 65% showed cardiac abnormality of left ventricular afterload, 59% showed increased afterload, and about 23% had decreased contractility. **(Lipshultz et al,1991)**

Overall, we have high quality evidence which shows limitation of dorsiflexion and range of motion (ROM) of joints are significant long-term side effects of treatment with vincristine and IT methotrexate. We also found high quality evidence associating the incidence of diabetes mellitus among ALL patients who received asparaginase and dexamethasone. Children who received doxorubicin therapy have impaired myocardial growth, progressive increase in left ventricular afterload, and reduced contractility.

Evidence to Recommendation for Febrile Neutropenia

Neutropenia is a common adverse event associated with chemotherapy among children with ALL. The treatment options we considered were antibiotics and GCSF. We searched PubMed using the terms “chemotherapy induced neutropenia” AND “neutropenia in cancer” AND “management”. One meta-analysis was reviewed with high quality evidence. The study included 14 randomized controlled trials enrolling a total of 1,553 participants comparing management of chemotherapy induced neutropenia in children with cancer employing antibiotics alone vs antibiotics + GCSF.

Our review showed that there was no difference between antibiotics vs. antibiotics + GCSF in terms of mortality as shown in 13 studies (p-value 0.19). There was also no difference in infection related mortality (p-value 0.23). However, 7 studies showed a significant reduction in the number of days of hospitalization (p= 0.03), while 9 studies showed faster recovery from fever (p= 0.02) and 3 studies showed shorter duration of antibiotic use in the antibiotic + GCSF than antibiotic alone (p= 0.03) group. In terms of laboratory outcomes, 5 studies showed improved ability for neutrophil recovery in the antibiotic + GCSF than antibiotic alone (p-value 0.0004). **(Rahul Maskhar et al)**

Overall, there is high quality evidence that the use of antibiotics + GCSF compared to antibiotics alone in the management of chemotherapy induced neutropenia in children has no effect on overall mortality and infection related mortality. However, the combination reduced the number of days of hospitalization, promoted faster recovery from fever and neutropenia and reduced duration of antibiotic use.

Evidence to Recommendation for Antibiotic Prophylaxis

Infections are undesirable treatment-related toxicities due to the chemotherapy treatment regimen in Pediatric ALL. This might be due to a decrease in absolute neutrophil count (ANC), inability of the patient's immune response to combat a normal flora in the body and doses of chemotherapeutic drugs given during a certain phase in the treatment protocol. We searched PubMed Search using the terms "Pediatric", "Acute Lymphoblastic Leukemia", "post chemotherapy", "infections", "treatment-related infections", "post chemotherapy", "Febrile Neutropenia". We reviewed a total of 9 studies with a total of 4459 patients. Seven studies were identified as observational studies (either retrospective and prospective cohorts) and two were multicenter studies. Five studies have shown moderate quality evidence due to its mixed group of population; 3 studies with high quality evidence.

Two studies **(Fouad et al 2020 and Yiping Zhu et al 2020)** have shown evidence that febrile neutropenia attack is increased during the reinduction phase at 34.6% **(Kar et al 2017)** and 67.2% **(Inaba et al 2017)** and early intensification phase at 24.8% **(Kar et al 2017)**. In addition to intensive chemotherapy, prolonged and profound febrile neutropenia have also attributed to several infections such as Invasive fungal disease **(Das et al 2018)**, neutropenic enterocolitis **(Fouad et al 2020)**, and respiratory infections **(Özdemir et al 2016)**. Furthermore, febrile neutropenia was noted to be one of the risk factors for all of the infections such as respiratory, lip/oral, skin, urinary, gastrointestinal, etc. **(Inaba, et al 2016)**. One study has shown that patients receiving induction chemotherapy are at higher risk of viral acute respiratory illness (incidence of 2.3 per 1000 patient-days) **(Hakim et al 2015)** which led to delayed chemotherapy and prolonged hospitalization. Septicemia was noted to be more common in the intermediate and high risk ALL (17.2%) than in low risk (9.1%) ALL. The incidence and pattern of septicemia was similar to reports of the western countries **(Yiping Zhu et al 2020)**. One of the most common risk factors of mortality **(Kar et al 2017)** and infection-related complications **(Inaba et al 2017)** were febrile neutropenia. Induction phase of leukemia, use of intensive chemotherapy and other factors which may have allowed bacterial invasion and colonization of the bowel wall leads to intestinal complications. **(Fouad et al 2020)**. The most common infection during chemotherapy includes mucositis – 33.4%, pneumonia – 24.7% **(Kar et al 2017)**, upper respiratory infection – 56.8% and bloodstream Infection – 31.5% **(Inaba et al 2017)**. Some of the less common infections are Ear infections, Skin and soft tissue infections, Urinary tract infections **(Inaba et al 2017)**. These infections have impacted the chemotherapy course in children with ALL **(Hakim et al 2015)**.

Laboratory workups such as C-reactive Protein (CRP) could assist in predicting patients with bacterial infection **(Kar et al 2017)**; respiratory specimen testing to identify ARI **(Hakim et al 2015)**; combination of blood, urine, feces and/or bronchoscopy culture to identify infectious organism **(Torres-Flores et al 2020)**. The common microorganisms isolated are: *Staphylococcus* sp., *P. aeruginosa* **(Inaba et al 2017)**; *Staphylococcus* sp., *S. epidermidis*, *E. coli* and *Klebsiella* sp. **(Zhu et al 2020)**; *Staphylococcus* sp., *Klebsiella pneumoniae*, *E. coli* (Kar et al 2017); *E. coli* ESBL, *E. faecalis*, *C. albicans.* **(Torres-Flores et al 2020)**

Overall, the most common risk factors of mortality and treatment-related complications were febrile neutropenia, remission-induction phase of chemotherapy and use of intensive chemotherapy regimen which predisposes the patient to infection-related complications.

Evidence to Recommendation for Specific Antibiotics for Prophylaxis

Infections during a certain phase of chemotherapy in pediatric ALL are common due to neutropenia and lowered immune system. It is important to use prophylactic antibiotics to help combat these common side effects and help the patients complete the treatment to avoid longer hospital days and lessen drug resistance. We searched PubMed using the terms “Acute Lymphoblastic Leukemia”, “prophylaxis”, “pediatric”, “chemotherapy”, “antibiotic”, “Cotrimoxazole’ and “Isoniazid”. We reviewed a total of 3 studies with moderate to high quality evidence. One article was a retrospective non-randomized review with 86 participants who received cotrimoxazole prophylaxis and 85 participants who had no prophylaxis. Another was a meta-analysis with a total of 109 trials with 13,579 participants. A randomized trial with a mixed population of 175 ALL patients and 418 HSCT participants for a total 18,822 participants. They have used cotrimoxazole and quinolones as the prophylactic antibiotic being studied.

Our review showed that the use of cotrimoxazole prophylaxis have shown a lesser case of patients with additional antibiotic therapy, lesser infection rate (p value of 0.003) and less culture positive result (25% vs 57%, *P* value of 0.07). More patients receiving Cotrimoxazole had no febrile episodes during the first 36 days of chemotherapy (29/86 vs 14/85, *P* = 0.02). **(Rungoe et al 2010)**. Use of quinolones vs cotrimoxazole as prophylaxis have also showed a more similar result in all-cause mortality (6.8% vs 5.5%), febrile episodes (63.8% vs 67.5%) and bacteremia rate (17.2% vs 20.5%) than those with no prophylaxis vs prophylaxis with a higher episode of bacteremia (20.9% vs 10.5%). **(Gafter-Gvili et al 2018)**. The benefits of antibiotic prophylaxis outweighed the harm such as adverse effects and development of resistance since all-cause mortality was reduced, infection resistant to drug taken (p value of 0.01). **(Gafter-Gvili et al 2018)**. Though there were no differences in the length of hospital stay and the development of resistance to specific antibiotic agents, C. difficile diarrhea was fewer in the Levofloxacin prophylaxis group. **(Alexander et al 2018)**.

Overall, there is a moderate to high quality of evidence which showed that Cotrimoxazole had lesser side effects and better results in the prevention of secondary infections during chemotherapy in children with ALL. Comparable effect was seen in cotrimoxazole, quinolones such as levofloxacin and may be used as prophylactic antibiotics for pediatric ALL.

7.8 Supportive and Palliative Care

Recommendation 26 - We advise evaluation of quality of life outcomes of patients and their families with high psychosocial risk through a psychosocial screening during diagnosis, treatment and final outcome. A validated measure should be used to identify those in need of psychosocial support. (High Quality Evidence, Strong Recommendation)

Recommendation 27- We recommend nutritional supplementation in ALL children like peanut based ready-to-use food, high quality protein blend formula given during chemotherapy to improve their nutritional status, reduce incidence of complications and decrease the costs of hospitalization. (Moderate Quality Evidence, Strong Recommendation).

Recommendation 28 - We advise assessment of activities of daily living (ADL) and identification of patients who require assistance among children with ALL to enhance patient care and promote better quality of life and safe living conditions. (High Quality Evidence, Strong Recommendation)

Recommendation 29 - We advise observance of proper oral care in children with ALL to prevent and manage oral complications during chemotherapy (Moderate Quality Evidence, Strong Recommendation)

Recommendation 30 - We advise referral to palliative care at any point in the course of illness of newly diagnosed children with ALL to address psychosocial concerns, symptom management and end-of-life care. (High Quality Evidence, Strong recommendation)

Recommendation 31 - We recommend use of the WHO analgesic ladder in the management of pain in children with ALL. (Moderate Quality Evidence, Strong Recommendation)

Recommendation 32 - We recommend low-dose oral ketamine for procedural analgesia in pediatric cancer patients undergoing lumbar puncture in a resource limited hospital setting. (High Quality Evidence, Strong Recommendation)

Evidence to Recommendation for Psychosocial Evaluation

Psychosocial is a term used in describing the intersection and interaction of social, cultural, and environmental influences on the mind and behavior. It Influences the psychological factors and social environment on well-being. We searched through PubMed and Google Scholar using the terms "psychosocial support" AND "acute lymphoblastic leukemia" AND "pediatric or children" AND "quality of life". We reviewed a total of 3 studies with high quality evidence. An observational study assessing parental functioning during maintenance treatment for childhood ALL and 2 randomized controlled trials evaluating quality of life in pediatric oncology patients, caregivers and siblings after a psychosocial screening, sleep hygiene and relaxation intervention among children receiving maintenance chemotherapy.

Our review showed that parents of pediatric patients with (ALL) undergo four (4) tests which measured sleep problems, distress, physical and mental components. These tests generally measure their quality of life. The results revealed that 40% of the parents scored high in the mean nine-item sleep problems index (SLP). In addition, 66% of them have higher mean distress scores. Furthermore, 36% scored high in terms of their mean mental component summary (MCS). It was evident that the sleep problems, distress and mental QoL impairment are prevalent among the parents of children with ALL patients across both the standard risk and moderate risk groups ($p=<0.001$) **(Rensen, 2020).** Pediatric cancer patients who received psychosocial assessment tool (PAT) summary describing low, medium, or high psychosocial risk have lower physical, social, emotional, and school function using the Pediatric Quality of Life Inventory (PedsQL) and has no significant changes over time **(Barrera, 2020**).

Utilizing sleep hygiene and relaxation intervention for children with ALL, it was noted that children in the intervention group increased their mean nighttime sleep duration by 35 minutes compared with the control group, however, this difference did not reach statistical significance (P = .30). Wake time after sleep onset in the intervention group decreased by 44 minutes as compared with the control group; this difference almost reached statistical significance (P = .08). Change from baseline on other objectively measured sleep outcomes such as daytime sleep duration, longest stretch of daytime and nighttime sleep, and number of nighttime awakenings were similar across groups. Most children (95% at baseline, 83% at follow-up) scored above the cut off on the Children's Sleep Habits Questionnaire (CSHQ), indicating clinically significant sleep disturbance. Preintervention and postintervention scores on the Family Inventory of Sleep Habits (FISH) measures were high (mean score 946 in both groups), indicating that families reported practicing good sleep habits before the intervention. There were no differences between groups in change from baseline on the CSHQ, FISH, or CCFS-P. The study established the probability and acceptability of a sleep hygiene and relaxation intervention for children undergoing maintenance chemotherapy for ALL **(Zupanec, 2017**)

Overall, there is high quality evidence showing that psychosocial effects while ongoing treatment for the newly diagnosed children with ALL needs to be attended. The psychosocial well-being of the patients, caregivers and siblings differ to what extent the psychosocial intervention was delivered.

Evidence to Recommendation for Nutritional Support

Acute and chronic malnutrition are common in many resource-limited settings. Acute malnutrition is associated with reduced immunity, an increase in severe chemotherapy-related side effects, altered pharmacokinetics such as higher serum levels of vincristine and other cytotoxic medications, additional surgical complications and increased morbidity and mortality. Nutritional support is important for patients undergoing chemotherapy with underlying malnutrition. We searched through Pubmed and Google Scholar using the search terms "children" AND "Acute Lymphoblastic Leukemia" AND "nutrition or nutritional intake" AND "diet".

We reviewed 4 studies with moderate to low quality evidence. Oral nutritional supplements (ONS) in the form of milk supplements may improve the nutritional status of children, reduce the incidence of complications, and decrease the costs of hospitalization. Use of nutritional supplements was associated with lower weight loss ($p < 0.05$), improved hemoglobin level and concentrations of total protein, albumin, and pre-albumin was also significantly higher ($p < 0.05$ and $p < 0.01$, respectively) for patients in the remission-induction phase of chemotherapy. The incidences of hypoalbuminemia, gastrointestinal complications, and infection was lower in patients taking the ONS ($p < 0.05$) (**Liang,2018).** To address acute malnutrition, a peanut based ready to use therapeutic food may be provided. In Malawi 7 of 18 patients had a >5% increase in corrected weight during chemotherapy. **(Israel,2009)**

Institutions support changeover from the Neutropenic diet to a more standardized opinion of safe food processing. The neutropenic diet offers no benefit over the food and safety guidelines (FSGs) in the prevention of infection, malnutrition and length of hospital stay. **(Polat et al 2020**). Adherence requires more effort for patients and families. Institutions caring for children with cancer can consider replacing ND guidelines with FSGs. **(Moody,2018).**

Overall, there is moderate to low quality evidence to support the nutritional needs of children diagnosed with Acute Lymphoblastic Leukemia in a low-income setting. Current guidelines are well suited for patients in a high income setting where most of the children are not malnourished upon diagnosis.

Evidence to Recommendation for Activities of Daily Living

Activities of daily living (ADLs) are essential and routine tasks that most young, healthy individuals can perform without assistance. The inability to accomplish essential activities of daily living may lead to unsafe conditions and poor quality of life. Activities of daily living in children includes bathing, dressing, shoe tying, grooming, hygiene, and feeding. School age children ADLSs include time management, chores/cleaning/laundry, care of others/pets, money skills (from coin identification to high school financial planning), shopping, transportation and meal preparation. We searched through Pubmed and Google Scholar using the search terms “pediatric or children” AND “acute lymphoblastic leukemia” AND “activities of daily living”. We reviewed 2 observational studies with high quality evidence. One study aimed to characterize motor functioning in children treated for ALL in relation to visual-spatial, fine-motor, visual-motor and academic skills. Another study assessed daily living activities in the domain of school age children with acute lymphoblastic leukemia.

Our review showed that out of the 50 children with acute lymphoblastic leukemia (ALL) from welfare pediatric teaching hospital and child central pediatric hospital who took the assessment tool, 28% of the patients can wear their clothes independently. In addition, 48% of the patients were able to walk, run and lift heavy things. Moreover, 50% were able to perform their duties in school, understand the subjects but got low marks. There were 42% of the children who had difficulty playing with toys that require effort, play with other children, and practice their hobbies. In terms of their appearance and hygiene, 32% of the patients found it difficult to shower, wear clothes and use the toilet. In terms of nutrition, 12% of patients experienced difficulty eating and drinking alone and washing their hands after every meal. Furthermore, 28% of the patients liked to isolate themselves and complained that they have few friends. Lastly, there are 18% of the patients having difficulty in sleeping **(Hatab, 2020).**

The results revealed ALL patients displayed significant impairments in motor ability across multiple facets of motor functioning compared to age and sex-matched controls (11.69% vs 2.93%, p=0.031). Specifically, results of the study converge with prior findings revealing pediatric ALL patients treated with chemotherapy only experience gross-motor impairments following intensive treatment. It was evident that there was a significant difference between the motor functioning and physical well-being of children with cancer compared to those without cancer (p=0.023). The appearance (p=0.04), health (p=0.001), flexibility (0.040) and endurance (p=0.039) of the pediatric cancer patients were also noted to have significant effects on their functioning. **(Oswald et al, 2020)**

Overall, there was high quality evidence that there was significant impairment in the motor functioning and physical well-being of children with cancer. Giving appropriate-aged activities will help improve their motor functioning and prevent it from immobilization.

Evidence to Recommendation for Oral Care

Acute Lymphoblastic Leukemia and its treatment can directly or indirectly affect oral health . The oral complications include mucositis, opportunistic infections, gingival inflammation and bleeding, xerostomia and carious lesions. Mucositis is a common and devastating side effect of chemotherapeutic agents in children undergoing chemotherapy. The prevention and management of mucositis are necessary to improve quality of life. We searched through PubMed and Google Scholar using the search terms “children” AND “Acute Lymphoblastic Leukemia” AND “oral care”.

We reviewed a total of 4 studies with moderate to low quality evidence. There were 3 randomized controlled trials and 1 observational study. Our review showed that the use 0.12% chlorhexidine gluconate and oral hygiene care can reduce the occurrence of oral complications (p = 0.007) odds ratio of 11.3 (CI: 1.86—69.11) in children with ALL undergoing antineoplastic chemotherapy (**Pinto,2006**). The use of an oral care protocol intervention may reduce the incidence of mucositis by 38%, severity of oral mucositis (P=0.000002) and related pain (P=0.0001) in pediatric cancer patients following chemotherapy (**Cheng, 2001**). However, there was moderate evidence to support the use of chlorhexidine had a significant decrease in the concentrations of micro-organism in the oral cavity during leukopenia yet there are more clinical problems associated with chlorhexidine-based product such as severe mucositis and increased CRP (**Pitten,2003).** Oral care at home is linked with the incidence and severity of mucositis (P=0.039). **(Devi,2019)**

Overall, there is moderate evidence on the importance of oral care during chemotherapy treatment. There is substantial evidence in addressing the oral care protocols used in various institutions to reduce chemotherapy-induced oral mucositis such as use of chlorhexidine-based product. However, the number of well-controlled and prospective experimental studies designed to test the effectiveness of particular oral care protocols in pediatric patients is limited. In addition, methodological difficulties which include small and heterogenous population may lead to difficulty in conducting research in children.

Evidence to Recommendation for Early Palliative Care

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care for children is the active total care of the child’s body, mind and spirit, and also involves giving support to the family. It begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease. Health providers must evaluate and alleviate a child’s physical, psychological, and social distress. Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited. Palliative care can be provided in tertiary care facilities, in community health centers and even in children’s homes. We searched through Pubmed and Google Scholar using the terms “palliative care” AND “pediatric” AND “acute lymphoblastic leukemia”. We reviewed a total of 5 studies, all were observational studies with moderate to high quality evidence.

Our review showed that the most common pediatric palliative care rendered were psychosocial support and management of physical symptoms at 52.62% and 31.3%, respectively. **(Doherty et al, 2020)** Pain (73.2%) and non-pain symptom (58.5%) such as loss of appetite, fatigue, skin problems or wound, dyspnea, fever, nausea and vomiting, abdominal distention, and somnolence are the common physical symptoms noted. Integration of Pediatric Palliative Care (PPC) is associated with fewer diagnostic/monitoring procedures among children in the end-of-life during the last 48 hours (OR: 0.16, 95% CI; 0.04-0.61) such as blood draws (57.1%), x-rays (50%), CT-scans/MRI (17.9%), surgeries, IV placement and EKG at 7.1%. **(Osenga et al, 2016)**. Among those who received PPC, the most common place of death were hospice ward (36.4%), local hospital (22.7%), oncology ward (5.7%) and emergency room (3.4%) **(Zhang et al, 2021)**. Perceived optimal timing of palliative care involvement were at the beginning of cancer therapy for patients and parents (59.8% and 50.4% respectively), if pain or symptom management was a problem (49.6% and 34.1% respectively), if the cancer got worse or came back (49.6% and 31.8% respectively) and throughout all of a child's cancer care (32.3% and 40.6% respectively). **(Levine et al, 2017)**

Overall, there is a high quality of evidence to show that referral to pediatric palliative care among newly diagnosed pediatric acute lymphoblastic leukemia would be beneficial to patients and their families. Indication includes pain and non-pain symptoms and psychosocial concerns. Furthermore, this recommendation is critical in the provision of early palliative care.

Evidence to Recommendation for Pain Management

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. A person's report of an experience as pain should be respected. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being. Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain. We searched through Pubmed and Google Scholar using the search terms "acute lymphoblastic leukemia" AND "children or pediatric" AND "pain management" and "cross sectional". We reviewed a total of 5 studies, 4 are observational studies and 1 blinded placebo-controlled trial with moderate to high quality of evidence.

Our review showed that the type of pain among pediatric leukemic patients are nociceptive pain (94.9%) and neuropathic pain (5.1%). About 53.8% were managed with WHO step-2 analgesia, followed by step-1 analgesia at 30.8% and 15.4% by step-3 analgesia. **(Geeta et al,2010)** Disease-related pain is common among patients requiring upgradation of WHO step ladder (63%) and those who do not require upgradation of WHO step ladder (59.3%) followed by treatment- related pain of 37% and 40.7% for those requiring upgradation of WHO step ladder and those who do not require, respectively. Furthermore, the most common reason for treatment-related pain were mucositis, procedure-related pain and others. **(Biji et al, 2019).**

WHO Three-Step Analgesic Ladder:

Step 1: Mild Pain (Non-opioid Analgesics)
- Aspirin
- Paracetamol
- NSAIDs
- ±Adjuvants

Step 2: Moderate Pain (Weak opioid Analgesics)
- Tramadol
- Codeine
- ±Non-opioids
- ±Adjuvants

Step 3: Severe Pain (Strong opioid Analgesics)
- Morphine
- Oxycodone
- Fentanyl
- Methadone
- ±Non-opioids
- ±Adjuvants

The 2012 WHO guidelines recently recommended the 2 – step strategy in managing pediatric cancer pain. Paracetamol and ibuprofen are the medicines of choice in the first step (mild pain). Morphine is the medicine of choice for the second step (moderate to severe pain,although other strong opioids should be considered and made available to ensure an alternative to morphine in case of intolerable side-effects. There is a need to update the guidelines once evidence is available using the 2-step approach.

Gabapentin (65.4%) and opioid (34.6%) provided relief for vincristine-related neuropathic pain during treatment for childhood acute lymphoblastic leukemia. **(Anghelescu et al, 2011)** Breakthrough pain is common in children with cancer who have persistent pain. Fifty (50%) percent of patients with acute lymphoblastic leukemia did not develop breakthrough pain however 37.5% reported breakthrough pain. **(Friedrichsdorf et al, 2007)**

Ketamine is a dissociative anesthetic agent, with excellent analgesic properties and a favorable safety profile. Parenteral ketamine (intravenous/ intramuscular) is often used for sedation during outpatient as well as inpatient procedures, including lumbar puncture, bone marrow aspiration, and biopsies, with good efficacy and tolerable adverse effects such as hypersalivation and tachycardia. Low-dose oral ketamine can be safely administered for procedural analgesia in pediatric cancer patients undergoing lumbar puncture. Administration of ketamine hydrochloride together with topical analgesia (EMLA) gave a lower pain score by the patient vs topical analgesia alone (2.0% vs 4.0%, p=0.046) **(Rayala et al, 2019)**.

Overall, there is moderate to high quality evidence that showed WHO step-ladder pain management is effective in the control of pain among pediatric ALL patients. Furthermore, low-dose oral

ketamine can be safely administered for procedural analgesia in pediatric cancer patients undergoing lumbar puncture in a resource limited hospital setting. This recommendation is critical in the delivery of pediatric pain management particularly among resource-limited settings.

7.9 HEALTH SYSTEM SUPPORT

Recommendation 33 - We recommend provision of health systems support interventions such as twinning programs, adoption of treatment protocols, financial support for patient and family needs, health insurance, access to medicines and creation of dedicated pediatric oncology units to improve survival outcomes in children with ALL. (Low Quality Evidence, Strong recommendation)

Evidence to Recommendation for Health System Support

Survival in childhood leukemia was pegged at 80% in high income countries compared to 5-60% in low-income countries and this is in part attributed to variation in health system capacity. *(Denburg, 2017)* A study that compared survival for childhood leukemia among children in the Philippines compared with Asian Americans and Caucasians in the United States showed survival rates of 32.9%, 80.1% and 89.1% respectively. **(Redaniel, 2010)** Again this disparity was largely attributed to health care system differences. Suggestions on collaboration of programs in developing and developed countries and more government spending on health to address these disparities have been put forward to improve childhood cancer survival. **(Pui & Ribeiro, 2003; Howard, 2004)**

We searched PubMed until 5 October 2021 using the search terms: "twinning program AND childhood leukemia AND improving survival" which yielded 5 results and enabled us to retrieve 1 relevant article. An article from our partner St. Jude Hospital on a multi-pronged health systems collaborative approach to improving childhood cancer care was also retrieved and included in this review. We also conducted another search "insurance AND childhood leukemia AND outcomes" with filter 0-18 years old and yielded 18 results, 3 of which were found relevant and included in this review. An article from our partner St. Jude Hospital on a multi-pronged health systems approach to improving childhood cancer care was also retrieved and included in this review. All in all, a total of 5 articles were included in this evidence review. The evidence base for these interventions however were all observational hence deemed to be of very low to low quality.

Collaborative partnerships between more advanced cancer programs with starting programs have been undertaken to improve childhood cancer care. A telemedicine twinning referral between a hospital in Recife, Brazil with the St Jude Children's Hospital was done with a weekly conference on the management of pediatric patients with ALL. This before and after study showed improvements in over-all survival of children with low-risk ALL (77% vs. 100%) and over-all survival of children with high risk ALL (58% vs. 78%). **(Pedrosa, 2017)** A multi-pronged health systems partnership providing patient and family support, dedicated pediatric oncology unit, uniform treatment protocols and support for medicines was shown to improve event-free 5 year survival rate in a pediatric hospital in Reclife Brazil with a comparative 5 year EFS of 32% before program was started to 47% in the beginning

implementation of the program and 63% in the recent full implementation of the program. **(Howard et al, 2004)**

Cost of care remain as a detriment to seeking diagnosis and treatment for childhood acute lymphoblastic leukemia in low-income settings. In Northeast Mexico, costs per motive of admission for childhood ALL and whether reasons for admission impacted hospital stay was analyzed. USD 239 was the mean cost per day for non-ICU stay but this increased to USD 1016 when patients stayed in pediatric ICUs. The top 3 highest cost per day based on reasons for admission were due to altered neurologic status, tumor lysis syndrome and electrolyte imbalance at USD 549, 388, 364 respectively. Of note as well was the lowest cost per day at USD 160 for chemotherapy and in the multivariate odds it had an OR of 0.316 (95% CI 0.186–0.536) which shows admissions with chemotherapy as a lesson reduced length of stay. This provides indirect evidence that investing on chemotherapy support is worthwhile.

Worldwide, insurance coverage for healthcare has been practiced to decrease the impact of catastrophic illness. A US study looking into insurance coverage and risk of death for 15 years and older with variety of cancers showed among others that for the 15-19 age groups having no insurance or public insurance compared with having private insurance increased risk of dying for ALL (no values reported but RR point estimate and CI is greater than 1), Hodgkin's lymphoma (RR 2.17 (95% CI1.06-4.17)) and Non-Hodgkin's Lymphoma (RR 2.36 (95% CI 1.26-4.41)) among others. For ALL it was also shown that increasing age showed increasing risk for poor outcomes among those without or with public insurance compared to those with private insurance. **(Colton, 2019)** In another cohort study in Mexico, involving 297 children with ALL from the period of 2007-2009, it was shown that children with <50% insurance coverage had more than 2x increase in hazard's ration for dying (>25% HR =2.4 (95%CI 1.35-4.42) and 25-<50% HR=2.2 (95%CI 1.18-4.28).

In summary, based on low quality evidence twinning programs between starting and more advanced pediatric cancer facilities, enrolment of patients to insurance programs and multi-pronged health systems approaches including establishment of pediatric oncology units, provision of patient and family support, adaption of uniform treatment protocols and financial assistance to medication could help improve survival outcomes for children with acute lymphoblastic leukemia. **(Pedrosa et al, 2017)** Research on health systems intervention utilizing clinical trial methodologies will help improve the evidence base for future recommendations.

8 DISCUSSION, DISSEMINATION AND IMPLEMENTATION

8.1 SUMMARY OF IMPLICATIONS OF THE GUIDELINE RECOMMENDATIONS

Guidelines include recommendations intended to optimize patient care that when used appropriately, make healthcare consistent and efficient. These guidelines need to be evidence-based, economically feasible and culturally acceptable to the country in the region of implementation to accomplish this task in lower-middle income countries. Local guidelines are more likely to be implemented because they are applicable to the specific environment and consider factors such as availability of resources, specialized skills and local culture. If guidelines are to be implemented, developers need to involve local stakeholders to improve the rates of implementation by identifying and removing barriers to its accomplishment in lower middle-income countries (LMIC). Local guidelines may recommend strategies aimed at achieving the best practicable standard of care.

8.2 RESOURCE IMPLICATIONS

Guidelines have been defined as "statements that include recommendations intended to optimize patient care". They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. They summarize and evaluate all available evidence at a point in time on a particular issue aiming to assist healthcare workers in selecting the best strategies for patient management. **(Graham, et al, 2011)**

Guidelines can positively change practice and patient outcome. They promote beneficial interventions while discouraging those that are ineffective or possibly dangerous. However, clinical practice guidelines do not in themselves authorize or outlaw treatment options. **(Grimshaw et al,2004; Pantin et al,2006; Bateman and Saha,2007)** When used appropriately, guidelines make healthcare more consistent and efficient. **(Woolf et al,1999, Pantin et al,2006)** There is evidence in literature to suggest that successful implementation of guidelines reduces mortality and morbidity. **(Olayemi et al, 2017)** It has also become more prevalent for guidelines to influence government spending on health. **(Durieux et al,2000)** Low Gross National Income, scarcity of doctors and poor healthcare infrastructure result in absence or unequal distribution of basic healthcare services in lower-middle income countries. **(Olayemi et al, 2017)**

In this particular setting, there is often a paucity of appropriately designed guidelines to assist healthcare workers in their care of cancer patients. In the absence of local guidelines, doctors and allied healthcare workers are faced with the dilemma of identifying a source of guideline that are relevant and applicable to their specific clinical setting. **(Grimmer et al, 2014)** While the use of guidelines produced by international organization and professional bodies may be helpful, there is evidence to support the fact that local guidelines are more likely to be implemented than those developed elsewhere. **(Bateman & Saha, 2007)**

In the Philippines, implementing the recommendations in this guideline may be adequate in some hospitals or setting. In some additional resources are needed which include health expertise, facilities and an adequate social environment. A pediatric oncologist and health workers trained in palliative care, social and behavioral support may be needed. Diagnostic and treatment capacity usually available in need to be setup or the patients may need to be referred to where they are available. The health system recommendations especially on health financing may need to be addressed by social or private health insurance and responsible government agencies.

8.3 Process of Guideline Dissemination and Implementation

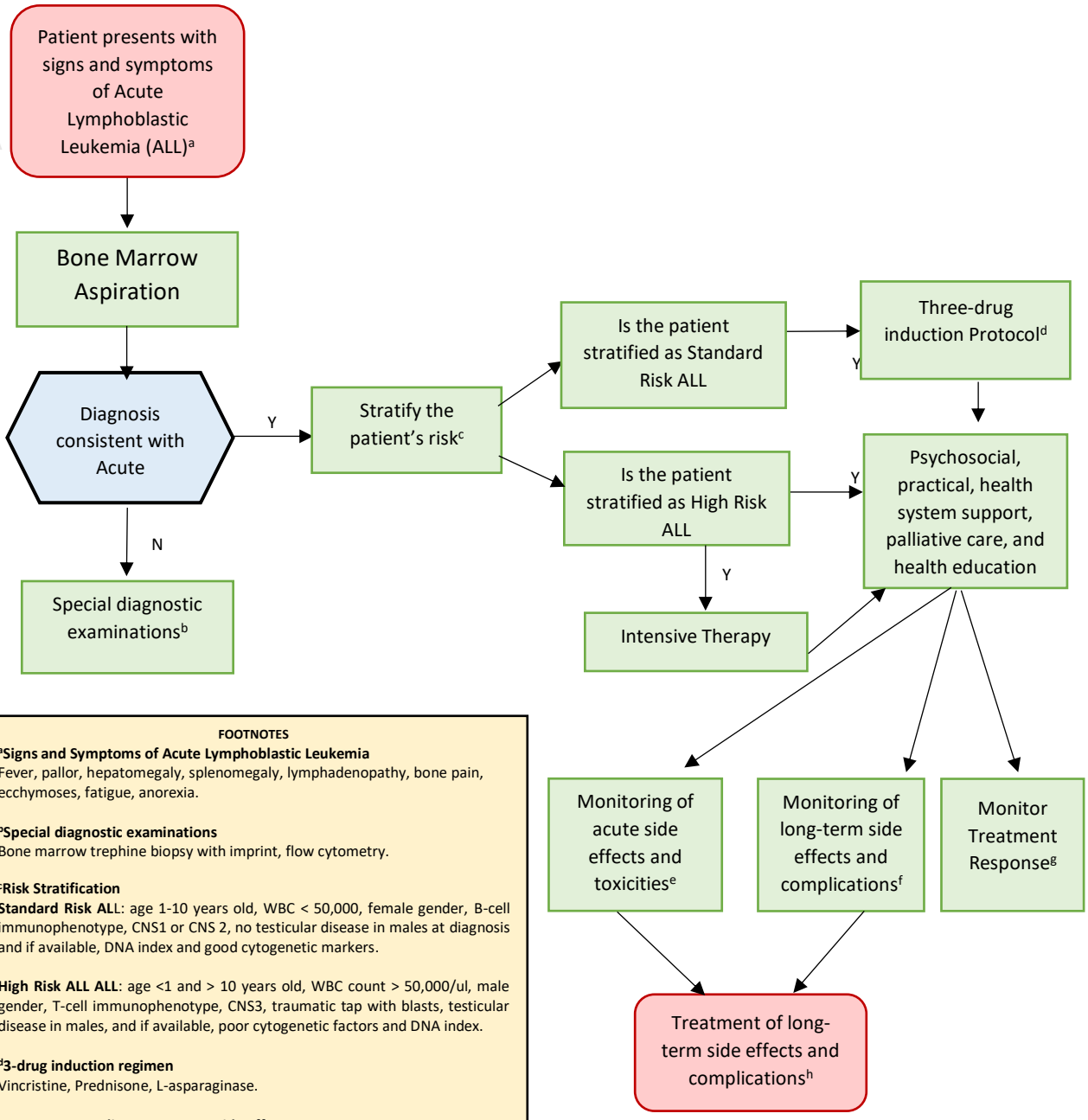
There is little or no documentation on the process for developing or updating guidelines in resource poor countries. **(Vernooij et al,2014)** To be reliable, guidelines must be relevant and reflect state-of-the-art medical practice. Other factors to be considered in guideline development include acceptability and the financial implications of implementation of a new clinical practice guideline. **(Davino-Ramaya et al, 2012)** The involvement of local stakeholders may improve the rates of implementation by identifying and removing barriers to their use, as there is a close association between stakeholder involvement, applicability and guideline implementation. **(Olayemi et al,2017)** Guidelines developed in collaboration with local experts should include suggestions on how they can be adapted for use in local situations.

Adaptation of existing guidelines to local environments may be a more cost-effective means of proving high quality guidelines. **(Fervers et al,2006)** However, this alternative requires careful planning to avoid additional costs to end-users. **(Harrison et al, 2013)** If a guideline requires a resource not widely available in lower-middle income countries, alternatives will be required. For guidelines to be successfully implemented, they must be applicable to the specific environment, based on factors such as availability and cost of required resources, specialized skills, population needs and values. **(Olayemi et al,2017)**

Effectiveness of CPG dissemination and/or implementation strategies among health care professionals (HCPs) in a cancer care context include group educational strategies, feedback on guideline compliance and providing reminders which were the most utilized strategies that correspond to positive significant changes in HCPs behavior and patient outcomes. **(Tomasone et al,2020)** Since this is specific to the local context, the TWG leave it to the health care providers and their health facility the method of adaptation and the tools they might need for implementation. The DOH can also use this guideline and develop standards of care for the management of children with ALL. Such standards can be used as monitoring or audit criteria by health facilities caring for children with ALL.

Below are our recommended algorithm and clinical audit checklist as tools for implementation. The algorithm is a simplified flow of the process of care that can be used to explain to the patient the process of management. The audit checklist can be used to assess the quality of care to every patient seen in the clinic. The checklist can be used by conducting a records review for every patient diagnosed and managed for Burkitt's Lymphoma. These tools are designed for SPMC as this is adapted to our process and setting. Other institution may have to modify these tools and make it relevant to their setting.

8.4 ALGORITHM



FOOTNOTES

[a]Signs and Symptoms of Acute Lymphoblastic Leukemia
Fever, pallor, hepatomegaly, splenomegaly, lymphadenopathy, bone pain, ecchymoses, fatigue, anorexia.

[b]Special diagnostic examinations
Bone marrow trephine biopsy with imprint, flow cytometry.

[c]Risk Stratification
Standard Risk ALL: age 1-10 years old, WBC < 50,000, female gender, B-cell immunophenotype, CNS1 or CNS 2, no testicular disease in males at diagnosis and if available, DNA index and good cytogenetic markers.

High Risk ALL ALL: age <1 and > 10 years old, WBC count > 50,000/ul, male gender, T-cell immunophenotype, CNS3, traumatic tap with blasts, testicular disease in males, and if available, poor cytogenetic factors and DNA index.

[d]3-drug induction regimen
Vincristine, Prednisone, L-asparaginase.

[e]Acute or Immediate Treatment Side Effects:
Febrile neutropoenia, sepsis, gastrointestinal symptoms, bleeding, hypersensitivity, anaphylaxis, pancreatitis, thrombosis.

[f]Long Term Treatment Side Effects:
Neuromuscular impairment, limitation of physical performance, diabetes mellitus, cardiotoxicity, secondary cancers, avascular necrosis/osteonecrosis, gonadal dysfunction/infertility, metabolic syndrome.

[g]Monitoring of Treatment Response:
MRD monitoring by PCR on Days 33 and 78, if MRD not available, then WBC and peripheral blast count after 1 week of steroid prephase and bone marrow blast count and platelet count at Day 28 of induction chemotherapy.

[h]Treatment of Long Term Side Effects and Complications:
Antibiotics, Granulocyte Colony Stimulating Factor (GCSF).

8.5 CLINICAL AUDIT CHECKLIST

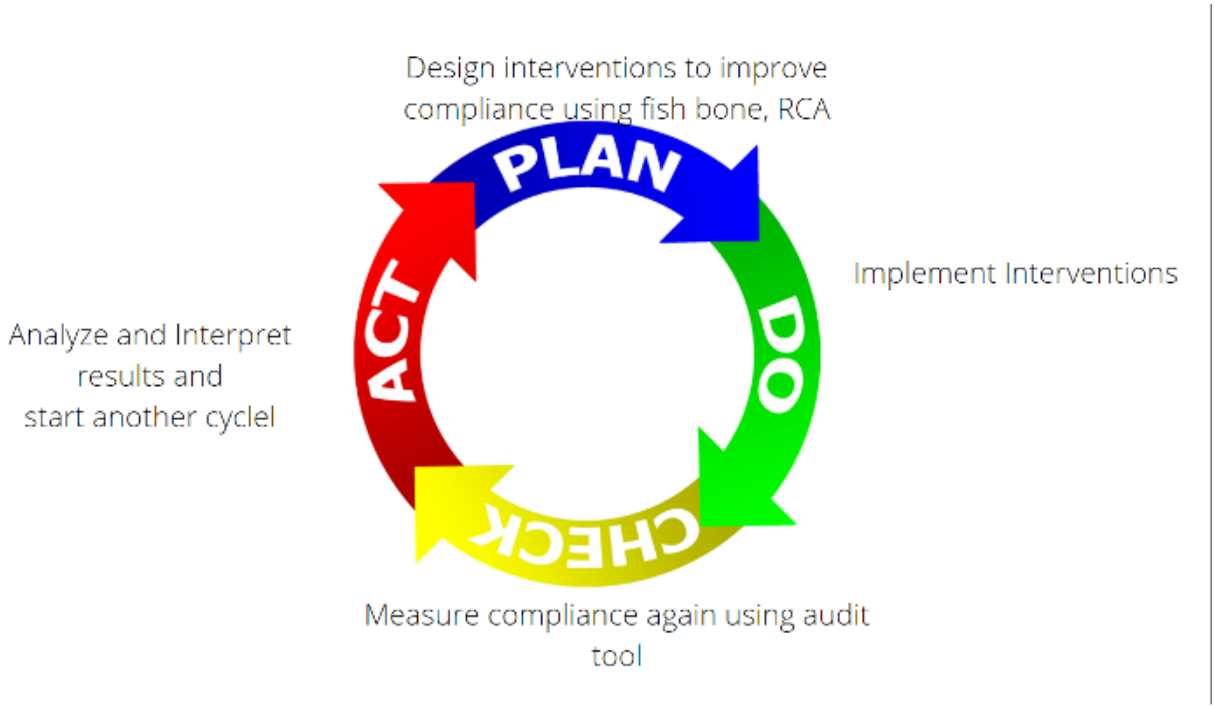
Instructions on Using the Chart Audit Tool

This tool is meant to measure physician's compliance to the standard of care process measures based on the Clinical Practice Guideline for the Diagnosis and Management of Acute Lymphoblastic Leukemia (ALL) developed in part by the SPMC-CCI ALL Guideline Development Group with funding support from the Department of Health.

This tool will be used to evaluate charts of children <19 years of age newly diagnosed with Acute Lymphoblastic Leukemia on initial admission and start of treatment. Before you begin, collect at least 30 charts for audit. After which, the audit group should agree on what minimum compliance rate you should meet for this cycle to establish that quality care for children with ALL is being done.

Please check the chart for presence of each of the criteria. This means that the criteria should explicitly be documented in the chart you are reviewing. If it is present, mark yes and if absent mark no. At the end, the total compliance score will be the number of items marked yes over the items of numbers marked no. Check the total compliance score per chart to the target score you set at the beginning. If compliance meets or exceeds target score, reinforce the ways to maintain it, if not you can start a quality improvement cycle following Figure 1 below.

Figure 1. Quality Improvement Cycle



General Data

Hospital Record Number	
Patient Initials	
Age/Sex	
Initial Impression	
Attending Physician	

Audit Tool for Initial Admission and Induction of Treatment for Children newly diagnosed with ALL

Criteria	Yes	No	What yes means
1. History elicited common signs and symptoms (Recom 3)			3 or more of the following has been elicited: fever, pallor, hepatomegaly, splenomegaly and lymphadenopathy, bone pain, ecchymoses, fatigue and anorexia.
2. Diagnosis of ALL with appropriate risk stratification was made (Recom 7-9)			-appropriately classified as Standard or High Risk based on the prognostic factors
3. BMA was ordered and performed. (Recom 4)			-BMA was ordered and performed
4. When available bone marrow flow cytometry was ordered and performed (Recom 6)			-Bone marrow flow cytometry ordered and performed
5. Recommended treatment protocol based on risk was used (Recom 11-14)			Standard Risk ALL: 3 drug induction protocol without an intensive consolidation but added delayed intensification. - Delayed first intrathecal treatment for CNS prophylaxis High Risk ALL: intensive therapy with intensive consolidation and delayed intensification during continuation phases. - Intrathecal treatment with cranial irradiation for CNS3 or overt CNS involvement.

6. Monitoring of immediate treatment effect is documented. (Recom 15-17, Recom 21)			All of the following should be present: 1) Immediate and Long Term Treatment Side Effects. 2) MRD monitoring by PCR on Days 33 and 78. If MRD not available, then WBC and peripheral blast count after 1 week of steroid prephase and bone marrow blast count and platelet count at Day 28 of induction chemotherapy.
7. Antibiotic prophylaxis given for children undergoing chemotherapy (Recom 23, 25)			-antibiotic prophylaxis ordered and administered in a timely manner
8. Management of Side effects of treatment was done and was appropriate. (Recom 22,24)			Febrile neutropenia – broad spectrum antibiotic with GCSF Appropriate sepsis work-up with CRP and blood culture
9. Health education to support treatment given (Recom 19)			Health education centering on adherence to treatment and follow up, explanation of treatment and side effects documented
10. Appropriate supportive and palliative care measures were instituted (Recom 26-31)			Does any or a combination of the following when appropriate: 1)ADL assessment 2)proper oral care advise 3) WHO analgesic ladder for pain 4) referral to palliative care
11. Offered health system support resources when needed (Recom 33)			Referral for financial support, support for medications and support groups done when needed

Total Compliance Score: (number of yes)/11 * 100% = ____/_____ * 100% = _____

8.6 Facilitators and Barriers to Guideline Dissemination and Implementation

There are several barriers to guideline implementation in LMIC. **(Puchalski et al, 2016)** There are reports that there is generally a slow uptake of guidelines in LMIC, which may result from lack of mutual understanding between guideline content developers and policymakers. **(Fretheim et al, 2006)** The inability to implement guidelines remains a challenge to the development of health systems in many LMIC. **(Panisset et al, 2012)** Poorly developed infrastructure along with other resource constraints limit uptake of guidelines that ultimately lead to impairment of clinical practice. This lack of material and human resources in LMICs has been well documented and is a key barrier to guideline implementation. **(Puchalski et al, 2016)** There needs to be improvement in the quality of facilities for adequate diagnosis and treatment before most guidelines can be implemented. In some countries, policymakers have come to understand that developing good relationships with guideline researchers reduced mutual mistrust and was an important way to facilitate knowledge transfer. **(Innvaer et al, 2002)** Patients have to travel long distances to access health care due to lack of healthcare facilities in LMIs. As a result, patients who lack the financial capability to pay for transportation and/or accommodation will not be able to benefit from any guideline that is implemented as part of routine medical practice. This is one of the reasons for abandonment of treatment in patients being managed for hematological malignancies. **(Slone et al, 2014)**

9 FUNDING

The development of this guideline was funded by the Department of Health. No funding was received from the pharmaceutical industry or other companies involved in manufacture, sales and distribution of products that were recommended in this guideline. The guideline development team and consensus panel declared no potential conflict of interest.

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11 APPENDICES

11.1 TECHNICAL WORKING GROUP

Name	Expertise	Role in Guideline Development	Conflict of Interest
Dr. Grace Ann Quitain-Pecson	Pediatric Hematologist/ Diagnosis, Screening, Treatment, Management of Complications, End of Life Care, Psychosocial Support and Care for Children with Malignant Hematologic Disease	Project Team Leader for ALL TWG	None
Dr. Maria Elinore A. Concha	Family and Community Medicine/ Prevention and Psychosocial Support, CPG Development	Assistant Project Team Leader for ALL TWG	None
Dr. Fernando Douglas A. Go	Pediatric Hematologist/ Diagnosis, Treatment, Management of Complications, End of Life Care, Psychosocial Support for Cancer patient and family members	Member for ALL TWG	None
Dr. Ma. Delta San Antonio-Aguilar	Pediatric Infectious and Tropical Diseases Specialist, Diagnosis, Treatment, Management of Infections in Children with Cancer	Member for ALL TWG	None
Dr. John Patrick Calanog Padilla	Anatomic and Clinical Pathologist/ Diagnosis, Morphology Reviews, Confirmatory Testing	Member for ALL TWG	None
Dr. Shella Akil-Bravo	Palliative and Hospice Care specifically ensuring Quality of Life for Pediatric Oncology patients, Pain management, End of life care, Psychosocial Support for cancer patient and family members	Member for ALL TWG	None
Dr. Jenny Pearl Carrasco-Librero	Pediatric Oncology Fellow-in-training, Diagnosis and treatment of Pediatric Oncology patients under the guidance of Hematology and Oncology Consultants, End of life care, Psychosocial Support for Cancer patient and family members	Member for ALL TWG	None

Dr. Hannah Grace B. Segocio	Pediatric Oncology Fellow-in-training, Diagnosis and treatment of Pediatric Oncology patients under the guidance of Hematology and Oncology Consultants, End of life care, Psychosocial Support for Cancer patient and family members	Member for ALL TWG	None
Carla Joy C. Costillas, RN	Pediatric Oncology Nursing/Infection Prevention	Member for ALL TWG	None
Katherene Guino-o, RN	Pediatric Oncology Nursing specializing in High Dependency Unit patients	Member for ALL TWG	None
Joy Mariz F. Dumayas, RN	Pediatric Oncology Nursing specializing in Outpatient Care	Member for ALL TWG	None
Kristine L. Jao, RPh	Pediatric Oncology Clinical Pharmacist specializing in chemotherapeutics drugs and other medications given to pediatric oncology patients	Member for ALL TWG	None
Janeva I. Ciudadano	Child Life Coordinator	Member for ALL TWG	None
Erika B. Cabel	Pediatric Oncology Social worker	Member for ALL TWG	None
Airene Joy Peralta	Pediatric Oncology DATA Manager	Member for ALL TWG	None
Dr. Seurinane Sean Española	Family and Community Medicine	Technical Writer for ALL TWG	None

11.2 CONSENSUS PANEL

Name	Expertise	Role in Guideline Development	Conflict of Interest
Crispin D.L. Dalisay Jr., MD	Pediatric Hematologist-Oncologist/ Diagnosis, Screening, Treatment, Management of Complications, End of Life Care, Psychosocial Support and Care for Children with Malignant and Benign Hematologic Diseases	Member, Consensus Panel	None
Aura Rhea D. Lanaban, MD	Palliative and Hospice Care specifically ensuring Quality of Life for Pediatric Oncology patients, Pain management, End of life care, Psychosocial Support for cancer patient and family members	Member, Consensus Panel	None
Jetty Jet R. Lu, MD	Practicing pediatrician and Pediatrics chief of a private general hospital	Member, Consensus Panel	None
Jo-anne Jajurie- Lobo, MD	Pediatric Infectious Disease and Tropical Medicine specialist and Pediatrics chief of a government/public hospital.	Member, Consensus Panel	None
Shiena P. Procullos	Child life coordinator of Kythe Foundation that focuses on quality of life among hospitalized children with cancer and other chronic illnesses	Member, Consensus Panel	None

11.3 CONSULTATION WITH STAKEHOLDERS

Prior to developing the scope and clinical questions for guideline recommendations, the TWG conducted a mini survey among patients and parents with ALL. The key questions were relevant issues they felt needed for the care of their children with ALL. The results are summarized in the graphs below.

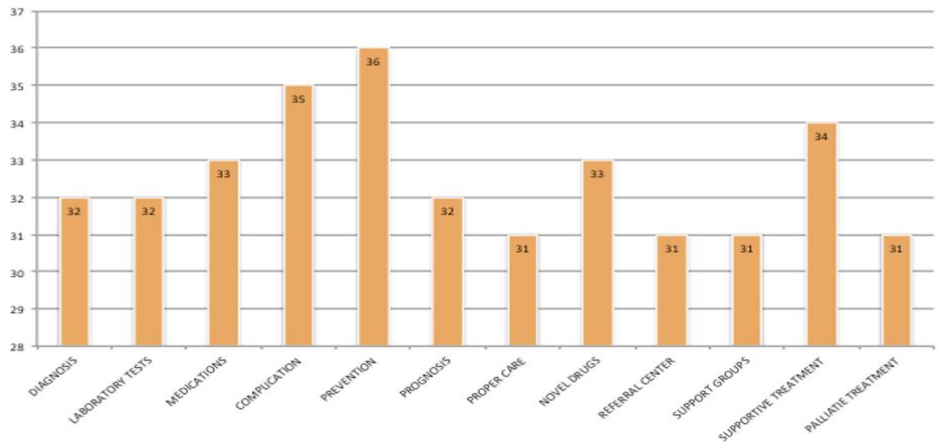

Figure 1. Knowledge about ALL in children and adolescents less than 19 years old

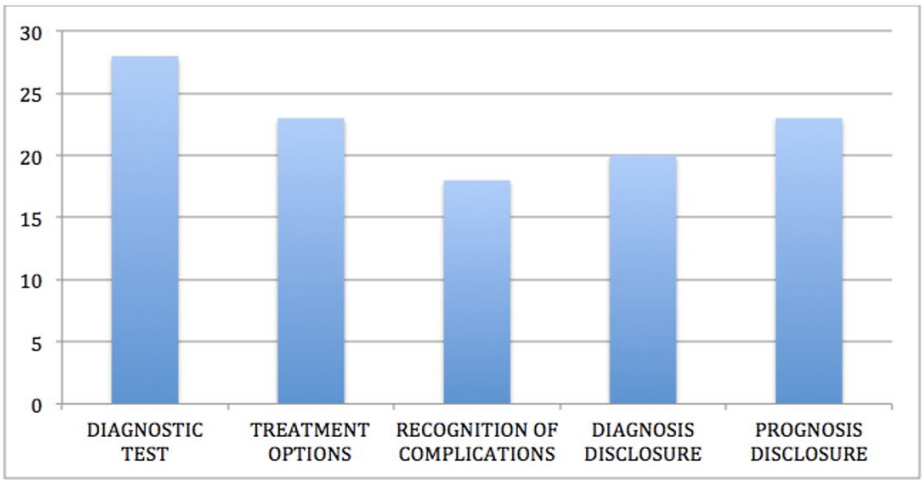

Figure 2. Room for Improvement in the care of children and adolescents less than 19 years old newly diagnosed with ALL

11.4 EVIDENCE TABLES

Screening and Prevention

Kwan Study

Author(s): ALL SCREENING GROUP
Date: 2021-07-06
Question: Should BREASTFEEDING be used for PREVENTION OF CHILDHOOD ALL?
Settings:
Bibliography: Kwan ML, Buffler PA, Abrams B, Kiley VA. Breastfeeding and the risk of childhood leukemia: a meta-analysis. Public Health Rep. 2004 Nov-Dec;119(6):521-35. doi: 10.1016/j.phr.2004.09.002. PMID: 15504444; PMCID: PMC1497668.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BREASTFEEDING	Control	Relative (95% CI)	Absolute		
SHORT TERM BREASTFEEDING (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
14	observational studies[1]	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	OR 0.88 (0.8 to 0.96)	-	⊕⊕OO LOW	IMPORTANT
LONG TERM BREASTFEEDING (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
14	observational studies[1]	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	dose response gradient[3]	6470 cases 0 controls	0%	OR 0.75 (0.67 to 0.85)[4]	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] case-control
[2] some studies showed effects crossing 1
[3] longer duration better response
[4] SES adjusted, total of 6470
[5] >20
[6] difference of 40% between intervention and control

Martin Study

Author(s): ALL SCREENING GROUP
Date: 2021-07-06
Question: Should BREASTFEEDING be used for prevention of childhood ALL?
Settings:
Bibliography: Martin RM, Gunnell D, Owen CG, Smith GD. Breast-feeding and childhood cancer: A systematic review with metaanalysis. Int J Cancer. 2005 Dec 20;117(6):1020-31. doi: 10.1002/ijc.21274. PMID: 15986434.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BREASTFEEDING	Control	Relative (95% CI)	Absolute		
<6 MONTHS DURATION OF BREASTFEEDING (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
12	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	-	0%	OR 0.93 (0.86 to 1)	-	⊕⊕⊕O MODERATE	IMPORTANT
>6 MONTHS DURATION OF BREASTFEEDING (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
13	observational studies[1]	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	-	0%	OR 0.81 (0.72 to 0.91)	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] case-control
[2] >6months more protective

Amitay Study

Author(s): ALL SCREENING GROUP
Date: 2021-07-06
Question: Should BREASTFEEDING be used for PREVENTION OF ALL?
Settings:
Bibliography: Amitay, Efrat L., and Lital Keinan-Boker. "Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review." JAMA pediatrics 169.6 (2015): e151025-e151025.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BREASTFEEDING	Control	Relative (95% CI)	Absolute		
RISK DEVELOPING CHILDHOOD ALL (timing of exposure mean 6 months; assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
17	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	OR 0.80 (0.72 to 0.9)	-	⊕⊕OO LOW	IMPORTANT
risk of developing childhood all (subgroup higher quality studies) (assessed with: odds ratio)												
8	observational studies[1]	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	6690 cases 13273 controls	0%	OR 0.86 (0.78 to 0.95)	-	⊕⊕⊕O MODERATE	IMPORTANT

[1] case-control
[2] 6 months or greater versus less than or never

Milne Study

Author(s): Fontanilla-Dumayas, RN and Alba-Concha, MD
Date: 2021-09-05
Question: Should paternal smoking be used for as risk factor for childhood all?
Settings:
Bibliography: Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, de Klerk NH, Armstrong BK. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol. 2012 Jan 1;175(1):43-53. doi: 10.1093/aje/kwr275. Epub 2011 Dec 5. PMID: 22143821.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paternal smoking	Control	Relative (95% CI)	Absolute		
eversmokingriskALL (assessed with: odds ratio)												
10	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	9323 cases	0 controls	OR 1.15 (1.06 to 1.24)	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
20cpdriskall												
7	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	2118 cases	0 controls	OR 1.44 (1.24 to 1.68)	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		

[1] case-control
[2] greater cig per day higher odds

Chunxia Study

Author(s): Fontanilla-Dumayas and Alba-Concha
Date: 2021-09-04
Question: Should paternal smoking be used for as risk factor for ALL?
Settings:
Bibliography: Chunxia D, Meifang W, Jianhua Z, Ruijuan Z, Xiue L, Zhuanzhen Z, Linhua Y. Tobacco smoke exposure and the risk of childhood acute lymphoblastic leukemia and acute myeloid leukemia: A meta-analysis. Medicine (Baltimore). 2019 Jul;98(28):e16454. doi: 10.1097/MD.0000000000016454. PMID: 31305478; PMCID: PMC6641792.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paternal smoking	Control	Relative (95% CI)	Absolute		
paternalsmokingriskallprecon (assessed with: odds ratio)												
8	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	-		OR 1.146 (1.009 to 1.302)	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
psallpreg												
8	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	-		OR 1.23 (0.989 to 1.530)	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
>20cigarsALL (assessed with: odds ratio)												
6	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	-		OR 1.3 (1.072 to 1.586)	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		

[1] case-control
[2] higher number of cigars per day greater risk

Cao Study

Author(s): Fontanilla-Dumayas and Alba-Concha
Date: 2021-09-04
Question: Should smoking be used in as risk factor for Childhood ALL?
Settings:
Bibliography: Cao Y, Lu J, Lu J. Paternal Smoking Before Conception and During Pregnancy Is Associated With an Increased Risk of Childhood Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis of 17 Case-Control Studies. J Pediatr Hematol Oncol. 2020 Jan;42(1):32-40. doi: 10.1097/MPH.0000000000001657. PMID: 31743318; PMCID: PMC6924935. Copy Download .nbib Format:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Smoking	Control	Relative (95% CI)	Absolute		
risk of ALL (preconceptionsmoking) (assessed with: odds ratio)												
8	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[1] dose response gradient[2]	5417 cases	11908 controls	OR 1.15 (1.04 to 1.27)	-	⊕⊕OO LOW	IMPORTANT
								0%		-		
risk of ALL during preg (assessed with: odds ratio)												
9	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[1] dose response gradient[2]	4313 cases	6267 controls	OR 1.20 (1.12 to 1.28)	-	⊕⊕OO LOW	IMPORTANT
								0%		-		

[1] note of publication bias
[2] longersmokingmoremarkedrisk

Mostert Study

Author(s):
Date: 2021-10-07
Question: Should parental education program be used for improving outcomes in childhood ALL?
Settings:
Bibliography: Mostert S, Sitaresmi MN, Gundy CM, Janes V, Sutaryo, Veerman AJ. Comparing childhood leukaemia treatment before and after the introduction of a parental education programme in Indonesia. Arch Dis Child. 2010 Jan;95(1):20-5. doi: 10.1136/adc.2008.154138. Epub 2009 Aug 12. PMID: 19679573.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parental education program	Control	Relative (95% CI)	Absolute		
efspoor (follow-up mean 2 years; assessed with: percentage event free survival)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/96 (29.2%)	16/120 (13.3%)	-	133 fewer per 1000 (from 133 fewer to 133 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
treatment refusal overall (follow-up mean 2 years; assessed with: treatment refusal over-all)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/119 (2.5%)	18/164 (11%)	-	110 fewer per 1000 (from 110 fewer to 110 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
treatment refusal poor (follow-up mean 2 years; assessed with: percentage who refused)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/96 (2.1%)	17/120 (14.2%)	-	142 fewer per 1000 (from 142 fewer to 142 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
treatmentrelateddeathoverall (follow-up mean 2 years; assessed with: percentage treatment related death)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/119 (36.1%)	38/164 (23.2%)	-	232 fewer per 1000 (from 232 fewer to 232 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
progressiveorrelapsedleukemiaoverall (follow-up mean 2 years; assessed with: percentage progressive or relapsed leukemia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/119 (6.7%)	30/164 (18.3%)	-	183 fewer per 1000 (from 183 fewer to 183 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
progressive or relapsed leukemia prosp (follow-up mean 2 years; assessed with: percentage progressive or relapsed leukemia among rich)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/23 (4.3%)	12/44 (27.3%)	-	273 fewer per 1000 (from 273 fewer to 273 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
treatment abandonment prosp (follow-up mean 2 years; assessed with: percentage treatment abandonment in prosperous group)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/23 (13%)	0/44 (0%)	-	-	⊕⊕OO LOW	CRITICAL

Sitaresmi Study

Author(s): ALL Screening and Prevention Team
Date: 2021-07-08
Question: Should addition of mediction diary book vs parental education and donated chemotherapy be used for improving outcomes in pediatric ALL?
Settings:
Bibliography: Sitaresmi MN, Mostert S, Gundy CM, Ismail D, Veerman AJ. A medication diary-book for pediatric patients with acute lymphoblastic leukemia in Indonesia. Pediatr Blood Cancer. 2013 Oct;60(10):1593-7. doi: 10.1002/pbc.24570. Epub 2013 Jun 3. PMID: 23733528.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Addition of medictio n diary book	Parental education and donated chemothera py	Relative (95% CI)	Absolute		
over-all 3 years event free survival (follow-up mean 3 years; assessed with: percentage who survived wtihout events)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/56 (41.1%)	11/53 (20.8%)	-	208 fewer per 1000 (from 208 fewer to 208 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
3 year EFS for educated mothers (follow-up mean 3; assessed with: percentage with event free survival)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/25 (60%)	7/25 (28%)	-	280 fewer per 1000 (from 280 fewer to 280 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
3 year EFS for noneducated (follow-up mean 3 years; assessed with: percentage with event free survival for non educated)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/31 (83.9%)	18/28 (64.3%)	-	643 fewer per 1000 (from 643 fewer to 643 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] small sample size, contamination and non use of the medication diary book

Di Giuseppe Study

Author(s):
Date: 2021-10-08
Question: Should education with DVD be used for reduced anxiety?
Settings:
Bibliography: Di Giuseppe, G., Pole, J. D., Abla, O., & Punnett, A. (2020). Impact of Videotaped Information on the Experience of Parents of Children with Acute Lymphoblastic Leukemia. Journal of cancer education : the official journal of the American Association for Cancer Education, 35(3), 479–484. https://doi.org/10.1007/s13187-019-1485-2

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education with DVD	Control	Relative (95% CI)	Absolute		
overall satisfaction (measured with: percentage satisfied; Better indicated by lower values)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	24	-	MD 100 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL
heightened anxiety (measured with: percentage with heightened anxiety; Better indicated by lower values)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24	24	-	MD 33.3 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL

[1] not all might have watched DVD same number of times, intervention might not be similar

Ghodsbin Study

Author(s):
Date: 2021-10-08
Question: Should educational intervention be used for childhood ALL improved outcomes?
Settings:
Bibliography: Ghodsbin F, Asadi N, Javanmardi Fard S, Kamali M. Effect of education on quality of life of family caregivers of children with leukemia referred to the Oncology Clinic at Kerman's Afzali-Poor Hospital (Iran), 2012. Invest Educ Enferm. 2014;32(1):41-8. doi: 10.17533/udea.iee.v32n1a05. PMID: 25229902.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Educational intervention	Control	Relative (95% CI)	Absolute		
differenceoverallQOL (follow-up mean 3 months; measured with: mean difference of overall qol; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 56.65 higher (26.95 to 86.35 higher)	⊕⊕⊕O MODERATE	IMPORTANT
difference in physical qol scores (follow-up mean 3 months; measured with: mean difference in physical qol scores; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 15.7 higher (14.8 to 21.6 higher)	⊕⊕⊕O MODERATE	IMPORTANT
difference in mental qol scores (Copy) (follow-up mean 3 months; measured with: mean difference in mental qol scores; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 49.9 higher (42.7 to 57.1 higher)	⊕⊕⊕O MODERATE	IMPORTANT
difference in social qol scores (Copy) (Copy) (follow-up mean 3 months; measured with: mean difference in social qol scores; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 31.3 higher (20.4 to 42.2 higher)	⊕⊕⊕O MODERATE	IMPORTANT
difference in spiritual qol scores (Copy) (Copy) (Copy) (follow-up mean 3 months; measured with: mean difference in spiritual qol scores; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 16.3 higher (5.8 to 26.8 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] convenience sampling

Assessment and Diagnosis

Clarke Study

Author(s): ALL group
Date: 2021-07-21
Question: Should hepatomegaly, splenomegaly, pallor and fever be used for diagnosing Pediatric|Acute Lymphoblastic Leukemia?
Settings: USA and UK
Bibliography: Clarke, R et al. 2016. Clinical presentation of childhood leukemia: a systematic review and meta-analysis. Archive of Disease in Childhood 101: 894-901.doi:10.1136/archdischild-2016-311251

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hepatomegaly, splenomegaly, pallor and fever	Control	Relative (95% CI)	Absolute		
hepatomegaly (follow-up 2 years)												
27	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1431/3084 (46.4%)	-	OR 64 (53 to 75)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
splenomegaly (follow-up 2 years)												
29	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1583/3084 (51.3%)	-	OR 61 (48 to 73)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
hepatosplenomegaly (follow-up 2 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/3084 (3.4%)	-	OR 42 (24 to 100)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
lymphadenopathy (follow-up 2 years)												
32	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1135/3084 (36.8%)	-	OR 41 (32 to 51)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
bruising (follow-up 2 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/3084 (1%)	-	OR 052 (37 to 66)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
petechiae (follow-up 2 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/3084 (2.8%)	-	OR 42 (36 to 49)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
bleeding tendency (follow-up 2 years)												
19	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	544/3084 (17.6%)	-	OR 38 (30 to 46)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
mucosal bleeding (follow-up 2 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/3084 (1.7%)	-	OR 26 (13 to 38)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
cutaneous bleeding (follow-up 2 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	171/3084 (5.5%)	-	OR 26 (14 to 38)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
purpura (follow-up 2 years)												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/3084 (5%)	-	OR 25 (14 to 37)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
epistaxis (follow-up 2 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/3084 (0.42%)	-	OR 10 (2 to 18)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
fever (follow-up 2 years)												
33	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1708/3084 (55.4%)	-	OR 53 (45 to 62)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
infections (follow-up 2 years)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/3084 (6%)	-	OR 49 (16 to 81)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
respiratory symptoms (follow-up 2 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/3084 (1.7%)	-	OR 22 (1 to 43)	-	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								0%		-		
URTI (follow-up 2 years)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/3084 (2.7%)	-	OR 20 (9 to 31)	-	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								0%		-		
sore throat (follow-up 2 years)												
20	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/3084 (1.4%)	-	OR 11 (3 to 25)	-	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								0%		-		
limb pain (follow-up 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	173/3084 (5.6%)	-	RR 43 (0 to 0)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
bone pain (follow-up 2 years)												
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	425/3084 (13.8%)	-	OR 26 (17 to 35)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
joint pain (follow-up 2 years)												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	258/3084 (8.4%)	-	OR 15 (5 to 25)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		

Louvigne Study

Author(s): ALL Group
Date: 2021-07-09
Question: Should Persistent Osteoarticular pain be used in early diagnosis of Pediatric and Adolescent ALL?
Settings: France
Bibliography: Louvigne, M et al. 2020. Persistent Osteoarticular pain in children: Early clinical and laboratory findings suggestive of acute lymphoblastic leukemia (a multicenter case control study of 147 patients). Pediatric Rheumatology 18:1; p1-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Persistent Osteoarticular pain	Control	Relative (95% CI)	Absolute		
joint pain (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	40/49 (81.6%)	98 / 98 (100%)	-	-	⊕⊕⊕O MODERATE	CRITICA
non articular pain (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	18/49 (36.7%)	98/98 (100%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
Diffuse initial presentation (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	42/49 (85.7%)	68/98 (69.4%)	-	69 fewer per 100 (from 69 fewer to 69 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Localized initial presentation (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/49 (14.3%)	30/98 (30.6%)	-	31 fewer per 100 (from 31 fewer to 31 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Fever (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	30/49 (61.2%)	12/98 (12.2%)	-	12 fewer per 100 (from 12 fewer to 12 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Asthenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	34/49 (69.4%)	7/98 (7.1%)	-	71 fewer per 1000 (from 71 fewer to 71 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Anorexia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12/49 (24.5%)	4/98 (4.1%)	-	4 fewer per 100 (from 4 fewer to 4 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
weight loss (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	10/49 (20.4%)	4/98 (4.1%)	-	4 fewer per 100 (from 4 fewer to 4 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
arthritis (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12/49 (24.5%)	80/98 (81.6%)	-	816 fewer per 1000 (from 816 fewer to 816 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
hepatomegaly (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	37/49 (75.5%)	2/98 (2%)	-	2 fewer per 100 (from 2 fewer to 2 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Splenomegaly (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	15/49 (30.6%)	1/98 (1%)	-	10 fewer per 1000 (from 10 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
lymphadenopathy (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	28/49 (57.1%)	1/98 (1%)	-	10 fewer per 1000 (from 10 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Anemia signs (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	25/49 (51%)	1/98 (1%)	-	1 fewer per 100 (from 1 fewer to 1 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	10/49 (20.4%)	0/98 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Jaime-Perez Study

Date: 2021-07-21
Question: Should Fever and organomegaly be used for diagnosing pediatric acute lymphoblastic leukemia?
Settings: Mexico
Bibliography: Jaime-Perez, J et.al. 2019. Revisiting the complete blood count and clinical findings at diagnosis of childhood acute lymphoblastic leukemia: 10-year experience at a single center. Hematology, Transfusion and Cell Therapy. 41(1):57-61

Quality assessment							No of patients	Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fever and organomegaly	Control	Relative (95% CI)	Absolute		
fatigue (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	126/203 (62.1%)	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
fever (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	122/203 (60.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
bone and joint pain (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	80/203 (39.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
hyporexia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	67/203 (33%)	-	-	-	⊕⊕⊕O MODERATE	NOT IMPORTANT
								0%		-		
weight loss (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	43/203 (21.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
hepatomegaly (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	159/203 (78.3%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
splenomegaly (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	128/203 (63.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
lymphadenopathy (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	116/203 (57.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
pallor (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	98/203 (48.3%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
purpura (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	61/203 (30%)	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
anemia + luekocytosis + thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	55/203 (27.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
anemia + leukopenia + thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	54/203 (26.6%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
anemia + thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	35/203 (17.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
anemia + leukopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	11/203 (5.4%)	203/0 (0%)	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
leukocytosis + thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	11/203 (5.4%)	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
anemia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	9/203 (4.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	8/203 (3.9%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
leukopenia + thrombocytopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/203 (3.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
anemia + leukocytosis (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/203 (3%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
leukocytosis (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/203 (1.5%)	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
leukopenia (follow-up 10 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/203 (0.99%)	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		

Zahid Study

Author(s): ALL group
Date: 2021-07-20
Question: Should fever, bone pain and lymphadenopathy be used for diagnosing acute lymphoblastic leukemia?
Settings: Pakistan
Bibliography: ZahidM et al. 1996. Acute Leukemias of Childhood: A Retrospective Analysis of 62 Cases. JPMA 46: 147-149.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fever, bone pain and lymphadenopathy	Control	Relative (95% CI)	Absolute		
Fever (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	49/62 (79%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Bone pain (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	42/62 (67.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Bleeding (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	29/62 (46.8%)	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
lymphadenopathy (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	41/62 (66.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
splenomegaly (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	37/62 (59.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
hepatomegaly (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	35/62 (56.5%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] No explanation was provided

Hassan Study

Author(s): ALL Group
Date: 2021-07-20
Question: Should fever, pallor and lymphadenopathy be used for diagnosing pediatric acute lymphoblastic leukemia?
Settings: Pakistan
Bibliography: Hassan, K. et al. 1992, ACUTE LEUKEMIA IN CHILDREN - FRENCH - AMERICAN - BRITISH (FAB) CLASSIFICATION AND ITS RELATION TO CLINICAL FEATURES. JPMA 42:49

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fever, pallor and lymphadenopathy	Control	Relative (95% CI)	Absolute		
Fever (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	45/45 (100%)	45/45 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
pallor (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	100/100 (100%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
bleeding gums (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	-	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
ecchymoses (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	24/45 (53.3%)	34/45 (75.6%)	-	756 fewer per 1000 (from 756 fewer to 756 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
petechiae (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/45 (15.6%)	11/45 (24.4%)	-	244 fewer per 1000 (from 244 fewer to 244 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
epistaxis (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/45 (15.6%)	16/45 (35.6%)	-	356 fewer per 1000 (from 356 fewer to 356 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
lymphadenopathy (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	45/45 (100%)	23/45 (51.1%)	-	511 fewer per 1000 (from 511 fewer to 511 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
hepatomegaly (follow-up 3 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	30/45 (66.7%)	34/45 (75.6%)	-	756 fewer per 1000 (from 756 fewer to 756 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] compared with AML

Biswas Study

Author(s): ALL group
Date: 2021-07-20
Question: Should fever, pallor and organomegaly be used in in diagnosing pediatric acute lymphoblastic leukemia?
Settings: India
Bibliography: Biswas, S et al. 2009. Childhood Acute Leukemia in West Bengal, India with a Emphasis on Uncommon Clinical Features. Asia Pacific Journal on Cancer Prevention, Vol 10; 903-906.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fever, pallor and organomegaly	Control	Relative (95% CI)	Absolute		
Fever (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	54/75 (72%)	13/14 (92.9%)	-	929 fewer per 1000 (from 929 fewer to 929 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
pallor (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	59/75 79%	8/14 (57.1%)	-	571 fewer per 1000 (from 571 fewer to 571 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
gum bleeding (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	15/75 (20.4%)	6/14 (42.9%)	-	429 fewer per 1000 (from 429 fewer to 429 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
bleeding from skin (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/75 (9.3%)	6/14 (42.9%)	-	429 fewer per 1000 (from 429 fewer to 429 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
lymphadenopathy												
0	No evidence available					none	-	-	-	-		
								0%		-		
lymphadenopathy (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	37 (50%)	5/18 (27.8%)	-	278 fewer per 1000 (from 278 fewer to 278 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
hepatomegaly (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	50 (66.7%)	11/14 (78.6%)	-	786 fewer per 1000 (from 786 fewer to 786 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
splenomegaly (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	50/75 (66.7%)	4/18 (22.2%)	-	222 fewer per 1000 (from 222 fewer to 222 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
sternal tenderness (follow-up 2 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/75 (1.3%)	1/18 (5.6%)	-	56 fewer per 1000 (from 56 fewer to 56 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Brix Study

Author(s): ALL group
Date: 2021-07-20
Question: Should polyarthritis be used for diagnosing pediatric acute lymphoblastic leukemia?
Settings: Germany
Bibliography: Brix, N et al. 2020. Identifying acute lymphoblastic leukemia mimicking juvenile idiopathic arthritis in children.PLOS ONE. https://doi.org/10.1371/journal.pone.0237530

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Polyarthritis	Control	Relative (95% CI)	Absolute		
polyarthritis (follow-up 20 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/26 (23.1%)	5/485 (1%)	-	10 fewer per 1000 (from 10 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
anemia (follow-up 20 years; assessed with: less than 10 gd/L)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	16/26 (61.5%)	48/485 (9.9%)	-	99 fewer per 1000 (from 99 fewer to 99 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
thrombocytopenia (follow-up 20 years; assessed with: less than 100 x10^9 /L)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	9/26 (34.6%)	2/485 (0.41%)	-	4 fewer per 1000 (from 4 fewer to 4 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
leukocytosis (follow-up 20 years; assessed with: more than 20 x 10^9 /L)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	4/26 (15.4%)	15/485 (3.1%)	-	31 fewer per 1000 (from 31 fewer to 31 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
leukopenia (follow-up 20 years; assessed with: less than 4 x 10^9 /L)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/26 (23.1%)	10/485 (2.1%)	-	21 fewer per 1000 (from 21 fewer to 21 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
neutropenia (follow-up 20 years; assessed with: less than 5 x 10^9/L)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	17/26 (65.4%)	5/485 (1%)	-	10 fewer per 1000 (from 10 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
LDH (follow-up 20 years; assessed with: >500 IU/L)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	16/26 (61.5%)	22/485 (4.5%)	-	45 fewer per 1000 (from 45 fewer to 45 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
CRP (follow-up 20 years; assessed with: more than 50mg/L)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	-	-	-	-	⊕⊕⊕O MODERATE	NOT IMPORTANT
								0%		-		
ESR (follow-up 20 years; assessed with: >50 mm/hr)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	-	-	-	-	⊕⊕⊕O MODERATE	NOT IMPORTANT

Tilak Study

Author(s): ALL Group
Question: Bone marrow aspiration compared to bone marrow Imprint in diagnosing Pediatric Acute Lymphoblastic Leukemia
Setting: India
Bibliography: Tilak, V et al. 2014. Value of Bone Marrow Imprint Smears in Early Diagnosis of Bone Marrow Pathologies Journal of Clinical and Diagnostic Research. 2014 Nov, Vol-8(11): FC01-FC03

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With bone marrow Imprint	With Bone marrow aspiration	Relative effect (95% CI)	Risk with bone marrow Imprint	Risk difference with Bone marrow aspiration
Sensitivity											
68 (1 observational study)	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ High	34/34 (100.0%)	30/34 (88.2%)	not estimable	1,000 per 1,000	CRITICAL
Specificity											
4 (1 observational study)	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ High	4/4 (100.0%)	0/0	not estimable	1,000 per 1,000	CRITICAL
Accuracy											
68 (1 observational study)	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	⊕⊕⊕⊕ High	34/34 (100.0%)	34/34 (100.0%)	not estimable	1,000 per 1,000	CRITICAL

CI: confidence interval

Manju Study

Author(s): ALL Group
Question: Bone Marrow Aspiration compared to Bone Marrow Trephine for diagnosing Pediatric Acute Lymphoblastic Leukemia?
Setting: India
Bibliography: Manju, et. al. 2016. Role of Bone Marrow Aspiration and Biopsy in Diagnosis of Hematological Disorders: A Prospective Study. J Pharma Biomed Sci. 06(03):150–154.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bone Marrow Aspiration	Bone Marrow Trephine	Relative (95% CI)	Absolute (95% CI)		
Sensitivity (follow-up: 30 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	8/8 (100.0%)	8/8 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity (follow-up: 30 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	1/1 (100.0%)	1/1 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy (follow-up: 30 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	8/8 (100.0%)	8/8 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval

Goyal Study

Author(s): ALL Group
Question: Bone marrow aspirate compared to bone marrow trephine biopsy for diagnosing Acute Lymphoblastic Leukemia
Setting: India
Bibliography: Goyal, Surbhi et al. 2014. Comparative Evaluation of Bone Marrow Aspirate with Trephine Biopsy in Hematological Disorders and Determination of Optimum Trephine Length in Lymphoma Infiltration. Mediterranean Journal of Hematology and Infectious Diseases, 6(1): e2014002, DOI: 10.4084/MJHID.2014.002

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bone marrow aspirate	bone marrow trephine biopsy	Relative (95% CI)	Absolute (95% CI)		
sensitivity of bone marrow aspiration (follow-up: 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	42/47 (89.4%)	42/47 (89.4%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of bone marrow aspiration (follow-up: 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	5/5 (100.0%)	5/5 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
accuracy of bone marrow aspirate (follow-up: 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	43/47 (91.5%)	47/47 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval

Chauchan Study

Author(s): ALL Group
Question: Bone marrow aspirate versus compared to bone marrow biopsy in diagnosis pediatric acute lymphoblastic leukemia
Setting: India
Bibliography: Chauchan, S et al. 2017. Evaluation of sensitivity and specificity of bone marrow trephine biopsy tests in an Indian teaching hospital. Journal of Medicine 54: 161-166

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With bone marrow biopsy	With bone marrow aspirate versus	Relative effect (95% CI)	Risk with bone marrow biopsy	Risk difference with bone marrow aspirate versus
Sensitivity											
256 (1 observational study)	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ High	128/128 (100.0%)	110/128 (85.9%)	Outcome not estimable	1,000 per 1,000	CRITICAL
Specificity											
21 (1 observational study)	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ High	1/1 (100.0%)	18/20 (90.0%)	Outcome not estimable	1,000 per 1,000	CRITICAL
Accuracy											
256 (1 observational study)	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ High	128/128 (100.0%)	128/128 (100.0%)	Outcome not estimable	1,000 per 1,000	CRITICAL

CI: confidence interval

Cheng Study

Author(s): ALL group
Question: Peripheral Flowcytometry compared to [comparison] for [health problem and/or population]
Setting: Department of Pathology, St. Jude Children's Research Hospital, Memphis, Tennessee
Bibliography: Cheng et al. 2018.Peripheral blood flow cytometry for the diagnosis of pediatric acute leukemia: Highly reliable with rare exceptions. Pediatric Blood Cancer. https://doi.org/10.1002/pbc.27453

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peripheral Flowcytometry	Bone Marrow Flowcytometry	Relative (95% CI)	Absolute (95% CI)		
Sensitivity of PBFC in B - ALL (follow-up: 4 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	107/108 (99.1%)	108/108 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of PBFC in B - ALL (follow-up: 4 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	1/1 (100.0%)	1/1 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of PBFC in B- ALL (follow-up: 4 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	108/108 (100.0%)	108/108 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity of PBFC in T - ALL (follow-up: 4 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	56/57 (98.2%)	57/57 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of PBFC in T - ALL (follow-up: 4 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	56/57 (98.2%)	57/57 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of PBFC in T - ALL (follow-up: 4 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	57/57 (100.0%)	57/57 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval

Paredes-Aguilar Study

Author(s): ALL Group
Question: Intracellular Antigens in Flowcytometry compared to for diagnosing Pediatric Acute Lymphoblastic Leukemia
Setting: Mexico
Bibliography: Paredes - Aguilar, R et al. 2001. Flow Cytometric Analysis of Cell Surface and Intracellular Antigens in the Diagnosis of Acute Leukemia. American Journal of Hematology 68:69-74.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intracellular Antigens in Flowcytometry		Relative (95% CI)	Absolute (95% CI)		
Sensitivity of CD79 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of CD79 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	65/74 (87.8%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of CD79 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity of CD22 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	72/74 (97.3%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of CD22 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	65/74 (87.8%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of CD22 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	IMPORTANT
Sensitivity of CD3 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intracellular Antigens in Flowcytometry		Relative (95% CI)	Absolute (95% CI)		
Specificity of CD3 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	72/74 (97.3%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of CD3 (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity of MPO (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of MPO (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	72/74 (88.6%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of MPO (follow-up: 18 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	74/74 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval

George Study

Author(s): ALL GROUP
Question: Morphologic assessment compared to flowcytometry, conventional cytogenetics, FISH or IHC for diagnosing Pediatric Acute Lymphoblastic Leukemia
Setting: USA
Bibliography: George, T et al. 2017. Evaluation Testing of Samples. Archives if Pathology & Laboratory Medicine. 141:1101 - 1106; doi:10.5858/arpa.2016-0398-CP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	morphologic assessment	flowcytometry, conventional cytogenetics, FISH or IHC	Relative (95% CI)	Absolute (95% CI)		
Sensitivity of morphologic assessment (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	232/233 (99.6%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of morphologic assessment (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	1/1 (100.0%)		not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of morphologic assessment (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	233/233 (100.0%)	233/233 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
sensitivity of flowcytometric analysis (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	232/233 (99.6%)	229/233 (98.3%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of flowcytometric Analysis (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	1/1 (100.0%)	1/1 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of flowcytometric analysis (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	233/233 (100.0%)	233/233 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity of conventional cytogenetics (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	233/233 (100.0%)	225/233 (96.6%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
specificity of conventional cytogenetics (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	1/1 (100.0%)	1/1 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of Cytogenetics (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	233/233 (100.0%)	233/233 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity of FISH (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	233/233 (100.0%)	198/233 (85.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Specificity of FISH (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	1/1 (100.0%)	35/35 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Accuracy of FISH (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	233/233 (100.0%)	233/233 (100.0%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity of immunohistochemistry (follow-up: 46 days)												
1	observational studies	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	233/233 (100.0%)	111/233 (47.6%)	not estimable		⊕⊕⊕⊕ High	CRITICAL
Sensitivity (follow-up: 46 days)												

Hunger Study

Question: Course of Acute Lymphoblastic Leukemia in Children's Oncology Group over 5 years
Setting: USA
Bibliography: Hunger, S et al. 2012. Improved Survival for Children and Adolescents With Acute Lymphoblastic Leukemia Between 1990 and 2005: A Report form the Children's Oncology Group. Journal of Clinical Oncology 30: 1663 - 1669
Author(s): ALL Group

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Age group < 1 year old (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	154	461	event rate 10 per 100 person year(s) (47.9 to 52)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group < 1 year old (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	148	461	event rate 10 per 100 person year(s) (48.1 to 52.4)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group < 1 year old (2000 to 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	159	461	event rate 10 per 100 person year(s) (53.2 to 58.6)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group 1 - 9.99 year old (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5599	16578	event rate 50 per 10 person year(s) (88.2 to 88.6)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group 1 - 9.99 years old (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5523	16578	event rate 50 per 100 person year(s) (91.7 to 92.1)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group 1 - 9.99 years old (2000 - 2005 ERA) (follow up: 15 years years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5456	16578	event rate 50 per 100 person year(s) (94.1 to 94.5)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group more than or equal to 10 years old (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1551	4587	event rate 37 per 100 person year(s) (70.8 to 72)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group more than or equal to 10 years old (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1498	4587	event rate 37 per 100 person year(s) (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group more than or equal to 10 years old (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1538	4587	event rate 37 per 100 person year(s) (81.6 to 82.6)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group 10 - 14.99 years old (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1094	3072	event rate 44 per 100 person year(s) (72.8 to 74.2)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group 10 - 14.99 years old (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1001	3072	event rate 44 per 100 person year(s) (78.9 to 80.3)	⊕⊕⊕⊕ HIGH	CRITICAL
Age group 10 - 14.99 years old (2000 - 2005 ERA)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	977	3072	event rate 44 per 100 person year(s) (84.7 to 86.2)	⊕⊕⊕⊕ HIGH	
Age group more than or equal to 15 years old (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	457	1515	event rate 29 per 100 (66.1 to 68.4)	⊕⊕⊕⊕ HIGH	IMPORTANT
Age group more than or equal to 15 years old (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	497	1515	event rate 29 per 100 person year(s) (72.9 to 75.1)	⊕⊕⊕⊕ HIGH	IMPORTANT
Age group more than or equal to 15 years old (2000 0 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	561	1515	event rate 29 per 100 person year(s) (75.9 to 78.5)	⊕⊕⊕⊕ HIGH	IMPORTANT
Sex: Male (1990 to 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4117	12155	event rate 42 per 100 person year(s) (82.7 to 83.3)	⊕⊕⊕⊕ HIGH	IMPORTANT
Sex: Male (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4057	12155	event rate 42 per 100 person year(s) (86.3 to 86.9)	⊕⊕⊕⊕ HIGH	IMPORTANT
Sex: Male (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3981	12155	event rate 42 per 100 person year(s) (89.9 to 90.5)	⊕⊕⊕⊕ HIGH	IMPORTANT

Sex: Female (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3187	9471	event rate 40 per 100 person year(s) (84.9 to 85.6)	⊕⊕⊕⊕ HIGH	IMPORTANT
Sex: Female (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3112	9471	event rate 40 per 100 person year(s) (89.5 to 90.1)	⊕⊕⊕⊕ HIGH	IMPORTANT
Sex: Female (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3172	9471	event rate 40 per 100 person year(s) (91 to 91.7)	⊕⊕⊕⊕ HIGH	IMPORTANT
Race: white (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5410	15759	event rate 35 per 100 person year(s) (86.3 to 86.8)	⊕⊕⊕⊕ HIGH	IMPORTANT
Race: white (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4890	15759	event rate 35 per 100 person	⊕⊕⊕⊕ HIGH	IMPORTANT

									year(s) (88.9 to 89.4)		
Race: white (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5242	15759	event rate 35 per 100 person year(s) (91.1 to 91.6)	⊕⊕⊕⊕ HIGH	IMPORTANT
Race: Black (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	535	1474	event rate 51 per 100 person year(s) (75.3 to 77.3)	⊕⊕⊕⊕ HIGH	IMPORTANT
Race: Black (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	472	1474	event rate 51 per 100 person year(s) (80.7 to 82.6)	⊕⊕⊕⊕ HIGH	IMPORTANT
Race: Black (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	425	1474	event rate 51 per 100 (87.8 to 89.9)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Hispanic (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	547	2589	event rate 31 per 100 person	⊕⊕⊕⊕ HIGH	IMPORTANT

									year(s) (82 to 83.8)		
Ethnicity: Hispanic (1995-1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	675	2589	event rate 31 per 100 person year(s) (86.2 to 87.6)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Hispanic (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1367	2589	event rate 31 per 100 person year(s) (87.6 to 88.8)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Non - Hispanic (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3626	12528	event rate 34 per 100 person year(s) (87 to 87.6)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Non - Hispanic (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3377	12528	event rate 34 per 100 person year(s) (88.5 to 89.1)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Non - Hispanic (2000 - 2005 ERA) (follow up: 15 years)											

1	randomised trials	not serious	not serious	not serious	not serious	strong association	5525	12528	event rate 34 per 100 person year(s) (91.4 to 91.9)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Unknown (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3131	6509	event rate 18 per 100 (80 to 80.7)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Unknown (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3117	6509	event rate 18 per 100 person year(s) (87.1 to 87.7)	⊕⊕⊕⊕ HIGH	IMPORTANT
Ethnicity: Unknown (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	261	6509	event rate 18 per 100 (83.8 to 86)	⊕⊕⊕⊕ HIGH	IMPORTANT
Immunophenotype: B cell (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5068	16880	event rate 41 per 100 person year(s) (84.9 to 85.4)	⊕⊕⊕⊕ HIGH	CRITICAL
Immnophenotype: B cell (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5830	16880	event rate 41 per 100 person year(s) (88.3 to 88.7)	⊕⊕⊕⊕ HIGH	CRITICAL
Immunophenotype: B cell (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	5982	16880	event rate 41 per 100 person year(s) (91.1 to 91.6)	⊕⊕⊕⊕ HIGH	CRITICAL
Immunophenotype: T cell (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	748	1831	event rate 41 per 100 person year(s) (91.1 to 91.6)	⊕⊕⊕⊕ HIGH	CRITICAL
Immunophenotype: T cell (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	624	1831	event rate 37 per 100 person year(s) (80.7 to 82.4)	⊕⊕⊕⊕ HIGH	CRITICAL
Immunophenotype: T cell (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	459	1831	event rate 37 per 100 person year(s) (81.6 to 83.8)	⊕⊕⊕⊕ HIGH	CRITICAL
NCI risk group: Standard risk (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4624	14154	event rate 49 per 100 person year(s) (90.2 to 90.7)	⊕⊕⊕⊕ HIGH	CRITICAL
NCI risk group: Standard risk (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4674	14154	event rate 49 per 100 person year(s) (92.7 to 93.1)	⊕⊕⊕⊕ HIGH	CRITICAL
NCI risk group: Standard risk (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4856	14154	event rate 49 per 100 person year(s) (81.6 to 83.8)	⊕⊕⊕⊕ HIGH	CRITICAL
NCI risk group: High risk (1990 - 1994 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	2680	7460	event rate 32 per 100 person year(s) (73.8 to 74.7)	⊕⊕⊕⊕ HIGH	CRITICAL
NCI risk group: High risk (1995 - 1999 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	2494	7460	event rate 32 per 100 person	⊕⊕⊕⊕ HIGH	CRITICAL
									year(s) (79.8 to 80.7)		
NCI risk group: High risk (2000 - 2005 ERA) (follow up: 15 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	2286	7460	event rate 32 per 100 person year(s) (82.9 to 84)	⊕⊕⊕⊕ HIGH	CRITICAL

Moghrabi Study

Question: Course of DFCI ALL consortium Protocol 95 -01 in Risk Stratification of Acute Lymphoblastic Leukemia over 5 years
Setting: Canada
Bibliography: **Moghrabi, A et al.** 2007. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. BLOOD, 1 February, Volume 109, Number 3.
Author(s): ALL group

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
DCFI risk group: standard (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	272	491	event rate 82.0% (80 to 84)	⊕⊕⊕⊕ High	CRITICAL
DCFI risk group: High (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	219	491	event rate 76.0% (74 to 78)	⊕⊕⊕⊕ High	CRITICAL
NCI risk group: Good-risk pre-B (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	299	491	event rate 86.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
NCI risk group: Poor-risk pre-B											
1	observational studies	not serious	not serious	not serious	not serious	strong association	121	491	event rate 70.0% (66 to 74)	⊕⊕⊕⊕ High	CRITICAL
NCI risk group: Good-risk T (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	12	491	event rate 83.0% (72 to 94)	⊕⊕⊕⊕ High	CRITICAL
NCI risk group: Poor risk T (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	40	491	event rate 85.0% (79 to 91)	⊕⊕⊕⊕ High	CRITICAL
< 1 y.o. (follow-up: 57 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	14	491	event rate 42.0% (29 to 55)	⊕⊕⊕⊕ High	CRITICAL
1 - 9 y.o. (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	385	491	event rate 84.0% (82 to 86)	⊕⊕⊕⊕ High	CRITICAL
10 - 18 y.o. (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	92	491	event rate 75.0% (70 to 80)	⊕⊕⊕⊕ High	CRITICAL
WBC: < 20.000 x109L (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	318	491	event rate 87.0% (85 to 89)	⊕⊕⊕⊕ High	CRITICAL
WBC: 20.000 – 49.999 x109L (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	76	491	event rate 71.0% (66 to 76)	⊕⊕⊕⊕ High	IMPORTANT
WBC: 50.00 – 99.999 x109L (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	43	491	event rate 79.0% (73 to 85)	⊕⊕⊕⊕ High	IMPORTANT
WBC: 100.000 x109L (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	54	491	event rate 66.0% (59 to 73)	⊕⊕⊕⊕ High	IMPORTANT
Male (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	274	491	event rate 79.0% (49 to 109)	⊕⊕⊕⊕ High	IMPORTANT
Female (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	217	491	event rate 84.0% (81 to 87)	⊕⊕⊕⊕ High	IMPORTANT

Immunophenotype: B-lineage (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	434	491	event rate 81.0% (79 to 83)	⊕⊕⊕⊕ High	CRITICAL
Immunophenotype: T cell (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	52	491	event rate 85.0% (80 to 90)	⊕⊕⊕⊕ High	CRITICAL
CNS at diagnosis: CNS1 (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	403	491	event rate 83.0% (79 to 85)	⊕⊕⊕⊕ High	CRITICAL
CNS at diagnosis: CNS2 (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	49	491	event rate 72.0% (65 to 77)	⊕⊕⊕⊕ High	CRITICAL
CNS at diagnosis: CNS3 (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	12	491	event rate 75.0% (62 to 88)	⊕⊕⊕⊕ High	CRITICAL
CNS at diagnosis: Traumatic (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	19	491	event rate 68.0% (57 to 79)	⊕⊕⊕⊕ High	IMPORTANT
Down Syndrome: No (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	477	491	event rate 82.0% (80 to 84)	⊕⊕⊕⊕ High	IMPORTANT
Down Syndrome: Yes (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	14	491	event rate 71.0% (59 to 83)	⊕⊕⊕⊕ High	IMPORTANT
Hyperdiploid > 50 (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	82	309	event rate 86.0% (82 to 90)	⊕⊕⊕⊕ High	IMPORTANT
Hyperdiploid <50 (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	23	309	event rate 73.0% (64 to 82)	⊕⊕⊕⊕ High	IMPORTANT
Diploid (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	134	491	event rate 84.3% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Pseudodiploid (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	54	309	event rate 71.0% (65 to 77)	⊕⊕⊕⊕ High	IMPORTANT
Hypodiploid (follow-up: 57 months)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	16	309	event rate 73.0% (61 to 85)	⊕⊕⊕⊕ High	IMPORTANT

Pui Study

Question: Course of outcome in Risk Stratification of Acute Lymphoblastic Leukemia over 5 years
Setting: USA
Bibliography:Pui, C et al.2004. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. BLOOD, Volume 104, Number 9.
Author(s):

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Risk: lower (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	116	117	event rate 88.1% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Risk: Higher (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	126	130	event rate 73.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
NCI (B lineage ALL) standard (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	111	112	event rate 87.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
NCI (B lineage ALL) High (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	88	90	event rate 76.7% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age: < 1 year old (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	10	10	event rate 70.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age: 1 to 10 years old (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	160	161	event rate 84.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age: > 10 years old (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	72	76	event rate 74.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Sex: Female (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	101	103	event rate 83.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Sex: Male (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	141	144	event rate 79.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Race: white (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	194	199	event rate 79.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Race: Black (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	45	45	event rate 86.5% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Race: Other (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3	3	event rate 100.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Leukocyte count: < 10 X 109 /L (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	108	111	event rate 82.7% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Leukocyte count: 10 to 49 x 109 /L (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	70	70	event rate 88.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Leukocyte count: 50 to 99 X 109 /L											

1	observational studies	not serious	not serious	not serious	not serious	strong association	27	28	event rate 78.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Leukocyte count: 100 x 109 /L (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	37	38	event rate 63.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS status: CNS1 (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	142	145	event rate 81.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS status: CNS2 (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	76	78	event rate 80.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS status: CNS3 (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	7	7	event rate 71.4% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS status: traumatic tap (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	17	17	event rate 82.4% (-- to --)	⊕⊕⊕⊕ High	CRITICAL

Immunophenotype: B cell receptor (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	199	202	event rate 82.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Immunophenotype: T cell precursor (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	41	43	event rate 71.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
DNA Index 1.16 or more (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	45	46	event rate 91.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
DNA index less than 1.6 (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	197	201	event rate 78.5% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
t (9;22)/ BCR ABL absent (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	228	232	event rate 82.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
t (9;22)/ BCR ABL present (follow-up: 4 years)											

1	observational studies	not serious	not serious	not serious	not serious	strong association	6	7	event rate 28.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
t(4;11)/ MLL-AF4 absent (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	199	204	event rate 82.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
t(4;11)/ MLL-AF4 present (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	7	7	event rate 42.9% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
t (1;19)? E2A-PBX1 Absent (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	196	201	event rate 81.0% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
t (1;19)? E2A-PBX1 Present (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	10	10	event rate 80.0% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
TEL-AML1 Present (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	39	39	event rate 84.5% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT

TEL-AML1 Present (follow-up: 4 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	129	133	event rate 78.8% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT

Schultz Study

Question: Course of Pediatric Oncology Group (POG) and Children's Cancer Group in Acute Lymphoblastic Leukemia over 5 years
Setting:
Bibliography: **Schultz, K et al.** 2007. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) . BLOOD,VOLUME 109, NUMBER 3 .
Author(s): ALL Group

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Sex: Male (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	849	4986	event rate 54.1 per 100 (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Sex: Male (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	208	6793	event rate 68.5 per 100 (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Sex: Female (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	680	4986	event rate 67.1 per 100 (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Sex: Female (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	198	6793	event rate 69.8 per 100 (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Race: African American (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	165	4968	event rate 53.1 per 100 (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Race: African American (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	36	6793	event rate 56.9% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Race: Hispanic (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	225	4968	event rate 54.3% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Race: Hispanic (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	29	6793	event rate 67.7% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Race: Others (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1139	4968	event rate 61.9% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Race: Others (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	340	6793	event rate 70.7% (-- to --)	⊕⊕⊕⊕ High	IMPORTANT
Age: 15 years old or less (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1360	4968	event rate 60.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age: 15 years old or less (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	343	6793	event rate 71.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age: More than 15 years old (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	169	4968	event rate 51.1% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age: More than 15 years old (CCG)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	63	6793	event rate 59.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-1 with ANY NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	4382	4968	event rate 75.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL

CNS-1 with ANY NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1037	6793	event rate 78.4% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-2 with ANY NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	326	4968	event rate 65.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-2 with ANY NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	70	6973	event rate 67.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-3 with ANY NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	105	4968	event rate 64.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-3 with ANY NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	21	6793	event rate 76.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-1 with STANDARD NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	3193	4968	event rate 79.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-1 with STANDARD NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	712	6793	event rate 81.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-2 with STANDARD NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	176	4968	event rate 70.1% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-2 with STANDARD NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	38	6793	event rate 68.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-3 with STANDARD NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	48	4968	event rate 71.8% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-3 with STANDARD NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	8	6973	event rate 75.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-1 with High NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1181	4968	event rate 64.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-1 with High NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	325	6793	event rate 72.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-2 with High NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	150	4968	event rate 59.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-2 with High NCI risk group (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	32	6793	event rate 65.6% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-3 with High NCI risk group (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	55	4968	event rate 58.7% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
CNS-3 with High NCI risk group (CCG) (follow-up: 7 years)											

1	observational studies	not serious	not serious	not serious	not serious	strong association	13	6793	event rate 76.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Testicular status at diagnosis: No Disease (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	2667	4968	event rate 71.4% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Testicular status at diagnosis: No Disease (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	618	6793	event rate 76.5% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Testicular status at diagnosis: with Disease (POG) (follow-up: 13 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	10	4968	event rate 90.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Testicular status at diagnosis: No Disease (CCG) (follow-up: 7 years)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	8	6793	event rate 62.5% (-- to --)	⊕⊕⊕⊕ High	CRITICAL

Vrooman Study

Author(s): ALL group
Date: 2021-07-09
Question: Should refining risk stratification be used in in Pediatric and Adolescent ALL??
Settings: US
Bibliography: Vrooman, L et al. 2018. Refining Risk Stratification in childhood B acute lymphoblastic leukemia: result of DFCI ALL Consortium Protocol 05-001. Blood advances vol.2 no. 12: p1449-1458.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Refining risk stratification	Control	Relative (95% CI)	Absolute		
Initial DFCI risk group: Standard (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	460/678 (67.8%)	-	RR 91 (88 to 94)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
Initial DFCI risk group: High (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	218/678 (32.2%)	-	RR 77 (071 to 82)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
Age at diagnosis: <10 years (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	531/678 (78.3%)	-	RR 89 (86 to 91)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
Age ate diagnosis: more than or equal to 10 years (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	147/678 (21.7%)	-	RR 79 (71 to 85)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
Age at diagnosis: 10 years but less than 15years (follow-up 6 years)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	97/678 (14.3%)	-	RR 85 (76 to 91)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
Age at diagnosis: more than or equal to 15 year (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	50/678 (7.4%)	-	RR 66 (51 to 78)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
WBC at diagnosis: <50												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	578/678 (85.3%)	-	RR 90 (87 to 92)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
WBC at diagnosis: more than or equal to 50 (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	100/678 (14.7%)	-	RR 70 (60 to 78)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
								0%		-		
Male (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	357/678 (52.7%)	-	RR 86 (82 to 89)	-	⊕⊕⊕⊕ MODERATE	IMPORTANT
								0%		-		
Female (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	321/678 (47.3%)	-	RR 87 (83 to 91)	-	⊕⊕⊕⊕ MODERATE	IMPORTANT
								0%		-		
CNS status at diagnosis: CNS1 (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	540/678 (79.6%)	-	RR 87 (84 to 90)	-	⊕⊕⊕⊕ MODERATE	CRITICAL
CNS status at dianosis: CNS2 (follow-up 6 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	90/678 (13.3%)	-	RR 86 (77 to 92)	-	⊕⊕⊕⊕ MODERATE	CRITICAL

Cytogenetics: ETV6-RUNX1 (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	154/678 (22.7%)	- 0%	RR 95 (90 to 98)	- -	⨁⨁⨁◯ MODERATE	CRITICAL
Cytogenetics: Hypodiploidy (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/678 (1.5%)	- 0%	RR 0 (41 to 95)	- -	⨁⨁⨁◯ MODERATE	IMPORTANT
Cytogenetics: KMT2A rearranged (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/678 (1.8%)	- 0%	RR 58 (27 to 80)	- -	⨁⨁⨁◯ MODERATE	IMPORTANT
cytogenetics: iAMP21 (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/678 (1.9%)	- 0%	RR 67 (33 to 86)	- -	⨁⨁⨁◯ MODERATE	IMPORTANT
Cytogenetics: TCF3-PBX1 (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/678 (3.4%)	- 0%	RR 82 (59 to 93)	- -	⨁⨁⨁◯ MODERATE	IMPORTANT
Cytogenetics: normal karyotype (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	128/678 (18.9%)	- 0%	RR 87 (79 to 92)	- -	⨁⨁⨁◯ MODERATE	IMPORTANT
Final DFCI risk group: standard (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	407/678 (60%)	- 0%	RR 94 (91 to 96)	- -	⨁⨁⨁◯ MODERATE	CRITICAL
Final DFCI risk group: High (follow-up 6 years)													
								0%		-		
CNS status at diagnosis: CNS3 (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/678 (0.88%)	- 0%	RR 100 (0 to 0)	- -	⨁⨁◯◯ MODERATE	
CNS status at diagnosis: traumatic with blasts (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/678 (3.5%)	- 0%	RR 75 (53 to 88)	- -	⨁⨁◯◯ MODERATE	CRITICAL
CNS status at dianosis: Traumatic without blasts (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/678 (2.7%)	- 0%	RR 0 (62 to 97)	- -	⨁⨁◯◯ MODERATE	IMPORTANT
Down syndrome (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/678 (3.7%)	- 0%	RR 95 (68 to 99)	- -	⨁⨁◯◯ MODERATE	CRITICAL
Cytogenetics: Hyperdiploidy (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	198/678 (29.2%)	- 0%	RR 89 (84 to 93)	- -	⨁⨁◯◯ MODERATE	CRITICAL
Cytogenetics: Trisomy chr 4 and 10 (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	121/678 (17.8%)	- 0%	RR 92 (86 to 96)	- -	⨁⨁◯◯ MODERATE	IMPORTANT
Cytogenetics: No double trisomy (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	77/678 (11.4%)	- 0%	RR 85 (74 to 91)	- -	⨁⨁◯◯ MODERATE	IMPORTANT
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	176/678 (26%)	- 0%	RR 84 (77 to 88)	- -	⨁⨁◯◯ MODERATE	CRITICAL
Input outcome name: very high (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	65/678 (9.6%)	- 0%	RR 79 (67 to 87)	- -	⨁⨁◯◯ MODERATE	CRITICAL
End induction MRD (Day 32): Low <10													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	488/678 (72%)	- 0%	RR 91 (88 to 93)	- -	⨁⨁◯◯ MODERATE	CRITICAL
Final DFCI risk group: High more than ore equal to 10 (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/678 (6.9%)	- 0%	RR 77 (62 to 87)	- -	⨁⨁◯◯ MODERATE	CRITICAL
Final DFCI risk group: intermediate/ unknown (follow-up 6 years)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	113/678 (16.7%)	- 0%	RR 87 (79 to 82)	- -	⨁⨁◯◯ MODERATE	IMPORTANT

Pharmacologic Intervention

Hunger and Howard Study

Author(s):
Date: 2021-09-20
Question: Should Regimen with Prednisone Prophase 60 mg/m2 with tapering to 40 mg/m2 along 3 drug induction using VCR/Pred/L-asparaginase without intensive consolidation or Delayed Intensification using Dexa/VCR/L-asparaginase/Extended Intrathecal chemotherapy prophylaxis for SR vs Regimen with Prednisone at 60 mg/m2 with 3 drug induction VCR/Pred/L-asparaginase for SR but addition of 4th drug anthracycline with BFM style consolidation Cyclophosphamide/Cytarabine/6MP for HR or 2 month Delayed Intensification Phase using Dexa/VCR/L-asparginase/IT Mtx for HR with cranial irradiation at 1200 cGy for CNS 1 and 1800 cGy for CNS3 for HR be used for childhood ALL?
Settings:
Bibliography: Hunger and Howard,2009

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Regimen with Prednisone Prophase 60 mg/m2 with tapering to 40 mg/m2 along 3 drug induction using VCR/Pred/L-asparaginase without intensive consolidation or Delayed Intensification using Dexa/VCR/L-asparaginase/Extended Intrathecal chemotherapy prophylaxis for SR	Regimen with Prednisone at 60 mg/m2 with 3 drug induction VCR/Pred/L-asparaginase for SR but addition of 4th drug anthracycline with BFM style consolidation Cyclophosphamide/Cytarabine/6MP for HR or 2 month Delayed Intensification Phase using Dexa/VCR/L-asparginase/IT Mtx for HR with cranial irradiation at 1200 cGy for CNS 1 and 1800 cGy for CNS3 for HR	Relative (95% CI)	Absolute	Quality	Importance
16 year Event Free Survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/321 (58.9%)	290/397 (73%)	-	730 fewer per 1000 (from 730 fewer to 730 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.806%		8 fewer per 1000 (from 8 fewer to 8 fewer)		
CNS Control Rate (assessed with: CNs Control Rate for Extended Intrathecal Chemotherapy as prophylaxis for SR vs Cranial Irradiation as prophylaxis for HR)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/321 (80.1%)	357/397 (89.9%)	RR 0.891 (0 to 0)	98 fewer per 1000 (from 899 fewer to	⊕⊕⊕⊕ HIGH	CRITICAL

CNS Control Rate (assessed with: CNs Control Rate for Extended Intrathecal Chemotherapy as prophylaxis for SR vs Cranial Irradiation as prophylaxis for HR)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/321 (80.1%)	357/397 (89.9%)	RR 0.891 (0 to 0)	98 fewer per 1000 (from 899 fewer to 899 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Absence of Excess Toxic Deaths (assessed with: Absence of Toxic Deaths with 3 drug induction for SR vs 4 drug induction for HR)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193/321 (60.1%)	159/397 (40.1%)	RR 1.498 (0 to 0)	199 more per 1000 (from 401 fewer to 401 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
6 year Event Free Survival (Copy) (assessed with: 6 yr EFS for Dexamethasone vs. Prednisone)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	272/321 (84.7%)	306/397 (77.1%)	RR 1.098 (0 to 0)	76 more per 1000 (from 771 fewer to 771 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
7 year EFS (assessed with: 7 year EFS for 3 drug Induction with DI for SR vs 3 or 4 drug induction with BFM Style Intensive Consolidation)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	266/321 (82.9%)	250/397 (63%)	-	630 fewer per 1000 (from 630 fewer to 630 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.315%		13 fewer per 1000 (from 13 fewer to		

Silverman Study (Long Term DFCI Protocols)

Author(s):
Date: 2021-06-21
Question: Should Induction Protocol 91-01(3 days Prednisone prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR ,Mtx 4 g/m2,IT Cytarabine) & 95-01 (L-asparaginase Erwinia or E. coli, + Dexrazoxane for HR) vs Induction Protocol 85-01(5 days E. coli L-asparaginase prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR, Mtx 40 mg/m2, IT cytarabine) & 87-01 (+ E.coli/Erwinia/PEG L-asparaginase prephase x 5 days) be used for children with Acute Lymphoblastic Leukemia?
Settings:
Bibliography: Silverman 2009 Long term results of DFCI Protocols

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction Protocol 91-01(3 days Prednisone prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR ,Mtx 4 g/m2,IT Cytarabine) & 95-01 (L-asparaginase Erwinia or E. coli, + Dexrazoxane for HR)	Induction Protocol 85-01(5 days E. coli L-asparaginase prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR, Mtx 40 mg/m2, IT cytarabine) & 87-01 (+ E.coli/Erwinia/PEG L-asparaginase prephase x 5 days)	Relative (95% CI)	Absolute		
Overall Remission-Induction Rate (assessed with: Remission Rate)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	851/868 (98%)	573/589 (97.3%)	RR 1.01 (0 to 0)	10 more per 1000 (from 973 fewer to 973 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Induction Failure (assessed with: Induction Failure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/867 (1.4%)	11/589 (1.9%)	RR 0.736 (0 to 0)	5 fewer per 1000 (from 19 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Induction Death (assessed with: Induction Death Rate)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/868 (0.69%)	5/589 (0.85%)	RR 0.811 (0 to 0)	2 fewer per 1000 (from 8 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Silverman Study DFCI Protocol - SR

Author(s):
Date: 2021-06-21
Question: Should DFCI Protocols 91-01 (3 days Pred prephase, VCR/Pred/Doxorubicin/Mtx/IT Cytarabine/CNS tx (VCR.6MP, no CrRT for SR girls, + CrRT 18 Gy SR boys, Intensification & Continuation (VCR/Dexamethasone/IV Mtx/oral or IV 6MP/ 30 weeks L-asparaginase either E. coli or PEG & 95-01 (+ L-asparaginase during induction & 20 weeks L-asparaginase either E.coli or Erwinia during intensification) vs DFCI Protocols 85-01 (L-asparaginase x 5 days prephase, VCR/Pred/Doxorubicin/IV Mtx/IT Cytarabine, CNS Tx (VCR/oral 6MP/IT Mtx/ CrRT 18Gy, Intensification & Continuation (VCRPred/6MP/IV Mtx, 20 weeks of L-asparaginase E. coli) & 87-01 (no CrRT) be used for Children with Standard Risk ALL ?
Settings:
Bibliography: Silverman 2009 Long term results of DFCI Protocols 1990s vs 1980s

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DFCI Protocols 91-01 (3 days Pred prephase, VCR/Pred/Doxorubicin/Mtx/IT Cytarabine/CNS tx (VCR.6MP, no CrRT for SR girls, + CrRT 18 Gy SR boys, Intensification & Continuation (VCR/Dexamethasone/IV Mtx/oral or IV 6MP/ 30 weeks L-asparaginase either E. coli or PEG & 95-01 (+ L-asparaginase during induction & 20 weeks L-asparaginase either E.coli or Erwinia during intensification)	DFCI Protocols 85-01 (L-asparaginase x 5 days prephase, VCR/Pred/Doxorubicin/IV Mtx/IT Cytarabine, CNS Tx (VCR/oral 6MP/IT Mtx/ CrRT 18Gy, Intensification & Continuation (VCRPred/6MP/IV Mtx, 20 weeks of L-asparaginase E. coli) & 87-01 (no CrRT)	Relative (95% CI)	Absolute		
Event Free Survival for Standard Risk ALL (assessed with: 10 year Event Free Survival)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	341/409 (83.4%)	181/224 (80.8%)	RR 1.032 (0 to 0)	26 more per 1000 (from 808 fewer to 808 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Survival for Standard Risk ALL (assessed with: 10 year Overall Survival)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	377/409 (92.2%)	206/224 (92%)	RR 1.002 (0 to 0)	2 more per 1000 (from 920 fewer to 920 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Silverman (ALL DFCI Protocols)

XAuthor(s):
Date: 2021-06-21
Question: Should Induction Protocol 91-01(3 days Prednisone prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR ,Mtx 4 g/m2,IT Cytarabine) & 95-01 (L-asparaginase Erwinia or E. coli, + Dexrazoxane for HR) vs Induction Protocol 85-01(5 days E. coli L-asparaginase prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR, Mtx 40 mg/m2, IT cytarabine) & 87-01 (+ E.coli/Erwinia/PEG L-asparaginase prephase x 5 days) be used for children with Acute Lymphoblastic Leukemia?
Settings:
Bibliography: Silverman 2009 Long term results of DFCI Protocols

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction Protocol 91-01(3 days Prednisone prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR ,Mtx 4 g/m2,IT Cytarabine) & 95-01 (L-asparaginase Erwinia or E. coli, + Dexrazoxane for HR)	Induction Protocol 85-01(5 days E. coli L-asparaginase prephase, VCR/Pred/Doxorubicin cumulative 60 mg/m2 for SR & 360 mg/m2 for HR, Mtx 40 mg/m2, IT cytarabine) & 87-01 (+ E.coli/Erwinia/PEG L-asparaginase prephase x 5 days)	Relative (95% CI)	Absolute		
Overall Remission-Induction Rate (assessed with: Remission Rate)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	851/868 (98%)	573/589 (97.3%)	RR 1.01 (0 to 0)	10 more per 1000 (from 973 fewer to 973 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Induction Failure (assessed with: Induction Failure)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/867 (1.4%)	11/589 (1.9%)	RR 0.736 (0 to 0)	5 fewer per 1000 (from 19 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Induction Death (assessed with: Induction Death Rate)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/868 (0.69%)	5/589 (0.85%)	RR 0.811 (0 to 0)	2 fewer per 1000 (from 8 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Silverman (CNS DIrected Therapy)

Author(s):
Date: 2021-06-21
Question: Should CNS directed treatment 91-01 (VCR, oral 6MP,IT Mtx, no CrRT for SR girls, + CrRT 18 Gy for boys and HR) & 95-01 (no CrRT for SR, + CrRT 18Gy for HR, + Doxorubicin 30 mg/m2) vs 85-01 (VCR, oral 6MP, IT Mtx, + CrRT 18 Gy for SR and +CrRT 24 Gy for HR) & 87-01 (no CrRT for SR, + CrRT 18Gy for HR, + Doxorubicin 30 mg/m2) be used for CNS Prophylaxis in childhood ALL?
Settings:
Bibliography: Silverman 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CNS directed treatment 91-01 (VCR, oral 6MP,IT Mtx, no CrRT for SR girls, + CrRT 18 Gy for boys and HR) & 95-01 (no CrRT for SR, + CrRT 18Gy for HR, + Doxorubicin 30 mg/m2)	85-01 (VCR, oral 6MP, IT Mtx, + CrRT 18 Gy for SR and +CrRT 24 Gy for HR) & 87-01 (no CrRT for SR, + CrRT 18Gy for HR, + Doxorubicin 30 mg/m2)	Relative (95% CI)	Absolute		
Isolated CNS Relapse (assessed with: 10 year Isolated CNS Relapse)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/868 (0.92%)	22/589 (3.7%)	RR 0.248 (0 to 0)	28 fewer per 1000 (from 37 fewer to 37 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Vrooman Study

Author(s):
Date: 2021-06-13
Question: Should Individualized Dose L-Asparaginase vs Fixed dose L-asparaginase be used for Post-induction treatment of childhood ALL?
Settings:
Bibliography: Vrooman 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individualized Dose L-Asparaginase	Fixed dose L-asparaginase	Relative (95% CI)	Absolute		
Event Free Survival (assessed with: 5 year EFS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	170/189 (89.9%)	160/195 (82.1%)	RR 1.06 (0 to 0)	49 more per 1000 (from 821 fewer to 821 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.91%		1 more per 1000 (from 9 fewer to 9 fewer)		
Overall Survival (assessed with: 5 year OS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	172/189 (91%)	181/195 (92.8%)	RR 0.98 (0 to 0)	19 fewer per 1000 (from 928 fewer to 928 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Skeletal Toxicity (assessed with: Osteonecrosis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/189 (10.1%)	56/195 (28.7%)	RR 0.35 (0 to 0)	187 fewer per 1000 (from 287 fewer to 287 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Toxicity (assessed with: Clinical Allergy)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/189 (21.2%)	39/195 (20%)	RR 1.06 (0 to 0)	12 more per 1000 (from 200 fewer to 200 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Toxicity (assessed with: Pancreatitis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/189 (3.2%)	10/195 (5.1%)	RR 0.63 (0 to 0)	19 fewer per 1000 (from 51 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Toxicity (assessed with: Thrombosis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/189 (3.7%)	16/195 (8.2%)	RR 0.45 (0 to 0)	45 fewer per 1000 (from 82 fewer to 82 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Hunger COG Trials

Author(s):
Date: 2021-06-12
Question: Should COG ALL-9 Era 2000-2005 Induction for SR(VCR/Dexa/L-Asparaginase/TIT) HR (VCR/Daunorubicin/Dexa/L-Aspa/TIT 2-4x) CNS Prophylaxis for SR (MD Mtx 2 g/m2/TIT x 3) HR (HD Mtx 3g/m2/TIT x4), Reinduction for HR only(VCR/Dauno/Dexa/6MP/L-Asparaginase/TIT x 1) Superconsolidation for HR only (Cyclo/Ara-C x 6 courses), Maintenance SR & HR (VCR/Dexa/6MP/Mtx/TIT x 8) vs COG ALL-8 Era 1990-1999 Induction 1a for SR & HR (VCR/Daunorubicin/Pred/L-Asparaginase/IT Mtx x 1/TIT 2), Induction 1b for SR (Cyclo/6MP/Ara-C/TIT x 2), HR (Dexa/6MP/VCR/HD Mtx 5 g/m2/TIT x 2/HD Ara-C/L-Asparaginase) Protocol M (HD Mtx 5 g/m2/6MP/TIT x 4), Reinduction for SR (VCR/Dexa/Doxo/L-Asparaginase/Cyclo/Ara-C/6TG/TIT x 2), HR (Dexa/6TG/HD Mtx/Vindesine/Daunorubicin/L-asparaginase/Ifosfamide/TIT x1), Maintenance for SR(6MP/Mtx/L-asparaginase) HR (6MPMtx) be used in children with ALL?
Settings:
Bibliography: Hunger et al 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	COG ALL-9 Era 2000-2005 Induction for SR(VCR/Dexa/L-Asparaginase/TIT) HR (VCR/Daunorubicin/Dexa/L-Aspa/TIT 2-4x) CNS Prophylaxis for SR (MD Mtx 2 g/m2/TIT x 3) HR (HD Mtx 3g/m2/TIT x4), Reinduction for HR only(VCR/Dauno/Dexa/6MP/L-Asparaginase/TIT x 1) Superconsolidation for HR only (Cyclo/Ara-C x 6 courses), Maintenance SR & HR (VCR/Dexa/6MP/Mtx/TIT x 8)	COG ALL-8 Era 1990-1999 Induction 1a for SR & HR (VCR/Daunorubicin/Pred/L-Asparaginase/IT Mtx x 1/TIT 2), Induction 1b for SR (Cyclo/6MP/Ara-C/TIT x 2), HR (Dexa/6MP/VCR/HD Mtx 5 g/m2/TIT x 2/HD Ara-C/L-Asparaginase) Protocol M (HD Mtx 5 g/m2/6MP/TIT x 4), Reinduction for SR (VCR/Dexa/Doxo/L-Asparaginase/Cyclo/Ara-C/6TG/TIT x 2), HR (Dexa/6TG/HD Mtx/Vindesine/Daunorubicin/L-asparaginase/Ifosfamide/TIT x1), Maintenance for SR(6MP/Mtx/L-asparaginase) HR (6MPMtx)	Relative (95% CI)	Absolute		
Overall Survival (assessed with: 5 year Overall Survival)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6466/7153 (90.4%)	12400/14473 (85.7%)	RR 1.05 (0 to 0)	43 more per 1000 (from 857 fewer to 857 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Incidence of Death (assessed with: 5 year Cumulative Incidence of Death After Relapse)												
Incidence of Death (assessed with: 5 year Cumulative Incidence of Death After Relapse)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	687/7153 (9.6%)	2076/14473 (14.3%)	RR 0.671 (0 to 0)	47 fewer per 1000 (from 143 fewer to 143 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Relapse/Disease Progression (assessed with: 5 year Relapse Rate/Disease Progression)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	515/7153 (7.2%)	1582/14473 (10.9%)	RR 0.66 (0 to 0)	37 fewer per 1000 (from 109 fewer to 109 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Treatment-Related Death (assessed with: 5 year Treatment-Related Death prior to Relapse)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/7153 (1.6%)	289/14473 (2%)	RR 0.8 (0 to 0)	4 fewer per 1000 (from 20 fewer to 20 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Survival (assessed with: 10 year OS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6466/7153 (90.4%)	11867/14473 (82%)	RR 1.102 (0 to 0)	84 more per 1000 (from 820 fewer to 820 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Pui Study (SJCRH Study)

Author(s):
Date: 2021-07-20
Question: Should SJCRH Total Therapy Study 13A(1991-1994) Remission Induction (IV Mtx 1 g/m2 for HR, 30 mg/m2 for SR, Etoposide, 2 additional weekly IT) Consolidation (HD Mtx 2 g/m2, 6MP, VCR, Pred, add L-Asparaginase for HR) Reinduction (VCR,Pred,L-asparaginase,IT x 15 doses for SR, IT x 22-26 doses for HR, + CrRT for T-cell ALL and WBC>100,000 or CNS 3) Continuation therapy (Dexamethasone instead of Pred) and Study 13B (Additional IT during continuation therapy) vs SJCRH Total Therapy Study 11(1984-88) Remission Induction x 6 weeks (Pred,VCR,Daunorubicin, L-asparaginase,Teniposide,Cytarabine) Consolidation HD Mtx 2 g/m2, Etoposide,Cyclophosphamide,6MP, oral Mtx,Teniposide,Cytarabine,Prednisone,VCR, IT x 9 doses for SR, +CrRT for CNS 2 & 3, total IT x 13-15 doses for HR) and Study 12(1988-1991) plus additional Teniposide and Cytarabine during Consolidation and IT x 13-20 doses) be used for children with ALL?
Settings:
Bibliography: Pui (2010), review of 5 studies

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJCRH Total Therapy Study 13A(1991-1994) Remission Induction (IV Mtx 1 g/m2 for HR, 30 mg/m2 for SR, Etoposide, 2 additional weekly IT) Consolidation (HD Mtx 2 g/m2, 6MP, VCR, Pred, add L-Asparaginase for HR) Reinduction (VCR,Pred,L-asparaginase,IT x 15 doses for SR, IT x 22-26 doses for HR, + CrRT for T-cell ALL and WBC>100,000 or CNS 3) Continuation therapy (Dexamethasone instead of Pred) and Study 13B (Additional IT during continuation therapy)	SJCRH Total Therapy Study 11(1984-88) Remission Induction x 6 weeks (Pred,VCR,Daunorubicin, L-asparaginase,Teniposide,Cytarabine) Consolidation HD Mtx 2 g/m2, Etoposide,Cyclophosphamide,6MP, oral Mtx,Teniposide,Cytarabine,Prednisone,VCR , IT x 9 doses for SR, +CrRT for CNS 2 & 3, total IT x 13-15 doses for HR) and Study 12(1988-1991) plus additional Teniposide and Cytarabine during Consolidation and IT x 13-20 doses)	Relative (95% CI)	Absolute	Quality	Importance
Event Free Survival (assessed with: 10 year EFS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	307/412 (74.5%)	357/546 (65.4%)	RR 1.139 (0 to 0)	91 more per 1000 (from 654 fewer to 654 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Overall Survival (assessed with: 10 year OS)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	333/412 (80.8%)	424/546 (77.7%)	RR 1.04 (0 to 0)	31 more per 1000 (from 777 fewer to 777 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Induction Failure (assessed with: Death from Induction Failure)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/412 (1.9%)	21/546 (3.8%)	RR 0.5 (0 to 0)	19 fewer per 1000 (from 38 fewer to 38 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Cumulative Risk of Death in Remission (assessed with: 10 year Cumulative Risk of Death in Remission)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/412 (2.7%)	9/546 (1.6%)	RR 1.68 (0 to 0)	11 more per 1000 (from 16 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Infection Death in Remission (assessed with: Death from Infection during Induction)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/412 (1.2%)	6/546 (1.1%)	RR 1.09 (0 to 0)	1 more per 1000 (from 11 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Hematologic Relapse (assessed with: Isolated BMA Relapse)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/412 (10%)	67/546 (12.3%)	RR 0.81 (0 to 0)	23 fewer per 1000 (from 123 fewer to 123 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
CNS Relapse (assessed with: Isolated CNS Relapse)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/412 (2.2%)	40/546 (7.3%)	RR 0.30 (0 to 0)	51 fewer per 1000 (from 73 fewer to 73 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Testicular Relapse (assessed with: Isolated Testicular Relapse)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/412 (0.24%)	3/546 (0.55%)	RR 0.436 (0 to 0)	3 fewer per 1000 (from 5 fewer to 5 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Second Cancer (assessed with: Incidence of Secondary Cancer)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/412 (5.8%)	30/546 (5.5%)	RR 1.05 (0 to 0)	3 more per 1000 (from 55 fewer to 55 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Pui Study (Induction Therapy)

Author(s):
Date: 2021-09-17
Question: Should prophylactic cranial irradiation vs risk-adjusted chemotherapy using Induction Pred/Mtx/Vincristine/Daunorubicin/L-asparaginase/Cyclophosphamide/Cytarabine/Mercaptopurine/IT cytarabine/Triple IT using Mtx,Hydrocortisone, Cytarabine; Consolidation with High-dose Mtx/6-MP/Triple IT; Early Continuation /Reinduction using alternating pulses of VCR/Dexamethasone/L-asparaginase/Doxorubicin/6MP/oral Mtx without cranial irradiation be used for childhood ALL?
Settings:
Bibliography: Pui, Campana, et al 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic cranial irradiation	Risk-adjusted chemotherapy using Induction Pred/Mtx/Vincristine/Daunorubicin/L-asparaginase/Cyclophosphamide/Cytarabine/Mercaptopurine/IT cytarabine/Triple IT using Mtx,Hydrocortisone, Cytarabine; Consolidation with High-dose Mtx/6-MP/Triple IT; Early Continuation /Reinduction using alternating pulses of VCR/Dexamethasone/L-asparaginase/Doxorubicin/6MP/oral Mtx without cranial irradiation	Relative (95% CI)	Absolute		
5 year Overall Event Free Survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	426/498 (85.5%)	-	855 fewer per 1000 (from 855 fewer to 855 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year EFS for Low Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	228/239 (95.4%)	-	954 fewer per 1000 (from 954 fewer to 954 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year EFS for Standard Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	179/217 (82.5%)	-	825 fewer per 1000 (from 825 fewer to 825 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year EFS for High Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	20/42 (47.6%)	-	476 fewer per 1000 (from 476 fewer to 476 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year Overall Survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	465/498 (93.4%)	-	934 fewer per 1000 (from 934 fewer to 934 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year OS for Low Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	236/239 (98.7%)	-	987 fewer per 1000 (from 987 fewer to 987 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year OS for Standard Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	201/217 (92.6%)	-	926 fewer per 1000 (from 926 fewer to 926 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year OS for High Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	28/42 (66.7%)	-	667 fewer per 1000 (from 667 fewer to 667 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Cumulative Risk of Isolated CNS Relapse												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	11/498 (2.2%)	-	22 fewer per 1000 (from 22 fewer to 22 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Cumutive Risk of Death from Toxic Effects during Chemotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	7/498 (1.4%)	-	14 fewer per 1000 (from 14 fewer to 14 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Osteonecrosis following chemotherapy for Standard Risk or High Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	28/259 (10.8%)	-	108 fewer per 1000 (from 108 fewer to 108 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Osteonecrosis following chemotherapy for Low Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	4/239 (1.7%)	-	17 fewer per 1000 (from 17 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Thrombosis during chemotherapy for Standard or High Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	31/259 (12%)	-	120 fewer per 1000 (from 120 fewer to 120 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Thrombosis during chemotherapy for Low Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	5/239 (2.1%)	-	21 fewer per 1000 (from 21 fewer to 21 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Hyperglycemia during chemotherapy for Standard Risk or High Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	32/259 (12.4%)	-	124 fewer per 1000 (from 124 fewer to 124 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Hyperglycemia during chemotherapy for Low Risk ALL												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	9/239 (3.8%)	-	38 fewer per 1000 (from 38 fewer to 38 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year Rate of Continuous Complete Remission												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/56 (73.2%)	64/71 (90.1%)	-	901 fewer per 1000 (from 901 fewer to 901 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.81%		8 fewer per 1000 (from 8 fewer to 8 fewer)		

Teuffel Study

Dexamethasone compared to Prednisone for Induction Treatment of children with ALL

Patient or population: patients with Induction Treatment of children with ALL
Settings:
Intervention: Dexamethasone
Comparison: Prednisone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Prednisone**	Corresponding risk **Dexamethasone**				
Event 5 year Event Rate	**Study population**		**RR 0.790** (0 to 0)	8380 (8 studies)	⊕⊕⊕⊕ **high**	
	205 per 1000	**162 per 1000** (0 to 0)				
	Moderate					
CNS Relapse 5 year Cumulative Incidence of CNS Relapse	**Study population**		**RR 0.515** (0 to 0)	8873 (8 studies)	⊕⊕⊕⊕ **high**	
	64 per 1000	**33 per 1000** (0 to 0)				
	Moderate					
Death During Induction Death During 4 week Induction	**Study population**		**RR 2.307** (0 to 0)	6677 (8 studies)	⊕⊕⊕⊕ **high**	
	8 per 1000	**18 per 1000** (0 to 0)				
	Moderate					
Neuropsychiatric Events Neuropsychiatric Toxicity	**Study population**		**RR 4.93** (0 to 0)	3022 (8 studies)	⊖⊕⊕⊕ **high**	
	7 per 1000	**36 per 1000** (0 to 0)				
	Moderate					
Skeletal Toxicity Osteonecrosis	**Study population**		**RR 1.147** (0 to 0)	7717 (8 studies)	⊖⊕⊕⊕ **high**	
	34 per 1000	**39 per 1000** (0 to 0)				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Vora Study

Author(s):
Date: 2021-09-16
Question: Should cranial radiotherapy vs without cranial radiotherapy be used for prevention or relapse among children with ALL?
Settings:
Bibliography: VORA, 2011, single arm meta-analysis from 10 cooperative groups

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranial radiotherapy	Without cranial radiotherapy	Relative (95% CI)	Absolute		
5 year Overall Survival												
101	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14961/16623 (90%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
5 year Cumulative Incidence of Any Event												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2892/16623 (17.4%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Subgroup Analysis with Overt CNS Involvement (assessed with: 5 year Overall Cumulative Incidence of Any Event)												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	105/327 (32.1%)	10/29 (34.5%)	RR 0.93 (0 to 0)	24 fewer per 1000 (from 345 fewer to 345 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Subgroup Analysis with Overt CNS Involvement (assessed with: 5 year Crude Cumulative Incidence of Isolated Bone Marrow Relapse)												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/377 (10.3%)	2/29 (6.9%)	RR 1.49 (0 to 0)	34 more per 1000 (from 69 fewer to 69 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Subgroup Analysis with Overt CNS Involvement (assessed with: 5 year Cumulative Incidence of Isolated CNS Relapse)												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/377 (4.2%)	5/29 (17.2%)	-	172 fewer per 1000 (from 172 fewer to 172 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Subgroup Analysis with Overt CNS Involvement (assessed with: 5 year Cumulative Incidence of Isolated CNS Relapse)												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/377 (4.2%)	5/29 (17.2%)	-	172 fewer per 1000 (from 172 fewer to 172 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.244%		2 fewer per 1000 (from 2 fewer to 2 fewer)		
Subgroup Analysis with Overt CNS Involvement (assessed with: 5 year Crude Cumulative Incidence of any CNS Relapse)												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/377 (6.9%)	5/29 (17.2%)	-	172 fewer per 1000 (from 172 fewer to 172 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.40%		4 fewer per 1000 (from 4 fewer to 4 fewer)		
5 year Mortality Rate												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3103/13855 (22.4%)	248/1208 (20.5%)	-	205 fewer per 1000 (from 205 fewer to 205 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.09%		11 fewer per 1000 (from 11 fewer to 11 fewer)		

Yeh Study

Interventions for [Condition] in [Population]

Outcomes	Intervention and Comparison intervention	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		With comparator	With intervention				
5 year Overall Survival							
	Delayed 1st intrathecal therapy using TIT (Mtx,Hydrocortisone, Cytarabine) and omission of prophylactic cranial irradiation/TIT with prophylactic cranial irradiation	**Study population**		**RR 0.956** (0 to 0)	1347 (1 study)	⊕⊕⊕⊕ **high**	
		829 per 1000	**793 per 1000** (0 to 0)				
		Moderate					
5 year Event Free Survival							
	Delayed 1st intrathecal therapy using TIT (Mtx,Hydrocortisone, Cytarabine) and omission of prophylactic cranial irradiation/TIT with prophylactic cranial irradiation	**Study population**		**RR 0.954** (0 to 0)	1347 (1 study)	⊕⊕⊕⊕ **high**	
		756 per 1000	**722 per 1000** (0 to 0)				
		Moderate					
Cumulative Risk of Isolated CNS Relapse							
	Delayed 1st intrathecal therapy using TIT (Mtx,Hydrocortisone, Cytarabine) and omission of prophylactic cranial irradiation/TIT with prophylactic cranial irradiation	**Study population**		**RR 0.35** (0 to 0)	1347 (1 study)	⊕⊕⊕⊕ **high**	
		40 per 1000	**14 per 1000** (0 to 0)				
		Moderate					

5 year Event Free Survival for Non CNS-1 status (CNS-2,CNS-3,Traumatic Lumbar Puncture with Blasts)					
Delayed 1st intrathecal therapy using TIT (Mtx,Hydrocortisone, Cytarabine) and omission of prophylactic cranial irradiation/TIT with prophylactic cranial irradiation	**Study population**		**RR 1.179** (0 to 0)	104 (1 study)	⊕⊕⊕⊕ **high**
	536 per 1000	**632 per 1000** (0 to 0)			
	Moderate				
Cumulative Risk of Isolated CNS Relapse for Non CNS-1 Status					
Delayed 1st intrathecal therapy using TIT (Mtx,Hydrocortisone, Cytarabine) and omission of prophylactic cranial irradiation/TIT with prophylactic cranial irradiation	**Study population**		**RR 0.549** (0 to 0)	104 (1 study)	⊕⊕⊕⊕ **high**
	71 per 1000	**39 per 1000** (0 to 0)			
	Moderate				

Sima Jeha Study

Author(s):
Date: 2021-06-08
Question: Should Extra doses ofTriple Intrathecal chemotherapy vs cranial radiation be used in children with ALL?
Settings: CNS Prophyiaxis
Bibliography: Sima Jeha (St. Jude Study) 2019

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extra doses ofTriple Intrathecal chemotherapy	Cranial radiation	Relative (95% CI)	Absolute		
CNS Relapse (assessed with: Isolated CNS Relapse)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/2545 (1.5%)	126/3150 (4%)	RR 0.375 (0 to 0)	25 fewer per 1000 (from 40 fewer to 40 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] No explanation was provided

Monitoring of Treatment Response and Adherence

Conter Study

Question: What is the EFS based on MRD of pediatric ALL patients
Bibliography: Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment & redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010; 115:3206 – 3214
Author(s):

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
5-year Event Free Survival MRD-SR <0.01% (assessed with: 5-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	81	1348	event rate 92.3% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
5-year Event Free Survival MRD-IR 0.01 to <0.1% (assessed with: 5-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	288	1647	event rate 77.6% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
5-year Event Free Survival MRD-HR 0.1% and above (assessed with: 5-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	86	189	event rate 50.1% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-SR + AGE 1-9 (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	1165	2589	event rate 93.5% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-SR + AGE 10-17 (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	183	1348	event rate 84.4%	⊕⊕⊕⊕ HIGH	CRITICAL

									(-- to --)		
EFS MRD-IR + AGE 1-9 (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	1298	1647	event rate 79% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-IR + AGE 10-17 (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	349	1647	event rate 72.3% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-HR + AGE 1-9 (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	126	189	event rate 50.2% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-HR + AGE 10-17 (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	63	189	event rate 50.3% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-SR + NCI-SR (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	1007	1348	event rate 94.1% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-SR + NCI-HR (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	341	1348	event rate	⊕⊕⊕⊕ HIGH	CRITICAL

									86.9% (-- to --)		
EFS MRD-IR + NCI-SR (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	1122	1647	event rate 80.3% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-IR + NCI-HR (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	525	1647	event rate 71.8% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-HR + NCI-SR (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	95	189	event rate 49.3% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
EFS MRD-HR + NCI-HR (assessed with: 5 year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	94	189	event rate 51.4% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL

cumulative incidence of relapse or MRD-SR (assessed with: percentage)											
1	observational studies	not serious	not serious	not serious	not serious	none	61	1348	event rate 6% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
cumulative incidence of relapse or MRD-IR (assessed with: percentage)											
1	observational studies	not serious	not serious	not serious	not serious	none	266	1647	event rate 21% (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
cumulative incidence of relapse or MRD-HR (assessed with: percentage)											
1	observational studies	not serious	not serious	not serious	not serious	none	60	189	event rate 34.9 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL

Scrideli Study

Question: Course of childhood ALL in terms of survival over 5 years
Bibliography: Scrideli, C. A., de Paula Queiróz, R., Bernardes, J. E., Defavery, R., Valera, E. T., & Tone, L. G. (2008). Use of simplified strategies to evaluate early treatment response in childhood acute lymphoblastic leukemia. Leukemia research, 30(8), 1049-1052. https://doi.org/10.1016/j.leukres.2005.11.021
Author(s): Scrideli et al

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95 % CI)		
Day 7 WBC <5000 event free survival (assessed with: 5-YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	71	84	event rate 78.8 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Day 7 WBC >5000 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	13	84	event rate 46.2 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Day 28 bone marrow blast <5% EFS (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	74	80	event rate 80.2 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Day 28 bone marrow blast >5% EFS (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	6	80	event rate 33.3 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
MRD (+) day 14 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	9	37	event rate 64.8 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
MRD (-) day 14 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	28	37	event rate 96.3 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
MRD (+) day 28 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	17	72	event rate 22.1 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
MRD (-) day 28 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	55	72	event rate 93.2 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
ALL-SR MRD (+) day 28 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none			event rate 33.3 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
ALL-HR MRD (+) day 28 event free survival (assessed with: 5 YEAR EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none			event rate 21.4 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL

Dai Study

Question: Course of childhood acute lymphoblastic leukemia in terms of survival over 3 years

Bibliography: Dai, Qingkai MDa,b; Shi, Rui MD, PhDa,b; Zhang, Ge MD, PhDa,b; Yang, Hui MDa,b; Wang, Yuefang MDa,b; Ye, Lei MDa,b; Peng, Luyun MDa,b; Guo, Siqi MDa,b; He, Jiajing MDa,b; Jiang, Yongmei MD, PhDa,b,*
Combined use of peripheral blood blast count and platelet count during and after induction therapy to predict prognosis in children with acute lymphoblastic leukemia, Medicine: April 16, 2021 - Volume 100 - Issue 15 - p e25548. doi: 10.1097/MD.0000000000025548

Author(s): Dai et al 2021

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95 % CI)		
Event free survival low blast, high platelet (assessed with: 3-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	315	415	event rate 86.3 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Event free survival high blast, high platelet (assessed with: 3-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	43	415	event rate 76.7 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Event free survival low blast, low platelet (assessed with: 3-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	45	415	event rate 70.8 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Event free survival high blast, low platelet (assessed with: 3-year EFS)											
1	observational studies	not serious	not serious	not serious	not serious	none	13	415	event rate 53.8 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Overall survival low blast d8, high platelet d33 (assessed with: 3-year OS)											
1	observational studies	not serious	not serious	not serious	not serious	none	315	415	event rate 90.1 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Overall survival high blast d8, high platelet d33 (assessed with: 3-year OS)											
1	observational studies	not serious	not serious	not serious	not serious	none	43	415	event rate 83.7 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Overall survival low blast d8, low platelet d33 (assessed with: 3-year OS)											
1	observational studies	not serious	not serious	not serious	not serious	none	45	415	event rate 79.6 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL
Overall survival high blast d8, low platelet d33 (assessed with: 3-year OS)											
1	observational studies	not serious	not serious	not serious	not serious	none	13	415	event rate 61.5 % (-- to --)	⊕⊕⊕⊕ HIGH	CRITICAL

Alam Study

Question: Course of pediatric ALL in treatment adherence over time
Setting:
Bibliography: Alam, A., & Kumar, A. (2018). Prevalence, predictors, causes of treatment refusal and abandonment in children with acute lymphoblastic leukaemia over 18 years in North India. Treatment phase affecting factors: A step towards better focussed counselling. Cancer epidemiology, 57, 53-69. https://doi.org/10.1016/j.canep.2018.07.011
Author(s): Alam et al 2018

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
treatment refusal (follow-up: mean 18 years; assessed with: prevalance)											
1	observational studies	not serious	not serious	not serious	not serious	none	96	572	event rate 16.8% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
treatment abandonment (follow-up: mean 18; assessed with: prevalence)											
1	observational studies	not serious	not serious	not serious	not serious	none	139	476	event rate 29.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age <1 refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	6	10	event rate 60.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age 1-5 refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	39	231	event rate 16.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age >5-10 refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	42	244	event rate 17.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age >10 refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	9	87	event rate 10.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
SES lower refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	83	392	event rate 21.2% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
SES middle refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	13	165	event rate 7.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
SES upper refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	0	15	event rate 0.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Residence urban refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	18	157	event rate 11.4% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Residence rural refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	78	415	event rate 18.8% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Father illiterate refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	51	222	event rate 24.8% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Father low refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	39	257	event rate	⊕⊕⊕⊕ High	CRITICAL

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
									15.2% (-- to --)		
Father high refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	6	93	event rate 6.5% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Financial constraint refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	57	139	event rate 59.4% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Belief about incurability refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	22	139	event rate 22.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age <1 abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	2	4	event rate 50.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age 1-5 abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	52	192	event rate 27.1% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age >5-10 abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	64	202	event rate 31.7% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Age >10 abandonment											

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
1	observational studies	not serious	not serious	not serious	not serious	none	21	78	event rate 26.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
SES lower abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	109	309	event rate 35.3% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
SES middle abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	21	152	event rate 19.1% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
SES upper abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	1	15	event rate 6.7% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Residence urban abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	25	139	event rate 18.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Residence rural abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	114	337	event rate 33.9% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Father illiterate abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	68	171	event rate 39.8% (-- to --)	⊕⊕⊕⊕ High	CRITICAL

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Father low abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	55	218	event rate 25.2% (- - to --)	⊕⊕⊕⊕ High	CRITICAL
Father high abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	16	87	event rate 18.4% (- - to --)	⊕⊕⊕⊕ High	CRITICAL
Financial constraint abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	48	129	event rate 34.5% (- - to --)	⊕⊕⊕⊕ High	CRITICAL
Belief about incurability abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	28	129	event rate 20.1% (- - to --)	⊕⊕⊕⊕ High	CRITICAL
Poor general condition abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	21	129	event rate 15.1% (- - to --)	⊕⊕⊕⊕ High	CRITICAL
No improvement of child abandonment											
1	observational studies	not serious	not serious	not serious	not serious	none	19	129	event rate 13.7% (- - to --)	⊕⊕⊕⊕ High	CRITICAL

Sitaresmi Study

Question: Course of childhood ALL in treatment adherence over 3-4 years
Setting: Indonesia
Bibliography: Sitaresmi, M. N., Mostert, S., Schook, R. M., Sutaryo, & Veerman, A. J. (2010). Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: an analysis of causes and consequences. Psycho-oncology, 19(4), 361–367. https://doi.org/10.1002/pon.1578.
Author(s): Sitaresmi et al 2010

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
patient refused/abandoned treatment											
1	observational studies	not serious	not serious	not serious	not serious	none	40	159	event rate 25.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: financial difficulties											
1	observational studies	not serious	not serious	not serious	not serious	none	22	37	event rate 60.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: belief about incurability											
1	observational studies	not serious	not serious	not serious	not serious	none	22	37	event rate 60.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: severe side effects											
1	observational studies	not serious	not serious	not serious	not serious	none	13	37	event rate 35.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: transportation difficulties											
1	observational studies	not serious	not serious	not serious	not serious	none	8	37	event rate 22.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: patient refusal											
1	observational studies	not serious	not serious	not serious	not serious	none	8	37	event rate 22%% (-- to --)	⊕⊕⊕⊕ High	CRITICAL

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
Reason: dissatisfaction with HC providers											
1	observational studies	not serious	not serious	not serious	not serious	none	4	37	event rate 11.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: no room availability											
1	observational studies	not serious	not serious	not serious	not serious	none	2	37	event rate 5.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reason: child looked healthy											
1	observational studies	not serious	not serious	not serious	not serious	none	2	37	event rate 5.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Remission induction phase											
1	observational studies	not serious	not serious	not serious	not serious	none	19	40	event rate 48.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Consolidation phase											
1	observational studies	not serious	not serious	not serious	not serious	none	5	40	event rate 12.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Reinduction phase											
1	observational studies	not serious	not serious	not serious	not serious	none	1	40	event rate 3.0% (-- to --)	⊕⊕⊕⊕ High	CRITICAL
Maintenance phase											
1	observational studies	not serious	not serious	not serious	not serious	none	10	40	event rate	⊕⊕⊕⊕ High	CRITICAL

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
									25.0% (-- to --)		

Alsous Study

adherence to oral maintenance chemotherapy compared to non-adherence to oral maintenance chemotherapy for children with ALL

Patient or population: patients with children with ALL
Settings:
Intervention: adherence to oral maintenance chemotherapy
Comparison: non-adherence to oral maintenance chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Non-adherence to oral maintenance chemotherapy**	Corresponding risk **Adherence to oral maintenance chemotherapy**				
Overall Adherence Overall Adherence Rate	**Study population**		**RR 4.2** (0 to 0)	104 (1 study)	⊕⊕⊖⊕ **high**[1,2]	
	192 per 1000	**808 per 1000** (0 to 0)				
	Moderate					
Levels of TGN & 6MP Levels of TGN & 6MP in packed RBC	**Study population**		**RR 5.49** (0 to 0)	104 (1 study)	⊕⊕⊖⊕ **high**[3]	
	154 per 1000	**845 per 1000** (0 to 0)				
	Moderate					
MARS questionnaire for parent/caregiver MARS score > or equal to 4.5	**Study population**		**RR 16.24** (0 to 0)	104 (1 study)	⊕⊕⊖⊕ **high**[4,5]	
	58 per 1000	**937 per 1000** (0 to 0)				
	Moderate					
MARS questionnaire for child MARS mean score > or equal to 4.5	**Study population**		Not estimable	104 (1 study)	⊕⊕⊕⊕ **high**[6,7]	
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Difference in the overall adherence rate is > 75% between intervention and control groups
[2] The higher the MARS score and levels of 6mp and TGN means the higher the adherence rate
[3] Difference between MARS mean scores of parents/caregivers were higher among adherent parents and caregivers
[4] The higher the MARS score, the more adherent the parent or caregiver
[5] Difference between MARS scores of children were higher by 100% among adherent children to medications
[6] MARS score of children > or equal to 4.5 had a higher adherence rate
[7] No explanation was provided

Kamal Study

non-adherence to oral 6MP maintenance chemotherapy by questionnaire and serum 6MP levels compared to adherence to both for children with ALL

Patient or population: patients with children with ALL
Settings:
Intervention: non-adherence to oral 6MP maintenance chemotherapy by questionnaire and serum 6MP levels
Comparison: adherence to both

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Adherence to both	Corresponding risk Non-adherence to oral 6MP maintenance chemotherapy by questionnaire and serum 6MP levels	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Over-all non-adherence rate Non-adherence to 6MP	**Study population**		Not estimable	129 (1 study)	⊕⊕⊕⊕ **high**[1,2]	
	Moderate					
Forgetfullness of the caregiver	**Study population**		Not estimable	72 (1 study)	⊕⊕⊕⊖ **moderate**[3]	
	Moderate					
Negligence of caregiver/parent	**Study population**		Not estimable	72 (1 study)	⊕⊕⊕⊖ **moderate**[4]	
	Moderate					
child's refusal to take 6MP	**Study population**		Not estimable	72 (1 study)	⊕⊕⊕⊖ **moderate**[5]	
	Moderate					
Drug unavailability	**Study population**		Not estimable	72 (1 study)	⊕⊕⊕⊖ **moderate**[6]	
	Moderate					
Medical Staff Error	**Study population**		Not estimable	72 (1 study)	⊕⊕⊕⊖ **moderate**[7]	
	Moderate					
Socioeconomic Status Low Socioeconomic Level	**Study population**		**RR 5.34** (0 to 0)	258 (1 study)	⊕⊕⊕⊕ **high**[8,9]	
	157 per 1000	**839 per 1000** (0 to 0)				
	Moderate					
Educational Level of caregiver/parent Non-educated caregiver/parent	**Study population**		**RR 1.76** (0 to 0)	258 (1 study)	⊕⊕⊕⊕ **high**[10]	
	364 per 1000	**640 per 1000** (0 to 0)				
	Moderate					

Educational Level of caregiver/parent Low educational level of caregiver/parent	**Study population**	**RR 2.81** (0 to 0)	274 (1 study)	⊖⊕⊕⊕ **high**[1]
	234 per 1000 **656 per 1000** (0 to 0)			
	Moderate			
Family number > 5	**Study population**	**RR 1.81** (0 to 0)	258 (1 study)	⊖⊕⊕⊕ **high**[2]
	331 per 1000 **598 per 1000** (0 to 0)			
	Moderate			
Cost to follow-up of hospital visits	**Study population**	**RR 1.51** (0 to 0)	258 (1 study)	⊖⊕⊕⊕ **high**[3]
	397 per 1000 **599 per 1000** (0 to 0)			
	Moderate			
Non-adherence based on serum 6MP level serum 6MP level < 9.3 ng	**Study population**	Not estimable	0 (1 study)	⊖⊕⊕⊕ **high**[4]
	Moderate			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

Yeoh Study

More than median length of treatment delays in chemotherapy compared to less than median length of treatment delays in chemotherapy for risk of relapses in childhood ALL

Patient or population: patients with risk of relapses in childhood ALL
Settings:
Intervention: More than median length of treatment delays in chemotherapy
Comparison: less than median length of treatment delays in chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Less than median length of treatment delays in chemotherapy**	Corresponding risk **More than median length of treatment delays in chemotherapy**				
Cumulative Risk of Relapse according to median length of delay	**Study population**		**RR 1.16** (0 to 0)	141 (1 study)	⊕⊕⊕⊕ **high**[1]	
	125 per 1000	**145 per 1000** (0 to 0)				
	Moderate					
Relapse in the Intensive Phase of Chemotherapy according to Median length of delay	**Study population**		**RR 1.16** (0 to 0)	141 (1 study)	⊕⊕⊕⊕ **high**[2]	
	125 per 1000	**145 per 1000** (0 to 0)				
	Moderate					
Relapse in the Maintenance Phase according to median length of delay	**Study population**		**RR 0.46** (0 to 0)	141 (1 study)	⊕⊕⊕⊕ **high**[3]	
	183 per 1000	**84 per 1000** (0 to 0)				
	Moderate					

Cumulative Risk of Relapse by quartile	**Study population**		**RR 0.279** (0 to 0)	63 (1 study)	⊕⊕⊕⊕ **high**
	179 per 1000	**50 per 1000** (0 to 0)			
	Moderate				
Relapse in the Intensive Phase of chemotherapy by quartile	**Study population**		**RR 0.994** (0 to 0)	64 (1 study)	⊕⊕⊕⊕ **high**
	172 per 1000	**171 per 1000** (0 to 0)			
	Moderate				
Relapse in the Maintenance Phase by quartile	**Study population**		Not estimable	0 (1 study)	See comment
	See comment	See comment			
	Moderate				
Low blood counts as cause of delay in the Intensive Phase of Chemotherapy	**Study population**		Not estimable	141 (1 study)	⊕⊕⊕⊖ **moderate**
	Moderate				
Low blood counts as cause of delay in the Maintenance Phase of Chemotherapy	**Study population**		Not estimable	141 (1 study)	⊕⊕⊕⊖ **moderate**
	Moderate				
Severe Infections as a cause of treatment delay in the Intensive Phase of chemotherapy	**Study population**		Not estimable	141 (1 study)	⊕⊕⊕⊖ **moderate**[4]
	Moderate				
Severe Infections as a cause of treatment delay in the Maintenance phase of chemotherapy	**Study population**		Not estimable	141 (1 study)	⊕⊕⊕⊖ **moderate**
	Moderate				
Febrile Neutropenia as a cause of treatment delay in the Intensive Phase of chemotherapy	**Study population**		Not estimable	141 (1 study)	⊕⊕⊕⊖ **moderate**
	Moderate				
Febrile Neutropenia as a cause of treatment delay in the Maintenance Phase of chemotherapy	**Study population**		Not estimable	141 (1 study)	⊕⊕⊕⊖ **moderate**
	Moderate				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Prognosis

Gupta Study

Question: Prognistic Factors for Childhood ALL
Setting:
Bibliography: Absolute Lymphocyte Count Recovery Independently Predicts Outcome in Childhood ALL: Experience from a Tertiary Care Center from a Developing Country
Author(s): Anshul Gupta, MD, FNB,* Gauri Kapoor, MD, PhD,* Sandeep Jain, DNB, FIAP,* and Ram Bajpai, Msc, PhDw

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other conside rations	Nº of events	Nº of individuals	%		
5 year overall survival with DAY 15 ALC >500											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	135	113	**84.1**	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year overall survival with Day 15 ALC <500 (follow up: 5 years; assessed with: ALC <500)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	77	42	54.4	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year relapse free survival with Day 15 ALC >500 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	135	107	**79.2**	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year relapse free survival with Day 15 ALC <500 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	77	32	41.3	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year event free survival with Day 15 ALC >500 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	135	55	**72.3**	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year event free survival with Day 15 ALC <500 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	77	47	34.8	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year overall survival with Day 29 ALC >1000 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	128	112	**88.1**	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year overall survival with Day 29 ALC <1000 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	84	40	47.8	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year relapse free survival with Day 29 ALC >1000 (follow up: 5 years; assessed with: ALC)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	128	110	**88.5**	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year relapse free survival with Day 29 ALC <1000 (follow up: 5 years)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	84	29.5	35.2	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year event free survival with Day 29 ALC >1000 (follow up: 5 years)											
1	observatio nal studies	not serious	not serious	not serious	not serious	strong associati on	128	99.5	**77.8**	⊕⊕⊕⊕ HIGH	IMPORTANT
5 year event free survival with Day 29 ALC <1000 (follow up: 5 years)											
1	observatio nal studies		not serious	not serious	not serious	strong associati on	84	27	32.6	⊕⊕⊕⊕ HIGH	IMPORTANT

5 year Relapse free survival with ALC Day 15 <500/uL (follow up: 5; assessed with: adjusted hazard ratio)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1		event rate 3.4 % (1.8 to 6.4)	⨁⨁⨁⨁ HIGH	IMPORTANT
5 year Event free survival with ALC Day 15 <500/uL (follow up: 5 years; assessed with: adjusted hazard ratio)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	-		undefined 2.5 SD (1.5 to 4.2)	⨁⨁⨁⨁ HIGH	IMPORTANT
5 year overall survival with ALC Day 15 <500/uL (follow up: 5 years; assessed with: adjusted hazard ratio)											
1	observational studies	not serious	not serious	not serious	not serious	strong association			event rate 2.0 % (1.1 to 3.7)	⨁⨁⨁⨁ HIGH	IMPORTANT
5 year relapse free survival with ALC D29 <1000/uL (follow up: 5 years; assessed with: adjusted hazard ratio)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	-		undefined 2.54 (1.4 to 4.7)	⨁⨁⨁⨁ HIGH	IMPORTANT

5 year event free survival with ALC <1000/uL (follow up: 5 years; assessed with: adjusted hazard ratio)											
1	observational studies	not serious	not serious	not serious	not serious	strong association			event rate 2.2 % (1.3 to 3.7)	⨁⨁⨁⨁ HIGH	IMPORTANT
5 year overall survival with ALC <1000/uL (follow up: 5 years; assessed with: adjusted hazard ratio)											
1	observational studies	not serious	not serious	not serious	not serious	strong association	-		undefined 2.3 (1.3 to 4.1)	⨁⨁⨁⨁ HIGH	

Rabin Study

Question:
Setting:
Bibliography: Absolute Lymphocyte Counts Refine MRD-Disease Based Risk Stratification in Childhood ALL. Pediatric Blood Cancer Sept 20112
Author(s): Karen Rabin et al

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Relapse free survival with ALC day 29 < 1500 cells/uL (follow up: 5 years; assessed with: 5 year)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	49	171	p 0.018 per HR 2.2 (1.1 to 4.2)	⨁⨁⨁⨁ HIGH	CRITICAL
RFS age <10 yrs at dx (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	141	171	P 0.001 per HR 0.28 (0.14 to 0.56)	⨁⨁⨁⨁ HIGH	CRITICAL
RFS initial WBC <50,000/cumm											
1	observational studies	not serious	not serious	not serious	not serious	strong association	158	171	HR per (0.23 to 1.9)	⨁⨁⨁⨁ HIGH	CRITICAL
RFS favorable cytogenetics											
1	observational studies	not serious	not serious	not serious	not serious	strong association	65	171	HR 0.32 per (0.14 to 0.74)	⨁⨁⨁⨁ HIGH	IMPORTANT
RFS MRD day 29 >0.01%											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	26	171	p 0.001 per HR 3.3 (1.6 to 6.7)	⨁⨁⨁⨁ HIGH	

Overall Survival ALC day 29 < 1500 cells/uL (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	49	171	p 0.001 per HR 7.0 (2.2 to 22.3)	⊕⊕⊕⊕ HIGH	
OS age at Dx <10 yrs											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	142	171	p 0.001 HR 0.13 (0.04 to 0.38)	⊕⊕⊕⊕ HIGH	
OS mean initial WBC <50,000/cumm (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	158	171	p 0.367 HR 0.50 (0.11 to 2.2)	⊕⊕⊕⊕ HIGH	
OS MRD day 29 > 0.01% (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	none	26	171	p 0.001 HR 6.6 (2.1 to 20.9)	⊕⊕⊕⊕ HIGH	

Winick Study

Question: Initial CSF finding as prognostic factor for relapse
Setting:
Bibliography: IMpact of Initial CSF findings on outcome of patients with standard and high risk B cell ALL
Author(s): naomi winick, et al

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate		
CNS 1, 5 yr EFS (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	7214	8174	85%, (SE 0.6%)	⊕⊕⊕⊕ HIGH	CRITICAL
CNS 2, 5 yr EFS (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	836	8174	76% (SE 2%)	⊕⊕⊕⊕ HIGH	CRITICAL
CNS 3, 5 yr EFS (follow up: 5 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	124	8174	76% (SE 5%) **p 0.001 %**	⊕⊕⊕⊕ HIGH	CRITICAL
CNS 1, OS (follow up: 8 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	7577	8174	92.7% (SE 0.4%)	⊕⊕⊕⊕ HIGH	CRITICAL
CNS 2, OS (follow up: 8 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	725	836	86.8% (SE 1.6%)	⊕⊕⊕⊕ HIGH	CRITICAL
CNS 3, OS (follow up: 8 years)											
1	observational studies	not serious	not serious	not serious	not serious	very strong association	101	124	82.1% (SE :4.7%), **p 0.001**	⊕⊕⊕⊕ HIGH	CRITICAL
Combined CNS relapse, CNS 1											
1	observational studies	not serious	not serious	not serious	not serious	strong association	202	7214	2.85% (SE 0.2%)%	⊕⊕⊕⊕ HIGH	CRITICAL
Combined CNS relapse, CNS 2											
1	observational studies	not serious	not serious	not serious	not serious	strong association	64	836	7.7% (SE 0.97)%	⊕⊕⊕⊕ HIGH	CRITICAL
Combined CNS relapse, CNS 3											
1	observational studies	not serious	not serious	not serious	not serious	strong association	6	124	5.1% (SE 2%) **p< 0.001**	⊕⊕⊕⊕ HIGH	CRITICAL
Isolated CNS relapse, CNS 1											
1	observational studies	not serious	not serious	not serious	not serious	strong association	144	7214	2% (SE 0.2%)	⊕⊕⊕⊕ HIGH	CRITICAL

Isolated CNS relapse, CNS 2											
1	observational studies	not serious	not serious	not serious	not serious	strong association	46	836	5.6% (SE 1.8%)	⊕⊕⊕⊕ HIGH	CRITICAL
Isolated CNS relapse, CNS 3											
1	observational studies	not serious	not serious	not serious	not serious	strong association	6	124	5.1% (SE 2%) **p <0.001**	⊕⊕⊕⊕ HIGH	CRITICAL
Bone marrow relapse, CNS 1											
1	observational studies	not serious	not serious	not serious	not serious	strong association	411	7214	5.7% (SE 0.3%)	⊕⊕⊕⊕ HIGH	CRITICAL
Bone marrow relapse, CNS 2											
1	observational studies	not serious	not serious	not serious	not serious	strong association	54	836	6.5% (SE 0.9)	⊕⊕⊕⊕ HIGH	
Bone marrow relapse, CNS 3											
1	observational studies	not serious	not serious	not serious	not serious	strong association	11	124	9.3% (SE 2.9%)' **p 0.08**	⊕⊕⊕⊕ HIGH	

S.M. Ng Study

Question: Course of [health condition] over [time]
Setting:
Bibliography: Age, Sex, Hb level and white cell count at diagnosis are important prognostic factors in children with ALL treated with BFM type protocol
Author(s): S.M. Ng et al

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Event Rate		
Treatment failure rate, age < 1 yr											
1	observational studies	not serious	not serious	not serious	not serious	strong association	18	23	78%%	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate , age > 1 yr											
1	observational studies	not serious	not serious	not serious	not serious	strong association	239	552	43% **p 0.0001**	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate, male											
1	observational studies	not serious	not serious	not serious	not serious	strong association	167	326	51%	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate, female											
1	observational studies	not serious	not serious	not serious	not serious	strong association	90	249	36% **p 0.0003**	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate, WCC <50,000											
1	observational studies	not serious	not serious	not serious	not serious	strong association	179	441	41%	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate, WCC >50,000											
1	observational studies	not serious	not serious	not serious	not serious	strong association	70	126	56% **p 0.003**	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate, Hb <11											
1	observational studies	not serious	not serious	not serious	not serious	strong association	199	481	41%	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure rate, Hb >11											
1	observational studies	not serious	not serious	not serious	not serious	strong association	41	72	57% **p 0.01**	⊕⊕⊕⊕ HIGH	CRITICAL

Side Effects and Complications

Ness (Methotrexate Study)

Author(s): ALL group
Date: 2021-06-07
Question: Should Methotrexate be used for Pediatric ALL?
Settings:
Bibliography: Ness, et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Control	Relative (95% CI)	Absolute		
Limited Walking Efficiency (assessed with: Neuromuscular Performance Testing)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	115/193 (59.6%)	38/193 (19.7%)	OR 5.8 (2.2 to 15.4)	390 more per 1000 (from 153 more to 594 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Limited Walking Efficiency (assessed with: Neuromuscular Performance Testing)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	86/193 (44.6%)	38/193 (19.7%)	OR 4.0 (1.5 to 10.7)	298 more per 1000 (from 72 more to 527 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Dorsiflexion Range (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	61/139 (43.9%)	41/139 (29.5%)	OR 3.4 (1.2 to 9.8)	29 more per 100 (from 4 more to 51 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Dorsiflexion Range (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	41/139 (29.5%)	41/139 (29.5%)	OR 2 (0.8 to 5.5)	16 more per 100 (from 4 fewer to 40 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Knee Extension Strength (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	37/125 (29.6%)	29/125 (23.2%)	OR 4.1 (1.3 to 13.2)	321 more per 1000 (from 50 more to 567 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Knee Extension Strength (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	39/125 (31.2%)	29/125 (23.2%)	OR 3.7 (1.2 to 11.2)	296 more per 1000 (from 34 more to 540 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] IT Methotrexate dose: 215-694mg/m2
[2] IT Methotrexate dose: 47-214mg/m2

Ness (Vincristine Study)

Author(s):
Date: 2021-06-17
Question: Should Vincristine be used for Pediatric ALL?
Settings:
Bibliography: Ness et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vincristine	Control	Relative (95% CI)	Absolute		
Limited Walking Efficiency (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	96/193 (49.7%)	-	OR 1.3 (0.9 to 2.1)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Limited Walking Efficiency (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	83/193 (43%)	-	OR 1 (0 to 0)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Dorsiflexion Range (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	51/139 (36.7%)	-	OR 1.5 (1 to 2.5)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Dorsiflexion Range (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	42/139 (30.2%)	-	OR 1 (0 to 0)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Knee Extension Strength (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	35/125 (28%)	-	OR 1.2 (0.7 to 2.1)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impaired Knee Extension Strength (assessed with: Neuromuscular Performance Test)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	40/125 (32%)	-	OR 1 (0 to 0)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Vincristine dose: 39-220mg/m2
[2] Vincristine dose: 3-38mg/m2

Williams Study

Author(s):
Date: 2021-06-22
Question: Should L-asparaginase be used for Children with ALL (<15 years at diagnosis)?
Settings:
Bibliography: Williams et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	L-asparaginase	Control	Relative (95% CI)	Absolute		
Diabetes mellitus (assessed with: Plasma glucose and Glycosylated hemoglobin (HgbA1c))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	64/978 (6.5%)	0%	OR 0.99 (0.94 to 1.04)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] L-asparaginase dose: per 1000units/m2 increase

Author(s):
Date: 2021-06-22
Question: Should Prednisone be used for Children with ALL (<15 years at diagnosis)?
Settings:
Bibliography: Williams et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone	Control	Relative (95% CI)	Absolute		
Diabetes mellitus (assessed with: Plasma glucose and Glycosylated hemoglobin (HgbA1c))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	62/951 (6.5%)	0%	OR 1.05 (0.98 to 1.12)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Prednisone dose (per 1000mg/m2)

Author(s):
Date: 2021-06-22
Question: Should Dexamethasone be used for Children with ALL (<15 years at diagnosis)?
Settings:
Bibliography: Williams et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Control	Relative (95% CI)	Absolute		
Diabetes mellitus (assessed with: Plasma glucose and Glycosylated hemoglobin (HgbA1c))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	20/208 (9.6%)	0%	OR 1.58 (1.05 to 2.37)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Dexamethasone dose (per 1000mg/m2)

Author(s):
Date: 2021-06-22
Question: Should L-asparaginase be used for Children with ALL (>15 years at diagnosis)?
Settings:
Bibliography: Williams et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	L-asparaginase	Control	Relative (95% CI)	Absolute		
Diabetes mellitus (assessed with: Plasma glucose and Glycosylated hemoglobin (HgbA1c))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	18/66 (27.3%)	-	OR 1.12 (1.02 to 1.23)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] L-asparaginase dose: per 1000units/m2 increase

Author(s):
Date: 2021-06-22
Question: Should Prednisone be used for Children with ALL (>15 years at diagnosis)?
Settings:
Bibliography: Williams et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisone	Control	Relative (95% CI)	Absolute		
Diabetes mellitus (assessed with: Plasma glucose and Glycosylated hemoglobin (HgbA1c))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	17/65 (26.2%)	0%	OR 1.07 (0.9 to 1.28)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Prednisone dose (per 1000mg/m2)

Author(s):
Date: 2021-06-22
Question: Should Dexamethasone be used for Children with ALL (>15 years at diagnosis)?
Settings:
Bibliography: Williams et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	Control	Relative (95% CI)	Absolute		
Diabetes mellitus (assessed with: Plasma glucose and Glycosylated hemoglobin (HgbA1c))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	7/23 (30.4%)	0%	OR 0.53 (0.15 to 1.84)	-	⊕⊕⊕O MODERATE	CRITICAL

[1] Dexamethasone dose (per 1000mg/m2)

Lipshultz Study

Author(s):
Date: 2021-09-11
Question: Should Doxorubicin be used for Children with ALL?
Settings:
Bibliography: Lipshultz SE, et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxorubicin	Control	Relative (95% CI)	Absolute		
Cardiac abnormality of left ventricular load (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	3/18 (16.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cardiac abnormality of left ventricular load (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	29/52 (55.8%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cardiac abnormality of left ventricular load (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[3]	31/42 (73.8%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cardiac abnormality of left ventricular load (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[4]	3/3 (100%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cardiac abnormality of left ventricular load (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[5]	63/97 (64.9%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Increased afterload (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	3/18 (16.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Increased afterload (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	26/52 (50%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Increased afterload (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[3]	28/42 (66.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Increased afterload (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[4]	3/3 (100%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Increased afterload (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[5]	57/97 (58.8%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Decreased contractility (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	-	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Decreased contractility (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	7/52 (13.5%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Decreased contractility (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[3]	12/42 (28.6%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Decreased contractility (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[4]	3/3 (100%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Decreased contractility (assessed with: History, 24-hour ambulatory electrocardiographic recording, exercise testing and Echocardiography)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[5]	22/97 (22.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] 45mg/m2
[2] 228mg-360mg/m2
[3] 361-477mg/m2
[4] >500mg/m2
[5] 228-550mg/m2

Maskhar Study

Author(s): Rahul Mhaskar et al
Question: CSF + antibiotics compared to antibiotics alone for chemo induced febrile neutropenia
Setting:
Bibliography: cochrane database sys review october 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CSF + antibiotics	antibiotics alone	Relative (95% CI)	Absolute (95% CI)		
overall mortality												
13	randomised trials	not serious	not serious	not serious	not serious	very strong association	688/1335 (51.5%)	647/1335 (48.5%)	**HR 0.74** (0.47 to 1.16)	**97 fewer per 1,000** (from 217 fewer to 52 more)	⨁⨁⨁⨁ HIGH	CRITICAL
infection related mortality												
10	randomised trials	not serious	not serious	not serious	not serious	very strong association	471/897 (52.5%)	426/897 (47.5%)	**RR 0.75** (0.47 to 1.20)	**119 fewer per 1,000** (from 252 fewer to 95 more)	⨁⨁⨁⨁ HIGH	CRITICAL
>10 days hospital stay												
7	randomised trials	not serious	not serious	not serious	not serious	very strong association	565/1087 (52.0%)	522/1087 (48.0%)	**RR 0.65** (0.44 to 0.95)	**168 fewer per 1,000** (from 269 fewer to 24 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Time to neutrophil recovery												
6	randomised trials	not serious	not serious	not serious	not serious	very strong association	419/794 (52.8%)	375/794 (47.2%)	**RR 0.52** (0.34 to 0.81)	**227 fewer per 1,000** (from 312 fewer to 90 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
recovery duration of neutropenia												
9	randomised trials	not serious	not serious	not serious	not serious	very strong association	588/1135 (51.8%)	547/1135 (48.2%)	**-1.7 --** (-2.65 to -0.76)	**-- per 1,000** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL

Recovery of fever												
9	randomised trials	not serious	not serious	not serious	not serious	very strong association	502/966 (52.0%)	462/966 (47.8%)	**-0.49 --** (-0.90 to -0.09)	**-- per 1,000** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL
Time withdrawal of antibiotic												
3	randomised trials	not serious	not serious	not serious	not serious	very strong association	233/457 (50.8%)	225/457 (49.2%)	**-1.5 --** (-2.83 to -0.18)	**-- per 1,000** (from -- to --)	⨁⨁⨁⨁ HIGH	CRITICAL
DVT												
4	randomised trials	not serious	not serious	not serious	not serious	very strong association	194/389 (49.9%)	195/389 (50.1%)	not estimable		⨁⨁⨁⨁ HIGH	CRITICAL

Fouad Study

Question: What are treatment-related infection following chemotherapy?

Setting: South Egypt Cancer Institute

Bibliography: Fouad ER, Morsy AM, Kamel HEM, Ali AM. Neutropenic enterocolitis in pediatric leukemia patients treated with intensive chemotherapy in Upper Egypt. Pediatr Investig. 2020 Mar 17;4(1):5-10. doi: 10.1002/ped4.12174. PMID: 32851335; PMCID: PMC7331293.

Author(s): ALL TWG

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
intestinal complications (1) (assessed with: patients with 1 episode of intestinal complications)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	67	77		⨁⨁⨁◯ MODERATE	CRITICAL
intestinal complications (2) (assessed with: patients with 2 episodes of intestinal complications)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	9	77		⨁⨁⨁◯ MODERATE	CRITICAL
intestinal complications (3) (assessed with: patients with 3 episodes of intestinal complications)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	1	77		⨁⨁⨁◯ MODERATE	CRITICAL
Mortality (assessed with: number of patient deaths with neutropenic enterocolitis)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	18	47		⨁⨁⨁◯ MODERATE	CRITICAL
Mortality (other intestinal complications) who had intestinal complications (assessed with: number of patient deaths)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	4	30		⨁⨁⨁◯ MODERATE	CRITICAL
intestinal complications (assessed with: number of episodes due to Neutropenic Enterocolitis)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	88		⨁⨁⨁◯ MODERATE	CRITICAL
neutropenic enterocolitis (assessed with: number of patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	47	77		⨁⨁⨁◯ MODERATE	CRITICAL

Explanations

a. mixed population: ALL and AML patients were included in the study

Yiping Zhu Study

Question: What are treatment-related infections during chemotherapy in pediatric ALL patients
Setting: 18 Centers in China
Bibliography: Yiping Zhu, Rong Yang, jiaoyang Cai, Jie Yu, Yanjing Tang, Yumei Chen, Ningling Wang, Hailong He, Xuedong Wu, frankie W.T. Cheng, Lirong Sun, Yingyi He, Xiuli Ju, Qun Hu, Runming Jiu, Kaili Pan, Yongjung Fang, Xiaowen Zhai, Hui Jiang, Chi-kong Li. 2020
Author(s): ALL TWG

№ of studies	Certainty assessment							Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Septicemia in Low Risk ALL patients (assessed with: number of patients)											
1	observational studies	not serious	not serious	not serious	not serious	none	196	2150		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in Intermediate/High Risk ALL (assessed with: number of patients)											
1	observational studies	not serious	not serious	not serious	not serious	none	331	1930		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in LR ALL during Induction phase (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	137	205		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in LR ALL during Consolidation Phase (weeks 8-15) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	29	205		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in LR ALL during Consolidation and Reinduction Phase (Weeks 16-34) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	19	205		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in LR ALL during Maintenance Phase (Weeks 35-125) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	20	205		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in Intermediate/HIgh Risk during Induction Phase (Week 1-7) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	99	355		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in Intermediate Risk/HR ALL during Consolidation Phase (Week 8-15) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	26	355		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in Intermediate Risk/HR ALL during Continuation and Reinduction Phase (Week 16-34) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	90	355		⨁⨁⨁⨁ HIGH	CRITICAL
Septicemia in Intermediate risk/HR ALL during Maintenance Phase (week 35-125) (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	40	355		⨁⨁⨁⨁ HIGH	CRITICAL
Mortality among patients with septicemia (assessed with: number of patients)											
1	observational studies	not serious	not serious	not serious	not serious	none [a]	19	527		⨁⨁⨁⨁ HIGH	CRITICAL

Explanations

a. The logistic regression analysis of the above factors was performed, and female gender, associated comorbidities and fungal infection were the significant factors

Kar Study (In-Patient)

Question: What are treatment-related infections following chemotherapy for pediatric ALL patients?
Setting: In-patient Hospital
Bibliography: Kar YD, Özdemir ZC, Bör Ö. Evaluation of febrile neutropenic attacks of pediatric hematology-oncology patients. Turk Pediatri Ars. 2017 Dec 1;52(4):213-220. doi: 10.5152/TurkPediatriArs.2017.5312. PMID: 29483801; PMCID: PMC5819859.
Author(s): ALL TWG

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
Febrile Neutropenia during Induction Phase of chemotherapy (assessed with: number of events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	20	133		⊕⊕⊕◯ MODERATE	CRITICAL
Febrile Neutropenia during Consolidation Phase of chemotherapy (assessed with: number of events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	29	133		⊕⊕⊕◯ MODERATE	CRITICAL
Febrile Neutropenia during Early Intensification Phase of Chemotherapy (assessed with: number of events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	33	133		⊕⊕⊕◯ MODERATE	CRITICAL
Febrile Neutropenia in Reinduction Phase of Chemotherapy (assessed with: number of events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	46	133		⊕⊕⊕◯ MODERATE	CRITICAL
Febrile Neutropenia in Maintenance Phase of Chemotherapy (assessed with: number of events)											

Question: What are treatment-related infections following chemotherapy for pediatric ALL patients?
Setting: In-patient Hospital
Bibliography: Kar YD, Özdemir ZC, Bör Ö. Evaluation of febrile neutropenic attacks of pediatric hematology-oncology patients. Turk Pediatri Ars. 2017 Dec 1;52(4):213-220. doi: 10.5152/TurkPediatriArs.2017.5312. PMID: 29483801; PMCID: PMC5819859.
Author(s): ALL TWG

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
Clinically documented Febrile Neutropenic Attack (assessed with: events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	81	200		⊕⊕⊕◯ MODERATE	CRITICAL
Microbiologically Documented Febrile Neutropenic Attack (assessed with: events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	73	200		⊕⊕⊕◯ MODERATE	CRITICAL
Fever of Unknown Origin (assessed with: events)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	46	200		⊕⊕⊕◯ MODERATE	CRITICAL

Explanations

a. mixed population with 50 ALL, 8 AML, NHL, 1HL. 1 Neuroblastoma, 1 Wilm's tumor

Das Study

Author(s): ALL TWG
Date: 2021-08-09
Question: What are treatment-related infections in Pediatric ALL following chemotherapy?
Settings: Government-owned, university hospital in North India
Bibliography: Anirban Das, Sagna Oberoi, Amita Trehan, Arunaloke Chakrabati, Deepak Bansal, Akshay K. Saxena, Kushaljit S. Sodhi, Nandita Kakkar, Radhika Srinivasan, 2016

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Control	Relative (95% CI)	Absolute		
Invasive Fungal Disease (assessed with: number of patients)												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/692 (6.6%)[2,3]	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Mortality (assessed with: number of patients[2])												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/55 (43.6%)[4]	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Invasive Fungal Disease (assessed with: number of patients[5])												
1	observational studies[5,6]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/346 (4.6%)[5]	-	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] retrospective study
[2] 55 IFD was noted with a mixed population of ALL (692) and AML (89)
[3] no fungal antibiotic prophylaxis was started for ALL population.
[4] deaths/number of patients who had IFD
[5] during the last 12 months of the study
[6] prospective

Ozdemir Study

Question: What are treatment-related infections following chemotherapy in Pediatric ALL patients?
Setting: Cerrahpaşa School of Medicine (CTF) Hospital
Bibliography: Özdemir N, Tüysüz G, Çelik N, Yantri L, Erginöz E, Apak H, Özkan A, Yildiz İ, Celkan T. Febrile neutropenia in children with acute lymphoblastic leukemia: single center experience. Turk Pediatri Ars. 2016 Jun 1;51(2):79-86. doi: 10.5152/TurkPediatriArs.2016.2757. PMID: 27489464; PMCID: PMC4959745.
Author(s): ALL TWG

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
Febrile Neutropenia in Fever with unknown origin (assessed with: episodes of FN in febrile patients ongoing chemotherapy)											
1	observational studies	not serious	not serious	not serious	not serious	none	177	299		⨁⨁⨁⨁ HIGH	CRITICAL
Success Rate (assessed with: completed response from chemotherapy)											
1	observational studies	not serious	not serious	not serious	not serious	none	81	96		⨁⨁⨁⨁ HIGH	CRITICAL
Respiratory Infections (assessed with: number of patients during FN attacks)											
1	observational studies	not serious	not serious	not serious	not serious	none	25	66		⨁⨁⨁⨁ HIGH	CRITICAL
ear infections (patients/FN attacks) (assessed with: number of patients during FN)											
1	observational studies	not serious	not serious	not serious	not serious	none	6	66		⨁⨁⨁⨁ HIGH	CRITICAL
GastroIntestinal Infections (assessed with: number of patients during FN attacks)											
1	observational studies	not serious	not serious	not serious	not serious	none	19	66		⨁⨁⨁⨁ HIGH	CRITICAL
fungal infections (assessed with: number of patients)											
1	observational studies	not serious	not serious	not serious	not serious	none	8	96		⨁⨁⨁⨁ HIGH	CRITICAL
bacterial infections (assessed with: number of microbiologically defined culture growths)											
1	observational studies	not serious	not serious	not serious	not serious	none	69	80		⨁⨁⨁⨁ HIGH	CRITICAL
viral infections (assessed with: number of microbiologically defined culture growths)											
1	observational studies	not serious	not serious	not serious	not serious	none	6	80		⨁⨁⨁⨁ HIGH	CRITICAL

Inaba Study

Author(s): ALL TWG
Date: 2021-08-08
Question: What are treatment-related infections following chemotherapy?
Settings: St. Jude Children's Research Hospital
Bibliography: H. Inaba et al, 2016

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Control	Relative (95% CI)	Absolute		
Mortality (assessed with: number of patients[1])												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	4/409 (0.98%)[3]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Induction Phase) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	153/308 (49.7%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Consolidation Phase) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	51/100 (51%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase - weeks 1-6) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	32/60 (53.3%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Reinduction I Phase - Weeks 7-9) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	82/122 (67.2%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase Weeks 10-16) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	79/142 (55.6%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Reinduction II Phase - Weeks 17-20) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	160/243 (65.8%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase - weeks 21-47) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	171/360 (47.5%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase - Weeks 48-71) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	160/369 (43.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase - Weeks 72-103) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	124/354 (35%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase - Weeks 104-120) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	47/168 (28%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile Neutropenia (Continuation Phase - Weeks 121-146) (assessed with: episodes)												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	24/126 (19%)[4]	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] during induction therapy
[2] retrospective study
[3] 2 of bacteremia; 2 of presumed septic shock
[4] episodes/all infections combined per phase of chemotherapy

Hakim Study

Question: What are treatment-related infections following chemotherapy in pediatric ALL?
Setting: St. Jude Children's Research Hospital (SJCRH) in Memphis, Tennessee
Bibliography: Hakim H, Dallas R, Zhou Y, Pei D, Cheng C, Flynn PM, Pui CH, Jeha S. Acute respiratory infections in children and adolescents with acute lymphoblastic leukemia. Cancer. 2016 Mar 1;122(5):798-805. doi: 10.1002/cncr.29833. Epub 2015 Dec 23. PMID: 26700662; PMCID: PMC4764417.
Author(s): ALL TWG

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
Acute Respiratory infections with viral etiology (assessed with: Episodes of Viral ARI in total number of ARI episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	133	269		⊕⊕⊕⊕ HIGH	CRITICAL
Acute Respiratory Infection without Viral Etiology (assessed with: episodes of non-viral ARI in total number of ARI episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	136	269		⊕⊕⊕⊕ HIGH	CRITICAL
Lower Respiratory Tract Infection (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	24	133		⊕⊕⊕⊕ HIGH	CRITICAL
Upper Respiratory Tract Infection (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	109	133		⊕⊕⊕⊕ HIGH	CRITICAL
co-infection with > 2 virus (assessed with: episodes)											
1	observational studies	not serious	not serious	not serious	not serious	none	6	133		⊕⊕⊕⊕ HIGH	CRITICAL

Torres-Flores Study

Question: What are treatment-related infections following chemotherapy in Pediatric ALL patients?
Setting: INCan Acute Leukemia Clinic
Bibliography: Jorge Torres-Flores,a Ramiro Espinoza-Zamora,a Jorge García-Méndez,b Eduardo Cervera-Ceballos,c Alejandro Sosa-Espinoza,c and Nidia Zapata-Cantoa,d et al 2020
Author(s): ALL TWG

Nº of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nº of events	Nº of individuals	Rate (95% CI)		
Respiratory Infection (assessed with: deaths in ALL patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	32	313	-	⊕⊕⊕◯ MODERATE	CRITICAL
ear and/or dental infections (assessed with: mortality on ALL patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	1	313	-	⊕⊕⊕◯ MODERATE	CRITICAL
Gastrointestinal Infections (assessed with: mortality in ALL patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	4	313	-	⊕⊕⊕◯ MODERATE	CRITICAL
skin and soft tissue infection (assessed with: mortality on ALL patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	8	313	-	⊕⊕⊕◯ MODERATE	CRITICAL
Catheter-associated infection (assessed with: mortality in ALL patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	4	313		⊕⊕⊕◯ MODERATE	CRITICAL
Genitourinary infection (assessed with: number of deaths in ALL patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	2	313		⊕⊕⊕◯ MODERATE	CRITICAL
Over-all mortality (assessed with: number of deaths over the number of number of ALL, AML, biphenotypic patients)											
1	observational studies	not serious	not serious	serious [a]	not serious	none	84	313		⊕⊕⊕◯ MODERATE	CRITICAL

Explanations

a. mixed population: ALL, AML, Biphenotypic leukemia, acute promyelocytic leukemia

Rungoe Study (Cotrimoxazole)

Author(s): ALL TWG
Date: 2021-06-06
Question: Should COTRIMOXAZOLE be used for Pediatric ALL patients ongoing chemotherapy?
Settings: Department of Paediatrics, Aarhus University Hospital, Skejby, Denmark.
Bibliography: C. Rungoe et al 2010

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	COTRIMOXAZOLE	Control	Relative (95% CI)	Absolute		
Effectivity (assessed with: number of patients who had no febrile episodes during chemotherapy)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	29/86 (33.7%)[1]	14/85 (16.5%)[2]	RR 2.07 (0 to 0)	176 more per 1000 (from 165 fewer to 165 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Infection (assessed with: number of patients who had bacteremic episodes)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	17/86 (19.8%)	38/85 (44.7%)	RR 0.45 (0 to 0)	246 fewer per 1000 (from 447 fewer to 447 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Additional Antibiotic Therapy (assessed with: number of patients with additional antibiotic therapy)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	59/86 (68.6%)[3]	69/85 (81.2%)[4]	RR 0.86 (0 to 0)	114 fewer per 1000 (from 812 fewer to 812 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Culture positive (assessed with: number of patients with a positive culture result[5])												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/86 (3.5%)	8/85 (9.4%)	RR 0.375 (0 to 0)	59 fewer per 1000 (from 94 fewer to 94 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Gafter-Gvili Study (Antibioitic)

Author(s): ALL TWG
Date: 2021-07-09
Question: Should ANTIBIOTIC PROPHYLAXIS vs NO PROPHYLAXIS be used for Pediatric ALL ?
Settings: various hospital/outpatient
Bibliography: Gafter-gvili et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ANTIBIOTIC PROPHYLAXIS	NO PROPHYLAXIS	Relative (95% CI)	Absolute		
All Cause-Mortality (assessed with: number of patients)												
46	randomised trials[1,2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/2863 (5.4%)	243/2772 (8.8%)	RR 0.66 (0.55 to 0.79)	30 fewer per 1000 (from 18 fewer to 39 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Febrile patients and outcomes (assessed with: number of patients who have encountered febrile episodes)												
54[1,3]	randomised trials[1,4]	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98/2945 (3.3%)	158/2832 (5.6%)	RR 0.80 (0.74 to 0.87)	11 fewer per 1000 (from 7 fewer to 15 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
bacteremia (assessed with: number of patients with baceremia)												
53	randomised trials[1,6]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	105/1000 (10.5%)	209/1000 (20.9%)	RR 0.50 (0.43 to 0.60)[7]	104 fewer per 1000 (from 84 fewer to 119 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

[1] meta-analysis
[2] 5635 paticipants
[3] 109 trilas with 13579 participants. 76 studies had adult participants; 26 studies had pediatric participants while 7 studies did not specify age-bracket.

Gafter-Gvili Study (Quinolones)

Author(s): ALL TWG
Date: 2021-07-09
Question: Should QUINOLONES vs COTRIMOXAZOLE (TMP-SMZ) be used for Cancer patients with afebrile neutropenia following chemotherapy?
Settings: hospital/outpatient
Bibliography: Gafter-Gvili et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	QUINOLONES	COTRIMOXAZOLE (TMP-SMZ)	Relative (95% CI)	Absolute		
All Cause-mortality												
10	randomised trials[1,2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	31/453 (6.8%)	22/402 (5.5%)	RR 1.07 (0.66 to 1.72)	4 more per 1000 (from 19 fewer to 39 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Febrile patients and episodes												
10	randomised trials[2,4]	no serious risk of bias	serious[3,5]	no serious indirectness	no serious imprecision	none	300/470 (63.8%)	311/461 (67.5%)	RR 0.92 (0.78 to 1.09)	54 fewer per 1000 (from 148 fewer to 61 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Bacteraemia												
10	randomised trials[2,4]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3,5]	none	81/470 (17.2%)	96/461 (20.8%)	RR 0.89 (0.56 to 1.42)	23 fewer per 1000 (from 92 fewer to 87 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] 917 participants
[2] meta-analysis
[3] allocation concealment was unclear in most of the trials.
[4] 931 participants
[5] due to heterogeneity

Alexander Study

Author(s): ALL TWG
Date: 2021-07-08
Question: Should LEVFLOXACIN PROPHYLAXIS be used for PEDIATRIC ALL?
Settings: US and Canada
Bibliography: S. Alexander et al 2021

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEVFLOXACIN PROPHYLAXIS	Control	Relative (95% CI)	Absolute		
Effectivity (assessed with: number of patients with bacteremia)												
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/96 (21.9%)[2]	43/99 (43.4%)[2]	RR 0.49 (0 to 0)	222 fewer per 1000 (from 434 fewer to 434 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
severe infections (assessed with: number of patients with severe infection as secondary outcome[3])												
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/306 (3.6%)	18/307 (5.9%)	RR 0.61 (0 to 0)	23 fewer per 1000 (from 59 fewer to 59 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
C. difficile diarrhea (assessed with: number of patients with C. difficile-associated diarrhea[4])												
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/306 (2.3%)	16/307 (5.2%)	RR 0.4375 (0 to 0)	29 fewer per 1000 (from 52 fewer to 52 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Development of new Resistance to Specific Agents in Bacteria Colonizing the stoll (assessed with: number of patients with resistance developing in colonizing organisms)												
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/43 (9.3%)[2]	4/45 (8.9%)	RR 1 (0 to 0)	0 fewer per 1000 (from 89 fewer to 89 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Duration of hospitalization stay (assessed with: mean (SE) Days per 30 patient days[6])												
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/9369 (0.28%)	25/9739 (0.26%)	-	3 fewer per 1000 (from 3 fewer to 3 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

[1] multi-center, open-label, randomized trial
[2] Total Acute leukemia (AML and relapsed ALL)
[3] defined as any grade 4 or 5 Common Terminology criteria for adverse events v 4.0 infections and includes clinically documented nonbacterial and bacterial infections
[4] as defined as a positive C. difficile test and doyumentation of grade 2 or higher diarrhea by CTCAE criteria
[5] levofloxacin
[6] for duration end points, the estimates re mean number of days per 30 days at risk during the infection observation period

Supportive and Palliative Care

Rensen Study

Author(s): ALL Group
Date: 2021-06-10
Question: Should psychosocial support be used for parental sleep, distress and quality of life?
Settings:
Bibliography: Rensen et al. 2020

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychosocial support	Control	Relative (95% CI)	Absolute		
Psychosocial support (assessed with: Sleep problem Index (SLP))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	48/121 (39.7%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Psychosocial support (assessed with: Distress thermometer (DT-P))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	80/121 (66.1%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Psychosocial support (assessed with: Physical component summary (PCS))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	16/121 (13.2%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Psychosocial support (assessed with: Mental component summary (MCS))												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	44/121 (36.4%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Barrera Study

Author(s): ALL Group
Date: 2021-07-20
Question: Should psychosocial screening be used for quality of life?
Settings: Canada
Bibliography: Barrera, 2019

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Psychosocial screening	Control	Relative (95% CI)	Absolute		
Quality of life (assessed with: Pediatric Quality of Life Inventory (PedsQL-4.0))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/16 (43.8%)	10/16 (62.5%)	-	625 fewer per 1000 (from 625 fewer to 625 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Quality of Life (assessed with: Caregiver Quality of Life Cancer Scale (CQOLCS))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/61 (57.4%)	27/61 (44.3%)	-	443 fewer per 1000 (from 443 fewer to 443 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Quality of Life (assessed with: Pediatric Quality of Life Inventory)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/15 (66.7%)	1/10 (10%)	-	100 fewer per 1000 (from 100 fewer to 100 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Zupanec Study

Author(s): Zupanec et al, 2017
Date: 2021-06-23
Question: Should sleep hygiene and relaxation intervention vs none be used in children with acute lymphoblastic leukemia?
Settings: canada
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sleep hygiene and relaxation intervention	None	Relative (95% CI)	Absolute		
Nighttime sleep (measured with: minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 35 higher (35 lower to 104 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
longest stretch of nighttime sleep (measured with: minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 2 lower (63 lower to 58 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
daytime sleep (measured with: minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 0.1 higher (28 lower to 28 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
longest stretch of daytime sleep (measured with: minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 1 higher (18 lower to 20 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
wake up time after sleep onset (measured with: minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 44 lower (93 lower to 5 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
number of nighttime awakenings (measured with: minutes; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 0.1 higher (5 lower to 5 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
CSHQ score (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 1 lower (9 lower to 6 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
CCFS-P score (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 3 lower (17 lower to 11 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
FISH score (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	9	-	MD 0.7 higher (4 lower to 5 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Liang Study

Author(s): ALL Group
Date: 2021-06-23
Question: Should Oral Nutritional Supplements (ONS) be used for children with acute lymphoblastic leukaemia during remission-induction chemotherapy?
Settings:
Bibliography: Liang et al (2018)

Quality assessment							No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral Nutritional Supplements (ONS)	Control	Relative (95% CI)	Absolute				
Weight loss (assessed with: weight in kg)														
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	ÂÂÂO MODERATE	CRITICAL		
Hypoproteinaemia (assessed with: Laboratory value)														
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/60 (15%)	32/67 (47.8%)	-	478 fewer per 1000 (from 478 fewer to 478 fewer)	ÂÂÂO MODERATE	CRITICAL		
Gastrointestinal complication (assessed with: Common Terminology Criteria for Adverse Events)														
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/60 (23.3%)	28/67 (41.8%)	-	418 fewer per 1000 (from 418 fewer to 418 fewer)	ÂÂÂO MODERATE	CRITICAL		
Infection														
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/60 (35%)	38/67 (56.7%)	-	567 fewer per 1000 (from 567 fewer to 567 fewer)	ÂÂÂO MODERATE	CRITICAL		
Blood Transfusion (assessed with: Laboratory value)														
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	ÂÂÂO MODERATE	CRITICAL		
Albumin Dosage (assessed with: Laboratory value)														
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	ÂÂÂO MODERATE			

Israel Study

Author(s): ALL Group
Date: 2021-08-25
Question: Should peanut based therapeutic ready to use food be used for children diagnosed with ALL?
Settings:
Bibliography: Israëls et al (2009)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peanut based therapeutic ready to use food	Control	Relative (95% CI)	Absolute		
Weight gain (assessed with: weight)												
1	randomised trials	serious[1,2]	no serious inconsistency	serious[1]	no serious imprecision	none	7/18 (38.9%)	-	-	-	ÂÂOO LOW	CRITICAL

[1] Difference in population, intervention is used on Wilm's tumor patients and no control was reported

Polat Study

Author(s): ALL group
Date: 2021-11-03
Question: Should neutropenic diet be used in children with Acute Lymphoblastic Leukemia?
Settings:
Bibliography: Polat et al (2020)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neutropenic diet	Control	Relative (95% CI)	Absolute		
Malnutrition (Moderate risk) (assessed with: clinical assessment)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/42 (64.3%)	15/42 (35.7%)	-	357 fewer per 1000 (from 357 fewer to 357 fewer)	ÂÂÂO MODERATE	CRITICAL
Malnutrition (Severe Risk) (assessed with: clinical assessment)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/18 (55.6%)	8/18 (44.4%)	-	444 fewer per 1000 (from 444 fewer to 444 fewer)	ÂÂÂO MODERATE	CRITICAL
Hospitalization duration (assessed with: number of days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	ÂÂÂO MODERATE	CRITICAL

[1] lack of randomization and blinding

Moody Study

Author(s): ALL group
Date: 2021-06-14
Question: Should neutropenic diet + FSG vs FSG be used for pediatric oncology patients?
Settings:
Bibliography: Moody, et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neutropenic diet + FSG	FSG	Relative (95% CI)	Absolute		
Neutropenic Infection (assessed with: clinical assessment)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	24/73 (32.9%)	27/77 (35.1%)	RR 0.89 (0 to 0)	39 fewer per 1000 (from 351 fewer to 351 fewer)	ÂÂOO LOW	CRITICAL
Proven Infection (assessed with: clinical assessment)												
1	randomised trials	serious[3]	no serious inconsistency	serious[2]	no serious imprecision	none	6/73 (8.2%)	8/77 (10.4%)	RR 0.07 (0 to 0)	97 fewer per 1000 (from 104 fewer to 104 fewer)	ÂÂOO LOW	CRITICAL

[1] Received anticancer treatment more likely to cause neutropenia: unclear (no large differences in types of malignancies, but stage of disease and exact treatment including doses not reported)

[2] difference in population

[3] Co-interventions (protective environment, antimicrobial prophylaxis, CVC care, oral care, hygiene practices, colony-stimulating factors): no large differences in hygiene practices and use of colony-stimulating factors; not reported for the other items (maybe not used at all)

Hatab Study

Author(s): ALL Group
Date: 2021-06-10
Question: Should activities of daily living and school be used for acute lymphoblastic leukemia?
Settings:
Bibliography: Hatab et al. 2020

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Activities of daily living and school	Control	Relative (95% CI)	Absolute		
activities of daily living (assessed with: Dressing activities)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/50 (28%)[1]	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
activities of daily living (assessed with: Activity and movement)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/50 (48%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
activities of daily living (assessed with: School activity)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/50 (50%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
activities of daily living (assessed with: Toys and hobbies)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/50 (42%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
activities of daily living (assessed with: Nutrition)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/50 (12%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
activities of daily living (assessed with: Social activity)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/50 (28%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
activities of daily living (assessed with: Social activity)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/50 (18%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

[1] A purposive sample of 50 children with acute lymphocytic leukemia at welfare pediatric teaching hospital and child central pediatric hospital.

Oswald Study

Author(s): ALL Group
Date: 2021-07-22
Question: Should activities of daily living and school be used for acute lymphoblastic leukemia?
Settings:
Bibliography: Oswald,2020

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Activities of daily living and school	Control	Relative (95% CI)	Absolute		
Activities of daily living (assessed with: Movement Assessment Battery for Children)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Physical Self Description Questionnaire)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Esteem)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Appearance)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Global Physical)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Body fat)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Health)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Sports Competence)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Activities of daily living (assessed with: Strength)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Activities of daily living (assessed with: Physical Activity)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%) 0%	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer) -	⊕⊕⊕⊕ HIGH	CRITICAL
Activities of daily living (assessed with: Flexibility)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%) 0%	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer) -	⊕⊕⊕⊕ HIGH	CRITICAL
Activities of daily living (assessed with: Endurance)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/53 (100%)	53/53 (100%) 0%	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer) -	⊕⊕⊕⊕ HIGH	CRITICAL

[1] No explanation was provided

Pinto Study

Author(s): ALL CPG
Date: 2021-06-14
Question: Should chlorhexidine gluconate 0.12% be used for patients diagnosed with Acute Lymphoblastic Leukemia undergoing chemotherapy??
Settings:
Bibliography: Pinto et al (2006),

Quality assessment							No of patients		Effect		Quality	Importance		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chlorhexidine gluconate 0.12%**	**Control**	**Relative (95% CI)**	**Absolute**				
Mucositis (assessed with: Clinical Assessment)														
1	**randomised trials**	**serious**	**no serious inconsistency**	**no serious indirectness**	**no serious imprecision**	**none**	**6/23 (26.1%)**	**8/10 (80%)**	**OR 11.3 (1.86 to 69.11)**	**178 more per 1000 (from 82 more to 196 more)**	**ÂÂÂO MODERATE**	**CRITICAL**		

Cheng Study

Author(s): ALL group
Date: 2021-09-06
Question: Should an Oral care protocol be used for children diagnosed with ALL?
Settings:
Bibliography: Cheng et al

Quality assessment							No of patients		Effect		Quality	Importance		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**An Oral care protocol**	**Control**	**Relative (95% CI)**	**Absolute**				
incidence of oral lesions (assessed with: clinical assessment)														
1	**randomised trials**	**serious [1]**	**no serious inconsistency**	**no serious indirectness**	**no serious imprecision**	**none**	**7/21 (33.3%)**	**15/21 (71.4%)** **0%**	**RR 0.46 (0 to 0)**	**386 fewer per 1000 (from 714 fewer to 714 fewer)** -	**ÂÂÂO MODERATE**	**CRITICAL**		
severity of oral mucositis (assessed with: Eilers' Oral Assessment Guide)														
1	**randomised trials**	**serious [1]**	**no serious inconsistency**	**no serious indirectness**	**no serious imprecision**	**none**	**-**	**-**	**Not estimable**	**-**	**ÂÂÂO MODERATE**	**CRITICAL**		
pain intensity (assessed with: Faces Scale)														
1	**randomised trials**	**serious [1]**	**no serious inconsistency**	**no serious indirectness**	**no serious imprecision**	**none**	**-**	**-**	**Not estimable**	**-**	**ÂÂÂO MODERATE**	**CRITICAL**		
Patients requiring local analgesic														
1	**randomised trials**	**serious [1]**	**no serious inconsistency**	**no serious indirectness**	**no serious imprecision**	**none**	**2/21 (9.5%)**	**9/21 (42.9%)**	**RR 0.22 (0 to 0)**	**334 fewer per 1000 (from 429 fewer to 429 fewer)**	**ÂÂÂO MODERATE**	**CRITICAL**		

[1] lack of concealment and blinding

Pitten Study

Author(s): ALL group
Date: 2021-10-04
Question: Should chlorhexidine-based oral rinse 0.3% be used in cancer patients with chemotherapy induced leukopenia?
Settings:
Bibliography: Pitten et al (2003)

Quality assessment							No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorhexidine-based oral rinse 0.3%	Control	Relative (95% CI)	Absolute				
CRP >50mg/L (assessed with: laboratory value)														
1	randomised trials	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	15/24 (62.5%)	8/23 (34.8%)	OR 3.13 (0.82 to 12.39)	278 more per 1000 (from 44 fewer to 521 more)	ÂÂÂO MODERATE	CRITICAL		
Severe Mucositis (assessed with: Clinical Assesment)														
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	9/24 (37.5%)	2/23 (8.7%)	OR 6.30 (1.02 to 49.67)	288 more per 1000 (from 2 more to 739 more)	ÂÂÂO MODERATE	CRITICAL		

[1] Differences in population

Devi Study

Author(s): ALL Group
Date: 2021-10-06
Question: Should oral care practice be used for children with Acute Lymphoblastic Leukemia?
Settings:
Bibliography: Devi et al (2019)

Quality assessment							No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral care practice	Control	Relative (95% CI)	Absolute				
Mucositis (assessed with: Oral Assessment Guide (OAG))														
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/34 (52.9%)	-	-	-	ÂOOO VERY LOW	CRITICAL		

[1] source of control group is implicit

Doherty Study

Author(s): Doherty, M., Power, L., & Thabet, C. (2020).
Date: 2021-08-30
Question: Should palliative care be used in among newly diagnosed patients with pediatric acute lymphoblastic leukemia??
Settings: Tertiary Hospital in Bangladesh
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative care	Control	Relative (95% CI)	Absolute		
type of cancer (assessed with: ALL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[1]	123/200 (61.5%)	407/738 (55.1%)	-	551 fewer per 1000 (from 551 fewer to 551 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
type of cancer (assessed with: AML)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	21/200 (10.5%)	82/738 (11.1%)	-	111 fewer per 1000 (from 111 fewer to 111 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
type of cancer (assessed with: NHL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	16/200 (8%)	74/738 (10%)	-	100 fewer per 1000 (from 100 fewer to 100 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Type of intervention (assessed with: Providing psycho social support for the child)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	305/580 (52.6%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Type of intervention (assessed with: management of physical symptoms)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	181/580 (31.2%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Type of intervention (assessed with: Group or individual psychosocial support for parent/caregiver)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	152/580 (26.2%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Type of intervention (assessed with: Family meeting to plan home-based end-of-life care)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	15/580 (2.6%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	60/82 (73.2%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
physical symptom (assessed with: Skin problems or wound)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	16/82 (19.5%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Weakness)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	9/82 (11%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

physical symptoms (assessed with: Constipation)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/82 (8.5%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Respiratory symptoms)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/82 (2.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Itching)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/82 (2.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Bleeding)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/82 (2.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Seizures)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/82 (2.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Weight loss)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/82 (2.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Vomiting)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/82 (1.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

physical symptoms (assessed with: Incontinence)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/82 (1.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Spasticity)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/82 (1.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Ear problems)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/82 (1.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Burn care)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/82 (1.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
physical symptoms (assessed with: Feeding issues)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/82 (1.2%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] 407 out of the 738 population were diagnosed of ALL which is about 55.1%

Osenga Study

Author(s): Osenga, K., Postier, A., Dreyfus, J., Foster, L., Teeple, W., & Friedrichsdorf, S. J. (2016).
Date: 2021-09-03
Question: Should palliative care be used in pediatric lymphoblastic leukemia??
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative care	Control	Relative (95% CI)	Absolute		
Diagnostic category (assessed with: Cardiology)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	9/28 (32.1%)	8/86 (9.3%)	-	93 fewer per 1000 (from 93 fewer to 93 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Diagnostic category (assessed with: Neonatal)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/28 (21.4%)	51/86 (59.3%)	-	593 fewer per 1000 (from 593 fewer to 593 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Diagnostic category (assessed with: Trauma/other)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/28 (25%)	24/86 (27.9%)	-	279 fewer per 1000 (from 279 fewer to 279 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Diagnostic category (assessed with: Hem/Onc)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/28 (21.4%)	3/86 (3.5%)	-	35 fewer per 1000 (from 35 fewer to 35 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: yes)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	17/28 (60.7%)	79/86 (91.9%)	OR 0.16 (0.04 to 0.61)	275 fewer per 1000 (from 45 fewer to 608 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: X-rays)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	14/28 (50%)	70/86 (81.4%)	OR 0.39 (0.13 to 1.16)	183 fewer per 1000 (from 451 fewer to 21 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: CT-scans/MRI)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	5/28 (17.9%)	18/86 (20.9%)	OR 0.46 (0.12 to 1.83)	101 fewer per 1000 (from 179 fewer to 117 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: Blood draws)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	16/28 (57.1%)	77/86 (89.5%)	OR 0.17 (0.05 to 0.60)	303 fewer per 1000 (from 58 fewer to 596 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

At least one diagnostic/monitoring procedure during last 48 hours (assessed with: Blood draws)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	16/28 (57.1%)	77/86 (89.5%)	OR 0.17 (0.05 to 0.60)	303 fewer per 1000 (from 58 fewer to 596 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: surgeries)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/28 (7.1%)	24/86 (27.9%)	OR 0.20 (0.04 to 1.05)	207 fewer per 1000 (from 264 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: IV placement)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/28 (7.1%)	37/86 (43%)	OR 0.07 (0.01 to 0.40)	380 fewer per 1000 (from 198 fewer to 423 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
At least one diagnostic/monitoring procedure during last 48 hours (assessed with: EKG)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/28 (7.1%)	8/86 (9.3%)	OR 0.11 (0.01 to 0.91)	82 fewer per 1000 (from 8 fewer to 92 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
End-of-life planning (assessed with: DNR ordered)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	22/28 (78.6%)	45/86 (52.3%)	OR 7.92 (2.02 to 31.12)	374 more per 1000 (from 166 more to 448 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

End-of-life planning (assessed with: CPR)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/28 (25%)	26/86 (30.2%)	OR 0.77 (0.29 to 2.03)	52 fewer per 1000 (from 191 fewer to 166 more)	⊕⊖⊖O MODERATE	CRITICAL
								0%		-		
End-of-life planning (assessed with: Social work consult)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	20/28 (71.4%)	85/86 (98.8%)	OR 0.04 (0.01 to 0.36)	216 fewer per 1000 (from 20 fewer to 529 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
End-of-life planning (assessed with: Chaplain/pastordend-of-life support)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	23/28 (82.1%)	75/86 (87.2%)	OR 0.38 (0.10 to 1.55)	151 fewer per 1000 (from 467 fewer to 41 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms and management of symptoms during last 72 hours (assessed with: Dyspnea)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	16/28 (57.1%)	28/86 (32.6%)	OR 2.88 (0.99 to 8.33)	256 more per 1000 (from 2 fewer to 475 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms and management of symptoms during last 72 hours (assessed with: Seizures/convulsions)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	10/28 (35.7%)	15/86 (17.4%)	OR 1.79 (0.54 to 5.95)	100 more per 1000 (from 72 fewer to 383 more)	⊕⊕⊖O MODERATE	CRITICAL
								0%		-		
Symptoms and management of symptoms during last 72 hours (assessed with: Terminal agitation)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	10/28 (35.7%)	15/86 (17.4%)	OR 1.84 (0.57 to 5.92)	108 more per 1000 (from 67 fewer to 381 more)	⊕⊕⊖O MODERATE	CRITICAL
								0%		-		

Zhang Study

Author(s): Zhang, A., Bing, L., Mi, Q., Zhou, F., & Wang, J. (2021)
Date: 2021-08-30
Question: Should palliative care be used in among newly diagnosed patients with pediatric acute lymphoblastic leukemia??
Settings: tertiary children's hospital in China
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative care	Control	Relative (95% CI)	Absolute		
most common primary diseases (assessed with: neuroblastoma)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	27/92 (29.3%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
most common primary diseases (assessed with: acute lymphoblastic leukemia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	21/92 (22.8%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
most common primary diseases (assessed with: acute myeloid leukemia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	15/92 (16.3%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Reason for referral to Pediatric Palliative Care (assessed with: Newly diagnosed malignancy)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	5/92 (5.4%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Reason for referral to Pediatric Palliative Care (assessed with: Tumor relapse or refractory tumors)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	76/92 (82.6%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Reason for referral to Pediatric Palliative Care (assessed with: Serious complications)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	11/92 (12%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	68/92 (73.9%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Loss of appetite)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	54/92 (58.7%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Fatigue)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/92 (57.6%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Fever)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	50/92 (54.3%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Dyspnea)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	49/92 (53.3%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Bleeding)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	38/92 (41.3%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Symptoms of children 1 month before death (assessed with: Nausea and vomiting)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	28/92 (30.4%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Abdominal distention)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	27/92 (29.3%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Somnolence)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	22/92 (23.9%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Symptoms of children 1 month before death (assessed with: Constipation)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	20/92 (21.7%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Place of death (assessed with: home)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	28/88 (31.8%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Place of death (assessed with: Hospice ward)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	32/88 (36.4%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Place of death (assessed with: Local hospital)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	20/88 (22.7%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Place of death (assessed with: Oncology ward)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	5/88 (5.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Place of death (assessed with: ER)													
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/88 (3.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Levine Study

Author(s): Levine, D. R., Mandrell, B. N., Sykes, A., Pritchard, M., Gibson, D., Symons, H. J., Wendler, D., & Baker, J. N. (2017).
Date: 2021-09-03
Question: Should palliative care be used in newly diagnosed pediatric acute lymphoblastic leukemia?
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palliative care	Control	Relative (95% CI)	Absolute		
Cancer type (assessed with: Brain tumor)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	20/127 (15.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: Leukemia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	38/127 (29.9%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: Lymphoma)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	26/127 (20.5%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: Solid tumor)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	41/127 (32.3%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
expressed opposition to early PC												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/127 (1.6%)	8/129 (6.2%)	-	62 fewer per 1000 (from 62 fewer to 62 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
a perceived detrimental effect of early PC (assessed with: it would interfere with their relationship with their oncologist)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/127 (4.7%)	5/129 (3.9%)	-	39 fewer per 1000 (from 39 fewer to 39 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
a perceived detrimental effect of early PC (assessed with: loss of hope for a cure)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/127 (2.4%)	10/129 (7.8%)	-	78 fewer per 1000 (from 78 fewer to 78 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
a perceived detrimental effect of early PC (assessed with: therapy interference)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/127 (2.4%)	2/129 (1.6%)	-	16 fewer per 1000 (from 16 fewer to 16 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Perceived Optimal Timing of Palliative Care Involvement (assessed with: At the Beginning of Cancer Therapy)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	76/127 (59.8%)	65/129 (50.4%)	-	504 fewer per 1000 (from 504 fewer to 504 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-	
Perceived Optimal Timing of Palliative Care Involvement (assessed with: if pain or symptom management was a problem)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	63/127 (49.6%)	44/129 (34.1%)	-	341 fewer per 1000 (from 341 fewer to 341 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-	
Perceived Optimal Timing of Palliative Care Involvement (assessed with: if the cancer got worse or came back)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	63/127 (49.6%)	41/129 (31.8%)	-	318 fewer per 1000 (from 318 fewer to 318 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-	
Perceived Optimal Timing of Palliative Care Involvement (assessed with: throughout all of a child's cancer care)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	41/127 (32.3%)	52/128 (40.6%)	-	406 fewer per 1000 (from 406 fewer to 406 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-	

Geeta Study

Author(s): Geeta, M. G., Geetha, P., Ajithkumar, V. T., Krishnakumar, P., Kumar, K. S., & Mathews, L. (2010).
Date: 2021-09-03
Question: Should pain management be used in among newly diagnosed pediatric acute lymphoblastic leukemia??
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain management	Control	Relative (95% CI)	Absolute		
pain (assessed with: nociceptive pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	37/39 (94.9%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
pain (assessed with: neuropathic pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	2/39 (5.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Treatment (assessed with: managed with Step-1 analgesia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12/39 (30.8%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Treatment (assessed with: managed with Step-2 analgesia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	21/39 (53.8%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Treatment (assessed with: managed with Step-3 analgesia)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/39 (15.4%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Biji Study

Author(s): Biji, M. S., Vinayagamoorthy, V., Jithin, T. K., Raghavan, V., Selvaraj, K., Duraisamy, K., Shringarpure, K., Abhinaa, S. S., Deenathayalan, V. P., Mehta, K., Rathi, P., & Mathews, L. (2019).
Date: 2021-09-04
Question: Should pain management be used in among newly diagnosed pediatric acute lymphoblastic leukemia??
Settings: Tertiary Cancer Center in Rural India
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain management	Control	Relative (95% CI)	Absolute		
Hematologic malignancy (assessed with: ALL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	63/93 (67.7%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Hematologic malignancy (assessed with: AML)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12/93 (12.9%)	-	-	-		CRITICAL
								0%		-		
Hematologic malignancy (assessed with: NHL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	10/93 (10.8%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Hematologic malignancy (assessed with: HL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/93 (7.5%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Hematologic malignancy (assessed with: MDS)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/93 (1.1%)	-	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
pain (assessed with: disease related pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	17/27 (63%)	35/59 (59.3%)	RR 0.90 (0.47 to 1.72)	59 fewer per 1000 (from 314 fewer to 427 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
pain (assessed with: treatment related pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	10/27 (37%)	24/59 (40.7%)	RR 0.90 (0.47 to 1.72)	41 fewer per 1000 (from 216 fewer to 293 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Nature of disease (assessed with: primary)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	15/27 (55.6%)	50/59 (84.7%)	RR 2.51 (1.40 to 4.51)	1000 more per 1000 (from 339 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
nature of disease (assessed with: relapse)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	11/27 (40.7%)	8/59 (13.6%)	RR 2.51 (1.40 to 4.51)	205 more per 1000 (from 54 more to 476 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Reason for treatment-related pain (assessed with: mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	8/27 (29.6%)	11/59 (18.6%)	-	186 fewer per 1000 (from 186 fewer to 186 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Reason for treatment-related pain (assessed with: procedure related pain)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/27 (3.7%)	7/59 (11.9%)	-	119 fewer per 1000 (from 119 fewer to 119 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Reason for treatment-related pain (assessed with: other)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	1/27 (3.7%)	5/59 (8.5%)	-	85 fewer per 1000 (from 85 fewer to 85 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

Anghelescu Study

Author(s): Anghelescu, D. L., Faughnan, L. G., Jeha, S., Relling, M. V., Hinds, P. S., Sandlund, J. T., Cheng, C., Pei, D., Hankins, G., Pauley, J. L., & Pui, C. H. (2011)
Date: 2021-09-03
Question: Should pain management be used in among newly diagnosed pediatric acute lymphoblastic leukemia??
Settings:
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain management	Control	Relative (95% CI)	Absolute		
Prevention and relief of VRNP (assessed with: Gabapentin)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	100/153 (65.4%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Prevention and relief of VRNP (assessed with: opioid)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	53/153 (34.6%)	-	-	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

Friedrichsdorf Study

Author(s): Friedrichsdorf, S. J., Finney, D., Bergin, M., Stevens, M., & Collins, J. J. (2007).
Date: 2021-09-04
Question: Should pain management be used in among newly diagnosed pediatric acute lymphoblastic leukemia??
Settings: Oncology Unit at the Children's Hospital at Westmead, Sydney, Australia
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pain management	Control	Relative (95% CI)	Absolute		
Cancer type (assessed with: ALL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/16 (37.5%)	6/12 (50%)	-	500 fewer per 1000 (from 500 fewer to 500 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: Ewing Sarcoma)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	4/16 (25%)	2/12 (16.7%)	-	167 fewer per 1000 (from 167 fewer to 167 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: AML)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/16 (18.8%)	1/12 (8.3%)	-	83 fewer per 1000 (from 83 fewer to 83 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: Osteosarcoma)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	0/16 (0%)	3/12 (25%)	-	250 fewer per 1000 (from 250 fewer to 250 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Cancer type (assessed with: others)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	3/16 (18.8%)	0/12 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Impact of Breakthrough Pain/CDI (measured with: Negative mood; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of Breakthrough pain (measured with: Interpersonal Problems; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	MD 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of Breakthrough pain (measured with: Ineffectiveness; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of breakthrough pain (measured with: Anhedonia; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL

Impact of Breakthrough Pain/CDI (measured with: Negative mood; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of Breakthrough pain (measured with: Interpersonal Problems; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	MD 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of Breakthrough pain (measured with: Ineffectiveness; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of breakthrough pain (measured with: Anhedonia; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Impact of breaktrough pain (measured with: Negative self-esteem; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12	16	-	mean 0 higher (0 to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL

Rayala Study

Author(s): Rayala, S., Bäckdahl, T., Reddy, N., Jacob, J., Gebre-Medhin, E., Karonen, E., Palat, G., Sinha, S., Schyman, T., Wiebe, T., Brun, E., & Segerlantz, M. (2019).
Date: 2021-09-04
Question: Should Ketamin plus EMLA vs Placebo plus EMLA be used in among newly diagnosed pediatric acute lymphoblastic leukemia??
Settings: Resource-Limited Cancer Hospital in India
Bibliography:

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamin plus EMLA	Placebo plus EMLA	Relative (95% CI)	Absolute		
Diagnosis (assessed with: ALL)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/26 (88.5%)	24/26 (92.3%)	-	923 fewer per 1000 (from 923 fewer to 923 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Diagnosis (assessed with: AML)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/26 (11.5%)	1/26 (3.8%)	-	38 fewer per 1000 (from 38 fewer to 38 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
Pain scores by patient (measured with: self-reported median pain score; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2	4	-	median 0 higher (0 to 0 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
pain scores by caregiver (measured with: self-reported median pain score ; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2	3	-	MD 0 higher (0 to 0 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Health System Support

Howard Study

Author(s):
Date: 2021-06-18
Question: Should improvement in health systems be used for improving outcomes in children with ALL?
Settings:
Bibliography: Howard SC, Pedrosa M, Lins M, Pedrosa A, Pui CH, Ribeiro RC, Pedrosa F. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. JAMA. 2004 May 26;291(20):2471-5. doi: 10.1001/jama.291.20.2471. PMID: 15161898..

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Improvement in health systems	Control	Relative (95% CI)	Absolute		
riskoftreatmentfailure1yearearlyvsrecent (follow-up mean 1 years; assessed with: relative risk of treatment failure)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	38/214 (17.8%)	32/83 (38.6%)	RR 2.4 (1.5 to 3.8)	540 more per 1000 (from 193 more to 1000 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
riskoftreatmentfailure1yearmiddlevsrecent (follow-up mean 1 years; assessed with: relative risk)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/214 (17.8%)	23/78 (29.5%)	RR 1.8 (1.1 to 3.1)	236 more per 1000 (from 29 more to 619 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
EFS5yearsearlyvsrecent (follow-up mean 5 years; assessed with: percentage event free survival)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	135/214 (63.1%)	27/83 (32.5%)	-	325 fewer per 1000 (from 325 fewer to 325 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
EFS5yearsmidvsrecent (follow-up mean 5 years; assessed with: percentage EFS)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	135/214 (63.1%)	37/78 (47.4%)	-	474 fewer per 1000 (from 474 fewer to 474 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] non randomized
[2] effect difference greater than 20 percent

Pedrosa Study

Author(s):
Date: 2021-06-18
Question: Should telemedicine referrals (twinning) be used for improving outcomes in childhood ALL?
Settings:
Bibliography: Pedrosa, F., Shaikh, F., Rivera, G., Ribeiro, R., & Qaddoumi, I. (2017). The Impact of Prospective Telemedicine Implementation in the Management of Childhood Acute Lymphoblastic Leukemia in Recife, Brazil. Telemedicine journal and e-health : the official journal of the American Telemedicine Association, 23(10), 863–867. https://doi.org/10.1089/tmj.2016.0273

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telemedicine referrals (twinning)	Control	Relative (95% CI)	Absolute		
Overall survival low risk (follow-up mean 4 years; assessed with: percentage of patients who survived)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	100/100 (100%)	77/100 (77%)	-	770 fewer per 1000 (from 770 fewer to 770 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
overall survival high risk (follow-up mean 4 years; assessed with: percentage survival)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	78/100 (78%)	58/100 (58%)	-	580 fewer per 1000 (from 580 fewer to 580 fewer)	⊕⊕OO LOW	
								0%		-		

overallmortality (assessed with: percentage mortality)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/100 (13%)	31/100 (31%)	-	310 fewer per 1000 (from 310 fewer to 310 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
early death (follow-up mean 4 years; assessed with: percentage death)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/100 (3%)	7/100 (7%)	-	70 fewer per 1000 (from 70 fewer to 70 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
relapse (follow-up mean 4 years; assessed with: percentage relapse)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] non randomized
[2] greater than 20% difference

Colton Study

Author(s):
Date: 2021-09-25
Question: Should insurance status be used for improvement in survival for children with ALL?
Settings:
Bibliography: Colton, M. D., Goulding, D., Beltrami, A., Cost, C., Franklin, A., Cockburn, M. G., & Green, A. L. (2019). A U.S. population-based study of insurance disparities in cancer survival among adolescents and young adults. Cancer medicine, 8(10), 4867–4874. https://doi.org/10.1002/cam4.2230

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Insurance status	Control	Relative (95% CI)	Absolute		
riskofdeathhodgkins (assessed with: relative risk)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	-	-	RR 2.17 (1.06 to 4.47)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
riskofdeathnonhodgkins (assessed with: relative risk)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	-	-	RR 2.36 (1.26 to 4.41)	-	⊕⊕OO LOW	
								0%		-		

[1] does not include burkitts and covers only 15-19
[2] relative risk point estimate more than 2x the risk

Jaime-Perez Study

Author(s): ALL group
Date: 2021-10-06
Question: Should REASON FOR ADMISSION UNDER POPULAR MEDICAL INSURANCE be used for AID IN TREATMENT OF CHILDHOOD ALL?
Settings:
Bibliography: Jaime-Pérez JC, Fernández LT, Jiménez-Castillo RA, Colunga-Pedraza JE, Padilla-Medina JR, Mancías-Guerra C, Gómez-Almaguer D. Hospitalization rate and costs in acute lymphoblastic leukemia of childhood in a low-income group: Financial impact in Northeast Mexico. Pediatr Blood Cancer. 2017 Dec;64(12). doi: 10.1002/pbc.26673. Epub 2017 Jun 9. PMID: 28598592.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	REASON FOR ADMISSION UNDER POPULAR MEDICAL INSURANCE	Control	Relative (95% CI)	Absolute		
MULTIVARIATE FEBRILE NEUTROPENIA (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	251/449 (55.9%)	-	OR 1.492 (0.986 to 2.258)	-	§§OO LOW	IMPORTANT
MULTIVARIATE CHEMOTHERAPY (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	118/449 (26.3%)	0%	OR 0.316 (0.186 to 0.536)	-	§§§O MODERATE	IMPORTANT
MULTIVARIATE ELECTROLYTE IMBALANCE (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	17/449 (3.8%)	0%	OR 0.474 (0.159 to 1.415)	-	§§OO LOW	IMPORTANT
MULTIVARIATE ADVERSE DRUG REACTION (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	15/449 (3.3%)	0%	OR 1.054 (0.343 to 3.234)	-	§§OO LOW	IMPORTANT
MULITIVARIATE ALTERED NEUROLOGIC STATUS (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	13/449 (2.9%)	0%	OR 1.319 (0.407 to 4.277)	-	§§OO LOW	IMPORTANT
MULTIVARIATE HEMORRHAGE (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	8/449 (1.8%)	0%	OR 0.666 (0.419 to 2.966)	-	§§OO LOW	IMPORTANT
MULTIVARIATE FEVER (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	6/449 (1.3%)	0%	OR 1.175 (0.225 to 6.136)	-	§§OO LOW	IMPORTANT
MULTIVARIATE RELAPSE (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	4/449 (0.89%)	0%	OR 1.078 (0.148 to 7.83)	-	§§OO LOW	IMPORTANT
MULTIVARIATE TUMOR LYSIS SYNDROME (assessed with: ODDS RATIO AND CONFIDENCE INTERVAL)												
observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none[1]	2/449 (0.45%)	-	OR 1.223 (0.073 to 20.357)	-	§§OO LOW	IMPORTANT