The Philippine Clinical Practice Guidelines on the Diagnosis, Management, Psychosocial Support and Palliative Care of Burkitt Lymphoma in Children and their Families

Southern Philippines Medical Center

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Technical Working Group

Jeannie B. Ong, MD
Team Leader

Cheryl Lyn A. Diez, MD
Assistant Team Leader

Technical Working Group Members
Allyne M. Aguelo, MD
Sheila Grace A. Bonostro, RSW
Tessa Marlou Faye L. Duo, RN
Andy Omar A. Elorde, MD
Ana A. Loseo, RN
Ma. Theresa Fedoc-Minguito, MD
Kristina Mae B. Montebon-Soriano, MD
Paul Joshua L. Sison, RPh
Irish May C. Solar, RN
Rojim J. Sorrosa, MD
Marlo T. Tampon, MD
Jose Bernardo D. Tengson
Rosie Mebelle Tongco, RN
Bai Johanna T. Zainal, MD

Consensus Panel
Fatima Inderah D. Disomimba
Mae Concepcion J. Dolendo, MD
Oscar P. Grageda, MD
Linell G. Malimbag, PhD, RN, FPCHA
Lilia M. Yu, MD

Steering Committee
Mae Concepcion J. Dolendo, MD
Project Lead

Steering Committee Members
Maria Elinore A. Concha, MD
Cheryl Lyn A. Diez, MD
Jeannie B. Ong, MD
Grace Anne Q. Pecson, MD

Noel L. Espallardo, MD
Adviser

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2 EXECUTIVE SUMMARY

2.1 BACKGROUND

Burkitt lymphoma (BL) is the most common type of non-Hodgkin lymphoma in children and adolescents accounting for 30–50% of all pediatric lymphomas. Despite its fast-growing nature, BL is one of the most curable forms of non-Hodgkin lymphoma. A child's probability of surviving cancer is dismal in less developed countries and extreme discomfort is likely in the absence of palliative care. Considering this situation and the lack of clinical practice guidelines for BL in our country, Southern Philippines Medical Center organized a Technical Working Group to develop Clinical Practice Guidelines (CPG) for Burkitt Lymphoma in children and adolescents. The aim was to provide recommendations regarding clinical assessment, diagnostic and ancillary tests, risk stratification, staging, prognosis, BL treatment and its side effects, supportive measures, palliative care and the involvement of the health system in managing pediatric patients afflicted with BL.

The SPMC-CCI BL 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) Consensus Panel Review and Evidence to Decision, and 5) External Review and Updating of Recommendations.

2.2 SUMMARY OF KEY RECOMMENDATIONS

Clinical Assessment

Recommendation 1: Among children suspected of having Burkitt Lymphoma, look for the following during physical examination: abdominal masses; lymphadenopathy; head and neck masses; evidence of bone marrow abnormalities like pallor, ecchymoses, bleeding, or petechiae; CNS involvement findings such as headache, dizziness, vomiting, paralysis and paresthesia; ascites and pleural effusion. *(High Quality Evidence; Strong Recommendation)*

Recommendation 2: Among children suspected of having Burkitt Lymphoma, ask for B symptoms in the clinical history such as fever, night sweats and weight loss. *(High Quality Evidence; Strong Recommendation)*

Recommendation 3: Aside from the common items in the history and physical examination recommended above, the physician must also be aware of atypical presentations such as thyroid mass, URTI, dyspnea, dysphagia, and cavernous sinus thrombosis. *(High Quality Evidence; Strong Recommendation)*

Diagnostic and Ancillary Tests

Recommendation 4: Among pediatric patients suspected of having Burkitt Lymphoma, do image-guided core needle biopsy for lymph nodes to establish histopathological diagnosis. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 5: Among pediatric patients suspected of having Burkitt Lymphoma with equivocal results from core needle biopsy, repeat image guided core needle biopsy or perform surgical excision biopsy of lymph nodes. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 6: Morphological features are the cornerstone in the diagnosis of Burkitt Lymphoma. If available, employ immunophenotypic, cytogenetic, and molecular tests to strongly establish or validate the diagnosis. *(High Quality Evidence; Strong Recommendation)*

Recommendation 7: Among pediatric patients diagnosed to have BL, offer CT imaging or PET scan for pretreatment staging and monitoring. If not available, ultrasound may be used. *(High Quality Evidence; Strong Recommendation)*

Staging, Risk Classification, and Prognosis

Recommendation 8: Among pediatric patients diagnosed with Burkitt Lymphoma, we recommend using the International Pediatric Non-Hodgkin Lymphoma Staging System. *(High Quality Evidence; Strong Recommendation)*

Recommendation 9: Among pediatric patients diagnosed with Burkitt Lymphoma, the French-American-British Mature B-Cell Lymphoma (FAB-LMB) or Berlin Frankfurt Munster (BFM) risk stratification can be used. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 10: In pediatric patients with Burkitt Lymphoma, identify the following prognostic factors: extent of the disease (CNS and bone marrow involvement, minimal disseminated disease*), age of patient at diagnosis, primary site of tumor, LDH level, presence of EBV*, and cytogenetic abnormalities* (*depending on availability). *(Moderate to High Quality Evidence; Strong Recommendation).*

Treatment and Side Effects

Recommendation 11: Among pediatric patients with newly diagnosed Burkitt Lymphoma with CNS and/or bone marrow involvement Burkitt Lymphoma (Group C patients or R3-R4), offer treatment that

includes Rituximab 375 mg/m2 x 4-6 doses added to systemic chemotherapy with FAB LMB Regimen *(High Quality Evidence)* or BFM Regimen *(Moderate Quality evidence; Strong Recommendation).*

Recommendation 12: Among pediatric patients with newly diagnosed Burkitt Lymphoma with Intermediate Risk (Group B) and Low Risk (Group A) or R1 and R2 risk stratification, offer treatment that includes systemic chemotherapy with FAB LMB Regimen or BFM Regimen. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 13: Among pediatric patients with Burkitt Lymphoma undergoing treatment, watch out for febrile neutropenia, hematologic toxicities (anemia, thrombocytopenia), infection, mucositis, and tumor lysis syndrome which are the most common side effects. Monitor also for possible gastric toxicities (diarrhea and constipation), kidney failure, and infusion-related reactions such as hypersensitivity reactions and hypotension (usually associated with Rituximab) that are less common side effects. *(Moderate Quality Evidence; Strong Recommendation)*

Side Effects and Management

Recommendation 14: Among children with Burkitt Lymphoma undergoing chemotherapy, watch out for the most common treatment-related infections such as febrile neutropenia and mucositis. *(High Quality Evidence; Strong Recommendation)*

Recommendation 15: Among children with Burkitt Lymphoma who develop febrile neutropenia, offer empiric antibiotic treatment. *(High Quality Evidence; Strong Recommendation)*

Recommendation 16: Among pediatric Burkitt Lymphoma patients with oral mucositis, offer Chlorhexidine mouthwash and anti-fungal treatment. In addition, oral care, antivirals, pain management using patient-controlled analgesia (PCA)/nurse-controlled analgesia (NCA) opioid administration, and intravenous Ketamine can be used as supportive management. *(High Quality evidence; Strong recommendation)*

Supportive and Palliative Care

Recommendation 17: Among Burkitt Lymphoma patients undergoing chemotherapy, consider nutritional support from pre-induction through post chemotherapy as supportive management. Use urate oxidase (Rasburicase) for the prevention and treatment of hyperuricemia in tumor lysis syndrome (if not available, the alternative treatment is Allopurinol). *(High Quality Evidence; Strong Recommendation)* Granulocyte colony- stimulating factor (GCSF) may reduce hospitalization days during neutropenic episodes. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendations 18: For Burkitt Lymphoma patients, recommend behavioral intervention like distraction, paced breathing and positive reinforcement to reduce parental rated pain, parental anxiety and usage of restraints during chemotherapy and cancer-related procedures. Counselling and skill-based interventions that aim to improve resilience, quality of life and psychological distress should also be offered. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 19 - Palliative care may be offered to pediatric patients with Burkitt lymphoma to improve overall quality of life and well-being. *(Low Quality Evidence; Strong Recommendation)*

Health System Recommendations

Recommendation 20: Treatment of pediatric Burkitt Lymphoma should be covered by PhilHealth and other health insurance companies because it is cost effective *(High **Q**uality Evidence; Strong Recommendation).* It should also be emphasized that having insurance can increase overall survival rate *(Low **Q**uality Evidence; Strong Recommendation).*

Recommendation 21: Among pediatric patients suspected of having Burkitt Lymphoma, encourage carers to improve their perspective of health-seeking behavior by participating in support groups and thorough health education discussions. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 22: Among pediatric patients suspected of having Burkitt Lymphoma, provide assistance to affected families, by considering their non-medical needs such as transportation and/or accommodation, access to financial assistance and psychosocial guidance. *(Moderate Quality Evidence; Strong Recommendation)*

3 BACKGROUND

Every year, an estimated 400,000 children aged 0–19 years develop cancer globally. (**Ward et al., 2019**) The Department of Health in the Philippines reported about 5,133 childhood cancer cases annually and the most common cases include acute lymphocytic leukemia, acute myelogenous leukemia, central nervous system (CNS) tumors, lymphoma, retinoblastoma, osteosarcoma, Wilms tumor, rhabdomyosarcoma, and neuroblastoma. Non-Hodgkin lymphoma (NHL) is the fourth most common malignant tumor in children. Burkitt lymphoma (BL) is the most common type of non-Hodgkin lymphoma in children and adolescents (**Miles et al., 2012**) accounting for 30–50% of all pediatric lymphomas. **(Huang et al., 2015)** BL is a fast-growing tumor and is associated with impaired immunity and is rapidly fatal if left untreated. However, despite its fast-growing nature, BL is one of the most curable forms of non-Hodgkin lymphoma. More than 90% of children with localized tumors and more than 85% with widespread disease are cured. Determining the precise histology is critical because clinical presentations and therapeutic strategies for the various lymphomas are distinct. Accurate and reliable histopathology diagnosis is crucial for confirmation of BL. There is no single parameter used as the gold standard for BL diagnosis. (**Arber et al., 2000**) The challenges of confidently establishing BL diagnoses is considerable amid severe limitations especially in lower middle-income countries (LMIC) such as the Philippines.

The Philippine Pediatric Society Disease Registry Program reported 403 cases of Burkitt Lymphoma from 2016 until October 2021. Seventy-three cases were from Davao Southern Mindanao Chapter. A total of 15 cases from 2013 to 2021 were diagnosed at the Southern Philippines Medical Center Children's Cancer Institute (SPMC-CCI). These numbers can be an underestimation of actual cases of BL since the cases reported were mainly from tertiary training institutions. In addition, only a proportion of the children who are registered receive appropriate treatment. From a survey of health care workers in 10 LMICs, including Bangladesh, Philippines, Tanzania, and Vietnam, only 15–37 percent of the expected patients were seen by health-care providers **[WHO 2021],** suggesting insufficient access to appropriate care. (**Ribeiro 2008**) A child's probability of surviving cancer is dismal in less developed countries, [**Ma X, Liu Y, 2018**] and extreme discomfort is likely in the absence of palliative care. [**American Cancer Society**] Considering this situation and the lack of clinical practice guidelines for BL in our country, Southern Philippines Medical Center organized a Technical Working Group to develop Clinical Practice Guidelines (CPG) for Burkitt Lymphoma in children and adolescents. The aim was to provide recommendations regarding clinical assessment, diagnostic and ancillary tests, risk stratification, staging, prognosis, BL treatment and its side effects, supportive measures, palliative care and the involvement of the health system in managing pediatric patients afflicted with BL. With this guideline, we hope to improve quality of cancer care to BL patients that may bring better patient outcomes, improve cost effectiveness, help authorities to decide on the approval of medicines, reagents and devices, and eventually identify areas of needed research.

The SPMC-CCI BL 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) Consensus Panel Review and Evidence to Decision, and 5) External Review and Updating of Recommendations.

4 SCOPE AND PURPOSE

4.1 TARGET POPULATION

The clinical practice guideline is intended for newly diagnosed Burkitt's Lymphoma patients less than 19 years old. This will cover all stages of the disease. The clinical practice guideline does not address relapsed or refractory Burkitt's Lymphoma. Recommendations on how to treat these conditions will be discussed in a separate clinical practice guideline. The clinical practice guideline does not address the other types of lymphoma other than Burkitt's Lymphoma.

4.2 TARGET USERS

The intended users are medical practitioners involved in the care of patients with Burkitt's Lymphoma namely primary care physicians and nurses, pediatric hematologist or oncologist, pathologists, palliative care and social workers. The goal of this clinical practice guideline is to inform and provide the local primary health care workers as well as the Specialists on current evidence-based practice on Burkitt's Lymphoma diagnosis and holistic management. This will assist them whenever they are faced with the dilemma of identifying a source of guideline that are relevant to their specific question that is answered by each recommendation. The primary health care physicians need to have an immediate and accurate initial evaluation of a presenting symptom and may take some additional evaluation, such as laboratory testing, imaging, and/or other diagnostic tests. A timely referral to Specialist is also warranted to treat the patient with BL competently.

5 OBJECTIVES

5.1 GENERAL OBJECTIVE

The main goal of the clinical practice guideline is to provide evidence-based recommendations on the early identification, diagnosis, assessment, management and provision of psychosocial support and quality of life for newly diagnosed Burkitt's lymphoma aged 19 years and below and their family.

5.2 SPECIFIC OBJECTIVES

- Provide and identify physical findings that can recognize early Burkitt's lymphoma.
- Provide the most accurate diagnostic test for the diagnosis of Burkitt's lymphoma
- Determine ancillary tests that are helpful in the diagnosis of Burkitt's lymphoma.
- Determine the most effective treatment for Burkitt's lymphoma including treatment related complications and toxicities.
- Provide recommendations on how to provide palliative care for patients diagnosed with Burtkitt Lymphoma

5.3 CLINICAL QUESTIONS ADDRESSED BY THE RECOMMENDATIONS

The clinical questions to be addressed with recommendations among newly diagnosed BL patient below 19 years old were grouped into the following:

- What are the early identification strategies?
- What should be the clinical assessment for patients with BL?
- What are the diagnostic and ancillary tests for patients with BL?
- What are the effective treatments and their complications?
- What are the monitoring tests during and post treatment for BL?
- What are the indicators of poor prognosis in BL?
- What are the supportive managements in patients with BL?
- Should palliative care be integrated for patients with Burkitt Lymphoma?
- How effective are integrative interventions in improving the quality of life among patients with Burkitt Lymphoma?
- Is counselling effective in relieving psychosocial and spiritual distress among patients with Burkitt Lymphoma?

- How do we initiate and integrate supportive care while patients are undergoing treatment for BL?
- Is national health insurance system and private insurance coverage for the treatment of BL cost effective?
- What are the factors affecting adherence/compliance to therapy of BL patients and how do we address them?

6 METHODS OF DEVELOPMENT

6.1 TECHNICAL WORKING GROUP

This guideline development for BL in children was funded by the Department of Health (DOH). A Steering Committee was formed from the Children's Cancer Institute (CCI) of the SPMC Department of Pediatrics assisted by the SPMC Training Office. The committee led the formation of the Technical Working Group to develop the guideline. The team was composed of a multi-specialty group that included pediatric oncologists, pediatric hematologists, clinical pathologists, palliative care specialists, family physicians, nurses, medical technologists and other allied health professionals. 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.

6.2 CONSENSUS PANEL

A Consensus Panel (CP) was convened to review the BL TWG recommendations. This consist of a pediatric hematologist, oncologist, pathologist, hospital administrator and charity foundation officer to represent community and family perspective. A draft document of the BL TWG recommendations and supporting evidence was sent to all CP members to review in preparation for the online meetings. The CP members were provided with a preliminary grading sheet that was populated prior to meeting and results reviewed after TWG presentation and scientific literature evidence to recommendations. The CP voted Weak, Moderate and Strong depending on the number of votes per recommendation.

6.3 CONSULTATION WITH CARE PROVIDERS, PATIENTS AND FAMILIES

The Technical Working Group consulted the target users of the guideline in a meeting. The meeting discussed relevant decisions to be made by the health care provider for BL patients. Consultations were also done with patients and families of children with BL. They are asked for relevant information and health care services that they need. The results of these consultations were summarized in the Appendix. From these consultations, the TWG was able to formulate the key questions to be answered by the guidelines as shown in Box 1. These initial questions were further refined as the search strategy, retrieval and appraisal of the evidence were being conducted.

6.4 EXTERNAL REVIEW

The CPG for Burkitt's lymphoma were sent to pediatric oncology training institutions such as the Philippine General Hospital/Oncology Divisions and the Philippine Children's Medical Center Cancer and Hematology Center through their respective section heads who subsequently assigned reviewers from their institution. Professional societies such as the Philippine Society of Pediatric Oncology and the Philippine Society of Pediatric Hematology were also requested to conduct external review using the AGREE Tool. The outcomes of external review process were submitted to the SPMC CCI Steering committee for discussion. The section heads designated their institutional reviewers. Pathologists and nurses were part of the CPG technical working group but not as external reviewers. Psychiatrists were not included in the external review process but social workers and child life coordinators were included in the TWG and Consensus Panel.

Box 1. Key Clinical Questions the TWG Tried to Address

Early identification

1. What is the effective screening strategy for early detection of Burkitt lymphoma?
2. What are the early signs and symptoms of Burkitt Lymphoma?

Clinical assessment

1. What are the signs and symptoms that are predictive of Burkitt Lymphoma?
2. Is there a "pathognomonic" or physical examination findings specific to in BL?

Diagnostic and ancillary tests

1. What are the is the reference standard diagnostic tests for Burkitt's Lymphoma?
2. What is the most cost-effective diagnostic modality for the diagnosis of Burkitt's Lymphoma?
3. How important is frozen section biopsy in determining Burkitt 's Lymphoma?
4. When is the accurate period to do diagnostic tests for patients suspected with Burkitt Lymphoma?
5. What are the molecular diagnostic tests and gene sequencing used to diagnose BL?
6. What are the imaging tests needed in Burkitt 's Lymphoma?
7. What is the better modality in diagnosing Burkitt 's Lymphoma?
8. CT scan vs MRi? Is Ultrasound and Xray also important?
9. What are the other laboratory tests that might be helpful in the diagnosis and prognosis of BL?
10. Do we have diagnostic criteria that correlate with the prognosis of the patient? Is there a test or set of tests used to stratify the patients according to prognosis?
11. What is the most effective test to determine subtypes for treatment prognostication? (immunochemistry, flowcytometry, karyotyping)

Treatment and Complications

1. What is the recommended treatment for Burkitt 's Lymphoma? (Chemotherapy/Surgery/Radiotherapy)
2. What is the standard chemotherapy regimen in the treatment of Burkitt 's Lymphoma? Stage 1 and 2? Stage 3 and residual disease? Stage 4 (CNS and BM Involvement)?
3. What is the efficacy and safety of Rituximab added to chemotherapy for to Burkitt 's Lymphoma?
4. What are the other novel therapy and targeted therapy for Burkitt 's Lymphoma?
5. What is the outcome of patients with Burkitt 's Lymphoma given standard treatment regimen, and Rituximab?
6. Is there a role of stem cell transplant (or BMT) in patients with BL?
7. What are the most common treatment complications of Burkitt 's Lymphoma?
8. How can Tumor lysis Syndrome be prevented and managed in patients with Burkitt's Lymphoma?
9. What are the parameters to monitor response to chemotherapy in patients with Burkitt 's Lymphoma?
10. What are the possible adverse reactions to chemotherapy in the treatment of Burkitt 's Lymphoma?
11. What are the precautionary measures to be done to avoid/lessen infection while on treatment of BL?
12. What are the surveillance monitoring tests to be done while ongoing and post treatment?
13. Is GCSF helpful in preventing febrile neutropenia for patients with Burkitt 's Lymphoma?
14. What are the factors affecting adherence/compliance to therapy of BL patients and how do we to address them?
15. What are the indicators of poor prognosis in Burkitt 's Lymphoma?
16. What are the signs of treatment failure in Burkitt 's Lymphoma?
17. What are the supportive management in patient with BL? (Blood transfusion, prophylactic antibiotics, hygiene)
18. What are dietary recommendations and restrictions for patients with BL?
19. What are the nursing interventions for patients receiving Rituximab?

Supprotive and Palliative Care

1. When is palliative care indicated for patients with Burkitt's Lymphoma?
2. How to assess and manage pain associated with Burkitt's Lymphoma?
3. How to identify patients with complex palliative needs?
4. When do I refer to palliative care specialists?
5. How to initiate and integrate supportive care while the patient is being treated?
6. How to identify patients with psychological, social, spiritual and physical distress?
7. How to provide psychosocial, emotional, spiritual support to newly diagnosed BL patients and their families giver?
8. How to disclose poor prognosis to patients with BL and their families?
9. Health systems recommendation
10. What are the referral services that help support pediatric BL?
11. Should a treatment protocol for BL suited for a community with limited resources be implemented to promote better compliance and therefore improve survival rate?
12. What should be the health insurance coverage for these patients?

6.5 SEARCHING, SELECTION AND ASSESSMENT OF THE EVIDENCE

Based on the agreed scope, the TWG team divided review assignments based on the grouping of the clinical questions. Consideration was given on the capacity and expertise of the team member in the assignments. There were 3-4 team members assigned per clinical review question. The members independently searched the scientific literature for relevant publications. From the agreed clinical review question, the key terms were identified and used for the search. The most common search terms were "Burkitt lymphoma", and "children". Depending on the clinical question, other terms like "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 types of articles were limited to clinical trials, systematic reviews, meta-analysis, and randomized controlled trials.

The titles and abstracts were independently reviewed by each TWG member for their relevance. They were included if the population studied were children with BL. Some articles were studies on non-Hodgkin's lymphoma but included a subgroup of BL. These were also included if the study addressed the other elements in the clinical review questions that are covered ie., clinical manifestations, risk factors, diagnostic test, treatment or prognosis. An inclusive approach ie., to include as many relevant articles was used at this stage. The TWG met and discussed the list and developed a consensus on which articles to include. The full-text articles of included titles and abstracts were retrieved.

The quality of the full text articles was evaluated using the GRADEPro approach. This approach used the parameters that include study design, limitations, inconsistency, indirectness, imprecision, publication bias and other considerations for quality assessment. GRADEPro was developed to assess the quality and summarize the results of effectiveness of interventions based on the prioritized outcomes. This was the approach used for clinical questions on intervention. GRADEPro gives a higher quality score for randomized control trial designs over observational studies. However, for clinical questions on clinical manifestations, risk, prognosis and diagnosis, study designs are usually usually observational. We used the modified GRADEPro approach and observational studies are graded accordingly. Using the same evaluation parameters for both GRADEPro for intervention questions and the modified GRADEPro for non-intervention questions, we classified the quality of evidence to high, moderate, low and very low quality. The data were extracted by the individual members of the team independently using a standardized data extraction form. The extracted data were verified by the other members of the team and entered into a GRADEPro software to generate the evidence table.

Before using the GRADEPro, the TWG prioritized the clinically important outcomes that should be considered when developing the recommendations. 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. 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.

6.6 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: clinical assessment, diagnostic and ancillary tests, staging, risk classification and prognosis, treatment and side effects, management of side effects, supportive and palliative care and health system recommendations. The recommendations were stated considering patient involvement in the decision making.

The quality of the evidence for 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.

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 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. The final grade of the recommendation was a combination of the quality of the evidence and the CP consensus.

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 BL.

6.7 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 CLINICAL ASSESSMENT

Recommendation 1: Among children suspected of having Burkitt Lymphoma, look for the following during physical examination: abdominal masses; lymphadenopathy; head and neck masses; evidence of bone marrow abnormalities like pallor, ecchymoses, bleeding, or petechiae; CNS involvement findings such as headache, dizziness, vomiting, paralysis and paresthesia; ascites and pleural effusion. ***(High Quality Evidence; Strong Recommendation)***

Recommendation 2: Among children suspected of having Burkitt Lymphoma, ask for B symptoms in the clinical history such as fever, night sweats and weight loss. ***(High Quality Evidence; Strong Recommendation)***

Recommendation 3: Aside from the common items in the history and physical examination recommended above, the physician must also be aware of atypical presentations such as thyroid mass, URTI, dyspnea, dysphagia, and cavernous sinus thrombosis. ***(High Quality Evidence; Strong Recommendation)***

Evidence to Recommendation on Clinical Assessment

Burkitt lymphoma is an aggressive B-cell Non-Hodgkin lymphoma. The patient may initially be seen by the medical community with symptoms affecting one or more anatomic sites. PubMed was utilized in searching related articles, studies and journals. MeSH terms used are: "Burkitt lymphoma", "signs and symptoms" and "children". A total of 28 studies reviewed, eight of which were selected.

All eight studies included with a total of 657 patients are of high-quality evidence. One high quality study noted that B symptoms were noted in 35% (**Huang et al., 2015**). In terms of physical examination findings, six high quality studies included abdominal tumors as one of the most common clinical presentations (52% mean percentage) **(Ertem et al., 1996; Mbulaiteye et al., 2009; Huang et al., 2015; Cavdar et al., 1994; Zheng et al., 2019)**. Lymphadenopathies (38%) were cited in five high quality studies **(Mbulaiteye et al., 2009; Huang et al., 2015; Cavdar et al., 1994; Anavi et al., 1990)**. Head and neck masses were mentioned in four studies (33%) **(Ertem et al., 1996; Mbulaiteye et al., 2009; Cavdar et al., 1994; Zheng et al., 2019)**. The less common clinical presentations of BL were bone marrow abnormalities (16%), ascites (13% and CNS involvement (13%) and pleural effusion (11%) **(Ertem et al., 1996; Mbulaiteye et al., 2009; Cavdar et al., 1994; Anavi et al., 1990; Zheng et al., 2019)**. The rest of the less common presentations of BL were liver involvement (6%), mediastinal (6%) and kidney presentations (6%); ovarian mass, skin nodule (3.7%); and least are testis involvement and breast mass (2.5%) **(Ertem et al., 1996; Cavdar et al., 1994)**

Overall, there is high-quality evidence suggesting B symptoms, abdominal tumors, lymphadenopathies, head and neck masses are common manifestations of BL. These are seen in at least 30% of patients. The less common manifestations are bone marrow abnormalities, ascites, CNS involvement and pleural effusion found in at least 10% of cases.

Evidence to Recommendation on Unusual Manifestation

Some Burkitt Lymphoma are unusual and highly aggressive forms of NHL are seen in pediatric age groups. Because of its extremely low prevalence, little is known about the pathogenesis and clinico-pathological features of this disease. PubMed was used in searching for related articles using the words "Burkitt lymphoma", “clinical presentations", signs and symptoms" and "children". Studies chosen were those with reports of being "rare" and "unusual". A total of eight (8) studies were reviewed, six (6) of which were eventually included.

The six studies included a total of 112 patients. One was high-quality evidence and five were moderate quality evidence. Most of these are case reports/observational studies, with one meta-analysis report. High quality evidence show that Upper Respiratory Tract Infections (URTIs) are common presentations in 80% of cases **(Periera et al., 2006; Banthia et al., 2003; Xeuereb et al., 2020)**. The rest of the five (5) moderate quality evidence suggested that the common atypical presentations of BL patients are thyroid mass 81% **(Hayashi et al., 2020)**; Dyspnea 61% **(Hayashi et al., 2020)**; and bone marrow presentations 38% **(Yang et al., 2020; Marginean et al., 2018)**. All are of moderate quality evidence studies. The less common atypical presentations are dysphagia (16%), cavernous sinus thrombosis and thyrotoxicosis (4.8%) **(Hayashi et al., 2020)**.

Overall, the most atypical presentations of BL are thyroid mass (81%), URTIs (80%), dyspnea (61.1%) and bone marrow presentations (anemia, bleeding, petechiae, ecchymosis) (38.4%). In addition, atypical presentations of BL are dysphagia (16.7%), cavernous sinus thrombosis (4.8%), and thyrotoxicosis (4.8%). These are based on moderate quality evidence.

7.2 Diagnostic and Ancillary Tests

Recommendation 4: Among pediatric patients suspected of having Burkitt Lymphoma, do image-guided core needle biopsy for lymph nodes to establish histopathological diagnosis. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 5: Among pediatric patients suspected of having Burkitt Lymphoma with equivocal results from core needle biopsy, repeat image guided core needle biopsy or perform surgical excision biopsy of lymph nodes. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 6: Morphological features are the cornerstone in the diagnosis of Burkitt Lymphoma. If available, employ immunophenotypic, cytogenetic, and molecular tests to strongly establish or validate the diagnosis. *(High Quality Evidence; Strong Recommendation)*

Recommendation 7: Among pediatric patients diagnosed to have BL, offer CT imaging or PET scan for pretreatment staging and monitoring. If not available, ultrasound may be used. ***(High Quality Evidence; Strong Recommendation)***

Evidence to Recommendation on Diagnosis

The diagnosis of BL is usually based on biopsy that can be performed with the following options i.e., fine needle, core needle or surgical. Fine needle aspiration biopsy specimens are obtained by a surgeon using a 22–25-gauge needle with multiple passes. In core needle biopsy, the puncture is performed by using standard percutaneous biopsy using a coaxial technique in all cases with a semi-automated biopsy gun that could obtain a core of tissue 17 mm long. A PubMed search was done with the terms "Burkitt lymphoma", "Pediatric", "Adolescent", "Core needle biopsy", and "Fine needle biopsy". Reference lists of articles were also searched through this approach. The recommendations are based on available published evidence. We reviewed a total of 15 published articles and 4 were included in the analysis with moderate quality evidence. There were 482 patients included in the studies.

In suspected lymphoma patients, fine needle aspiration biopsy is not recommended due to its high rate of non-diagnostic samples and incomplete classification of lymphoma. Nevertheless, there is a high diagnostic accuracy rate reported in the initial diagnosis of lymphoma for fine needle aspiration biopsy if in conjunction with flow cytometry having an accuracy of 95%, sensitivity 93% and specificity 100%. **(Dong et al., 2010)** For those with suspected lymphoma in whom a lymph node is not easily accessible for fine needle aspiration biopsy, core needle biopsy with hemato-pathology slide examination with or without concurrent sub-typing is appropriate for diagnosis which has an accuracy of 98.4%, sensitivity of 100% and specificity 100%. **(Loubeyre et al., 2009)**. Core needle biopsy revealed high diagnostic yield equivalent to surgical excision biopsy for suspected lymphoma. Core needle biopsy successful biopsy rate of 89% was comparable to surgical biopsy rate of 93.5% (p=0.25). Core needle biopsy provided minimal invasiveness, shorter waiting time to diagnosis and easily accessible. **(Chatani et al.,2020)**

Two studies **(deKerviler et al., 2000 and Loubeyre et al., 2009)** of 221 patients assessed core needle biopsy through confirmatory subtyping. Both studies provided good quality of evidence that morphology through biopsy can accurately diagnose lymphoma with confirmatory test using subtyping. Image-guided core needle biopsy is a cost efficient, safe and time-saving diagnostic tool for the evaluation of suspected lymphoma. Only for samples showing non-diagnostic or equivocal cases, it is recommended to consider re-biopsy or surgical excision biopsy. **(Nguyen et al., 2014)** Overall, there is moderate quality evidence that would recommend image guided core needle biopsy as the diagnostic procedure of choice in the diagnosis of patients with suspected lymphoma.

Evidence to Recommendation on Diagnostic Tests

A vast number of leukemias and lymphomas are diagnosed without the use of molecular, genetic and cytogenetic studies. Morphologic features as seen from histopathological samples remain the cornerstone of the evaluation of these malignancies. In Burkitt Lymphoma, however, a combination of morphologic, immunophenotypic, cytogenetic/molecular parameters are employed in its diagnosis. No single parameter can be used as the gold standard for diagnosis of Burkitt Lymphoma. (**Arber, 2000)**

Burkitt Lymphoma tumor cells usually have rounded nuclei with finely clumped chromatin and multiple basophilic, medium-sized, para-centrally located nucleoli. Their cytoplasm is deeply basophilic and usually contains lipid vacuoles. These tumor cells are seen with a diffuse, monotonous pattern of growth and many mitotic figures. A so-called "starry sky" pattern is usually present due to numerous tingible body macrophages. (**WHO 2016)**

Tissue biopsies of suspected Burkitt Lymphoma tumors are also subjected to immunophenotypic or molecular tests such as the following: Ki-67, B-cell markers (CD19, CD20, CD22, CD79a, PAX5), germinal center markers (CD10, BCL6), and MYC protein. The molecular hallmark of BL is the translocation of MYC at band 8q24 to the IGH region on chromosome 14q32, t (8;14) (q24; q32), or less commonly to the IGK locus on 2p12 [t (2;8)] or the IGL locus on 22q11 [t (8;22)]. However, MYC translocations are not specific for BL, and may occur in other types of lymphoma. Furthermore, additional chromosomal abnormalities may also occur in BL: (a) gains of 1 q, 7, and 12; (b) losses of 6q, 13q32-34, and 17p. (**WHO 2016**) When used for the diagnosis of Burkitt Lymphoma, molecular tests have high sensitivity and negative predictive (NP) values and cytogenetics have high specificity and positive predictive (PP) values. Molecular tests have sensitivity and negative predictive value results of 100% compared to 48 - 93% only if molecular tests were not employed in diagnostics. Cytogenetics have specificity and positive predictive value results of 100% compared to only 16% (specificity) and 39% (PPV) when cytogenetics is not employed. Accuracy of molecular testing (62% & 95%) and cytogenetic testing (48%) is high or at par with the accuracy of the previous and current BL diagnostic modalities (69%, 95%, and 34%) when used in the diagnosis of BL. (**Dave et al. 2006; Poirel et al.2008; Boerma et al. 2008**)

Studies dealing with review of previously diagnosed Burkitt Lymphoma cases showed that using specific molecular tests yielded more BL identified cases compared to previous and current BL diagnostic modalities. Pathological diagnosis identified 25 BL cases out of 71 lymphoma cases under study. With molecular testing, however, 52 out of 71 cases were identified as BL. (**Dave et al., 2006**) With the use of cytogenetics, 76% of lymphoma cases under study were identified as BL compared to 60% only in the absence of cytogenetic testing. (**Poirel et al.,2008**) Using molecular testing, 97 out of 299 lymphoma cases were identified as BL compared to 81 out of 299 lymphoma cases identified by pathological diagnosis. (**Boerma et al., 2008**) Specificity and positive predictive (PP) values of purely molecular tests, however, are low compared to the current WHO diagnostic criteria for BL since a combination of morphologic, molecular, cytogenetic, and clinical presentations are being considered in the current WHO BL diagnostic criteria. Two studies using molecular testing reported specificity of 41% and 93% (**Dave et al. 2006; Boerma et al. 2008**) compared to 100% specificity when using the current WHO diagnostic criteria for BL diagnosis.

However, in cases where, cytogenetics and molecular tests are not available, a novel flow cytometric antibody CD44 measurement can also be an alternative method to differentiate BL from diffuse large B cell lymphoma (DLBCL) . Eight articles were found at PubMed about the significance of CD44 among patients with BL but only 2 cross sectional studies with complete data were included. CD44 deficiency is a consistent finding in childhood Burkitt Lymphoma as proven by both studies. One high quality study **(Schniederjan 2**010) and 1 moderate quality evidence (**Attarbaschi, 2007**) demonstrated that CD44 is low or absent in BL while high in DLBCL with average sensitivity of 94.2%, specificity of 84.5%, PPV of 91.5%, NPV of 90.1 and accuracy of 91.5%. Overall, there is a moderate to high quality of

evidence that flow cytometry immunophenotyping using CD44 aids in distinguishing BL from DLBCL. This can be included in the immunophenotyping panel if one needs to differentiate BL from DLBCL in a clinical trial to further strengthen this evidence.

Overall, we found moderate to high quality evidence that suggest molecular testing (including cytogenetics) is accurate in the diagnosis of BL. However, the use of specific molecular tests or cytogenetics alone for the diagnosis of BL is not recommended.

Evidence to Recommendations on Imaging Studies

Aside from biopsy, radiologic imaging has also been tested for the diagnosis of BL. The options available for radiologic imaging are ultrasound, CT and PET scan. The role of ultrasound in the diagnostic workup of BL demonstrates that abdominal ultrasound provides more accurate staging than clinical examination alone. (**Marjerrison et al. 2021**) Ultrasonography is a widely accepted initial imaging workup; therefore, recognition of the sonographic features of BL should contribute to its early diagnosis and initiation of treatment. **(Okamoto et al. 2018)** A careful ultrasound assessment of all abdominal organs conducted with the use of convex and linear probes increases the chances of establishing an adequate diagnosis. (**Brodzisz et al. 2013)** Accurate initial staging is of primary importance, especially in children, as over-treatment increases the risk of long-term side-effects, and advanced stages require an aggressive therapeutic regimen. PET scan is significantly more sensitive than conventional CT in the management of aggressive pediatric mature B cell NHL. CT scan has a relatively high sensitivity and specificity for pretreatment staging of lymphoma. PET/CT had significant implications in terms of early assessment of treatment response. (Raef Riad et al. 2010) PET/CT should be the first modality for all purposes in initial staging, evaluating, treatment response and follow-up.

A PubMed search was done with the MeSH terms ‘‘pediatric Burkitt lymphoma”, ‘‘radiologic imaging”,” diagnostic test”, “sonography”. A total of 31 published evidence with inclusion of 6 studies and a total of 411 patients were included in this pertinent question. Using the modified GRADE-pro, our analysis included 2 high quality studies (**Rahman et al. 2016; Kamona et al. 2003)** and 4 moderate quality studies **(Riad et al. 2010; Marjerrison et al. 2012; Okamoto et al. 2018; Brodzisz et al. 2013)**. The sensitivity (Se), specificity (Sp), and predictive values (PV) of PET scan during management of pediatric mature B cell non-Hodgkin’s lymphoma (NHL) in comparison with conventional computed tomography (CT) scan were identified. In BL, sensitivity was 91.3% for PET, and 66.7% for CT ($p = 0.08$). Specificity was 85.7% for PET, while was 58.7%for CT ($p < 0.001$). PPV and NPV were 40.5% and 98.4%, for PET, while 14.3% and 94.4% for CT scan ($p < 0.001$, and 0.05 respectively **(Rahman et al.2016)**. 8F-FDG PET/CT is a useful method in the management of pediatric lymphomas wherein it showed great value in initial staging of lymphomas **(Riad et al. 2010)**. PET CT is not recommended in routine follow up after complete remission. It has a low PPV due to post therapeutic inflammation taken denoting high false positivity rather than true relapse. (**Rahman et al., 2016)**

Overall, we found moderate to high quality evidence that showed PET scan to be more sensitive than conventional CT. It can have significant implications in terms of early assessment of treatment response as it allows accurate characterization of residuals. However, PET/CT scan is not readily available everywhere. CT scan is also recommended as an invaluable tool in the characterization of the

disease processes in children with Burkitt lymphoma. Provision of an Ultrasound at diagnosis in resource poor settings is also useful.

7.3 STAGING, RISK CLASSIFICATION, AND PROGNOSIS

Recommendation 8: Among pediatric patients diagnosed with Burkitt Lymphoma, we recommend using the International Pediatric Non-Hodgkin Lymphoma Staging System. ***(High Quality Evidence; Strong Recommendation)***

Recommendation 9: Among pediatric patients diagnosed with Burkitt Lymphoma, the French-American-British Mature B-Cell Lymphoma (FAB-LMB) or Berlin Frankfurt Munster (BFM) risk stratification can be used. ***(Moderate Quality Evidence; Strong Recommendation)***

Recommendation 10: In pediatric patients with Burkitt Lymphoma, identify the following prognostic factors: extent of the disease (CNS and bone marrow involvement, minimal disseminated disease*), age of patient at diagnosis, primary site of tumor, LDH level, presence of EBV*, and cytogenetic abnormalities* (*depending on availability). ***(Moderate to High Quality Evidence; Strong Recommendation).***

Evidence to Recommendation on Staging

For more than 3 decades, pediatricians used the Murphy/St. Jude Childhood NHL staging classification in determining the stage of Burkitt lymphoma among children. Since then, the pathologic classification of NHL has changed significantly, and major limitations of the said staging classification include lack of consideration of new distinct pediatric NHL histologic entities; absence of recognition of frequent skin, bone, kidney, ovarian, and other organ involvement; and lack of newer precise methods to detect bone marrow and CNS involvement, minimal disease quantification, and highly sensitive imaging technologies.

To address these limitations, a revised system was made by an international multidisciplinary expert panel in 2015 and named it as the International Pediatric NHL Staging System (IPNHLSS). Evidence-based disease distribution and behavior were reviewed from multiple pediatric cooperative group NHL studies incorporating new histologic entities, extra-nodal dissemination, improved diagnostic methods, and advanced imaging technology. This revised international staging system includes modifications in stage definitions and the inclusion of new information, such as additional staging information, to incorporate recent medical progress. This will facilitate more precise staging for children and adolescents with Burkitt Lymphoma. Thus, we recommend the use of the revised IPNHLSS, as detailed in the table below. Our report presents this proposed revised staging classification of childhood and adolescent NHL, representing a multidisciplinary international collaboration of experts in childhood and adolescent NHL **(Rosolen et al. 2016)**.

Box 2 International Pediatric Non-Hodgkin Lymphoma Staging System

Stage I Single tumor with exclusion of mediastinum and abdomen (N; EN; B or S: EN-B, EN-S)
Stage II Single EN tumor with regional node involvement ≥ Two N areas on same side of diaphragm Primary GI tract tumor (usually in ileocecal area), ± involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of tumor to adjacent organs, it should be regarded as stage III)
Stage III ≥ Two EN tumors including EN –B or EN-S) above and or below diaphragm ≥ Two N areas above and below diaphragm Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumor [usually in ileocecal region] ± involvement of associated mesenteric nodes that is completely resectable) Any paraspinal or epidural tumor, regardless of whether other sites are involved Single B lesion with concomitant involvement of EN and/or non regional N sites
Stage IV Any of the above findings with initial involvement of CNS (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods
NOTE. For each stage, type of examination and degree of BM and CNS involvement should be specified. Based on classification proposed by Murphy. Abbreviations: B, bone; BM, bone marrow; EN, extranodal; N, nodal; S, skin.

Box 3 Additional Staging Information

BM involvement

Stage IV disease, resulting from BM involvement, is currently defined by morphologic evidence of 5% blasts or lymphoma cells by BM aspiration; this applies to any histologic subtype and will be maintained in IPNHLSS.

For each stage, type and degree of BM involvement (by BM aspiration) should be specified, using abbreviations below to identify involvement

- BMm: BM positivity by morphology (specify % lymphoma cells) BMi:
- BM positivity by immunophenotypic methods (immunohistochemical or flow-cytometric analysis; specify % lymphoma cells)
- BMc: BM positivity by cytogenetic or FISH analysis (specify % lymphoma cells)
- BMmol: BM positivity by molecular techniques (PCR based; specify level of involvement)

Same approach should be used for PB involvement (ie, PBm, PBi, PBc, PBmol)

Definition of BM involvement should be obtained from analysis of bilateral BM aspirates and BM Biopsy.

CNS involvement

- CNS is considered involved in case of:
  - Any CNS tumor mass (identified by imaging techniques [i.e., CT, MRI])
  - Cranial nerve palsy that cannot be explained by extradural lesions
  - Blasts morphologically identified in CSF
- Condition that defines CNS positivity should be specified: CNS positive/ mass, CNS positive/palsy, CNS positive/blasts
- CSF status: CSF positivity is based on morphologic evidence of lymphoma cells
- CSF should be considered positive when any No. of blasts is detected
- CSF unknown (not performed, technical difficulties)
- Similar to BM, type of CSF involvement should be described whenever possible
  - CSFm: CSF positivity by morphology (specify No. of blasts/L)
  - CSFi: CSF positivity by immunophenotype methods (immunohistochemical or flow cytometric analysis; specify % lymphoma cells)
  - CSFc: CSF positive by cytogenetic or FISH analysis (specify % lymphoma cells)
  - CSFmol: CSF positivity by molecular techniques (PCR based; specify level of involvement)

NOTE. Until sufficient data are available, PET should be used with caution for staging, and PET results should be compared and discussed in light of other more consolidated imaging approaches.

Abbreviations: BM, bone marrow; CT, computed tomography; FISH, fluorescent in situ hybridization; IPNHLSS, International Pediatric Non-Hodgkin Lymphoma Staging System; MRI, magnetic resonance imaging; PB, peripheral blood; PBc, PB positivity by cytogenetic or FISH analysis; PBi, PB positivity by immunophenotype methods; PBm, PB positivity by morphology; PBmol, PB positivity by molecular techniques; PCR, polymerase chain reaction; PET, positron emission tomography.

Evidence to Recommendation on Risk Stratification

Several prognostic factors have been associated with influencing event-free survival (EFS) in children with Burkitt lymphoma. Identification of prognostic factors to aid treatment refinement is a persistent goal for specialists involved in treatment of childhood lymphoma. The French-American-British Mature B-Cell Lymphoma (FAB-LMB) protocols have categorized the risk-based treatment into three strata, where risk group A includes completely resected stage I/abdominal II disease and group C includes patients with CNS involvement or extensive (> 25%) involvement of the bone marrow (BM); Group B includes all patients not eligible for Group A or C. The Berlin Frankfurt Munster (BFM) protocols instead categorized the survival outcome based on four groupings, where Risk 1 includes completely resected stage I or II disease, Risk 2 includes stage I or II but not resected or those with stage III disease and LDH < 500 U/L. Those belonging to Risk 3 are stage III disease with LDH ≥ 500 to < 1000 U/L or those with stage IV and LDH < 1000 U/L and CNS negative. Risk 4 includes stage III or IV with LDH ≥ 1000 U/L and/or CNS positive. Treatment recommendations for pediatric patients with BL are based on either of this risk group classification.

One moderate quality study which was participated by 161 treatment centers determined the survival outcome of patients with NHL based on FAB-LMB groupings: Group A as low risk (limited or those with resected stage I and abdominal completely resected stage II); Group B (intermediate risk) those not belonging to Group A or B; and Group C as a High-Risk group (advanced or with bone marrow involvement and/or CNS disease). This study compared the EFS of those children with BL belonging to Group A versus those belonging to Group B and C with EFS of 99% versus 84% respectively. Those belonging to Group A (EFS 99.2%) were compared to Group B alone (EFS 89.9%). Further results showed Group A and B (EFS of 94%) to Group C (EFS of 79%); Group B (EFS 89%) to Group C (EFS of 79%); and group A alone (EFS of 99.2%) compared to Group C alone (EFS of 78.9%). (**Cairo et al. 2007)**

Another high quality study utilizing BFM risk stratification protocol categorized the patients according to serum LDH in addition to stage of the disease. This study compared the EFS of patients belonging to R1 versus R2 (100% vs 96%), EFS of patients with R2 versus R3 (96% vs 78%) and the EFS of patients with R3 versus R4 (90 % vs 70%). The EFS of stage III and IV B-ALL was lower if their LDH ≥ 1,000 U/L than those with LDH < 1000 (RR = 6.450; P < .0017). There is a high quality of evidence that determines the survival outcome based on 4 groupings: Risk 1 as low risk , Risk 2 and 3 as intermediate risk and Risk 4 as a high-risk group (**Reiter et al. 1999**).

RISK STRATIFICATION GROUP

	French-American-British (LMB-89)	Berlin-Frankfurt-Munster (BFM-90)
LOW RISK	**Group A** Resected stage I and abdominal completely resected stage II	**Risk 1** Stage I or II, completely resected
	Group B All patients not in Group A or C	**Risk 2** Stage I or II not resected Stage III with LDH < 500 U/L
		Risk 3 Stage III with LDH ≥ 500 to < 1000 U/L Stage IV with LDH < 1000 U/L and CNS negative
HIGH RISK	**Group C** Advanced or with bone marrow involvement and/or CNS disease.	**Risk 4** Stage III or IV with LDH ≥ 1000 U/L and/or CNS positive

Evidence to Recommendation on Prognosis

Many studies have contributed to the identification of possible risk factors for a bad prognosis, such as age, gender, CNS or marrow involvement, and chromosomal abnormalities. Bulky disease, estimated through staging systems, resection status and serum LDH levels, seem to be important adverse prognostic factors. The identifiable prognostic factors that may affect the survival of patients with BL were investigated, and grouped according to extent of the disease, non-modifiable factors such as the age of the patient and primary sites of the tumor and some laboratory tests like serum LDH levels, presence of Epstein Barr Virus (EBV) and cytogenetic abnormalities. To identify these factors, our PubMed search retrieved 20 full articles and 10 were included in this analysis with a total number of 1,962 patients.

Extent of disease has also been used as a prognostic factor. Advanced stage compared to early stage gives poorer EFS 86.6% versus 98.8% (**Woessmann et al. 2005**). Combination of advanced stage, poor resectability, and CNS disease gave an EFS of 82.6% and failure free survival (FFS) of 77.3% compared to 94% EFS and 94.9% FFS to those with early stage, resectability and absence of CNS disease with a HR of 3.58. **(Woessmann et al2005)** This finding has a HIGH quality and critical importance based on GRADE-pro. Two high-quality studies identify minimal disseminated disease (MDD) a poor-prognosis subgroup among children with high-risk BL with a HR of 4.74 (**Mussolin et al., 2012**). MDD positivity was the only prognostic factor that retained its adverse prognostic value on progression free survival (PFS) in the multivariate analysis; P = 0.04; HR 2.6 with 95% CI ,1.1 - 6.5. (**Pillon et al. 2016**)

Bone marrow and CNS involvement have also been tested as prognostic factors. One high quality study proved that the presence of lymphoma cells in the bone marrow biopsy gives a 2-year cumulative survival rate of 70% while those without bone marrow involvement gives 100%. (**Chen et al. 2018**) This study also compared those patients with bone marrow involvement with more than 25% to those with less than 25%. This gives a 2-year cumulative survival rate of 63.6% versus 100% respectively. Another high-quality study demonstrated that the presence of isolated CNS disease is associated with a poor EFS of 70% compared to 88.2% EFS to those without CNS disease. (**Woessmann et al. 2005**) One moderate quality evidence showed that the presence of both CNS disease and BM positivity gives an EFS of 61% compared to 91% for those without CNS disease and bone marrow

involvement. The relative failure rate (RFR) is high at 4.9% (**Cairo et al., 2007).** Same result was observed in another moderate quality study demonstrating the presence of both CNS disease and BM positivity gives an EFS of 62% compared to 89% for those without CNS disease and bone marrow involvement (**Belgaumi et al., 2016**). This study also reported that the presence of both CNS disease and Bone marrow disease has an EFS of 52.9% compared to 73% to those with BM involvement but without CNS disease.

One high quality study determined that age is an important prognostic factor among patients with BL. This included a total of 364 pediatric patients (146 patients were older than 10 years old while 218 patients were younger than 10 years of age). In univariate analysis of patients of the combined risk groups R3 and R4 and age older than 10 years ($P < .01$) were associated with inferior FFS of only 40% versus 60% of those younger than 10 years old and advanced risk. In a Cox regression model with the co-variables age younger than 10 years versus 10 years or older, and risk group R3 versus R4, the hazard ratio was 3.59 (95% CI, 1.30-9.93; $P < .014$) (**Woessman et al., 2005**). Another high quality study using the survival analysis of 13 Surveillance, Epidemiology, and End Results registries from 1992 through 2001 which included 2442 children, adolescents and young adults up to 24 years old patients of NHL. Subgroup analysis was made out of 216 Burkitt lymphoma patients belonging to 0-19 years of age. A 5-year overall cause-specific survival with multivariate Cox proportional hazards to obtain hazard ratios (HRs) and their 95% confidence interval was modelled. Adolescents were more likely to die within 5 years of NHL diagnosis compared with younger children (HR, 2.4; 95% CI, 1.7-3.3) We found that 5-year survival rates were lower among adolescents than among children 0-14 years old. Adolescents are increasingly being recognized as a group with unique biological and psychosocial traits that may affect their cancer survival. (**Tai et al. 2010)**.

Another prognostic factor that may be considered is the primary site of the tumor. A major risk factor that was identified involving 1,111 patients was the association of an inferior outcome in mediastinum primary site compared to patients with peripheral node primaries. There's a higher treatment failure rate associated with mediastinal disease and abdominal/retroperitoneal disease (relative failure rate, 4.5 and 2.7, respectively) versus patients with peripheral node primaries (**Cairo et al.2007**).

Some laboratory tests that affect survival of children's BL offer to improve chemotherapy regimens and increase long-term survival. We searched for the evidence and retrieved 15 articles but only 6 studies were relevant and included. Six studies involving 2,310 patients discussed the importance of LDH. Two high quality studies (**Chen, et al. 2018; Reiter et al. 1999**) proving that LDH level more than 2x the upper limit of normal or LDH > or equal to 500 U/L has a lower 2-year cumulative survival rate. Increased LDH (more than 2x the upper limit of normal versus lower than 2x ULN) is an independent risk factor associated with a significant increase in treatment failure rate (relative risk of 2.0 – **Cairo et al.,2007**). One high quality evidence (**Sandlund, 1997**) and 1 moderate quality evidence that pediatric patients with BL had a poorer EFS and OS if their LDH level is more than 500 U/L than those with LDH less than 500 U/L. (**Belgaumi et al., 2016**). Another high-quality evidence that LDH value above the median value had an independently negative prognostic value ($P < 0.0001$). In multivariate Cox regression analysis, only higher LDH value was confirmed as significantly associated with increased risk of failure ($P < 0,0001$; HR of 6.1; 95% C], 2.7- 13.6). Another high quality study (**Reiter, 1999)** showed that the pEFS was significantly lower for patient with stage III/IV/B-ALL if their LDH values are greater

than 1,000 U/L as compared with those with LDH values less than 1,000 U/L. In a Cox regression analysis with the co-variables stage (stage III v stage IV1B-ALL) and LDH (1,000 versus 1,000 U/L), LDH greater than 1,000 U/L was the superimposed predictor for treatment outcome (risk ratio, 6.450; P = .0017).

The relationship between Burkitt's lymphoma and blood levels of Epstein-Barr Virus in children in one high quality study found that the EBV load in blood might be a diagnostic and prognostic marker for the onset and monitoring of BL in African children. A statistically significant association was found between BL and EBV detection in peripheral blood, with a predominance of EBV type 1. Sixty percent of BL patients had EBV detectable in peripheral blood compared to 30% in control; (OR = 4.77, 95% CI = 1.71 – 13.33, p value = 0.003). Children with BL had higher viral load in their peripheral blood than EBV positive controls. (**Kabyemera et al. 2013**). Another high-quality evidence study in this context, determined that plasma EBV DNA would be an implementable and valuable clinical biomarker for BL diagnosis and treatment. In this study, although few children had assessable plasma for EBV DNA at clinical relapse, the proportion with detectable viremia was similar to mid-treatment and completion timepoints, but viremia level was higher at relapse when detected. Among children with baseline plasma EBV detected, survival was significantly worse for patients with baseline level ≥6 $\log_{10}$copies/mL versus <6 $\log_{10}$copies/mL (p=0.0002). Additionally, after cytotoxic treatment initiation, survival was worse for children with persistent mid-treatment plasma EBV detection versus those without (p=0.041). To conclude, quantitative plasma EBV DNA demonstrated potential utility for diagnosis, prognosis, and response assessment in a prospective pediatric BL (**Westmoreland, 2017)**.

Another important examination that could help in prognosticating patients with BL is to employ cytogenetic tests. Through cytogenetics, it is known that the molecular hallmark of BL is the translocation of MYC at band 8q24 to the IGH region on chromosome 14q32. Additional chromosomal abnormalities may also occur in BL, these include the following: gains of 1q, 7, and 12 and losses of 6q, 13q32-34, and 17p. These abnormalities may play a role in the progression of the disease. (**2016 WHO Classification of Tumors of Hematologic and Lymphoid Tissues**). We reviewed and included one article of high-quality evidence that used cytogenetics in risk group stratification of Burkitt Lymphoma. Specifically, presence of 7q+, 13q deletion and cytogenetic complexity (more than 3 cytogenetic abnormalities) are associated with poorer outcomes. **(Poirel et al. 2008).** On the other hand, there is no significant difference as to outcomes in BL patients with or without 8q24 rearrangement. **(Poirel et al. 2008)**

Overall, there is moderate to high quality evidence that extent of the disease such as CNS and bone marrow involvement, presence of minimal disseminated disease, age of the patient at diagnosis, primary site of the tumor, LDH level, presence of EBV and cytogenetic abnormalities will help in determining the prognosis of children with BL.

7.4 Treatment and Side Effects

Recommendation 11: Among pediatric patients with newly diagnosed Burkitt Lymphoma with CNS and/or bone marrow involvement Burkitt Lymphoma (Group C patients or R3-R4), offer treatment

that includes Rituximab 375 mg/m2 x 4-6 doses added to systemic chemotherapy with FAB LMB Regimen *(High Quality Evidence)* or BFM Regimen *(Moderate Quality evidence; Strong Recommendation).*

Recommendation 12: Among pediatric patients with newly diagnosed Burkitt Lymphoma with Intermediate Risk (Group B) and Low Risk (Group A) or R1 and R2 risk stratification, offer treatment that includes systemic chemotherapy with FAB LMB Regimen or BFM Regimen. *(Moderate Quality Evidence; Strong Recommendation)*

Recommendation 13: Among pediatric patients with Burkitt Lymphoma undergoing treatment, watch out for febrile neutropenia, hematologic toxicities (anemia, thrombocytopenia), infection, mucositis, and tumor lysis syndrome which are the most common side effects. Monitor also for possible gastric toxicities (diarrhea and constipation), kidney failure, and infusion-related reactions such as hypersensitivity reactions and hypotension (usually associated with Rituximab) that are less common side effects. *(Moderate Quality Evidence; Strong Recommendation)*

Evidence to Recommendation for Treatment

Historically the survival of pediatric Burkitt Lymphoma has been poor; using low dose Cyclophosphamide is ineffective (**San Roman et al. 2013**). The addition of Vincristine to the Malawi 28 day BL treatment protocol did not improve survival (**Depani et al. 2015**). Systemic chemotherapy with CHOP did not also improve outcomes in Pediatric BL compared to less intensive regimens in Malawi (**Stanley et al. 2016**)

Classical lymphoma regimens using anthracycline, vincristine (VCR), cyclophosphamide (CPM), and prednisone with CNS prophylaxis were also initially used for the treatment of children with BL/ L3 acute lymphoblastic leukemia (L3ALL) but failed to achieve complete response (CR) in advanced disease.

Recent improvement in the treatment of Burkitt Lymphoma among children usually involves brief duration, high intensity chemotherapy regimens that is associated with improved outcome with survival rates higher than 90% even in patients with central nervous system (CNS) involvement or L3ALL. The addition of monoclonal antibody therapy with Rituximab shows promise for improved outcomes and reduced toxic effects.

Our PubMed search yielded 53 articles and 9 studies with a total of 1,134 patients included in this review. One was high quality **(Minnard Colin et al., 2020)** while 8 were moderate quality evidence **(Goldman et al. 2014; Zijun Zhen et al. 2020; Aydin et al. 2019; Sun XF 2007; Sun XF et al. 2006; Bouda et al. 2019; Stanley et al. 2015; Park et al. 2011)**

One high quality study noted that Rituximab added to standard LMB chemotherapy markedly prolonged EFS and OS among children and adolescent with high risk Burkitt Lymphoma, with 3-year EFS/OS of 93.9 (95% CI, 89.1–96.7)/ 95.1 (95% CI, 90.5–97.5) **(Minard-Colin et al. 2020)**. Two moderate quality evidence noted with Rituximab 375 mg/m2 plus systemic chemotherapy, one with LMB 96 for the treatment of children and adolescent with CNS and/or Bone Marrow Positive Burkitt Lymphoma (Group C patients) with 3 years EFS and OS of 93% and 90% **(Goldman et al. 2014);** and the other with

Systemic Chemotherapy with BFM 90 Protocol, with 3 years EFS and OS of 81.2 given Rituximab (375 mg/m2) x 1-3 doses + Systemic Chemotherapy with BFM 90 Protocol and 3 years EFS 96.8 and OS 96.7 given Rituximab (375 mg/m2) x 4 -6 doses **(Zijun Zhen et al. 2020)**

Moderate quality evidence was also noted in pediatric Burkitt Lymphoma given systemic chemotherapy only with FAB LMB 96 regimens showing 3- and 5-year Overall Survival (OS) and Event Free Survival (EFS) of 86.8% and 81.6% **(Park et al. 2011)**, 90.8% and 87.4% (**Aydin et al. 2019**). Patients in Group B or Intermediate Risk received COP (Cyclophosphamide, Vincristine and Prednisone) as prophase, 2 courses of COPADM (Cyclophosphamide, Vincristine, Prednisone, Doxorubicin and Methotrexate) as induction, 2 courses of CYM (Cytarabine, Methotrexate, TIT, Folinic acid) as consolidation and maintenance chemotherapy (Vincristine, Prednisone Methotrexate, Folinic acid, Cyclophosphamide, Doxorubicin, TIT), with 5 years OS and EFS of 95% and 93% **(Aydin et al. 2019)**. Patients in High Risk Group C received COP (Cyclophosphamide, Vincristine and Prednisone) as prophase, 2 courses of COPADM (Cyclophosphamide, Vincristine, Prednisone, Doxorubicin and Methotrexate) as induction, 2 courses of CYM (Cytarabine, Methotrexate, TIT, Folinic acid) as consolidation and 4 maintenance chemotherapy cycles (Vincristine, Prednisone, Methotrexate, Folinic acid, Cyclophosphamide, Doxorubicin, TIT), with 5 years OS and EFS of 78% and 62% **(Aydin B et al. 2019)**

An equivalent moderate quality of evidence was also noted by giving systemic chemotherapy with Modified B-NHL-BFM-90 protocol among Burkitt Lymphoma in Chinese children and adolescents, with tolerable toxicity **(Sun XF at al.2007)**. EFS of BFM 90 regimen for Pediatric Burkitt Lymphoma is 85.5% for all patients and for Group R1, R2, R3 and stage III and IV of 100%, 84%, 72%, 80% respectively. With EFS For Low risk, moderate risk and high-risk group of 100%.92% and & 70% (**Sun XF. 2006**). EFS and OS for those Pediatric Burkitt Lymphoma given Anthracycline based systemic chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP), with 18 months Overall Survival of 29%, for Stage I/II 51% OS, for Stage III 28% OS, for stage IV 17% OS **(Stanley et al. 2016)**. For pediatric Burkitt Lymphoma patients given GFAOP Lymphomes Malins B (GFALMB) 2009: prephase with cyclophosphamide followed by 2 induction courses (Cyclophosphamide, Vincristine, Prednisone, High Dose Methotrexate (HDMTX)), 2 consolidation courses (Cytarabine, HDMTX) and maintenance phase only for stage IV, Overall Survival for Stage II bulky disease is 63%, stage III disease 60% and for stage IV, 31%, with one year OS of 60% for all patients. **(Bouda et al., 2019)**

Overall, there is moderate quality evidence to show that the following standard regimen improve survival in Burkitt Lymphoma: FAB LMB 96 regimens with 3- and 5-year OS and EFS of 86.8% and 81.6% **(Park et al. 2011)**, 90.8% and 87.4% **(Aydin et al. 2019)** and BFM 90 Regimen with anEFS 85.5% **(Sun XF et al. 2006).** There is high to moderate quality of evidence to show that rituximab added to standard regimen resulted in improved survival among group C BL and R2-R4 patients.

Response Monitoring and Follow Up

A standardized system to describe response evaluation is clinically important. In an effort to address these issues, a multi-disciplinary group of experts in the management of adults with lymphomas convened to develop a uniform approach to describing treatment response for malignant lymphomas. This initiative was referred to as International Harmonization Project (Cheson, et al 1999). This system was widely adapted, with an updated set of guidelines published in 2007 (Cheson, et al 2007). In this system Complete Remission (CR) indicated disappearance of all the disease, Partial Remission (PR) indicated regression, >50% reduction in tumor size, Stable Disease (SD) – indicated non CR, non PR and non PD (progressive disease). PD indicated > 50 increase in size of old lesions or the development of new lesions.

Once response has been assessed, further imaging studies should be performed judiciously and prompted by clinical indications. A careful history, physical examination and good clinical judgement are the cornerstone of patient follow up. Laboratory testing at follow up visits should include CBC and serum chemistries, including LDH and other relevant blood test. (Sandlund 2012, Cheson et al 2007). The frequency of follow-up should decrease, with visits being reduced from every 3 months during the first 2 years, to every 6 months for the next 3 years, and then annually thereafter to monitor for late relapse and treatment-related adverse effects.(Cheson et al, 2014)

Table 1. Systemic Chemotherapy: BFM R1 and LMB Group A.

	BFM	LMB
Group	R1	Group A
Definition	Stage I and II, completely resected	Stage I and II, completely resected
No of Courses	2	2
Dexamethasone	10 mg/m2 x 10 days	
Cytarabine	150 mg/m2 every 12 hours day 4	
Etoposide	100 mg/m2 day 4 and 5	
Methotrexate	1 gm/m2m over 4 hrs	
Cyclophosphamide	200 mg/m2 x 5 days	500 mg/m2 day 1 -3
Ifosfamide	800mg/m2 x 5 days	
Vincristine	1.5 mg/m2	2.0 mg/m2 day 1 and day 6

Table 2. Systemic Chemotherapy: BFM R2 and LMB Group B

	BFM	LMB
Group	R2	Group B
Definition	Stage I - III, LDH < 500	Not resected I and II, III, and LDH < 2x ULN IV CNS (-) and BM < 25%
No of Courses	4 (V-A-B-A-B)	4 (COP – COPADM x 2 – CYM x 2)
Dexamethasone	10 mg/m2 x day 1-5	
Cytarabine	150 mg/m2 every 12 hours day 4 and 5	100 mg/m2 over 24 hours on day 2-6
Etoposide	100 mg/m2 day 4 and 5	
Methotrexate	1 gm/m2m over 4 hrs.	3 grams/m2 over 3 hours on day 1
Cyclophosphamide	200 mg/m2 x days 2-4	250 mg/m2 day 2-4
Ifosfamide	800mg/m2 x days 2-4	
Vincristine	1.5 mg/m2 day 1	2.0 mg/m2 day 1
Prednisone		60 mg/m2 day 1 -6
Doxorubicin	25 mg/m2 days 4 and 5	60 mg/m2 day 1

Table 3. Systemic Chemotherapy: BFM R3 and LMB Group B

	BFM	LMB
Group	R3	Group B
Definition	Stage III, LDH ≥ 500 U/L, < 1,000 U/L IV B LDH < 1000 U/L and CNS -	Not resected I and II,III, and LDH > 2x ULN IV CNS (-) and BM < 25%
No of Courses	4 (V-AA-BB-CC-AA-BB)	4 (COP – COPADM x 2 – CYM x 2)
Dexamethasone	(AA) 10 mg/m2 x day 1-5 (CC) 20 mg/m2 days 1 -5	
Cytarabine	(AA)150 mg/m2 every 12 hours day 4 and 5 (CC) 3 gms/m2 x days 1 -5	100 mg/m2 over 24 hours day 2-6
Etoposide	(AA) 100 mg/m2 days 4 and 5 (BB) 100 mg/m2 days 3 and 5	
Methotrexate	(AA BB) 5 gm/m2m over 24 hrs day 1	3 grams/m2 over 3 hours day 1
Cyclophosphamide	200 mg/m2 x days 2-4	250 mg/m2 day 2-4
Ifosfamide	(AA) 800mg/m2 x days 2-4	
Vincristine Vendesine	(AA) 1.5 mg/m2 day 1 (CC) 1.5 mg/m2 day 3	2.0 mg/m2 day 1
Prednisone		60 mg/m2 day 1 -5

Table 4. Systemic Chemotherapy: BFM R4 and LMB Group C

	BFM	LMB
Group	R4	Group C
Definition	Stage III, LDH ≥ 500 U/L, < 1,000 U/L IV B AL LDH < 1000 U/L and CNS +	B AL, CNS +
No of Courses	6 (V-AA-BB-CC-AA-BB-CC)	6 (COP – COPADM x COPADM2 – CYVEx2-M1-M2)
Dexamethasone	(AA) 10 mg/m2 x day 1-5 (CC) 20 mg/m2 days 1 -5	
Cytarabine	A)150mg/m2 x day 4 and 5 (CC) 3 gms/m2 x days 1 and 2	(CYVE 1 and M2) 50 mg/m2 over 12 hours day 1-5 (CYVE) 3 gm/m2 days 2-5
Etoposide	(AA) 100 mg/m2 days 4 and 5 (BB) 100 mg/m2 days 3 - 5	(CYVE) 200mg/m2 days 2-5 (M2) 150 mg/m2 days 1-3
Methotrexate	(AA BB) 5 gm/m2 over 24 hrs day 1	(COPADM and M1) 8 grams/m2 over 4 hours day 1
Methotrexate	(AA BB) 5 gm/m2 over 24 hrs day 1	(COPADM and M1) 8 grams/m2 over 4 hours day 1
Cyclophosphamide	(BB) 200 mg/m2 x days 2-4	(COPADM) 250 mg/m2 day 2-4 (COPADM2) 500 mg/m2 day 2-4 (M1) 500 mg/m2 days 2 and 3
Ifosfamide	(AA) 800mg/m2 x days 2-4	
Vincristine	(AA) 1.5 mg/m2 day 1	(COPADM and M1) 2.0 mg/m2 day
Prednisone		(COPADM and M1) 60 mg/m2 day 1 -5
Doxorubicin	(BB) 25 mg/m2 days 4 and 5	(COPADM and M1) 60 mg/m2 day 2

Table 5. Medicines and Side Effects

Drugs	Side Effects
Rituximab	Fever, chills, fatigue, hypotension and other infusion related symptoms, anaphylactoid events, tumor lysis syndrome, infections, febrile neutropenia or neutropenia
Vincristine	Local necrosis if extravasation occurs, jaw pain, paresis, constipation, neurotoxicity, alopecia, paralytic ileus, hyponatremia, SIADH
Vindesine	Paresthesia, autonomic neuropathy, cranial nerve toxicity, peripheral neuropathy, ileus, acute pneumonitis
Cyclophosphamide	Myelosuppression, nausea, vomiting, alopecia, hemorrhagic cystitis, sterility, hepatotoxicity, hypersensitivity, sterility, hyperpigmentation, secondary malignancies
Ifosfamide	Myelosuppression, nausea, vomiting, alopecia, cranial nerve toxicity, encephalopathy, hypersensitivity, hemorrhagic cystitis, renal toxicity
Doxorubicin	Local necrosis if extravasation occurs, cardiotoxicity, bone marrow suppression, mucosal ulceration, nausea, vomiting, alopecia, red or orange discoloration of urine
Etoposide	Bone marrow suppression, alopecia, headache, fever, hypotension, nausea, vomiting, anaphylactic reaction, secondary malignancies
Cytarabine	Bone marrow suppression, nausea, vomiting, oral ulceration, fever and arthralgia, diarrhea, mucosal membrane inflammation, ulceration, bleeding, alopecia, anemia, flu-like syndrome, encephalopathy, hypersensitivity, cerebellar syndrome Intrathecal administration: Headache, stiff neck, lethargy, nausea, and vomiting
Methotrexate	Hepatotoxicity, neurotoxicity, mucositis, liver dysfunction, bone marrow depression, renal failure, mucosal membrane inflammation, ulceration and bleeding, diarrhea, hyperpigmentation Intrathecal administration: Headache, stiff neck, lethargy, nausea, vomiting, confusion, seizures
Dexamethasone	Gastric irritation, glycosuria, hyperglycemia, nausea, osteoporosis, irritability, headache, dizziness, increased appetite, sleeping problems, acne, weight gain (mainly in the face and abdomen), fluid and salt retention, hypertension, hypokalemia, increased white blood count but decreased numbers of infection-fighting cells, decreased muscle mass and muscle weakness, impaired wound healing, decreased growth, and thin, fragile skin
Prednisone	Gastric irritation, hirsutism, fluid and salt retention, hypertension, hypokalemia, irritability, glycosuria, hyperglycemia, increased appetite, weight gain (especially in the face and abdomen), acne, headache, dizziness, sleeping problems, fatigue or weakness, increased sweating, increased white blood cell count, increased risk of infection, decreased muscle mass and muscle weakness, impaired wound healing and growth, osteoporosis, pancreatitis, seizures and mental disability
Hydrocortisone	Salt and fluid retention, hypertension, potassium loss, muscle weakness, loss of muscle mass. Severe arthralgia, aseptic necrosis, of femoral and humeral head osteoporosis, peptic ulcer Intrathecal administration: Headache, nausea, vomiting, and fever
Folinic Acid	Allergic reactions (rash, pruritus, erythema)
GCSF	Bone pain, leukocytosis, rash allergic reactions, fever, chills, headache, malaise, nausea, hypotension, shortness of breath and splenomegaly

Evidence to Recommendation for Treatment Complications

Burkitt Lymphoma is a common and aggressive type of mature B-cell Non-Hodgkin's Lymphoma in children and adolescents. Modern treatment regimens which include short, high-intensity multi-agent chemotherapy can achieve excellent outcomes. In some cases, it is given in combination with anti-CD20 monoclonal antibodies (Rituximab) which can further improve results. However, aggressive treatment regimens entail various treatment-related side effects and complications that may increase the risk of mortality. The most common side effects are myelosuppression, febrile neutropenia, hematologic toxicities such as anemia and thrombocytopenia, infections, mucositis, and tumor lysis syndrome.

A PubMed search was done with the MeSH terms "Burkitt lymphoma", "Children", "Adolescents", or "Pediatric", and "Treatment Complications". Reference lists of articles were also searched through this approach. A total of 26 published pieces of evidence were reviewed and 11 were included in the analysis. Two (2) were Randomized Control Trial/Study **(Minard-Colin et al. 2020 and Woessmann et al.,2004)** and the rest were observational studies. Three (3) were high quality **(Celkan et al. 2011; Stanley et al. 2016, and Béogo et al. 2011)**, while eight (8) were moderate quality evidences **(Minard-Colin et al. 2020; Woessmann et al. 2004; Zhen et al. 2020; Sun et al. 2006; Gerrard et al. 2008; Baena-Gómez et al. 2015; Mansoor et al. 2019; and Belgaumi, AF et al. 2016).** There was a total of 1,607 patients in all 11 studies.

Two studies mentioned that the most common complication during treatment is myelosuppression **(Celkan et al. 2010; Sun et al. 2006)**. This is generally expected from chemotherapy regimens, but severity should be properly assessed in order to reduce mortality. However, there was no numerical data to support it. One high quality study reported that hematologic toxicities were noted in 65% of patients **(Celkan et al.2011).** There is moderate to high quality evidence showing that the following are the most common complications during treatment: 1) Febrile Neutropenia (64.2%); 2) Infection (60.3%); 3) Hematologic Toxicities (59.9%) – i.e., anemia and thrombocytopenia; 4) Mucositis (41.9%) – most common side effect attributed to Methotrexate dose **(Sun et al.2006)**; and 5) Tumor Lysis Syndrome (17.7%) – considered an oncological emergency. **(Baena-Gómez et al., 2015)** The less common complications are1) Gastric Toxicities (12.2%) – i.e., constipation, diarrhea; 2) Kidney Failure (3.4%) - usually secondary to tumor lysis syndrome; 3) Infusion-related Reactions – most commonly attributed to Rituximab. **(Zhen et al. 2020)**

7.5 Side Effects and Management

Recommendation 14: Among children with Burkitt Lymphoma undergoing chemotherapy, watch out for the most common treatment-related infections such as febrile neutropenia and mucositis. ***(High Quality Evidence; Strong Recommendation)***

Recommendation 15: Among children with Burkitt Lymphoma who develop febrile neutropenia, offer empiric antibiotic treatment. ***(High Quality Evidence; Strong Recommendation)***

Recommendation 16: Among pediatric Burkitt Lymphoma patients with oral mucositis, offer Chlorhexidine mouthwash and anti-fungal treatment. In addition, oral care, antivirals, pain management using patient-controlled analgesia (PCA)/nurse-controlled analgesia (NCA) opioid administration, and intravenous Ketamine can be used as supportive management. ***(High Quality evidence; Strong recommendation)***

Evidence to Recommendation on Side Effects of Treatment

There were 139 studies retrieved using the search terms.. Forty-two (42) studies specific for Burkitt Lymphoma among children were included for review. Five (5) studies were found to be the best articles to answer the clinical practice guideline question. The five studies included a total of 566 patients. **(Minard-Colin et al.2020; Srinivasan et al. 2020; Wessels et al.2000; Badr et al., 2016.)** Four studies are of high-quality evidence. One study is of moderate quality evidence.

One high quality study noted that febrile neutropenia was observed in 91.7% while stomatitis was seen in 77.5%. **(Minard-Colin et al., 2020**). It also showed that the addition of Rituximab to LMB chemotherapy increased overall survival of patients but was associated with higher incidence of infections (febrile neutropenia and stomatitis). There is high-quality evidence noted that profound neutropenia was significantly seen at a higher rate among malnourished children with p value of 0.012. OR 12, 95%CI 1.5 – infinitely **(Israels et al.2009)**. Another high-quality study showed that febrile neutropenia was the leading complication in 73.5% with p value of <0.001 and was associated with several documented infections particularly mucositis at 54.9%. Other infections encountered during neutropenic episodes were respiratory infection (45.1%), gastrointestinal infection (38.9%) and skin infection (23.9%). **(Badr et al. 2016)** The remaining high-quality study observed febrile neutropenia at 2.6 episodes/patient (73.7%) and severe mucositis at 1.9 episodes/patient (73.7%) in patients treated with LMB protocol and were significantly associated with undernourished children with a p value of 0.002 **(Wessels et al. 2000)**. Furthermore, another study, which was of moderate quality, reported that Rituximab was associated with more episodes of febrile neutropenia (90.5%) and pneumonia (38.1%). **(Srinivasan et al. 2020)**

Overall, there is high quality evidence suggesting febrile neutropenia and mucositis were the most common chemotherapy induced infections among children with Burkitt Lymphoma.

Evidence to Recommendation on Management of Side Effects

We retrieved a total of 2,542 articles during the search strategy period. We reviewed a total of 12 published evidence and a total of 6 studies included in the analysis with a total of 793 patients. Most of these are prospective randomized study, prospective open label randomized study, systematic review and prospective longitudinal cohort studies. Four were high quality evidence **(Oguz et al. 2006; Kebudi et al. 2001; Hurrel et al. 2019; Mazhari et al. 2018)**, while 2 were moderate quality evidence **(Ariffin et al, 2006; Lee et al.2015)**

There is high to moderate quality study showing Cefepime as treatment for Febrile Neutropenia. Cefepime and meropenem are useful as monotherapy for treatment of febrile episodes in neutropenic children. Comparison of success rates show that Cefepime has 65.6% or 21 out of 32 participants and Meropenem has 60.6% or 20 out of 33 participants **(Oguz et al.2006) with**. GRADE-pro result is high quality. Cefepime and ceftazidime were both effective in febrile neutropenic children as empiric monotherapy. Comparing success rates, Cefepime has 62.5% or 20 out of 32 participants and Ceftazidime has 61.3% or 19 out of 31 participants **(Kebudi et al. 2001)**. Resulting in a high-quality study in GRADE-pro. Cefepime monotherapy is a safe and favorable option for treatment of febrile neutropenia with a success rate of 60.8% and moderate quality evidence on GRADE-Pro. **(Ariffin et al.2006)**

There is moderate to high quality evidence suggesting that the lesser use of oral care protocol was significantly associated with the severity of oral mucositis. Chlorhexidine (CHX) mouthwash provided a useful option to maintain some form of oral care when brushing becomes too uncomfortable. The use of CHX increases as the severity of OM increases with p value of <0.0001 and GRADEpro result of high quality. Likewise, pain management was a significant component of oral mucositis management. The use of patient-controlled analgesia (PCA)/ nurse controlled analgesia (NCA) for opioid administration and IV Ketamine was associated significantly with oral mucositis severity p value of <0.0001 and GRADEpro result of high quality. The use of antivirals and antifungals were associated significantly with oral mucositis severity p value of <0.0001 and GRADEpro result of high quality. (**Hurrel et al. 2019)**. Individuals taking mineral derivatives during cancer therapies are less likely to experience peak oral mucositis than those without. **(Lee et al.2015)**. Palifermin could reduce the incidence, severity, and duration of oral mucositis significantly. **(Mazhari et al. 2018)**

Overall, there is moderate-high quality evidence in managing treatment-related infections. For the first episode of febrile neutropenia, empiric antibiotics are Ceftazidime, Cefepime and Meropenem. These have the same efficacy and safety among patients with febrile neutropenia. However, the culture result and antibiogram report of the institution must be considered. For oral mucositis, aside from the use of antifungals and chlorhexidine mouthwash, it is recommended to have oral care protocols plus use of analgesia and antivirals. Mineral derivatives and Palifermin are likewise highly recommended by early studies.

7.6 SUPPORTIVE AND PALLIATIVE CARE

Recommendation 17: Among Burkitt Lymphoma patients undergoing chemotherapy, consider nutritional support from pre-induction through post chemotherapy as supportive management. Use urate oxidase (Rasburicase) for the prevention and treatment of hyperuricemia in tumor lysis syndrome (if not available, the alternative treatment is Allopurinol). ***(High Quality Evidence; Strong Recommendation)*** **Granulocyte colony- stimulating factor (GCSF) may reduce hospitalization days during neutropenic episodes.** ***(Moderate Quality Evidence; Strong Recommendation)***

Recommendations 18: For Burkitt Lymphoma patients, recommend behavioral intervention like distraction, paced breathing and positive reinforcement to reduce parental rated pain, parental anxiety and usage of restraints during chemotherapy and cancer-related procedures. Counselling and skill-based interventions that aim to improve resilience, quality of life and psychological distress should also be offered. ***(Moderate Quality Evidence; Strong Recommendation)***

Recommendation 19 - Palliative care may be offered to pediatric patients with Burkitt lymphoma to improve overall quality of life and well-being. ***(Low Quality Evidence; Strong Recommendation)***

Evidence to Recommendation on Supportive Care

In recent years, treatment of pediatric Burkitt Lymphoma has greatly improved outcomes. Despite this, each treatment regimen has side effects and complications which demand the need for supportive care treatments in conjunction with chemotherapy. These supportive management may help in preventing certain side effects to occur or progress to more severe complications that may pose a higher risk of mortality. Optimizing patient status before, during, and after any treatment is essential in order to achieve the desired outcomes.

A PubMed search was done with the MeSH terms "Burkitt lymphoma", "Children", "Adolescents", or "Pediatric", "Supportive Treatments", "Tumor Lysis Syndrome", "Nutritional Supplement", and "Granulocyte-Colony Stimulating Factor". Reference lists of articles were also searched through this approach. A total of 20 published pieces of evidence were reviewed and 5 were included in the analysis. Three (3) were Randomized Control Trial/Study **(Goldman et al.2001; Tsurusawa et al. 2015; Patte et al. 2002)** and 2 were observational studies **(Hesseling et al.2018; Wössmann et al. 2003).** Two (2) were high quality **(Hesseling et al. 2018 and Goldman et al. 2001)**, while three were moderate quality evidence (**Tsurusawa et al. 2015; Wössmann et al. 2003; Patte et al. 2002).** There was a total of 742 patients in all 5 studies.

One high quality study noted that a cohort of patients who received enteral nutritional support prior to induction of chemotherapy had a death rate of only 5.6% compared to 18.6% of another cohort who did not receive it **(Hesseling et al. 2018).** In two moderate quality studies, the incidence of febrile neutropenia (FN) was compared in a group of patients receiving GCSF against a control group. The results showed a slight difference in the incidence rate of FN (85.6% vs 88.2% respectively) which was deemed insignificant. However, there was also a decrease in the duration of the FN (39 vs 50 average mean number of days) and hospitalization (66 vs 79 average mean number of days) which altogether, may be more beneficial in terms of reducing the risk in developing hospital or healthcare-associated infections **(Tsurusawa et al. 2015;Patte et al. 2002)**.

One high quality study compared rasburicase (recombinant urate oxidase) to allopurinol in addressing hyperuricemia. Mean uric acid AUC_{0-96} was significantly lower in the rasburicase group (128.1 mg/dL.hr) than in the allopurinol group (328.5 mg/dL.hr). The reduction in plasma uric acid levels after 4 hours of the first dose is 86.0% for the rasburicase group and 12.1% in the allopurinol group. The number of patients hyperuricemic at baseline (uric acid > 8 mg/dL at T = 0) who achieved a uric acid level less than 8 mg/dL by 4 hours is 100% for the rasburicase group and null for the allopurinol group. Thus, demonstrating that rasburicase is a more potent and faster acting hypouricemic agent than oral

allopurinol (Goldman, S. C., et al 2001). This is supported by another moderate quality study wherein, 16.1% was the reported frequency of TLS for patients in period 1, compared to 12.3% in period 3 where urate oxidase was used prophylactically. Therefore, patients who have higher risk to develop TLS will benefit from the prophylactic use of urate oxidase **(Wössmann et al. 2003)**.

There is moderate to high quality evidence suggesting that nutritional support before, during, and after treatment; the use of urate oxidase for the prevention and treatment of hyperuricemia in tumor lysis syndrome;), and granulocyte colony-stimulating factor (GCSF) in reducing the duration of neutropenic episodes and hospitalization days, are suitable supportive care treatments for pediatric Burkitt Lymphoma patients undergoing chemotherapy. Allopurinol is the usual treatment in most countries especially LMICs due to unavailability of rasburicase can still be used as alternative.

Evidence to Recommendation on Behavioral Intervention

Integrative interventions make use of cognitive, physical, and interventional modalities as adjunct to conventional Burkitt Lymphoma management. The ultimate goal is to improve the patient's and family's quality of life. **(WHO 2019)** Integrative approaches help alleviate physical, social and spiritual suffering while undergoing cancer treatment. Attentional distraction, paced breathing, and positive reinforcements are integrative interventions that are recommended in conjunction with standards of care for patients with Burkitt Lymphoma. The following search terms were used, "Burkitts Lymphoma", "Integrative Medicine", "Quality of Life ''and "Pediatric Cancer ''in MEDLINE. Filters were activated to limit the search process to identify papers that are relevant to the research question. The search yielded 386 articles. These were narrowed to 10 articles which included systematic reviews, meta-analysis and randomized controlled clinical trials. Most of the studies applied interventions like hypnosis and comprehensive programs that will require regular home visitations. Some articles only focused on one aspect of the quality of life like fatigue and level of physical activity. These were not found to be applicable in our local setting.

Only one article was found to be relevant in answering the focused clinical question. Behavioral interventions like parental coaching, attentional distraction, and positive reinforcement were postulated to reduce parental anxiety and patient distress. The study included 23 children who completed all three interventions and were regularly accompanied by their parents in the outpatient clinic. After initial assessment, the patients were randomly assigned to either the Behavioral Intervention group (n=13) or the Attention Control group (n=10). The Behavioral Intervention group consisted of instructions for attentional distraction, paced breathing and positive reinforcement. Distraction involved parental coaching with the use of party blowers during venipunctures. The patients were asked to breathe while the parents were counting out loud until the procedure was finished. Positive reinforcement consisted of tangible rewards like stickers of their favorite cartoon character until the venipuncture procedure is done. Behavioral intervention was assisted by a psychologist. In the Attention Control Group, the parents were instructed to use whatever techniques they found helpful to control their child's distress during venipunctures. No psychologist intervention was provided. Results of the study showed that behavioral interventions showed a reduction in parental rated pain (p-value < 0.001), parental anxiety

(p-value <0.01), and reduction in the use of restraints for children undergoing procedures (OR 0.29, 95% CI: 0.04 – 1.94; p-value <0.05). (Manne et al. 1990) There is moderate quality evidence based on one study supporting the use of integrative interventions like distraction, paced breathing and positive reinforcement to reduce parental anxiety and child distress during procedures for cancer treatment.

Evidence to Recommendation on and Physical and Psychosocial Intervention

The diagnosis of cancer can cause psychosocial and spiritual distress for children and their parents. Counseling interventions for children with cancer and their parents aim to improve behavior, relieve mental, emotional and spiritual distress. Counseling also helps improve resiliency while undergoing cancer treatment. The following search terms were used: ‘‘Burkitt’s Lymphoma”, ‘‘Pediatric Cancer OR Children’s Cancer”, and ‘‘counseling” in PubMed. Filters were activated to limit the search process to identify papers that are relevant to the research question. The search yielded 232 articles. These were narrowed to five articles which included three systematic reviews and two randomized controlled clinical trials.

One study focused on investigating the effect of combined physical and psychosocial intervention in improving the health-related quality of life and psychosocial functioning of children with cancer and their parents. The intervention group was composed of a highly intensive physical training focusing on cardiovascular health and muscle strength. This was also combined with psychosocial training using an individualized structured program to improve socio-emotional functioning and coping with disease-related effects. The intervention group was compared with the control group (care as usual). There was a substantial dropout rate of around 22%. The results did not show significant effects in the health-related quality of life or psychosocial functioning. **(van Djik-Lokkart.2015)** Promoting Resilience in Stress Management (PRISM) is a brief skill- based intervention aimed at stress management, goal setting, cognitive reframing, and meaning making. The PRISM brief strategic intervention was compared with the Usual Care Group in a randomized controlled clinical trial consisting of adolescents diagnosed with a new cancer before enrolment and receiving systemic chemotherapy or diagnosed with progressive, recurrent or refractory cancer at any time before enrolment. PRISM intervention consisted of four one-on-one sessions lasting for 30 to 50 minutes per session facilitated every other week (Table 1). Sessions five, six and seven were offered as optional opportunities for continuing to practice and share skills. These were given on top of the usual patient and hospital visits as part of the standards of care for cancer patients. These were delivered primarily by non-clinical staff who received standardized training and mock sessions. The control arm consisted only of usual or standard oncologic care. Patient reported resilience was the study’s primary outcome using the 10-item Connor-Davidson Resilience Scale (CDRISC- 10). Secondary outcomes included quality of life (PedsQL or Pediatric Quality of Life), psychological distress (Kessler-6 Psychological Distress Scale), anxiety and depression (HADS-D or Hospital Anxiety and Depression Scale). Outcomes were measured at six months. The results of the study showed that PRISM showed higher resilience (95% CI: 0 .5- 5.4; p-value 0.02), cancer -specific quality of life (95% CI: 2.6- 1 6.7; p-value 0.01), and lower psychological distress (95% CI: –4. 1 to – 0.2; p-value 0.03). **(Rosenberg et al. 2018)** There is moderate quality of evidence based on one

study supporting counselling and skill-based interventions in improving resilience, quality of life and alleviating psychological distress.

Table 6. PRISM Components

Session	Breakdown	Skills taught during the session	Format
1	Managing stress	Mindfulness techniques, relaxation strategies, obtaining social support	One-on-one
2	Goal setting	Setting specific, realistic, desirable goals; planning for roadblocks	One-on-one
3	Positive reframing	Recognizing negative self-talk; replacing it with realistic, positive, manageable thoughts	One-on-one
4	Meaning making	Identifying benefits, purpose, meaning, or legacy from cancer experience	One-on-one
5	Coming together	Discussion about what was learned, what helped, and what loved ones can do to help	Family Meeting
6	Boosters	Check-in visits to practice, further develop, and track skills	One-on-One
7	Cheat sheets	Between- session exercises to practice, further develop, and track skills	Paper and Pencil

Evidence to Recommendation on Palliative Care

Pediatric palliative care represents a special, albeit closely related field to adult palliative care. WHO's definition of palliative care appropriate for children and their families encompass the principles that apply to other pediatric chronic disorders **(WHO1998)** 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 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. It can be provided in tertiary care facilities, in community health centers and even in children's homes.

Pediatric palliative care may be offered since Burkitt Lymphoma is a life-threatening disease. The following search terms were used "Burkitt's Lymphoma", "Palliative Care", "Quality of Life '' and

“children '' in MEDLINE. Filters were activated to limit the search process to identify papers that are relevant to the research question. A total of 198 articles were reviewed. These were narrowed to 10 articles. Six full-text articles were reviewed. Two of these were systematic reviews. Both studies showed improvement in the quality of life, but one systematic review included patients with both malignant and non-malignant conditions. (Marcus et al 2020) This study was not included in the summary of evidence because of lack of directness.

Specialized Pediatric Palliative Care (SPPC) was the main intervention which involved a set of services addressed to improve illness experience and quality of life anytime from diagnosis to end-of-life. The principles of care were adherent to the WHO definition of palliative care. The study included pediatric patients aged 18 years and below with malignancies and their families. The studies were included in the systematic review if SPPC group was compared to a control group. Outcomes of interest included child/family outcomes, downstream health care utilization, and processes related to goal-concordant care. Opportunity to plan such as communication, decision-making and advance care planning was included as an outcome as well as patterns of end-of-life care, details related to Pediatric Palliative Care (PPC)-oncology collaboration and bereavement outcomes. Pediatric palliative care intervention timing, delivery, feasibility, and acceptability were also described. There were 28 studies included in this qualitative synthesis. There were no randomized controlled trials. Among these studies, 15 mentioned the involvement of a physician, advance practice provider (n=9), nurses and chaplains (n=10), social workers (n=12), child life specialists (n=5), and psychologist (n=1). No study mentioned grief or bereavement care counselors. Specialized Pediatric Palliative Care was integrated if there were triggers during the clinical encounter such as disease progression or poor prognosis. Integration of pediatric palliative care showed improvement in the physical symptoms such as pain, fatigue, nausea, vomiting, constipation, anxiety, seizures, breathlessness and impaired speech. The experience of pain was the main trigger for specialist pediatric palliative care referral. Patients receiving palliative care showed higher rates of comprehensive assessment, documentation and interventions to address any distress. SPPC integration also showed improvement in the overall quality of life and well-being of children with cancer. There was greater improvement in the assessment of the patient’s emotional and mental health state. Parental evaluations also improved from baseline. Furthermore, family and caregiver satisfaction with their patient’s care improved with SPPC integration. Both families and patient’s caregivers had positive experiences across different domains like symptom management, psychosocial support, and communication. (Kaye et al. 2021)

There is low quality of evidence supporting the integration of pediatric palliative care for patients with Burkitt Lymphoma due to the indirectness of these studies.

7.7 HEALTH SYSTEM RECOMMENDATIONS

Recommendation 20: Treatment of pediatric Burkitt Lymphoma should be covered by PhilHealth and other health insurance companies because it is cost effective *(High Quality Evidence; Strong Recommendation).* It should also be emphasized that having insurance can increase overall survival rate *(Low Quality Evidence; Strong Recommendation).*

Recommendation 21: Among pediatric patients suspected of having Burkitt Lymphoma, encourage carers to improve their perspective of health-seeking behavior by participating in support groups and thorough health education discussions. ***(Moderate Quality Evidence; Strong Recommendation)***

Recommendation 22: Among pediatric patients suspected of having Burkitt Lymphoma, provide assistance to affected families by considering their non-medical needs such as transportation and/or accommodation, access to financial assistance and psychosocial guidance. ***(Moderate Quality Evidence; Strong Recommendation)***

Evidence to Recommendation on Health Systems

The key search terms for the Health System question were Cost Effectiveness AND Burkitt Lymphoma AND Overall Survival Rate AND National Insurance in PubMed. Five studies tackled the impact of health systems on pediatric BL. There were 4 systematic reviews among these 5 studies. (**Denburg et al.2019; Fung et al.2019; Cuevas et al.2013; Bhakta et al. 2012)**

Pediatric-cancer care has been largely neglected in low-income and mid-income countries. An estimated 160,000 new cases of cancer are diagnosed annually in children younger than 15 years of age. Only 20% - 30% of patients (mostly on HIC) are thought to be adequately diagnosed and treated. Paradoxically, most cases of childhood cancer, if diagnosed at an early stage, are highly curable if treatment is available. Furthermore, today's effective treatment regimens are relatively simple, inexpensive and well-established. **(Ribeiro et al. 2008)**

The overall survival of children with cancer as postulated from interviews with local healthcare professionals is dismal in Bangladesh, Philippines, Senegal, Tanzania, and Vietnam, but is much better in countries like Ukraine and Venezuela. Egypt, Honduras, and Morocco rank in between these two groups. Overall survival was significantly related to several socioeconomic and health-related indices established by international agencies, including total annual health-care expenditure, per capita GDP, per capita GNI, and the number of physicians and nurses per 1000 population, but only annual government healthcare spending per capita was independently correlated. **(Ribeiro et al. 2008)**

Table 7. Correlation of health and economic indicators with pediatric cancer postulated 5-year survival in the surveyed countries

	Pearson's correlation coefficient (r)	Pearson (r2)	p
Government annual health-care expenditure per capita	0.939	0.882	<0.0001
Total annual health-care expenditure per capita	0.872	0.760	0.001
Per capita GDP (Gross Doestic Product)	0.777	0.603	0.008
Per capita GNI (Gross National Income)	0.756	0.572	0.011
Physicians per thousand population	0.749	0.560	0.013
Nurses per thousand population	0.712	0.506	0.032
Human development index	0.631	0.398	0.050
Human poverty index	−0.593	0.351	0.093
Under-5 mortality	−0.577	0.333	0.081

In the USA and other high-income countries (HIC), about 90% of children with the most common types of malignancies such as ALL, Burkitt Lymphoma and Wilms tumor survive long term with minimal disability. However, while overall childhood cancer cure rates in HIC approach 80%, event-free survival rates in low-income and middle-income countries (LMIC) range from 5% to 40%. **(Bhakta et al. 2012)**

A study using cost-of-illness analysis through cost identification and effectiveness approach to analyze the cost of treatment and its effect on the overall survival rate among the 122 children with confirmed diagnosis of BL. Fifty-five percent (95% CI, 45% to 64%) were alive two years after diagnosis. Patients with low-risk disease (Ziegler Stages A, B, and AR) had a statistically significantly higher 2-year OS (66%: 95% CI 51% to 77%) compared to patients with High-risk disease (Ziegler Stages C and D) 45%; 95% CI 31% to 58%). The cost per Disability Adjusted Life Years (DALY) averted in the treatment group was US$97 (Int$301). Cumulative estimate of national DALYs averted through treatment was 8,607 years, and the total national annual cost of treatment was US$834,879 (Int$2,590,845). This demonstrated a favorable cost DALY averted. **(Denburg et al. 2019)**

The systematic review highlighted two moderate quality evidence studies from Denburg et al (2019) and Hesseling et al (2013) directly focusing on the cost effectiveness of BL treatment and overall rate of survival. Among 122 patients included in the Uganda report, cost effectiveness of treatment has Mean Difference (MD) 0.55 higher (0.45 to 0.64 higher) overall survival rates (Denburg et al, 2019). Likewise, in Malawi an average of MD 0.57 higher (0.43 to 0.73 higher) overall survival rate are recorded amongst the 44 patients included in the study (Hesseling et al, 2013). Both studies indicated a favorable cost per DALY averted making it among the most comprehensive studies showcasing correlation between cost effectiveness of treatment and overall survival rate for Burkitt Lymphoma. Although some of the studies included in the systematic review did not account for the key cost input underestimating true treatment cost, the cost per DALY averted were nonetheless substantially lower than per capita Gross Domestic Product (GDP).

In 2006 the Mexican government provided a Fund for Protection Against Catastrophic Expenditures (FPGC) to support financially healthcare of high-cost illness such as cancer. A retrospective study from 2006-2009 looked into coverage of 3,821 new cancer cases that included Non-Hodgkins Lymphoma (NHL). An increase of 3.3% to 55.3% coverage was noted during the study period. Overall survival was measured using Kaplan-Meier curves and Cox proportional hazards regression modeling. Survival rates for NHL at 36 months was 40.1% (95%CI 25.1-54.5) compared to ALL (50%), AML (30.5%), Hodgkin Lymphoma (74.5%), CNS tumors (32.8%), bone tumors (33.4%) and retinoblastoma (59.2%). Although data was not specific to Burkitt Lymphoma, the study demonstrates the feasibility of increasing support for high-cost illness like cancer and the wide variability in survival experiences across cancers and places in the Mexico region. **(Cuevas et al. 2013)**

The Malawi cost effectiveness study of treating Burkitt Lymphoma by Bhakta et al,by **(Bhakta et al., 2012)** demonstrated better outcomes using a short-course (30days) regimen in Malawi with 48% cure rate for children with BL. The cost of chemotherapeutic and supportive care drugs was reported as less than US$50 per child, representing less than 1% of the calculated US$14,243 threshold for very cost-effective BL treatment. Actual estimated costs of treatment, at US$50, were far lower, although this figure only accounted for the costs of chemotherapy and is likely an underestimate. **(Bhakta et al. 2012).** The primary outcome of the study was presented as "very cost effective" with a 1:1 ratio of the cost to prevent one DALY to the annual gross domestic product per capita. The study by Denburg et al coincided with that of Bhakta et al, as the former's conclusion states that the annual per patient cost per BL treatment program is US$ 1,351.72 which is in line with the WHO-CHOICE cost-effectiveness threshold. In general, the Denburg et al and Bhakta et al studies of suggested high quality of evidence, using modified GRADEPro, while the other two studies by Alastair, Funge et al and Cuevas et al. suggested moderate quality of evidence on the cost effectiveness of BL treatment support.

Evidence to Recommendation on Financing

Using PubMed research platform key search questions National Insurance AND Pediatric Cancer AND Survival Rate we found one study to supporting our recommendation on financing BL treatment. **(Colton et al.2019)** The study used the Surveillance, Epidemiologic and End Results (SEER) database to identify 66,556 AYA (15 to 39 years old) patients between 2007 and 2014 among the US population and focused on International Classification of Childhood Cancer (ICCC) subcategory. . AYA were grouped into two insurance categories: private insurance and others, and no insurance. The participants have diverse representation in respect to social and financial resources. Among this age group, participants experienced significant transitions with education, employment, and family or partner relationship and therefore may be more susceptible to poor health outcomes associated with socioeconomic status (SES). SES is a predictor of failure to complete recommended therapy and AYA patients with greater financial stress may forgo medical treatments.

The findings reported an increased risk of death among those with public or no insurance compared to private insurance for most cancer types and age groups. The largest hazards of death (with 95% CI) were associated with public/no insurance in the multivariable models among 25-29-year-olds with Hodgkin lymphoma and other gliomas 3.27 (1.81, 5.94) and 2.93 (1.34, 6.39), respectively. Due to significant indirectness of the study population to Burkitt lymphoma, the was rated low quality of

evidence using GRADEPro. However, this study provides a model of how SES and insurance coverage affects clinical outcomes among patients with catastrophic illness such as cancer.

Evidence to Recommendation on Social Issues

Abandonment of pediatric cancer treatment is a common problem in developing countries. It is important to try to prevent this as failure to complete treatment generally increases the risk of relapse. This is especially important in a resource limited setting where the allocation of health resources must be carefully considered**. (Israels et al.2008)** Using PubMed, 10 studies were reviewed and 4 were found relevant to the key question.

A total of 179 patients were included in the 4 studies: 1 had low quality evidence on GRADEpro and 3 were moderate quality evidence. The very low quality evidence study was an observational study with 32 participants. The study reported Guardians' 'perspective affecting treatment adherence include consultation with a traditional healer (84%); decision making (6%); concept concerning disease (18.8 %); absence from home (18.8%); and perception of the hospital care (21.9%). **(Chirambo et al.2008)**

The moderate quality evidence was also an observational study with 121 participants. Most guardians or parents had low socioeconomic status and low educational attainment, out of 41 participants, 9 parents (22.0%) had no formal education (fathers), and were among the 15 (36.6%) whose primary source of income was subsistence farming. Eighteen (43.9%) of their parents (mothers) had no formal education. Thirteen (31.7%) of the parents withdrew their children against medical advice or left the hospital because they could not afford the cost of confirmatory tests and could not afford the cost of treatment. Twelve (57.1%) of the 22 properly discharged survivors did not keep any follow-up appointments, due to financial constraints. Eleven (26.8%) of 41 participants consulted a traditional healer and 13 (31.7%) consulted an unorthodox practitioner **(Meremikwu, et al. 2005).**

Another study with moderate quality of evidence had a total of 80 patients. Distance from home to hospital made no difference in completing chemotherapy courses, citing that 25% of patients were living inside the hospital district while 32% were living outside the hospital district **(De Boer et al. 2009).** The study of Njuguna et al. (2014) with 26 participants identified 3 factors that lead to abandonment of treatment. This included financial difficulties (46%), inadequate access to health insurance (46 %), and transportation difficulties (23%).

In summary, based on moderate quality of evidence, the most common factors that affect treatment adherence patients include consult with traditional or spiritual healers, absence from home, distance to hospital, and financial difficulties. These factors increase treatment abandonment and increase risk of relapse.

8 DISCUSSION, DISSEMINATION AND IMPLEMENTATION

The creation of guideline recommendations on Burkitt lymphoma is congruent with the spirit of RA 11215 National Integrated Cancer Control Act (NICCA) which is to have an equitable access to quality services across the cancer control continuum. This is accomplished by enhancing the oncology manpower skills to practice harmonized clinical practice guidelines (CPGs) on priority cancers such as childhood cancer and multidisciplinary approach to cancer management (NICCSP). Clinical guidelines should become a consistent part of clinical practice. Every day, clinical decisions at the bedside, rules of operation at hospitals and clinics, and health spending by governments and insurers are being influenced by guidelines. As defined by the Institute of Medicine, clinical guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." (**Field MJ et al.1990**). Burkitt lymphoma being a fast-growing tumor should be diagnosed and treated promptly. The recommendations on clinical assessment, diagnostic and ancillary tests will help the primary care physicians, specialists, nurses, and other basic health care workers on early recognition and diagnostic approach of BL. While sections on risk factors, treatment, monitoring of adverse events, prognosis and supportive/palliative care apply at the level of centers of high complexity, government or private cancer centers and specialized medical and infrastructure for specialized care. The recommendations on health systems will help Philhealth and private insurance to create guidelines in qualifying measurement for health insurance. This will address the economic burden among Filipino families afflicted with cancer by reducing financial hardship among cancer patients, persons living with cancer and cancer survivors. These guidelines will enhance the supportive care and diagnostic capabilities, decrease abandonment of therapy and late diagnosis, along with establishment of uniform treatment guidelines adapted to local resources, thus reducing the overall mortality of children with BL.

8.1 RECOMMENDED PROCESS OF DISSEMINATION AND IMPLEMENTATION

The recommendations in this guideline will be disseminated through a broad network of national partners, including the Department of Health, Philippine Medical Association and its component societies such as the Philippine Pediatric Society (PPS), Philippine Society of Pediatric Oncology (PSPO), Philippine Society of Pediatric Hematology (PSPH) Philippine Society of Hematology and Blood Transfusion (PSHBT), and Philippine Society of Pathology (PSP). This will also be shared to Philippine Oncology Nurses Association (PONA), Philippine Pharmacist Association, and the Philippine Health Insurance Corporation (Philhealth). Strategic dissemination to key stakeholders will ensure that the guideline reaches the users most likely to benefit from it.

As for the guideline document publication, these may be published in several formats, including a short version for busy clinicians which encapsulates the recommendations, a lengthy monograph

which summarizes the scientific evidence and rationale, and a consumer version for the patient. This may also include producing a lay version which enables patients to better understand the goals of treatment, the different treatment options and the benefits and risks of each option (**Martinez 2012**). It is also important to organize an annual national forum on a disease at which people share their experiences and take part in training and education programs.

The medicines recommended in this document are on the WHO Model List of Essential Medicines (WHO, Model list of essential medicines for children). Essential medicines are intended to be always available within the context of functioning health systems in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford. The Model List is a guide for the development of national and institutional essential medicine lists. Within this context, program managers will need to ensure that adequate quantities of required drugs in the recommended dosages are available to health workers. These drugs would normally be provided through existing health system supply chains.

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.

8.2 ALGORITHM

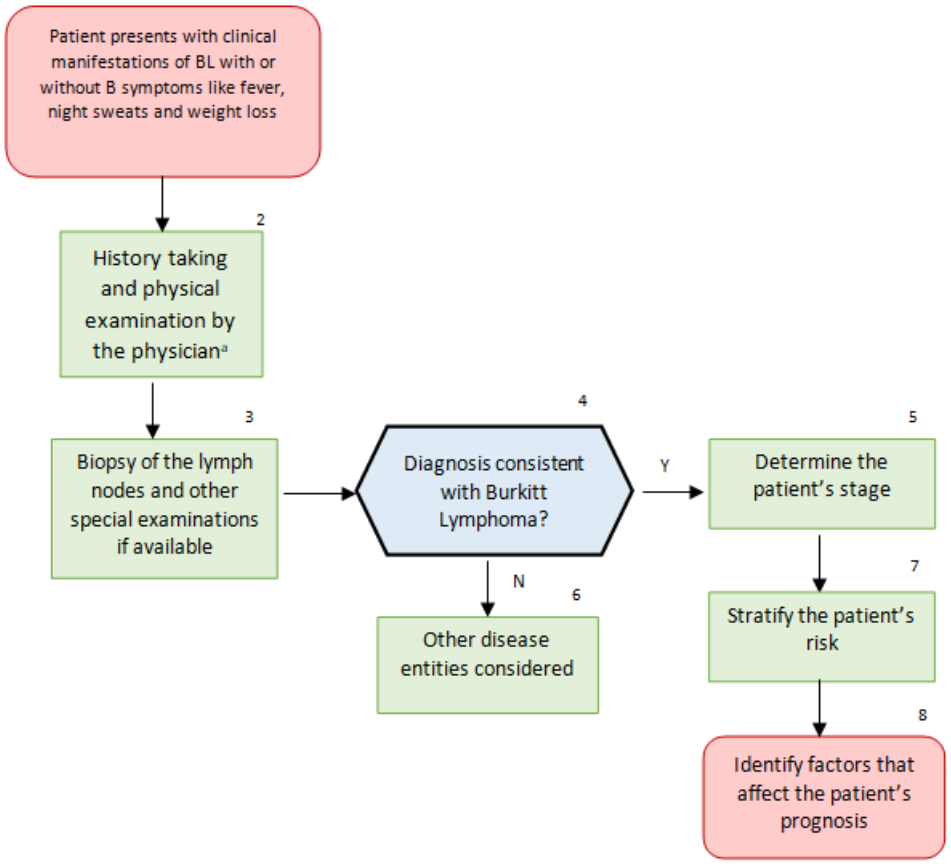


Figure 1. Decision Algorithm for the diagnosis, staging risk stratification and prognosis of Burkitt Lymphoma in Children

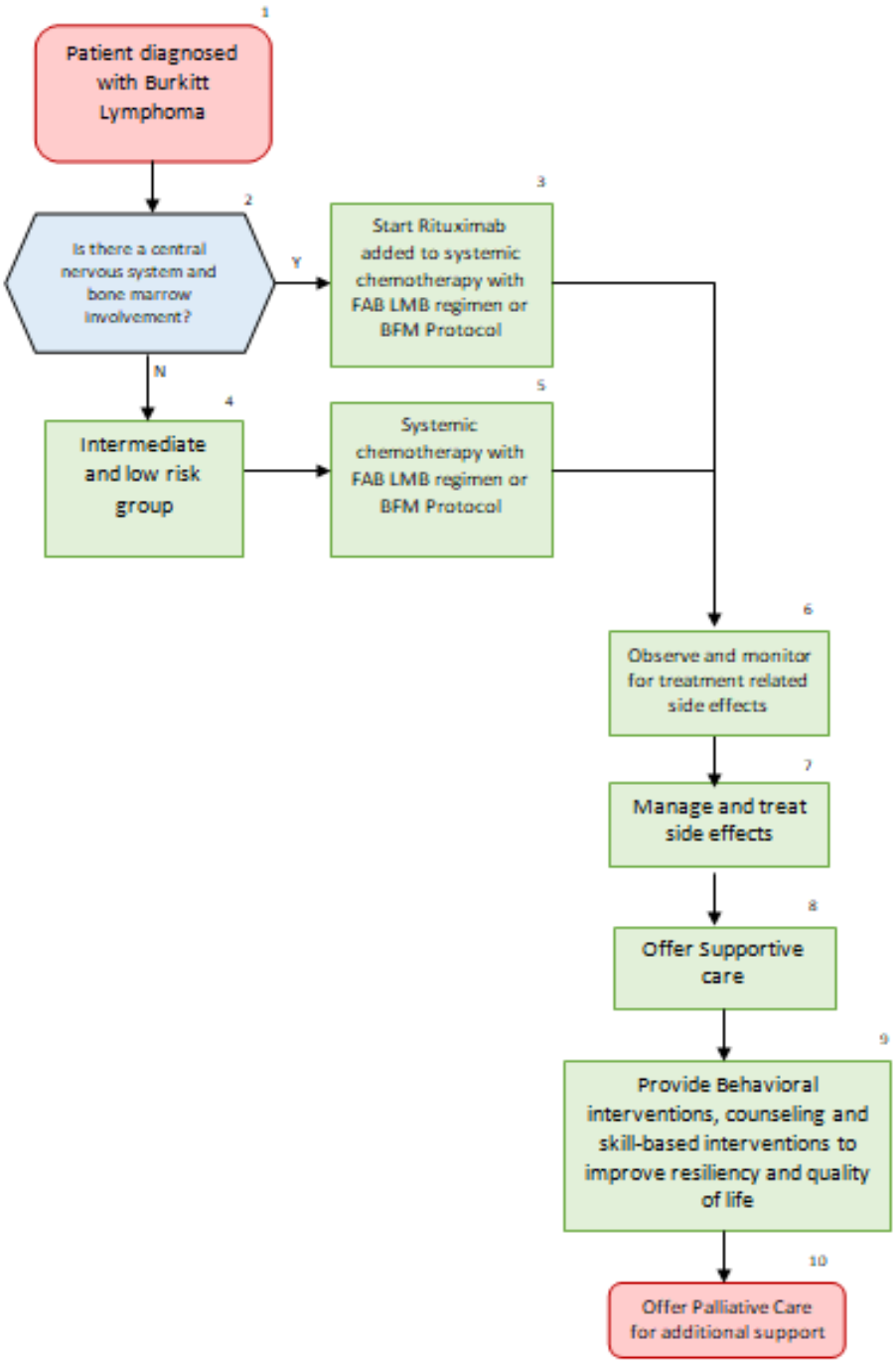


Figure 2. Treatment and Management Algorithm Burkitt Lymphoma in Children.

8.3 CLINICAL AUDIT CHECKLIST

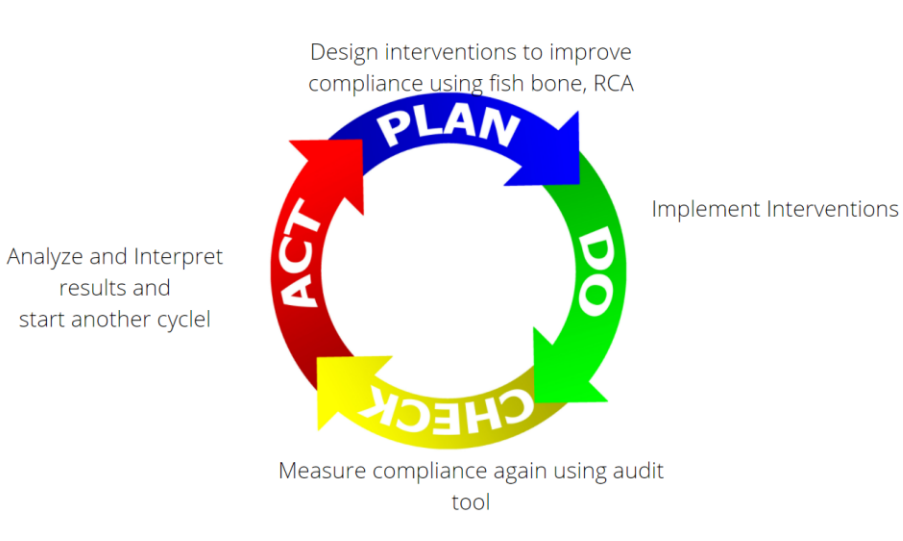
Instructions on Using the Chart Audit Tool

This tool is meant to measure physician's compliance to the standard of care process measures based on the Philippine Clinical Practice Guidelines on the Diagnosis, Management, Psychosocial Support and Palliative Care of Burkitt Lymphoma in Children and their Families developed in part by the SPMC-CCI BL 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 Burkitt Lymphoma. This will be for initial admission and beginning 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 3 below.

Figure 3. Quality Improvement Cycle



SOUTHERN PHILIPPINES MEDICAL CENTER CHILDREN'S CANCER INSTITUTE
CHART AUDIT TOOL FOR BURKITT LYMPHOMA

General Data

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

Audit Tool for Initial Admission and Induction of Treatment for Children with BL

Criteria	Yes	No	What yes means
1. Elicit history of B symptoms. (Rec 2)			-fever, night sweats and weight loss were asked in the history
2. Physical examination included palpation of masses, neurologic exam, presence of ascites or pleural effusion and examination of skin and mucosa for signs of bleeding (Rec 1)			-palpation for abdominal masses, neck masses, lymph nodes -Neurologic examination -Presence of ascites or pleural effusion -evidence of pallor, ecchymosis, petechiae
3. Image guided core needle biopsy for diagnosis was done. Surgical excision biopsy as an alternative if core needle biopsy fails was done (Rec 4-5)			Evidence that image guided core needle biopsy of lymph nodes was done or surgical excision biopsy if needed
4. Ancillary procedures such as immunophenotypic, cytogenetic and molecular tests were done. (Rec 6)			Said procedures were ordered and done.
5. CT or PET Scan or ultrasound if both are not available was ordered as part of pre-treatment staging (Rec 7)			Said procedures were ordered and done
6. Diagnosis includes stage of BL and risk stratification (Rec 8-9)			-Staging done and utilized the International Pediatric Non-Hodgkin Lymphoma Staging System -Risk stratification done using either French-American-British Mature B-Cell Lymphoma (FAB-LMB) or Berlin Frankfurt Munster (BFM) risk stratification
7. Appropriate treatment started based on risk and CNS and/or bone marrow involvement (Rec 11-12)			-Group C patients (R3 or R4) -Rituximab 375 mg/m2 x 4-6 doses added to systemic chemotherapy with FAB LMB Regimen -Group B or Group A – FAB LMB or BFM Regimen
8. Treatment related side effects were noted if applicable (Rec 13-14)			-Any of the following treatment related side effects were monitored: 1. febrile neutropenia 2. anemia, thrombocytopenia 3. infection 4. mucositis, and 5. tumor lysis syndrome 6. diarrhea and constipation 7.kidney failure 8. infusion-related reactions
9. Appropriate treatment started to address side effects of chemotherapy (Rec 15-16)			-Any one of the following interventions to address side effect: 1. febrile neutropenia – antibiotics 2. mucositis – chlorhexidine and antifungal treatment
10. Appropriate supportive and palliative care referral done if needed. (Rec 17-19)			Any one or a combination of the following when applicable was done: 1. Nutritional support 2. Palliative care referral 3. Urate oxidase or Allopurinol for tumor lysis syndrome
11. Referral to ancillary health services offered to the patient and family (Rec 19-22)			Any one or a combination of the following when applicable: 1. Referral to support groups 2. Enrolment to PHIC and referral for logistic support if needed

Total Compliance Score = (Total number of yes/total items) * 100% = (_____/_____) *100% = _____

8.4 RESOURCE IMPLICATION

Resource implications or affordability and cost effectiveness for each recommendation in this guideline should be explored. At the minimum, a qualitative description that can serve as a gross indicator of the number of resources needed, relative to current practice, should be provided (**Edejer, 2006**). For cost-effectiveness, there are concerns about the generalizability of results from a single cost-effective analysis (CEA) or even a systematic review of a CEA. A systematic review of sources of variability frequently mentions volume and costs of resources consumed as a source of variability (**Sculpher MJ.2004**). For costs, more specifically prices, general principles for adaptation are available (**Hutton G. 2005**). Affordability or resource implications was considered in these guidelines because each recommendation provides basic information that will allow guideline users to work out the cost implications for their own service (**Philips Z. 2004**). The resource implications of each individual recommendation were considered when implementation issues were being discussed. Alternative tests or drugs were offered if certain laboratory or medicine is not available locally.

8.5 MONITORING OF DISSEMINATION AND IMPLEMENTATION

Dissemination and implementation of these recommendations on pediatric BL are focused not just on health care professionals but also to other multidisciplinary teams, patients and their families. Monitoring and evaluation should be built into the implementation process, in order to provide important lessons for uptake and further implementation. Improvement of health care can be enhanced by the dissemination of recommendations that are easy to find and easy to understand by patients. The monitoring and evaluation strategy will endeavor to ensure that the existing patient monitoring tools at health facilities and communities will contain information on recognition and management of BL patients. However, the data could be collected periodically through special surveys or program reviews (**WHO, 2015**). Regarding monitoring and evaluation of their impact on quality of care, priority should be given to the strong recommendations.

Global and country level efforts are underway under CUREAlll: WHO Global Initiative for Childhood Cancer and the DOH, The National Integrated Cancer Control Strategic Plan 2021-2030 (CUREAll-WHO, 2015; NICCSP) with a program's vision of "Cancer-free Philippines (Philippines Free from the Burden of Cancer)". The DOH will help in monitoring the implementation of this guideline using multilevel intervention addresses at least three levels of the multilayer system (e.g., the individual, the team of health-care providers, the health-care organization or the community where the organization is located), reflecting the whole of government, whole of society, health in all policies, and multisectoral collaboration (NICCSP). Such interventions target at least three sources of influence upon health behavior that may ultimately result in improved patient and population outcomes.

8.6 Facilitators and Barriers to Dissemination and Implementation

Translating evidence from CPGs into practice is a challenging process as it involves making changes at the individual, organizational or health system levels. Assessing barriers and facilitators to the use of clinical practice guidelines is the first step in the local adaptation and uptake of evidence **(Grol R. 2003)**. One systematic meta-review reported five contexts to group the barriers and facilitators (**Correa VC.et al. 2020)**; these contexts are the political and social, the health organizational system, the guideline, the health professional and the patient context. Commonly mentioned about political and social barriers are the absence of a leader that establishes priorities and manages the implementation process **[Busetto L.2016)**, lack of coordination and disagreement with colleagues. With regards to health organizational system context, the most mentioned barriers are the lack of time allowed for researching, studying and implementing the guidelines [**Rubio-Valera.2014)**. Additional barriers were a shortage of hospital resources and equipment [**Flottorp SA,2013**). As to the CPG context, the most mentioned barriers were a lack of clarity in the CPG and a belief that the evidence in the guidelines is incorrect (**Lau R. 2016).** The health professional as the context of the barrier may happen due to the ignorance of the existence of the CPGs or recommendations, or a lack of familiarity with the guideline recommendations [**Wood E. 2017)**. While the most frequent barriers in the patient context were the unawareness of patients regarding the guideline, negative attitude of the patient towards the guide, reluctance to follow the recommendations, expectations in contrast to the opinion of the doctor **[Cochrane Ll. 2007**], lack of family support, and inadequate patient–doctor relationships (**De Vleminck A.2013**). While specifically for lymphoma clinical guidelines, a pilot mixed-methods research study was conducted and there were three themes emerging from the interviews in the interpretation of the results related to barriers. These include patient comorbidities, inadequate use of technology, and medical insurance. Physicians in academic practices reported more difficulty in adhering to lymphoma CPGs in all domains than did physicians in nonacademic practices. Older, more experienced physicians reported less difficulty adhering to the lymphoma CPGs in organizational and professional attitude domains than the younger physicians. . To best serve the physician and the patient, we need to find ways to improve CPG adherence. Tactics such as improving the methodology of CPG formation, using information technology, and creating ways to change physician attitudes and behavior are all viable options. (**Munteanu M.2019)**.

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11 APPENDICES

11.1 TECHNICAL WORKING GROUP

Name	Expertise	Role in Guideline Development	Conflict of Interest
Jeannie B. Ong, MD	Pediatric Hematology/Screening and Diagnosis, Treatment of Pediatric Cancer and Management of bleeding and other complications of cancer, end of life care and psychosocial and family support	Project Team Leader for BL TWG	None
Cheryl Lyn A. Diez, MD	Pediatric Hematology/Oncology, Screening and Diagnosis, Treatment of Pediatric Cancer and Management of bleeding and other complications of cancer, end of life care and psychosocial and family support	Assistant Team Leader	None
Rojim Sorrosa, 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	TWG Member	None
Marlon Tampon, MD	Pediatric Oncology Fellow-In-Training, can evaluate in patients and outpatients in the ward and OPD, has clinical assessment of common hematologic and oncologic problem (neutropenic fever, relapse of tumor, fluid imbalance, mucositis, nausea), able to perform technical skills (successful lumbar punctures, placement of a bone marrow aspirate needles, and proper examination of a peripheral blood smear)	TWG Member	None

Bai Johanna Zainal, MD	Pediatric Oncology Fellow-In-Training, can evaluate in patients and out patients in the ward and OPD, has clinical assessment of common hematologic and oncologic problem (neutropenic fever, relapse of tumor, fluid imbalance, mucositis, nausea), able to perform technical skills (successful lumbar punctures, placement of a bone marrow aspirate needles, and proper examination of a peripheral blood smear)	TWG Member	None
Andy Omar Elorde, MD	Palliative Care Medicine Fellow in training, renders quality of life services such as psychosocial, emotional and spiritual support for both patient and family members. I also cater to their immediate symptomatic concerns such as physical pain (Pain control management).	TWG Member	None
Allyne M. Aguelo, MD	Pediatric infectious disease specialist and infection control.	TWG Member	None
Ma. Theresa Fedoc-Minguito, MD	Clinical Pathologist	TWG Member	None
Irish May C. Solar, RN, MAN	CCI ward Unit Manager for four years, NICU nurse for two years, IV insertion	TWG Member	None
Ana Loseo, RN	Infection Preventionist Nurse focusing on overall status of patients, staff and carers, staff and environment, Supervising febrile neutropenia, monitors phlebitis, mucositis and wound infection.	TWG Member	None
Rosie Mebelle D. Tongco	Pediatric Oncology Nurse Pediatric Palliative Nurse	TWG Member	None
Paul Joshua Sison, RPh	Clinical Pharmacy, checking and monitoring of drug usage, drug interactions and compatibilities and dispensing of drugs	TWG Member	
Tessa Marlou Faye L. Duo, RN	Data manager, gather and collect pertinent data relative to patients for studies and research, knowledgeable in powerpoint presentation and excel	TWG Member	None

Sheila Grace A. Bonostro	Social Worker, intake interview, data gathering and referral.	TWG BL Member	None
Jose Bernardo D. Tengson	CCI Administrative / Technical Writing skills / knowledgeable in various IT application, background on Accounting, Financial and Risk Management, adept with the Government Procurement Act; attending to patients and carers social support and other needs.	TWG BL Member	None
Kristina Mae B. Montebon-Soriano, MD	General Pediatrics	Technical Writer for BL TWG	None

11.2 CONSENSUS PANEL

Name	Expertise	Role in Guideline Development	Conflict of Interest
Fatima Inderah D. Disomimba	Community worker and President, House of Hope Foundation for Kids with Cancer	Member, Consensus Panel	None
Mae Concepcion J. Dolendo, MD	Pediatric oncologist and council member of the National Integrated Cancer Control Council. St Jude Global Medical Lead and WHO focus person for pediatric oncology in the Philippines.	Member, Consensus Panel	None
Oscar P Grageda, MD	Senior Pathologist, private hospital CEO and president.	Member, Consensus Panel	None
Linell G. Malimbag, PhD	Academician and private hospital administrator	Member, Consensus Panel	None
Lilia M. Yu MD	Pediatric Hematologist. Screening and Diagnosis, Treatment of Pediatric Cancer and Management of bleeding and other complications of cancer, end of life care and psychosocial and family support	Member, Consensus Panel	None

11.3 CONSULTATION WITH STAKEHOLDERS

The Burkitt Lymphoma Technical Working Group (BL TWG) identified all patients less than 19 years old diagnosed with BL registered at the Southern Philippines Medical Center Children's Cancer Institute (SPMC-CCI0. SPMC is the biggest DOH retained tertiary government hospital in Mindanao and end referral center for pediatric cancer patients. The group also identified BL managed from private institutions, pediatric residents in training and nurses who handled cases of BL in children.

A total of 15 patients with Burkitt Lymphoma from a tertiary level government hospital and a private hospital were identified. Three families from the government hospital and a family from a private institution were included in the survey. The team also interviewed six resident physicians who handled Burkitt Lymphoma patients. Among them were five pediatric residents belonging to both public and private hospitals and one pathology resident. A total of five oncology nurses were interviewed.

All respondents were made to answer three questions: 1) What are the things you want to know as a patient's carer or as a family member of someone with Burkitt Lymphoma? 2) What are the important things to you regarding the treatment / medication of Burkitt Lymphoma? 3) In your experience, what do you think should be improved in treating patients with Burkitt Lymphoma?

The questions were translated to the preferred vernacular language. The data manager recorded and transcribed the answers for each question. Video teleconferencing software was used to conduct key informant interviews and informal surveys. The results of the survey showed that the respondents wanted to know more about the following aspects of BL:

- How to diagnose this disease
- What laboratory tests to order
- Appropriate medications and novel therapy that is available
- How to prevent this disease
- The complications of treatment
- Availability of support groups
- What palliative treatment
- Availability of referral centers for BL

Most of the respondents seem to emphasize on the effectiveness of the medicines used for BL, the cost of the treatment, availability of insurance coverage that will cover the whole treatment including supportive care, diagnostic tests and issues about prognosis. The decision to define the key questions of this proposed guideline was based on the respondents 'answers.

11.4 EVIDENCE TABLES

Clinical Assessment

Question: Should B symptoms be used for Diagnosis of Burkitt Lymphoma in Children?[1]
Bibliography: Huang,et.al. 2015

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With B symptoms		Risk with Control	Risk difference with B symptoms (95% CI)
diagnosis of BL (CRITICAL OUTCOME; assessed with: B symptoms)											
92 (1 study[2])	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1]	-	32/92 (34.8%)	-	See comment	See comment

Clinical Assessment

[1] B SYMPTOMS: fever, night sweat, weight loss
[2] case reports

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Abdominal tumors be used for Diagnosis of Burkitt Lymphoma in Children?
Bibliography: Ertem, et. al. 1996 Mbulaiteye, et. al. 1992-2005 Huang et al 2015 Cavdar, et. al. 1994 Patton et al.

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects
							With Control	With Abdominal tumors		Risk with Control / Risk difference with Abdominal tumors (95% CI)
diagnosis of BL (CRITICAL OUTCOME; assessed with: Abdominal tumors)										
584 (5 studies)	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1] due to risk of bias, large effect	-	305/584 (52.2%)	-	**Study population** - **Moderate** -

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should head and neck masses be used for Dagnosis of Burkitts Lymphoma in Children?

Bibliography: Ertem, et. al. 1996 Mbulaiteye, et. al. 1992-2005 Cavdar, et. al. 1994 Zheng, et. al. 2019 Huang,et.al. 2015 Hong,et.al.2019

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Head and neck masses		Risk with Control	Risk difference with Head and neck masses (95% CI)
diagnosis of BL (CRITICAL OUTCOME)											
700 (6 studies)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁◯◯ **LOW**[1]	-	229/700 (32.7%)	-	**Study population**	
											-
										Moderate	
											-

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should pleural effusion be used for diagnosis of Burkitt lymphoma in Children?
Bibliography: Ertem, et al 1996 Cavdar, et. al 1994

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Plueral effusion**		**Risk with Control**	**Risk difference with Plueral effusion** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
144 (2 studies)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1]	-	16/144 (11.1%)	-	**Study population**	
											-
										Moderate	
											-

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should bone marrow abnormalities be used for Diagnosis of Burkitts Lymphoma in Children?
Bibliography: Ertem, et. al.1996 Mbulaiteye, et. al. 1992-2005 Patton, et al Cavdar, et. al.1994

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Bone marrow abnormalities**		**Risk with Control**	**Risk difference with Bone marrow abnormalities** (95% CI)
New Outcome (CRITICAL OUTCOME)											
457 (4 studies)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1]	-	72/457 (15.8%)	-	**Study population**	
											-
										Moderate	
											-

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Ascites be used for Diagnosis of Burkitt Lymphoma in Children?
Bibliography: Ertem, et. al. 1996 Cavdar et. al. 1994

Quality assessment							Summary of Findings		
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**
							With Control / **With Ascitis**		**Risk with Control** / **Risk difference with Ascitis** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)									
144 (2 studies)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1]	- / 19/144 (13.2%)	-	**Study population** / -
									Moderate / -

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should CNS involvement be used for Diagnosis of Burkitts Lymphoma in Children?
Bibliography: Ertem et. al. 1996 Anavi, et. al. 1990 Cavdar, et al. 1994 Zheng, et al 2019 Patton, et al

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control / **With CNS involvement**		**Risk with Control**	**Risk difference with CNS involvement** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)										
227 (5 studies)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1]	- / 30/227 (13.2%)	-	**Study population**	
										-
									Moderate	
										-

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Lymphadenopathies be used for Diagnosis of Burkitts Lymphoma in Children?
Bibliography: Mbulaiteye, et. al. 1992-2005 Huang, et.al. 2015 Anavi,et.al. 1990 Cavdar,et.al. 1994 Patton, et al

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Lymphadenopathies		Risk with Control	Risk difference with Lymphadenopathies (95% CI)
diagnosis of BL (CRITICAL OUTCOME)											
517 (5 studies)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**[1]	-	195/517 (37.7%)	-	**Study population**	
											-
										Moderate	
											-

[1] No explanation was provided

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Liver involvement be used for Diagnosis of Burkitt Lymphoma in children?
Bibliography: Ertem, et.al. 1996

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control / **With Liver involvement**		**Risk with Control**	**Risk difference with Liver involvement** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)										
63 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	- / 4/63 (6.3%)	-	**Study population**	
										-
									Moderate	
										-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Mediastinum presentation be used for Diagnosis of Burkitt Lymphoma in children?
Bibliography: Ertem, et.al. 1996

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Mediastinum presentation		Risk with Control	Risk difference with Mediastinum presentation (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
63 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	-	4/63 (6.3%)	-	**Study population**	
											-
										Moderate	
											-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Testis involvement be used for Diagnosis of Burkitt Lymphoma?
Bibliography: Ertem, et. al. 1996 Haung, et. al. 2015 Cavdar,et. al. 1994

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Testis involvement**		**Risk with Control**	**Risk difference with Testis involvement** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
236 (3 studies)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	-	6/236 (2.5%)	-	**Study population**	
											-
										Moderate	
											-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Ovarian mass be used for Diagnosis of Burkitt Lymphoma in children?
Bibliography: Cavdar, et.al. 1994

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Ovarian mass**		**Risk with Control**	**Risk difference with Ovarian mass** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
81 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	-	3/81 (3.7%)	-	**Study population**	
											-
										Moderate	
											-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Kidney presentation be used for Diagnosis of Burkitt Lymphoma in children?
Bibliography: Ertem, et. al. 1996

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Kidney presentation		Risk with Control	Risk difference with Kidney presentation (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
63 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	-	4/63 (6.3%)	-	**Study population**	
											-
										Moderate	
											-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Breast mass be used for Diagnosis for Burkitt Lymphoma in children?
Bibliography: Cavdar, et. al. 1994

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Control	**With Breast mass**		**Risk with Control**	**Risk difference with Breast mass** (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
81 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	-	2/81 (2.5%)	-	**Study population**	
											-
										Moderate	
											-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Question: Should Skin nodule be used for Diagnosis for Burkitt Lymphoma in children?
Bibliography: Cavdar, et.al. 1994

Quality assessment							Summary of Findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Skin nodule		Risk with Control	Risk difference with Skin nodule (95% CI)
Diagnosis of BL (CRITICAL OUTCOME)											
81 (1 study)	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨀⨀ **LOW**	-	3/81 (3.7%)	-	**Study population**	
											-
										Moderate	
											-

	Design Score	Risks of Bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence						
Case Report	4	0	0	0	0	4

Legend: 4-High; 3- moderate; 2-Low; 1-Very low

Diagnostic and Ancillary Tests

Question: Core needle biopsy for diagnosis of Burkitt Lymphoma
Bibliography: de Kerviler E, Guermazi A, Zagdanski AM, Meignin V, Gossot D, Oksenhendler E, Mariette X, Brice P, Frija J. August 2000.

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	core needle biopsy	Relative (95% CI)	Absolute (95% CI)		
SENSITIVITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	147/157 (93.6%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
SPECIFICITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1/1 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
POSITIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	147/147 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
NEGATIVE PREDICTIVE OUTCOME											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1/11 (9.1%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
ACCURACY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	147/158 (93.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Retrospective Cohort	4	0	0	-1	0	3

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Among pediatric patients with suspected lymphoma, what is the best surgical diagnostic procedure for diagnosis of Burkitt Lymphoma?
Bibliography: Dong HY, Harris NL, Preffer FI, Pitman MB. May 2001

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fine needle aspiration biopsy	Relative (95% CI)	Absolute (95% CI)		
SENSITIVITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	93/100 (93.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
SPECIFICITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	39/39 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
POSITIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	100/100 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
NEGATIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	39/46 (84.8%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
ACCURACY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	132/139 (95.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

Dong HY et al. May 2001	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Retrospective	4	0	0	-1	0	3

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Core needle biopsy for diagnosis of Burkitt Lymphoma
Bibliography: Loubeyre P, McKee TA, Copercini M, Rosset A, Dietrich PY.June 2009

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	core needle biopsy	Relative (95% CI)	Absolute (95% CI)		
SENSITIVITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	62/62 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
SPECIFICITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1/1 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
POSITIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	62/62 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
NEGATIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	1/1 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
ACCURACY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	62/63 (98.4%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

Loubeyre P et al. June 2009	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Observational	4	0	0	-1	0	3

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Should core needle biopsy be used for diagnosis of Burkitt lymphoma?
Bibliography: Nguyen BM, Halprin C, Olimpiadi Y, Traum P, Yeh JJ, Dauphine C. December 2014

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	core needle biopsy	Relative (95% CI)	Absolute (95% CI)		
SENSITIVITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	37/37 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
SPECIFICITY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	36/36 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
POSITIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	37/37 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
NEGATIVE PREDICTIVE VALUE											
1	observational studies	not serious	not serious	not serious	not serious	strong association	36/36 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
ACCURACY											
1	observational studies	not serious	not serious	not serious	not serious	strong association	73/73 (100.0%)	not estimable		⊕⊕⊕◯ MODERATE	

Nguyen BM et al. December 2014	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Observational	4	0	0	-1	0	3

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Should MOLECULAR TESTING vs CURRENT WHO BL DIAGNOSTIC CRITERIA be used for DIAGNOSIS OF BL?
Bibliography: Dave et al 2006

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MOLECULAR TESTING	CURRENT WHO BL DIAGNOSTIC CRITERIA	Relative (95% CI)	Absolute		
ACCURACY (assessed with: (TP+TN)/(TP+TN+FP+FN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	62/100 (62%)	69/100 (69%)	-	690 fewer per 1000 (from 690 fewer to 690 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
SENSITIVITY (assessed with: TP/(TP+FN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	100/100 (100%)	48/100 (48%)	-	480 fewer per 1000 (from 480 fewer to 480 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
SPECIFICITY (assessed with: TN/(TN+FP) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	41/100 (41%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
POSITIVE PREDICTIVE VALUE (assessed with: TP/(TP+FP) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	48/100 (48%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
NEGATIVE PREDICTIVE VALUE (assessed with: TN/((FN+TN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	100/100 (100%)	41/100 (41%)	-	410 fewer per 1000 (from 410 fewer to 410 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cross Sectional	4	0	0	0	0	4

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Should CYTOGENETIC TESTING vs CONVENTIONAL (WITHOUT CYTOGENETICS) be used for DIAGNOSIS OF BURKITT LYMPHOMA?
Bibliography: Poirel et al 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYTOGENETIC TESTING	CONVENTIONAL (WITHOUT CYTOGENETICS)	Relative (95% CI)	Absolute		
ACCURACY (assessed with: (TP+TN)/(TP+TN+FP+FN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	48/100 (48%)	34/100 (34%)	-	340 fewer per 1000 (from 340 fewer to 340 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
SENSITIVITY (assessed with: TP/(TP+FN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	42/100 (42%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
SPECIFICITY (assessed with: TN/(TN+FP) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	100/100 (100%)	16/100 (16%)	-	160 fewer per 1000 (from 160 fewer to 160 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
POSITIVE PREDICTIVE VALUE (assessed with: TP/(TP+FP) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	100/100 (100%)	39/100 (39%)	-	390 fewer per 1000 (from 390 fewer to 390 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		
NEGATIVE PREDICTIVE VALUE (assessed with: TN/((FN+TN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	18/100 (18%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	ÂÂÂO MODERATE	CRITICAL
								0%		-		

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cross Sectional	4	0	0	0	0	4

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Should MOLECULAR DIAGNOSIS vs PATHOLOGICAL DIAGNOSIS be used for BURKITT LYMPHOMA?
Bibliography: Boerma et al 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MOLECULAR DIAGNOSIS	PATHOLOGICAL DIAGNOSIS	Relative (95% CI)	Absolute		
ACCURACY (assessed with: (TP+TN)/(TP+TN+FP+FN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	95/100 (95%)	95/100 (95%)	-	950 fewer per 1000 (from 950 fewer to 950 fewer)	ÅÅÅO MODERATE	CRITICAL
								0%		-		
SENSITIVITY (assessed with: TP/(TP+FN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	100/100 (100%)	86/100 (86%)	-	860 fewer per 1000 (from 860 fewer to 860 fewer)	ÅÅÅO MODERATE	CRITICAL
								0%		-		
SPECIFICITY (assessed with: TN/(TN+FP) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1[1]	93/100 (93%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	ÅÅÅO MODERATE	CRITICAL
								0%		-		
POSITIVE PREDICTIVE VALUE (assessed with: TP/(TP+FP) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	84/100 (84%)	100/100 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	ÅÅÅO MODERATE	CRITICAL
								0%		-		
NEGATIVE PREDICTIVE VALUE (assessed with: TN/((FN+TN) X 100)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	100/100 (100%)	93/100 (93%)	-	930 fewer per 1000 (from 930 fewer to 930 fewer)	ÅÅÅO MODERATE	CRITICAL
								0%		-		

[1] No explanation was provided

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cross Sectional	4	0	0	0	0	4

4-High; 3-Moderate; 2-Low; 1-Very Low

Note:

1) Pathological Diagnosis is Based on current WHO Criteria: Morphologic (microscopic), Immunophenotypic and Cytogenetics Findings which include the following a.Presence of c-MYC translocation, b. Ki-67 of >90% c. CD10 and/or BCL6 POSITIVE, & d. CD20 OR CD19 POSITIVE.

2) Molecular Diagnosis is Based on: a. high c-MYC target genes expression, b. High GC-B cell genes expression, c. Low level MHC-1 gene expression & d. Low level Nuclear Factor-κB target genes expression which are determined by the ff: Oligonucleotide microarray (ID of specific DNA markers by molecular hybridization) & RNA interference.

Question: Should CYTOGENETICS be used for RISK GROUP STRATIFICATION IN BL?
Bibliography: Poirel et al 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYTOGENETICS	Control	Relative (95% CI)	Absolute		
8q24 rearrangement (assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] reduced effect for RR >> 1 or RR << 1[1]	152/182 (83.5%)	154/182 (84.6%)	-	846 fewer per 1000 (from 846 fewer to 846 fewer)	ÂÂÂÂ HIGH	CRITICAL
								0%		-		
7q+ (assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] reduced effect for RR >> 1 or RR << 1[1]	138/182 (75.8%)	154/182 (84.6%)[2]	-	846 fewer per 1000 (from 846 fewer to 846 fewer)	ÂÂÂÂ HIGH	CRITICAL
								0%		-		
13q deletion (assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] reduced effect for RR >> 1 or RR << 1[1]	126/182 (69.2%)	156/182 (85.7%)[3]	-	857 fewer per 1000 (from 857 fewer to 857 fewer)	ÂÂÂÂ HIGH	CRITICAL
								0%		-		
More than 3 cytogenetic abnormalities (assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] reduced effect for RR >> 1 or RR << 1[1]	135/182 (74.2%)	159/182 (87.4%)[4]	-	874 fewer per 1000 (from 874 fewer to 874 fewer)	ÂÂÂÂ HIGH	CRITICAL
								0%		-		

[1] Control - BL with no 8q24 rearrangement; [2] Control - BL with no addition at 7q; [3] Control - BL with no 13q deletion; [4] Control - BL with only 1-3 cytogenetic abnormality

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Case Control	4	0	0	0	0	4

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Should CD44 deficiency be used for differentiating Burkitt lymphoma from other mature B cell lymphoma?
Bibliography: S. Schniederjan, et al 2010 A Attarbaschi, et al 2007

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CD44 deficiency	Control	Relative (95% CI)	Absolute		
Low CD 44 used in Diagnosis of BL (follow-up median 2 years; assessed with: Sensitivity)												
2	observational studies	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	49/52 (94.2%)	2/19 (10.5%)	-	11 fewer per 100 (from 11 fewer to 11 fewer)	⊡⊡⊡⊡ MODERATE	CRITICAL
specificity of Low CD44 in diagnosing BL (follow-up median 2 years; assessed with: Specificity)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	60/71 (84.5%)	0%	-	-	⊡⊡⊡⊡ MODERATE	CRITICAL
positive predictive value of low CD44 in diagnosing BL (follow-up median 2 years; assessed with: PPV)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	65/71 (91.5%)	-	-	-	⊡⊡⊡⊡ MODERATE	CRITICAL
								0%		-		
negative predictive value of low CD44 in diagnosis BL (assessed with: NPV)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	64/71 (90.1%)	-	-	-	⊡⊡⊡⊡ MODERATE	CRITICAL
								0%		-		
Accuracy of low CD44 in diagnosing BL (follow-up median 2 years; assessed with: Accuracy)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	65/71 (91.5%)	-	-	-	⊡⊡⊡⊡ MODERATE	CRITICAL
								0%		-		

[1] No explanation was provided; [2] large difference from control

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Attarbaschi, et al 2007 Cross-sectional	4	-1	0	0	0	3
Schniederjan, et al 2010Cross-sectional	4	0	0	0	0	4

4-High; 3-Moderate; 2-Low; 1-Very Low

Reference	Okamoto T, Sekiya A, Daifu T, Doi R, Kobayashi H. Primary jejunal Burkitt lymphoma in a child: ultrasonic detection. J Surg Case Rep. 2018 May 14;2018(5):rjy090. doi: 10.1093/jscr/rjy090. PMID: 29770187; PMCID: PMC5951082.			
Objective	To present a 4-year-old boy with primary jejunal BL with intussusception mimicking presentation, in which initial abdominal US allowed sustainable detection and characterization of the intestinal lesion. Jejunotomy was performed and histopathological analysis revealed a 'starry sky' pattern and c-myc split signals characteristic of BL.			
Study Design	Case report			
Bias	Well- defined broad spectrum of population? NO Comparison with reference standard? (Yes/No) no Adequate period of follow- up? (Yes/No) YES			
Description of Test	Focused sonography was performed using a Toshiba Aplio 400 PVT-375BT transducer with the pediatric abdominal setting at a 5-MHz frequency. This revealed a circumscribed area of homogenously low echogenicity without wall stratification in the submucosal area of the intestine Power Doppler sonography detected abundant blood flow signals in the same area.			
Test	Sensitivity	Specificity	Accuracy	Likelihood ration
Consistency	Heterogeneity? (Yes/No)	NO		
Conclusion	Ultrasonography is a widely accepted initial imaging workup; therefore, recognition of the sonographic features of BL should contribute to its early diagnosis and initiation of treatment.			

	DESIGN SCORE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	QUALITY SCORE	QUALITY
CASE REPORT	4	0	0	-1	0	3	MODERATE

Reference	Brodzisz A, Woźniak MM, Dudkiewicz E, Grabowski D, Stefaniak J, Wieczorek AP, Kowalczyk J. Ultrasound presentation of abdominal non-Hodgkin lymphomas in pediatric patients. J Ultrason. 2013 Dec;13(55):373-8. doi: 10.15557/JoU.2013.0040. Epub 2013 Dec 30. PMID: 26672593; PMCID: PMC4579673.			
Objective	The aim of this paper was to review the ultrasound manifestation of abdominal Burkitt lymphoma in children.			
Study Design	Case Studies			
Bias	Well- defined broad spectrum of population? NO (children between 2-17 years old) Comparison with reference standard? (Yes/No) Adequate period of follow- up? YES			
Description of Test	Ultrasound examinations were conducted with the use of a Siemens scanner with a convex transducer of 3.5–5 MHz and a high-frequency linear array transducer of L4 – 7.5 MHz. The following modes were used: B-mode, color and power Doppler as well as tissue harmonic imaging (THI). The gastrointestinal tract was assessed using an ultrasound set-up for organs located superfi cially (set-up "small parts").			
Test	Sensitivity	Specificity	Accuracy	Likelihood ration
Consistency	Heterogeneity? (Yes/No)	NO		
Conclusion	The clinical and ultrasound picture of abdominal Burkitt lymphoma in children is variable. A careful ultrasound assessment of all abdominal organs conducted with the use of convex and linear probes increases the chances of establishing an adequate diagnosis.			

	DESIGN SCORE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	QUALITY SCORE	QUALITY
CASE REPORT	4	0	0	-1	0	3	MODERATE

Reference	Marjerrison S, Fernandez CV, Price VE, Njume E, Hesseling P. The use of ultrasound in endemic Burkitt lymphoma in Cameroon. Pediatric Blood Cancer. 2012 Mar;58(3):352-5. doi: 10.1002/pbc.23050. Epub 2011 Mar 2. PMID: 21370431.			
Objective	This study was designed to examine the contribution of Ultrasound as a diagnostic tool in the Malawi 2002/03 trial at the BBH site.			
Study Design	retrospective chart review			
Bias	Well- defined broad spectrum of population? 95 patients with clinically identified eBL Comparison with reference standard? (Yes/No) yes Adequate period of follow- up? YES			
Description of Test				
Test	Sensitivity	Specificity	Accuracy	Likelihood ration
Consistency	Heterogeneity? (Yes/No)	yes		
Conclusion	We demonstrate that Ultrasound provides more accurate staging of eBL than clinical examination. Abdominal involvement is more common than previously reported and appears to be as frequent as disease of the jaw at presentation.			

	DESIGN SCORE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	QUALITY SCORE	QUALITY
Observational study	4	0	0	-1	0	3	MODERATE

Author(s): BL GROUP
Date: 2021-06-07
Question: Should PETSCAN vs CT SCAN be used for PEDIATRIC BURKITT'S LYMPHOMA IN DETERMINING THE EXTENT OF DISEASE?
Settings:
Bibliography: H. Abdel Rahman et al.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PETSCAN	CT SCAN	Relative (95% CI)	Absolute		
SENSITIVITY (follow-up median 42 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	115/126 (91.3%)	84/126 (66.7%)	RR 1.37 (0 to 0)	247 more per 1000 (from 667 fewer to 667 fewer)	⊕⊕◯◯ LOW	CRITICAL
								0%		-		
SPECIFICITY (follow-up median 42)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/126 (85.7%)	74/126 (58.7%)	RR 1.45 (0 to 0)	264 more per 1000 (from 587 fewer to 587 fewer)	⊕⊕◯◯ LOW	CRITICAL
								0%		-		
PPV: positive predictive value (follow-up median 42 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/126 (40.5%)	18/126 (14.3%)	RR 2.83 (0 to 0)	261 more per 1000 (from 143 fewer to 143 fewer)	⊕⊕◯◯ LOW	CRITICAL
								0%		-		
NPV: negative predictive value (follow-up median 42 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	124/126 (98.4%)	119/126 (94.4%)	RR 1.04 (0 to 0)	38 more per 1000 (from 944 fewer to 944 fewer)	⊕⊕◯◯ LOW	CRITICAL
								0%		-		

	DESIGN SCORE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	QUALITY SCORE	QUALITY
CROSS-SECTIONAL	4	0	0	0	0	4	HIGH

Author(s):
Date: 2021-06-24
Question: Should PET/CT vs CONVENTIONAL IMAGING be used for MALIGNANT PEDIATRIC LYMPHOMA?
Settings:
Bibliography: Riad R, Omar W, Kotb M, Hafez M, Sidhom I, Zamzam M, Zaky I, Abdel-Dayem H.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PET/CT	CONVENTIONAL IMAGING	Relative (95% CI)	Absolute		
SENSITIVITY (follow-up mean 6.8 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/51 (100%)	42/51 (82.4%)	RR 1.21 (0 to 0)	173 more per 1000 (from 824 fewer to 824 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
SPECIFICITY (follow-up mean 6.8 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/51 (98%)	34/51 (66.7%)	RR 1.47 (0 to 0)	313 more per 1000 (from 667 fewer to 667 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
PPV: positive predictive value (follow-up mean 6.8 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/51 (86.3%)	13/51 (25.5%)	RR 3.38 (0 to 0)	607 more per 1000 (from 255 fewer to 255 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
NPV: negative predictive value (follow-up mean 6.8 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/51 (100%)	49/51 (96.1%)	RR 1.04 (0 to 0)	38 more per 1000 (from 961 fewer to 961 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
ACCURACY (follow-up mean 6.8 months)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/51 (98%)	35/51 (68.6%)	RR 1.43 (0 to 0)	295 more per 1000 (from 686 fewer to 686 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		

	DESIGN SCORE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	QUALITY SCORE	QUALITY
CROSS-SECTIONAL	4	0	-1	0	0	3	MODERATE

Author(s): BL GROUP
Date: 2021-07-19
Question: Should CT scan be used for Pediatric Burkitt lymphoma?
Settings:
Bibliography: Kamona, A.A., El-Khatib, M.A., Swaidan, M.Y. et al. Pediatric Burkitt's lymphoma: CT findings. Abdom Imaging 32, 381–386 (2007). https://doi.org/10.1007/s00261-006-9069-0

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT scan	Control	Relative (95% CI)	Absolute		
Extra-nodal involvement: GASTRO-INTESTINAL TRACT (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	19/33 (57.6%)	- 0%	-	- -	⊕OOO VERY LOW	CRITICAL
Extra-nodal involvement: KIDNEYS (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	9/33 (27.3%)	- 0%	-	- -	⊕OOO VERY LOW	CRITICAL
Extra-nodal involvement: PERITONEUM (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	8/33 (24.2%)	- 0%	-	- -	⊕OOO VERY LOW	CRITICAL
Extra-nodal involvement: LIVER (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	4/33 (12.1%)	- 0%	-	- -	⊕OOO VERY LOW	CRITICAL
Extra-nodal involvement: SPLEEN (follow-up median 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	3/33 (9.1%)	- 0%	-	- -	⊕OOO VERY LOW	CRITICAL

Cont.

Extra-nodal involvement: ADRENALS (follow-up median 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	3/33 (9.1%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			
Extra-nodal involvement: PANCREAS (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	1/33 (3%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			
Extra-nodal involvement: HEAD AND NECK (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	8/33 (24.2%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			
Extra-nodal involvement: BONE (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	4/33 (12.1%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			
Extra-nodal involvement: LUNG (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	3/33 (9.1%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			
Extra-nodal involvement: HEART (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	2/33 (6.1%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			
Extra-nodal involvement: SKIN (follow-up mean 5.9 years)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious	no serious imprecision	none	2/33 (6.1%)	-	-	-	⊕OOO VERY LOW	CRITICAL
								0%	-			

[1] cases of Burkitt□s lymphoma (BL)

	DESIGN SCORE	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	QUALITY SCORE	QUALITY
CROSS-SECTIONAL	4	0	0	0	0	4	HIGH

Staging, Risk Classification, and Prognosis

Question: Should BFM 90 Risk group 1 vs risk group 2 be used for prognostication among children with BL?
Settings: Germany/Austria/Switzerland
Bibliography: Reiter, Schrappe, et al 1999

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BFM 90 Risk group 1	Risk group 2	Relative (95% CI)	Absolute		
Prognosis (follow-up median 4.2 years; assessed with: EFS)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/17 (100%)	161/167 (96.4%)	-	964 fewer per 1000 (from 964 fewer to 964 fewer)	⨁⨁⨁⨁ HIGH	
								0%		-		

Question: Should BFM-90 risk group 2 vs group 3 be used for prognostication among children with BL??
Settings: Germany, Austria, Switzerland
Bibliography: Reiter, Schrappe, et al 1999

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BFM-90 risk group 2	Group 3	Relative (95% CI)	Absolute		
Prognosis (follow-up median 4.2 years; assessed with: EFS)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	161/167 (96.4%)	137/175 (78.3%)		783 fewer per 1000 (from 783 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

Question: Should BFM-90 risk group 3 vs group 4 be used for prognostication among children with BL??
Settings: Germany, Austria, Switzerland
Bibliography: Reiter, Schrappe, et al 1999

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BFM-90 risk group 3	Group 4	Relative (95% CI)	Absolute		
Prognosis (follow-up median 4.2 years; assessed with: EFS)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/158 (90.5%)	59/84 (70.2%)	RR 6.45 (0 to 0)	1000 more per 1000 (from 702 fewer to 702 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

Question: Should **MDD positive vs MDD negative BM be** used for Prognostication among children with BL?
Bibliography: Mussolin, Pillon, et al 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDD positive	MDD negative BM	Relative (95% CI)	Absolute		
3 years PFS (follow-up mean 2 years; assessed with: PFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] reduced effect for RR >>1 or RR << 1	22/32 (68.8%)	29/31 (93.5%)	HR 4.74 (1 to 22.8)	65 more per 1000 (from 0 more to 65 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] more than 20percent

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Mussolin, et al 2012						
Cohort	4	0	0	0	0	4

Question: Should LDH <500 vs LDH>500 be used for risk stratification of Burkitt's lymphoma in children?
Bibliography: Chen 2018 Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LDH <500	LDH>500	Relative (95% CI)	Absolute		
risk stratification (follow-up median 42 months; assessed with: prognosis; 2.5 yrs EFS)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association reduced effect for RR >> 1 or RR << 1[1]	598/616 (97.1%)	359/472 (76.1%)	RFR 2 (1.3 to 3.2)	761 more per 1000 (from 228 more to 1000 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] difference is more than 20

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Chen 2018	4	0	0	0	0	4
Cairo M, Sposto R, 2012 Cohort	4	0	0	0	0	4

4-High; 3-Moderate; 2-Low; 1-Very Low

Question: Should advanced stage be used for prognostication among children with BL?
Settings: Austria, Germany, Switzerland
Bibliography: Woessmann et al, 2004

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advanced stage	Control	Relative (95% CI)	Absolute		
Prognosis/Risk Stratification (follow-up median 3.3 years; assessed with: EFS/FFS)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	no serious imprecision	strong association	220/254 (86.6%)	170/172 (98.8%)	-	988 fewer per 1000 (from 988 fewer to 988 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] includes both BL and DLBCL

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Woessmann, et. al- 2004						
Cohort	4	0	0	0	0	4

Question: Should advanced stage, resectability, high LDH and CNS disease be used for prognostication among children with BL?
Settings: Austria, Germany, Switzerland
Bibliography: Woessmann et al, 2004.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advanced stage, resectability, high LDH and CNS disease	Control	Relative (95% CI)	Absolute		
Prognosis/risk stratification (follow-up median 3.3 years; assessed with: EFS)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	no serious imprecision	none	185/224 (82.6%)	264/281 (94%)	-	940 fewer per 1000 (from 940 fewer to 940 fewer)	⊟⊟⊟⊟ HIGH	CRITICAL
								0%		-		

[1] Includes both BL and DLBCL

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Woessmann, et. al- 2004						
Cohort	4	0	0	0	0	4

Question: Should advanced stage, resectability, high LDH and CNS disease be used for prognostication among children with BL?
Settings: Austria, Germany, Switzerland
Bibliography: Woessmann et al, 2004.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advanced stage, resectability, high LDH and CNS disease	Control	Relative (95% CI)	Absolute		
prognosis/risk stratification (follow-up median 1 years; assessed with: FFS (Failure Free survival))												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	no serious imprecision	increased effect for RR ~1[2]	51/66 (77.3%)	111/117 (94.9%)	HR 3.58 (1.31 to 9.7)	51 more per 1000 (from 31 more to 51 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		

[1] both BL and DLBCL included in the study
[2] HR is more than 1

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Woessmann, et. al- 2004						
Cohort	4	0	0	0	0	4

Question: Should presence of CNS disease vs absence of CNS disease be used for prognostication among children with BL?
Settings: Austria, Germany, Switzerland
Bibliography: Woessmann et al, 2004

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of CNS disease	Absence of CNS disease	Relative (95% CI)	Absolute		
prognosis/Risk stratification (follow-up median 3.3 years; assessed with: EFS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	no serious imprecision	strong association[2]	28/40 (70%)	410/465 (88.2%)	-	882 fewer per 1000 (from 882 fewer to 882 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] Involved BL and DLBC but EFS between the 2 is not significant
[2] difference id significant

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Woessmann et al, 2004						
Cohort	4	0	0	0	0	4

Question: Should **BM+ and CNS + be used for prognostication among children with BL**?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BM+ and CNS +	Control	Relative (95% CI)	Absolute		
Risk/Prognosis (follow-up median 4.5 years; assessed with: EFS/OS)												
1	observational studies/cohort	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] increased effect for RR ~1[2]	42/68 (61.8%)	759/833 (91.1%)	RFR 4.9 (1.6 to 15)	1000 more per 1000 (from 547 more to 1000 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] Large difference
[2] RR is high

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	0	0	4

Question: Should BM+ and CNS + (Group 5) vs BM+ and CNS - (Group 4) be used for poor prognosis among children with BL?
Settings: Saudi Arabia
Bibliography: Belgaumi et al, 2016.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BM+ and CNS + (Group5)	BM+ and CNS - (Group 4)	Relative (95% CI)	Absolute		
risk/prognosis (follow-up median 6.2 years; assessed with: EFS)												
1	observational studies					none	-	-	-	-		CRITICAL
								0%		-		
prognosis /risk (follow-up median 6.2 years; assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	9/17 (52.9%)	11/15 (73.3%)	-	733 fewer per 1000 (from 733 fewer to 733 fewer)	⊡⊡⊡⊡ LOW	CRITICAL
								0%		-		

[1] Includes 87% BL population
[2] significant difference of EFS >20

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Belgaumi, et al- 2016						
Prospective Cohort	4	0	0	-1	0	3

Question: Should BM+ and CNS (+) vs BM - and CNS (-) be used for prognostication among children with BL?
Settings: Saudi Arabia
Bibliography: Belgaumi, et al- 2016

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BM+ and CNS (+)	BM - and CNS(-)	Relative (95% CI)	Absolute		
Risk /Prognosis (follow-up median 6.2 years; assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	20/32 (62.5%)	33/37 (89.2%)	-	892 fewer per 1000 (from 892 fewer to 892 fewer)	⊡⊡⊡⊡ LOW	CRITICAL
								0%		-		

[1] Includes 60 BL and 9 DLBCL
[2] EFS difference is very significant between the 2

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Belgaumi et al, 2016						
Prospective Cohort	4	0	0	-1	0	3

Question: Should bone marrow biopsy positive vs bone marrow biopsy negative be used for prognostication among children with BL?
Settings: China
Bibliography: Chen, et al 2018

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bone marrow biopsy positive	Bone marrow biopsy negative	Relative (95% CI)	Absolute		
prognosis/risk (follow-up median 31 months; assessed with: Cum survival rate)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	no serious imprecision	none	12/17 (70.6%)	12/12 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] includes BL and DLBCL but outcome difference of the 2: NOT significant

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Chen 2018						
	4	0	0	0	0	4

Question: Should **Bone marrow tumor cells >25% vs BM tumor cells <25% be used for prognostication of BL among children?**
Settings: China
Bibliography: Chen, et al 2018

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bone marrow tumor cells >25 %	BM tumor cells <25%	Relative (95% CI)	Absolute		
risk/prognosis (assessed with: 2 year cum survival rate)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/11 (63.6%)	5/5 (100%)	-	1000 fewer per 1000 (from 1000 fewer to 1000 fewer)	⨁⨁⨁⨁ LOW	CRITICAL
								0%		-		

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Chen 2018						
	4	0	0	0	0	4

Question: Should mediastinal primary site vs peripheral lymph node be used for prognostication among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mediastinal primary site	Peripheral lymph node	Relative (95% CI)	Absolute		
prognosis (follow-up median 4.5 years; assessed with: RFR)												
1	observational studies/cohort	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	increased effect for RR ~1[2]	54/0 (0%)	120/0 (0%)	RFR 4.5 (0 to 0)	-	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] also involves few DLBCL
[2] RFR is 4.5

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should abdominal or retroperitoneal primary site vs peripheral lymph node be used for prognostication among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abdominal or retroperitoneal primary site	Peripheral lymph node	Relative (95% CI)	Absolute		
prognosis (follow-up median 4.5 years; assessed with: RFR)												
1	observational studies/cohort	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	increased effect for RR ~1[2]	574/0 (0%)	120/0 (0%)	RFR 2.7 (0 to 0)	-	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] Involves mostly BL but includes also DLBCL
[2] RFR is 2.7

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should 10 years old and older vs less than 10 years old be used for prognostication of BL?
Settings: Austria, Germany, Switzerland
Bibliography: Woessmann et al, 2004

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	10 years old and older	Less than 10 years old	Relative (95% CI)	Absolute		
prognosis (follow-up median 3.3 years; assessed with: FFS)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	increased effect for RR ~1[2]	146/364 (40.1%)	218/364 (59.9%)	HR 2.62 (01.09 to 9.93)	310 more per 1000 (from 32 more to 401 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] BL and DLBCL but according to study no significant difference in the result of the 2
[2] significant HR
Given: (146 and 218 are number of cases per age group) HR and statement that Inferior FFS of 10 years old and above compared to less than 10 years old

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Woessmann et al, 2004						
Cohort	4	0	0	0	0	4

Question: Should female sex vs male sex be used for prognostication among children with BL?
Settings: Austria, Germany, Switzerland
Bibliography: Woessmann et al, 2004

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Female sex	Male sex	Relative (95% CI)	Absolute		
Prognosis (follow-up median 1 years; assessed with: FFS)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	increased effect for RR ~1[2]	0/87 (0%)	0/277 (0%)	HR 2.84 (1.16 to 6.92)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] Includes both BL and DLBCL
[2] HR is more than 1

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Woessmann, et. al, 2004						
Cohort	4	0	0	0	0	4

Question: Should Risk Group C vs Risk group A and Risk Group B be used for risk stratification among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk Group C	Risk group A and Risk Group B	Relative (95% CI)	Absolute		
risk stratification (follow-up median 4.5 years; assessed with: EFS)												
1	observational studies/cohort	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	588/744 (79%)	345/367 (94%)	-	940 fewer per 1000 (from 940 fewer to 940 fewer)	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] includes BL and DLBL
[2] difference in EFS is large

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should Risk group A vs risk group B and C be used for prognostication among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk group A	Risk group B and C	Relative (95% CI)	Absolute		
risk stratification (follow-up median 4.5 years; assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	131/132 (99.2%)	822/979 (84%)	-	840 fewer per 1000 (from 840 fewer to 840 fewer)	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] includes BL and DLBCL
[2] Large difference ... better EFS if risk group A

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should Risk Group B vs Risk group A be used for prognostication among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk Group B	Risk group A	Relative (95% CI)	Absolute		
risk stratification (assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	209/235 (88.9%)	131/132 (99.2%)	-	992 fewer per 1000 (from 992 fewer to 992 fewer)	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] Includes BL and DLBCL, no sub study for BL
[2] Large difference of EFS

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should Risk group C vs risk group B be used for prognostication among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk group C	Risk group B	Relative (95% CI)	Absolute		
risk stratification (follow-up median 4.5 years; assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	587/744 (78.9%)	209/235 (88.9%)	-	889 fewer per 1000 (from 889 fewer to 889 fewer)	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] includes BL and DLBCL
[2] large difference between the 2 groups

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should risk group C vs risk group A be used for prognostication among children with BL?
Settings: COG/UKCCSF/SFOP
Bibliography: Cairo M, Sposto R, 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk group C	Risk group A	Relative (95% CI)	Absolute		
Risk stratification (follow-up median 4.5 years; assessed with: EFS)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	587/744 (78.9%)	131/132 (99.2%)	-	992 fewer per 1000 (from 992 fewer to 992 fewer)	⨁⨁⨁◯ LOW	CRITICAL
								0%		-		

[1] includes BL and few DLBCL
[2] Large difference of EFS

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cairo M,Sposto R, 2012						
Cohort	4	0	0	-1	0	3

Question: Should positive EBV be used for diagnosis and prognosis of BL in children?
Settings: Tanzania, Africa
Bibliography: Kabyemera, et al 2013 (BMC Pediatrics)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Positive EBV	Control	Relative (95% CI)	Absolute		
diagnosis and prognosis (timing of exposure median 7 months; assessed with: odds ratio)												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[1,2]	no serious imprecision	increased effect for RR ~1[3]	35 cases 70 controls		OR 4.77 (1.71 to 13.33)	-	???? LOW	CRITICAL
								0%		-		

[1] 21 of 35 BL positive for EBV
[2] 32 cases of 35 BL, 1 DLBCL, NOS
[3] OR is 4.7
Overall, these findings suggest that EBV load in blood might be a diagnostic and prognostic marker for the onset and monitoring of NHL in African children. EBV detection in blood is less invasive and expensive than EBV detection in histological samples.

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Kabyemera 2013						
Case-control	4	0	0	0	0	4

Treatment and Side Effects

Question: Should Rituximab (375mg/m2) x 6 cycles plus systemic chemotherapy with FAB/LMB 96 protocol compared to systemic chemotherapy with FAB/LMB 96 Protocol for the treatment of high risk, high grade Pediatric Burkitt Lymphoma
Bibliography: Minard Colin V et al, 2020

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Should Rituximab (375mg/m2) x 6 cycles plus systemic chemotherapy with FAB/LMB 96 protocol**	**systemic chemotherapy with FAB/LMB 96 Protocol**	**Relative (95% CI)**	**Absolute (95% CI)**		
Event Free Survival (3 years) (follow-up: median 39.9 months)												
1	randomized trials	not serious	not serious	not serious	not serious	strong association	154/164 (93.9%)	136/164 (82.9%)	**RR 1.14** (-- to --)	**116 more per 1,000** (from -- to --)	⊕⊕⊕⊕ High	CRITICAL
								0.0%		**0 fewer per 1,000** (from -- to --)		
Overall Survival (3 years) (follow-up: median 39.1 months)												
1	randomized trials	not serious	not serious	not serious	not serious	strong association	156/164 (95.1%)	143/164 (87.2%)	**RR 1.09** (-- to --)	**78 more per 1,000** (from -- to --)	⊕⊕⊕⊕ High	CRITICAL
								0.0%		**0 fewer per 1,000** (from -- to --)		

CI: confidence interval; **RR:** risk ratio

Question: Should Rituximab 375mg/m2 plus systemic chemotherapy with LMB 96 be used for the treatment of children and adolescents with CNS and/or Bone Marrow Positive Burkitt Lymphoma (Group C patients)?

Bibliography: Goldman, S., Smith, L., Galardy, P., Perkins, S. L., Frazer, J. K., Sanger, W., Anderson, J. R., Gross, T. G., Weinstein, H., Harrison, L., Shiramizu, B., Barth, M., & Cairo, M. S. (2014). Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: a Children's Oncology Group Report. *British journal of haematology*, *167*(3), 394–401.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab 375mg/m2 plus systemic chemotherapy with LMB 96		Relative (95% CI)	Absolute (95% CI)		
3 year Event Free Survival (follow up: median 3.6 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	36/40 (90.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 year Overall Survival (follow up: median 3.6 years)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	36/40 (90.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 year Event Free Survival among CNS + BL patients (follow up: median 35 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	13.95/15 (93.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should Rituximab (375 mg/m2) x 1-3 doses + Systemic Chemotherapy with BFM 90 Protocol compared to Systemic Chemotherapy with BFM 90 Protocol be used for the treatment of Pediatric Burkitt Lymphoma?

Bibliography: Zijun Zhen, Jia Zhu, Juan Wang, Suying Lu, Feifei Sun, Junting Huang & Xiaofei Sun (2020): Rituximab is highly effective in children and adolescents with Burkitt lymphoma in Risk Groups R2 to R4, Pediatric Hematology and Oncology.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab (375 mg) x 1-3 doses + Systemic Chemotherapy with BFM 90 Protocol	Systemic Chemotherapy with BFM 90 Protocol	Relative (95% CI)	Absolute (95% CI)		
3 year Event Free Survival (follow up: median 36 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	12.99/16 (81.2%)	40.768/49 (83.2%)	**RR 0.97** (-- to --)	**25 fewer per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL
3 year Overall Survival (follow up: median 36 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	12.99/16 (81.2%)	34.89/41 (85.1%)	**RR 0.95** (-- to --)	**43 fewer per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Question: Should Rituximab (375mg/m2) X 4-6 doses + Systemic Chemotherapy with BFM 90 protocol compared to Systemic Chemotherapy with BFM 90 Protocol be used for the treatment of Pediatric Burkitt Lymphoma?

Bibliography: Zijun Zhen, Jia Zhu, Juan Wang, Suying Lu, Feifei Sun, Junting Huang & Xiaofei Sun (2020): Rituximab is highly effective in children and adolescents with Burkitt lymphoma in Risk Groups R2 to R4, Pediatric Hematology and Oncology.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rituximab (375mg/m2) X 4-6 doses + Systemic Chemotherapy with BFM 90 protocol**	**Systemic Chemotherapy with BFM 90 Protocol**	**Relative (95% CI)**	**Absolute (95% CI)**		
3 year Event Free Survival (follow up: median 36 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	39.68/41 (96.8%)	40.76/49 (83.2%)	**OR 1.16** (-- to --)	**20 more per 1,000** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL
3 year Overall Survival (follow up: median 36 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	39.64/41 (96.7%)	41.69/49 (85.1%)	**RR 1.13** (-- to --)	**111 more per 1,000** (from -- to --)	⨁⨁⨁◯ MODERATE	CRITICAL

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

Question: Should FAB LMB 96 regimen with 2 courses of COPAD be used for the treatment of Pediatric Burkitt Lymphoma in risk group A (low risk)?
Bibliography: Aydin B, et al, 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FAB LMB 96 regimen with 2 courses of COPAD**		**Relative (95% CI)**	**Absolute (95% CI)**		
No evidence of disease (follow up: range 17 months to 57 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	2/2 (100.0%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should FAB LMB 96 regimen with COP as prophase, 2 courses of COPADM (1 and 2) as induction, 2 courses of CYM as consolidation, and 1 maintenance chemotherapy course (COPADM3) be used for the treatment of Pediatric Burkitt Lymphoma in Group B (intermediate risk)?

Bibliography: Aydin B, et al; 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FAB LMB 96 regimen with COP as prophase, 2 courses of COPADM (1 and 2) as induction, 2 courses of CYM as consolidation, and 1 maintenance chemotherapy course (COPADM3)**		**Relative (95% CI)**	**Absolute (95% CI)**		
5 year Event Free Survival for Group B (Intermediate Risk) patients (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	38.13/41 (93.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
5 year Overall Survival for Group B (Intermediate Risk) patients (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	38.95/41 (95.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
New outcome												

CI: Confidence interval

Question: Should FAB LMB 96 regimen with COP as prophase, 2 courses of COPADM (1 and 2) as induction, 2 courses of CYVE as consolidation, and 4 maintenance courses be used as treatment for Pediatric Burkitt Lymphoma in risk group C (High Risk)?

Bibliography: Aydin B, et al; 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FAB LMB 96 regimen with COP as prophase, 2 courses of COPADM (1 and 2) as induction, 2 courses of CYVE as consolidation, and 4 maintenance courses		Relative (95% CI)	Absolute (95% CI)		
5 year Event Free Survival for high risk patients (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	8.68/14 (62.0%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL
5 year Overall Survival of high risk patients (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	10.92/14 (78.0%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should FAB LMB 96 Regimen be used for the treatment of Pediatric Burkitt Lymphoma patients?
Bibliography: Aydin, B et al; 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FAB LMB 96 Regimen		Relative (95% CI)	Absolute (95% CI)		
5 year Event Free Survival (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	49.81/57 (87.4%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL
5 year Overall Survival (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	51.75/57 (90.8%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL
Complete Response at End Of Induction (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	33.06/57 (58.0%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL
Residual Tumor at End of Induction (follow up: median 50 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	24/57 (42.1%)		not estimable		⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should LMB 96 protocol compared to D-COMP or CCG 106B be used for the treatment of Pediatric Burkitt Lymphoma?
Bibliography: Park E.S.et al; 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMB 96 protocol	D-COMP or CCG 106B	Relative (95% CI)	Absolute (95% CI)		
Event Free Survival (follow up: median 72 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	31/38 (81.6%)	25.916/38 (68.2%)	**RR 1.19** (-- to --)	**130 more per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL
Overall Survival (follow up: median 72 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	32.98/38 (86.8%)	15.99/22 (72.7%)	**RR 1.19** (-- to --)	**138 more per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Question: Should FAB LMB 96 Regimen be used for the treatment of Pediatric Burkitt Lymphoma?
Bibliography: Aydin B et al, 2019 and Park ES et al, 2011.

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Treatment						
Cross Sectional	4	0	0	0	0	4

Question: Should Systemic chemotherapy with BFM 90 protocol be used for the treatment of Pediatric Burkitt Lymphoma?

Bibliography: Sun, X-F, et al 2006

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Systemic chemotherapy BFM 90 protocol		Relative (95% CI)	Absolute (95% CI)		
Event Free Survival for all patients (follow up: median 24 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	47/55 (85.5%)	0.0%	not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
Event Free Survival for group R1 (follow up: median 24 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	55/55 (100.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
Event Free Survival for group R2 (follow up: median 24 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	46.2/55 (84.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
Event Free Survival for group R3 (follow up: median 24 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	39.6/55 (72.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
Event Free Survival for patients with Stage III/IV disease (follow up: median 24 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	44/55 (80.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

Question: Should Systemic chemotherapy with Modified B NHL BFM 90 Protocol be used for the treatment of Pediatric Burkitt Lymphoma?

Bibliography: Sun XF et al; 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Systemic chemotherapy with Modified B NHL BFM 90 Protocol		Relative (95% CI)	Absolute (95% CI)		
3 years Event Free Survival for stage I/II (follow up: median 33 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	31/31 (100.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 years Event Free Survival for stage III/IV (follow up: median 33 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	25.42/31 (82.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 years Event Free Survival for Low Risk Group (follow up: median 33 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	31/31 (100.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 years Event Free Survival for Moderate Risk Group (follow up: median 33 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	28.52/31 (92.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 years Event Free Survival for High Risk Group (follow up: median 33 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	21.7/31 (70.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
3 years Event Free Survival for all patients (follow up: median 33 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	26.66/31 (86.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should Anthracycline based systemic chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) be used for the treatment of Pediatric Burkitt Lymphoma?

Bibliography: Stanley, GC et al 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anthracycline based systemic chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP)		Relative (95% CI)	Absolute (95% CI)		
18 months Overall Survival (follow up: mean 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	21.17/73 (29.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
18 mos Overall Survival for Stage I/II (follow up: median 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	6.12/12 (51.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
18 mos Overall Survival for Stage III (follow up: mean 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	10.08/36 (28.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
18 mos Overall Survival for Stage IV (follow up: mean 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	4.25/25 (17.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should GFAOP Lymhomes Malins B (GFALMB) 2009: prephase with cyclophosphamide followed by 2 induction courses (Cyclophosphamide, Vincristine Prednisone, High Dose Methotrexate (HDMTX)), 2 consolidation courses (cytarabine,HDMTX) and maintenance phase only for stage IV be used for the treatment of Pediatric Burkitt Lymphoma?

Bibliography: Bouda, GC, et al, 2019

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GFAOP Lymhomes Malins B (GFALMB) 2009: prephase with cyclophosphamide followed by 2 induction courses (Cyclophosphamide, Vincristine Prednisone, High Dose Methotrexate (HDMTX)), 2 consolidation courses (cytarabine,HDMTX) and maintenance phase only for stage IV		Relative (95% CI)	Absolute (95% CI)		
One year Overall Survival (follow up: median 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	240/400 (60.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
One year Overall Survival in patients with Stage II bulky disease (follow up: median 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	16.38/26 (63.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
One year Overall Survival in patients with Stage III disease (follow up: median 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	182.4/304 (60.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL
One year Overall Survival in patients with Stage IV disease (follow up: median 12 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	22/71 (31.0%)		not estimable		⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

Question: Should FDG-PET compared to Conventional Imaging be used for monitoring response post induction in Pediatric Burkitt Lymphoma
Bibliography: Clement Bailly et al, 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FDG-PET	Conventional Imaging	Relative (95% CI)	Absolute (95% CI)		
Sensitivity (follow up: median 45 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	15.75/21 (75.0%)	5.25/21 (25.0%)	**RR 3** (-- to --)	**500 more per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL
Specificity (follow up: median 45 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	17.22/21 (82.0%)	9.87/21 (47.0%)	**RR 1.74** (-- to --)	**348 more per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL
Positive Predictive Value (follow up: median 45 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	10.5/21 (50.0%)	2.1/21 (10.0%)	**RR 5** (-- to --)	**400 more per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL
Negative Predictive Value (follow up: median 45 months)												
1	observational studies	not serious	not serious	not serious	not serious	strong association	19.53/21 (93.0%)	15.33/21 (73.0%)	**RR 1.27** (-- to --)	**197 more per 1,000** (from -- to --)	⊕⊕⊕◯ MODERATE	CRITICAL

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

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Treatment Response Monitoring						
Cross Sectional	4	0	0	0	0	4

TREATMENT COMPLICATIONS

Question: Should Rituximab-Chemotherapy (LMB-96 Protocol) vs Chemotherapy (LMB-96 Protocol) be used for Pediatric Burkitt Lymphoma?
Bibliography: Minard-Colin V, et al. (2020)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab-Chemotherapy (LMB-96 Protocol)	Chemotherapy (LMB-96 Protocol)	Relative (95% CI)	Absolute		
Febrile Neutropenia												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	150/162 (92.6%)	139/153 (90.8%)	-	908 fewer per 1000 (from 908 fewer to 908 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Stomatitis/Mucositis												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	129/162 (79.6%)	115/153 (75.2%)	-	752 fewer per 1000 (from 752 fewer to 752 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Gastric Toxicities (Enteritis)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	39/162 (24.1%)	24/153 (15.7%)	-	157 fewer per 1000 (from 157 fewer to 157 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Infection												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	95/162 (58.6%)	75/153 (49%)	-	490 fewer per 1000 (from 490 fewer to 490 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		

[1] Population is not specific to BL alone despite being the majority.

Question: Should Modified NHL-BFM-95 Protocol be used for Pediatric Burkitt Lymphoma?

Bibliography: Woessmann, W., et al (2004)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified NHL-BFM-95 Protocol	Control	Relative (95% CI)	Absolute		
Mucositis												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	351/505 (69.5%)	0%	-	-	⨁⨁⨁◯ MODERATE	CRITICAL

[1] Population is not specific to BL alone despite being the majority.

Question: Should NHL-BFM-95 Protocol ± Rituximab be used for Pediatric Burkitt Lymphoma?

Bibliography: Zhen, Z., et al (2020) Celkan, T. T., et al (2011)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NHL-BFM-95 Protocol ± Rituximab	Control	Relative (95% CI)	Absolute		
Febrile Neutropenia												
2	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	127/151 (84.1%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Hematologic Toxicities												
2	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	62/151 (41.1%)	0%	-	-	⨁◯◯◯ VERY LOW	
Mucositis												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/103 (17.5%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Tumor Lysis Syndrome												
2	observational studies	serious[2]	no serious inconsistency	serious[2]	no serious imprecision	none	22/151 (14.6%)	0%	-	-	⨁◯◯◯ VERY LOW	

[1] Study design falls under observational studies.

[2] One study included BLL as part of the population.

Intervention Zhen, Z., et al (2020)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	-1	0	3	MODERATE

Intervention Celkan, T. T., et al (2010)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	0	0	4	HIGH

Question: Should Modified NHL-BFM-90 Protocol be used for Pediatric Burkitt Lymphoma?
Settings: China
Bibliography: Sun, X. F., et al (2006)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modified NHL-BFM-90 Protocol	Control	Relative (95% CI)	Absolute		
Hematologic Toxicities												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	42/55 (76.4%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Tumor Lysis Syndrome												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	5/55 (9.1%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL

[1] Study design falls under observational studies.
[2] The study included large cell lymphoma in the population.

Intervention Sun, X. F., et al (2006)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	-1	0	3	MODERATE

Question: Should COPAD chemotherapy be used for Pediatric Burkitt Lymphoma?
Bibliography: Gerrard, M., et al (2008)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	COPAD chemotherapy	Control	Relative (95% CI)	Absolute		
Mucositis												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	6/132 (4.5%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Infection												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/132 (40.9%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Gastric Toxicities (Constipation)												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	29/132 (22%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL

[1] Study design falls under observational studies.

[2] Population is not specific to BL.

Intervention Gerrard, M., et al (2008)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Cohort	4	0	0	-1	0	3	MODERATE

Question: Should LMB-2001 Protocol (NHL 04) be used for Pediatric Burkitt Lymphoma?
Bibliography: Baena-Gómez, M. A., et al (2015)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMB-2001 Protocol (NHL 04)	Control	Relative (95% CI)	Absolute		
Febrile Neutropenia												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	19/20 (95%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Mucositis												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	14/20 (70%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Anemia												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	12/20 (60%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Thrombocytopenia												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	15/20 (75%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Infection												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	17/20 (85%)	0%	-	-	⨁◯◯◯ VERY LOW	
Gastric Toxicities (Hepatotoxicity)												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	10/20 (50%)	0%	-	-	⨁◯◯◯ VERY LOW	

[1] Study design falls under observational studies.
[2] Population is not specific to BL

Intervention Baena-Gómez, M. A., et al (2015)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	-1	0	3	MODERATE

Author(s): BL Group
Date: 2021-07-16

Question: Should LMB Protocol be used for Pediatric Burkitt Lymphoma?
Settings: Pakistan
Bibliography: Mansoor, R., et al (2019)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMB Protocol	Control	Relative (95% CI)	Absolute		
Tumor Lysis Syndrome												
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	48/233 (20.6%)	0%	OR 7.84 (3.16 to 19.44)	-	⨁⨁⨁◯ VERY LOW	CRITICAL

[1] Study design falls under observational studies.
[2] Population is not specific to BL.

Intervention Mansoor, R., et al (2019)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	-1	0	3	MODERATE

Question: Should CHOP Protocol be used for Pediatric Burkitt Lymphoma?
Settings: Kamuzu Central Hospital, Lilongwe, Malawi
Bibliography: Stanley, C. C. et al (2016)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHOP Protocol	Control	Relative (95% CI)	Absolute		
Neutropenia												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/69 (24.6%)	0%	-	-	⨁⨁⨁◯ VERY LOW	CRITICAL
Anemia												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/69 (42%)	0%	-	-	⨁⨁⨁◯ VERY LOW	CRITICAL

[1] Study design falls under observational studies.

Intervention Stanley, C. C., et al (2016)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Prospective Cohort	4	0	0	0	0	4	HIGH

Question: Should Cyclophosphamide & Methotrexate Therapy be used for Pediatric Burkitt Lymphoma?
Settings: Bobo Dioulasso, Burkina Faso (West Africa)
Bibliography: Béogo, R., et al (2011)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclophosphamide & Methotrexate Therapy	Control	Relative (95% CI)	Absolute		
Febrile Neutropenia												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/58 (32.8%)	0%	-	-	⨁⨁◯◯ VERY LOW	CRITICAL
Anemia												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/58 (39.7%)	0%	-	-	⨁⨁◯◯ VERY LOW	CRITICAL

[1] Study design falls under observational studies.

Intervention Béogo, R., et al (2011)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	0	0	4	HIGH

Side Effects and Management

Question: Should Rituximab plus LMB chemotherapy vs LMB chemotherapy be used for the treatment of Burkitt Lymphoma?
Bibliography: Minard-Colin, et al., 2020.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab-Chemotherapy (LMB-96 Protocol)	Chemotherapy (LMB-96 Protocol)	Relative (95% CI)	Absolute		
Febrile Neutropenia (follow-up median 39.9 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	No serious indirectness	no serious imprecision	none	150/162 (92.6%)	139/153 (90.8%)	RR 1.02 (0.954 to 1.09)	18more per 1000 (from 42 fewer to 82 more)	⨁⨁⨁⨁ HIGH	CRITICAL

Author(s):
Date: 2021-07-03
Question: **Should cyclophosphamide, intrathecal hydrocortisone and methotrexate protocol and malnutrition associated with febrile**
Settings: Blantyre, Malawi?
Bibliography: Israel, et al., 2009

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Malawi BL treatment protocol	Control	Relative (95% CI)	Absolute		
Neutropenic episode in malnourished BL (assessed with: complete blood count)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[1]	28/56 (50%)	9/25 (36%)	OR 1.4 (0.5 to 3.7)[2]	81 more per 1000 (from 140 fewer to 315 more)	⊕⊕⊕O MODERATE	CRITICAL
Profound neutropenia in malnourished BL (assessed with: complete blood count)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[3] reduced effect for RR >> 1 or RR << 1[4]	12/56 (21.4%)	0/25 (0%)	OR 12 (0 to 0)[5]	-	⊕⊕⊕⊕ HIGH	CRITICAL
Prolonged neutropenia in malnourished BL												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/56 (12.5%)	0/25 (0%)	_[6]	-	⊕⊕OO LOW	CRITICAL
Febrile Neutropenia in malnourised BL												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/56 (17.9%)	1/25 (4%)	OR 3 (0.6 to 28)[2]	71 more per 1000 (from 16 fewer to 498 more)	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Most (62.1%) of neutropenic episodes occured after second course of chemotherapy

[2] After correcion of confounders.

[3] After correcting the possible confounders for association of malnutrition with neutropenic episodes, profound neutropenia remained with an OR of 12 (95% CI, 1.5 to infinitely; P-value of 0.014)

[4] HIV, disease stage and bone marrow involvement were considered possible confounders affecting results

[5] After correction of confounders, the association between malnutrition and profound neutropenia still remained significant at OR 12 (95% CI, 1.5 to infinitely; P value 0.014)

[6] Association of malnutrion and prolonged neutropenia after correction of confounders was not significant, with an odds ratio of 5.9 (95% CI 0.7 to infinitely; P-value 0.119

Author(s):
Date: 2021-07-04
Question: Should rituximab be used for pediatric Burkitt Lymphoma?
Settings: India
Bibliography: Srinivasan, et al., 2020

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	Control	Relative (95% CI)	Absolute		
Febrile Neutropenia												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2] increased effect for RR ~1[1]	38/42 (90.5%)[3]	29/43 (67.4%)	RR 1.34 (1.066 to 1.688)	229 more per 1000 (from 45 more to 464 more)	⊖⊖⊖O MODERATE	CRITICAL

[1] Most of the patients (nine or 21.4%) with bone marrow involvement were treated with rituximab, while two (4.7%) were not treated with rituximab (P value 0.02). More advanced stage of disease might increase treatment-related toxicity. Furthermore, the study is limited by its retrospective nature and insufficient evidence to attribute toxicities entirely to rituximab given the strong interplay between chemo toxicity, immune dysfunction, malnutrition and infection in the study's patients.

[2] No explanation

[3] P-value 0.02

Author(s):
Date: 2021-07-04
Question: **Should high dose LMB protocol for B-cell lymphoma induced febrile neutropenia and severe mucositis?**
Settings: Tygerberg Hospital, Africa
Bibliography: Wessels, G and Hesseling, PB, 2000.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMB-89 protocol	Control	Relative (95% CI)	Absolute		
Febrile episodes												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[2]	14/19 (73.7%) [3]	-	-	-	⊖⊖⊖⊖ HIGH	CRITICAL

[1] No explanation

[2] Febrile neutropenia and severe mucositis were noted following courses of high-dose MTX, cyclophosphamide and doxorubicin

[3] 37 febrile episodes (2.6 episodes per patient) noted among the 14 patients under LMB-89 protocol

Author(s):
Date: 2021-07-04
Question: Should high-dose chemotherapy be used in pediatric cancer patients?
Settings: Egypt
Bibliography: Badr, M et al., 2016

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose chemotherapy	Control	Relative (95% CI)	Absolute		
First time neutropenia												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[2]	32/113 (28.3%)	-	-	-	⊖⊖⊖⊖ HIGH	CRITICAL
Recurrent neutropenia												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[2]	81/113 (71.7%)	-	-	-	⊖⊖⊖⊖ HIGH	CRITICAL
Febrile neutropenia												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[2]	37/50 (74%)	-	-	-	⊖⊖⊖⊖ HIGH	CRITICAL

[1] No explanation

[2] Different chemotherapy protocols were associated with a variable suppressive effect on bone marrow

Author(s): BL group
Date: 2021-07-03
Question: Should Rituximab plus LMB chemotherapy vs LMB chemotherapy alone be used for treatment of Burkitt Lymphoma?
Settings:
Bibliography: Minard-Colin, et al., 2020.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab plus LMB chemotherapy	LMB chemotherapy alone	Relative (95% CI)	Absolute		
Stomatitis (follow-up median 39.9 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	129/162 (79.6%)	115/153 (75.2%)	RR 1.06 (0.94 to 1.194)	45 more per 1000 (from 45 fewer to 146 more)	⊖⊖⊖⊖ HIGH	CRITICAL

Author(s):
Date: 2021-07-04
Question: Should LMB-89 protocol be used for undernourished children with B-cell lymphoma?
Settings: Tygerberg Hospital, Africa
Bibliography: Wessels, G and Hesseling, PB, 2000.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMB-89 protocol	Control	Relative (95% CI)	Absolute		
Severe mucositis												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[2]	14/19 (73.7%) [3]	-	-	-	⊖⊖⊖⊖ HIGH	CRITICAL

[1] No explanation

[2] Febrile neutropenia and severe mucositis were noted following courses of high-dose MTX, cyclophosphamide and doxorubicin

[3] Total of 26 episodes of severe mucositis, or 1.9 episodes per patient, was recorded

Author(s):
Date: 2021-07-04
Question: Should high-dose chemotherapy be used in pediatric cancer patients?
Settings: Egypt
Bibliography: Badr, M et al., 2016

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose chemotherapy	Control	Relative (95% CI)	Absolute		
Mucositis												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] increased effect for RR ~1[2] dose response gradient[3]	62/113 (54.9%)[4]	-	-	-	⊖⊖⊖⊖ HIGH	CRITICAL

[1] No explanation

[2] Neutropenia cases complicated with mucositis exhibited lower ANC count compared with non-complicated cases

[3] Different chemotherapy protocols were associated with a variable suppressive effect on bone marrow

[4] Patients with mucositis and GIT infection have significantly lower ANC counts with p-values of 0.01 and 0.02 respectively

Question: Should cefepime vs meropenem be used for Febrile Neutropenia in children?
Bibliography: Oguz et al.2006

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefepime	Meropenem	Relative (95% CI)	Absolute		
effectivity (assessed with: Incidence)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[1]	21/32 (65.6%)	20/33 (60.6%)	RR 1.05 (0 to 0)	30 more per 1000 (from 606 fewer to 606 fewer)	⊟⊟⊟⊟ HIGH	CRITICAL
								0%		-		

[1] good success rate

Question: Should Cefepime vs Ceftazidine be used for Febrile Neutropenia?
Bibliography: Kebudi et al. 2001

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefepime	Ceftazidine	Relative (95% CI)	Absolute		
effectivity (assessed with: success rate)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[1]	20/32 (62.5%)	19/31 (61.3%)	RR 1.05 (0 to 0)	31 more per 1000 (from 613 fewer to 613 fewer)	⊟⊟⊟⊟ HIGH	CRITICAL
								0%		-		

[1] No explanation was provided

Question: Should Cefepime be used for treatment of Febrile Neutropenia in children?
Bibliography: Ariffin et al. 2006

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefepime	Control	Relative (95% CI)	Absolute		
effectivity (assessed with: success rate)												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	80/ 133 (60%)	-	-	-	⨁⨁⨁◯ MODERATE	CRITICAL

[1] case reports

Question: Should oral care protocol, Chlorhexidine mouthwash, pain management, antiviral, antifungal and supportive care be used for post chemotherapy oral mucositis?

Bibliography: Hurrell 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 protocol, Chlorhexidine mouthwash, pain management, antiviral, antifungal and supportive care	Control	Relative (95% CI)	Absolute		
effectivity by use oral care protocol (assessed with: improvement of oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 0.12 (0.04 to 0.36)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of chlorhexidine mouthwash (assessed with: improvement of oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 15.73 (4.60 to 53.70)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of PCA/NCA (morphine and fentanyl) (assessed with: improvement of Oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 3.2 (2.2 to 4.8)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of IV Ketamine (assessed with: improvement of Oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 3.3 (2.0 to 5.9)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of antivirals (assessed with: improvement of Oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 1.8 (1.3 to 2.6)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of antifungal (assessed with: improvement of Oral Mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 1.4 (1.0 to 2.0)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of IVT (assessed with: improvement of Oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 2.7 (1.8 to 3.9)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		
effectivity by use of TPN (assessed with: improvement of Oral mucositis)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	-	-	OR 2.3 (1.5 to 3.3)	-	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

Author(s):
Date: 2021-07-09
Question: Should mineral derivatives be used for oral mucositis during cancer therapy?
Settings:
Bibliography: Lee

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mineral derivatives	Control	Relative (95% CI)	Absolute		
peak incidence of oral mucositis												
13	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	g 0 (0 to -0.2)[2]	-	⊖⊖⊖O MODERATE	
								0%		-		
duration of oral mucositis (Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	g 0.2 lower (0.1 higher to 0.5 lower)[3]	⊖⊖⊖⊖ HIGH	
onset of oral mucositis (Better indicated by higher values)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	g 0.5 lower (0.1 to 0.9 lower)[4]	⊖⊖⊖⊖ HIGH	
pain incidence (measured with: visual analog scale; Better indicated by lower values)												
5	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	g 0.01 lower (0.7 higher to 0.7 lower)[6]	⊖⊖⊖O MODERATE	
analgesic use												
5	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	g 0 (0 to -0.7)[8]	-	⊖⊖OO LOW	
								0%		-		

[1] Noted significant heterogeneity (i.e. different protocols and diverse cancer therapies) among studies included with I^2 of 61%

[2] patients given mineral derivates were less likely to experience peak OM vs those without treatment (g = -0.47, 95% CI −0.7 to −0.2, p = 0.0006)

[3] OM mean durations did not significantly differ between mineral derivative and control groups (g = −0.2, 95% CI 0.1 to −0.5, p = 0.128)

[4] Times to OM onset reported in five studies were significantly delayed in treated participants (g =−0.5, 95% CI−0.8 to−0.2, p = 0.0002)

[5] Significant heterogeneity among studies included with I^2 of 68%

[6] Experiencing pain was less likely in treated participants (g = −0.5, 95% CI −0.1 to −0.9, p = 0.01)

[7] Heterogeneity among studies is significant at I^2 79. Furthermore, some studies included did not have blinding, allocation concealment (Lambrecht and Markiewicz) and has missing exclusion criteria (Markiewicz)

[8] Analgesic use was no different across groups (g = −0.01, 95% CI 0.7 to −0.7, p = 0.977).

Author(s):
Date: 2021-07-08
Question: Should low-level laser therapy be used for oral mucositis in pedia patients receiving cancer therapy?
Settings:
Bibliography: Mazhari, et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-level laser therapy	Control	Relative (95% CI)	Absolute		
oral mucositis incidence												
3	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 2.87 (0.294 to 27.997)[2]	- -	⊕⊕⊕⊕ HIGH	

[1] 2 articles included have low risk bias and 1 article has high risk bias. Performing sensitivity analyses based on excluding the study having high risk of bias from the analyses led to similar results

[2] LLT did not show significant efficacy in decreasing incidence of OM (OR 2.87, CI 0.294-27.997; P= 0.364)

Author(s):
Date: 2021-07-08
Question: Should palifermin be used for oral mucositis in pediatric patients receiving cancer therapy?
Settings:
Bibliography: Mazhari

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Palifermin	Control	Relative (95% CI)	Absolute		
incidence of oral mucositis (Luchesse)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 11.870 (3.532 to 39.889)[2]	- -	⊕⊕⊕⊕ HIGH	
incidence of oral mucositis (Luchesse 2)												
1	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 3.551 (1.034 to 12.200)[3]	- -	⊕⊕⊕⊕ HIGH	
incidence of oral mucositis (Vitale)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 2.944 (0.888 to 9.764)[4]	- -	⊕⊕OO LOW	
incidence of oral mucositis (Lauritano)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 3.667 (0.95 to 14.028)[5]	- -	⊕⊕OO LOW	
incidence of oral mucositis (Czyzewski)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 2.935 (1.039 to 8.289)[6]	- -	⊕⊕OO LOW	

[1] low risk of bias as shown in Table 3 of journal

[2] palifermin significantly decreases incidence of OM with an OR of 11.87 (CI 3.532, 39.889; P-value 0.000)

[3] Palifermin significantly decreases incidence of OM with an OR of 3.551 (CI 1.034-12.200; P value 0.044)

[4] There was no significant difference in the incidence of OM in palifernin treated patients and control, with OR of 2.944 (CI 0.888-9.764, P value 0.077)

[5] Palifermin does not significantly decrease incidence of oral mucositis, with OR of 3.667 (CI 0.958-14.028, P value 0.058)

[6] Palifermin significantly decreases incidence of oral mucositis, with OR of 2.935 (CI 1.039-8.289, P value 0.042)

Supportive and Palliative

Question: Should Rasburicase vs Allopurinol be used for Pediatric Burkitt Lymphoma?
Settings:
Bibliography: Goldman, S. C., et al (2001)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rasburicase	Allopurinol	Relative (95% CI)	Absolute		
Hyperuricemia (assessed with: AUC 0-96 for mean uric acid)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	very strong association[2]	0/10 (0%)	5/5 (100%)	RR 2.6 (2 to 3.4)	1000 more per 1000 (from 1000 more to 1000 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								0%		-		

[1] Population size is a bit small and not specific to BL.
[2] All patients in the rasburicase group had significant decrease in plasma uric acid and maintained normal levels.

Question: Should Rasburicase be used for Pediatric Burkitt Lymphoma?
Bibliography: Wössmann, W., et al (2003)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rasburicase	Control	Relative (95% CI)	Absolute		
Tumor Lysis Syndrome (assessed with: Incidence Rate)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/130 (12.3%)	35/218 (16.1%)	-	161 fewer per 1000 (from 161 fewer to 161 fewer)	⨁⨁⨁◯ VERY LOW	CRITICAL
								0%		-		

[1] Study design falls under observational studies.

Intervention Wössmann, W., et al (2003)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Retrospective Cohort	4	0	0	-1	0	3	MODERATE

Question: Should Nutritional Support be used for Pediatric Burkitt Lymphoma?
Bibliography: Hesseling, P. B., et al (2018)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutritional Support	Control	Relative (95% CI)	Absolute		
Death Rate												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/72 (5.6%)	24/129 (18.6%)	-	186 fewer per 1000 (from 186 fewer to 186 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
MUAC < 3rd Centile												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/70 (10%)	11/70 (15.7%)	-	157 fewer per 1000 (from 157 fewer to 157 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
TSF increase > 0.5cm												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/70 (57.1%)	0%	-	-	⨁◯◯◯ VERY LOW	CRITICAL
TSF < 3rd Centile												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	33/70 (47.1%)	-	471 fewer per 1000 (from 471 fewer to 471 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		

[1] Study design falls under observational studies.

Intervention Hesseling, P. B., et al (2018)	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score	Quality
Prospective Cohort	4	0	0	0	0	4	HIGH

Question: Should G-CSF be used for Pediatric Burkitt Lymphoma?

Bibliography: Tsurusawa, M., et al (2015) Patte, C., et al (2002)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G-CSF	Control	Relative (95% CI)	Absolute		
Incidence of Febrile Neutropenia												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	856/1000 (85.6%)	882/1000 (88.2%)	-	882 fewer per 1000 (from 882 fewer to 882 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Mean number of days of Neutropenia												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	39/0 (0%)	50/0 (0%)	-	-	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Neutropenia < 500 ANC												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	915/1000 (91.5%)	990/1000 (99%)	-	990 fewer per 1000 (from 990 fewer to 990 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Mean number of hospitalization days												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	66/0 (0%)	79/0 (0%)	-	-	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		

[1] Population is not specific to BL.

Question: Integrative interventions compared to standard oncological care for pediatric patient's aged 19 years old and below with Burkitt Lymphoma
Bibliography: Mann SI et al. Behavioral Intervention to Reduce Child and Parent Distress During Venipuncture. Journal of Consulting and Clinical Psychology. 1990,Vol.58.No.5.565-572

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	integrative interventions	standard oncological care	Relative (95% CI)	Absolute (95% CI)		
Parental rated pain (assessed with: A modified version of the Procedure Behavior Rating Scale (PBRS;Katz,Kellerman,&Siegel,1980))												
1	randomised trials	serious [a]	not serious	serious [b]	serious	strong association all plausible residual confounding would reduce the demonstrated effect	29.38	47.6	-	**0** (0 to 0)	⊕⊕⊕◯ MODERATE	CRITICAL
Parent anxiety (assessed with: A modified version of the Procedure Behavior Rating Scale (PBRS; Katz ,Kellerman, & Siegel, 1980))												
1	randomised trials	serious [a]	not serious	serious	serious	strong association all plausible residual confounding would reduce the demonstrated effect	26	47	-	**0** (0 to 0)	⊕⊕⊕◯ MODERATE	CRITICAL
Use of restraints												
1	randomised trials	serious [a]	not serious	serious [b]	serious	strong association all plausible residual confounding would reduce the demonstrated effect	7/13 (53.8%)	8/10 (80.0%)	0.29 (0.04 – 1.94)		⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval
a. Short term follow-up
b. Inclusive of all types of invasive cancer

Question: Counseling compared to Usual Care for pediatric patient's aged 19 years old and below with Burkitt Lymphoma

Bibliography: Rosenberg AR et al. Promoting Resilience in Adolescents and Young Adults With Cancer: Results From the PRISM Randomized Controlled Trial; DOI : 10. 1002/ cncr .31666, Received: 13 April 201 8; 2 May 20 1 8; 27 May 201 8 , September 19, 20 18 in Wiley Online Library Revised: Accepted: Published online (wileyonlinelibrary.com)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	counseling	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Resilience (follow up: mean 9 months; assessed with: Connor Davidson Resilience Scale)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	29	28	3.0 (0.5- 5.4)	**0** (0 to 0)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of Life (follow up: mean 9 months; assessed with: CDRISC 10 or 10 item Connor Davidson Resilience Scale; Cancer Specific Quality of Life or PedsQL Cancer Module; Global Pyshcological Distress or Kessler-6)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	66	65	9.6 (2.6 - 16.7)	**0** (0 to 0)	⊕⊕⊕◯ MODERATE	CRITICAL
Psychological Distress (follow up: mean 9 months; assessed with: Kessler - 6)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	6	8	−2. 1 (− 4. 1 to − 0 .2)	**0** (0 to 0)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval

a. Inclusive of solid and non-solid cancers

Question: How effective is pediatric palliative care among 19 year old patients and below diagnosed with Burkitt Lymphoma?

Bibliography: Kaye, EC, Weaver MS, DeWitt LH, Byers E, Stevens SE, Lukowski J, Shih B, Zalud, K, Applegarth J, Wong HN, Baker JN, and Ullrich CK. The Impact of Specialty Palliative Care in Pediatric Oncology: A Systematic Review. J Pain Symptom Manage. 2021 May; 61(5): 1060-1076. https://doi.org/10.1016/j.jpainsymman.2020.12.003

Study Design	**Design Score**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality Score**	**Certainty**
Systematic Review	4	-1	-1	-1	0	1	Low quality

Health System

Question: Should cost of treatment and the overall survival rate be used in pediatric Burkitt's lymphoma for its inclusion in the National Insurance Program?
Settings: Low Middle Income Countries
Bibliography: Denburg AE, et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cost of treatment and the overall survival rate	Control	Relative (95% CI)	Absolute		
122 patients enrolled to Burkitt's Lymphoma Treatment Study (measured with: Cost of DALY averted; Better indicated by higher values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	122	-	-	MD 55 higher (45 to 64 higher)[1]	ÅÅÅÅ HIGH	CRITICAL
Overall survival by stage-based risk group (Low Risk Ziegler Stage A, B, AR) (measured with: Cost of DALY averted; Better indicated by higher values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	122	-	-	MD 66 higher (51 to 77 higher)[2]	ÅÅÅÅ HIGH	CRITICAL
Overall survival by stage-based risk group (High Risk Ziegler Stage C, D) (measured with: Cost of DALY averted; Better indicated by higher values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	122	-	-	MD 45 higher (31 to 58 higher)[3]	ÅÅÅÅ HIGH	

[1] Among the 122 children with confirmed diagnosis of BL, 55% (95% CI, 45% to 64%) were alive at years of diagnosis
[2] Patients with low-risk disease (Ziegler Stages A, B, and AR) had a statistically significantly higher 2-year OS (66%: 95% CI 51% to 77%)
[3] Patient with High-risk disease (Ziegler Stages C and D) 45%; 95% CI 31% to 58%)

Should cost of treatment and the overall survival rate be used in pediatric Burkitt's lymphoma for its inclusion in the National Insurance Program?

Patient or population: Pediatric Burkitt's lymphoma
Settings: Low Middle Income Countries
Intervention: cost of treatment and the overall survival rate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Cost of treatment and the overall survival rate**				
122 patients enrolled to Burkitt's Lymphoma Treatment Study	The mean 122 patients enrolled to Burkitt's lymphoma treatment study in the control groups was **1351.72 US Dollar**[1]	The mean 122 patients enrolled to Burkitt's lymphoma treatment study in the intervention groups was **55 higher** (45 to 64 higher)[2]		122 (1 study)	⊕⊕⊕⊕ **high**	Substantial burden of 26 DALYs averted per treated case. The cost per DALY averted in the base case was US$97 (Int$301). Cumulative estimates of National DALYS averted through treatment is 8607 years and annual National costs of treatment amounting to US$834,879.00 (Int$ 834,879.00). **The ratio of cost per DALY averted to per capita GDP** was 0.14, reflecting a very cost-effective intervention as per WHO-CHOICE norm.**
Overall survival by stage-based risk group (Low Risk Ziegler Stage A, B, AR)	The mean overall survival by stage-based risk group (low risk Ziegler stage a, b, ar) in the control groups was **1351.72 US Dollar**[1]	The mean overall survival by stage-based risk group (low risk Ziegler stage a, b, ar) in the intervention groups was **66 higher** (51 to 77 higher)[3]		122 (1 study)	⊕⊕⊕⊕ **high**	
Overall survival by stage-based risk group (High Risk Ziegler Stage C, D)	The mean overall survival by stage-based risk group (high risk Ziegler stage c, d) in the control groups was **1351.72 US Dollar**[1]	The mean overall survival by stage-based risk group (high risk Ziegler stage c, d) in the intervention groups was **45 higher** (31 to 58 higher)[4]		122 (1 study)	⊕⊕⊕⊕ **high**	

*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).

Question: Should cost of treatment and the overall survival rate be used in pediatric Burkitt's lymphoma for its inclusion in the National Insurance Program?

Bibliography: Alastair Fung, et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	National and/Private Insurance Company	Control	Relative (95% CI)	Absolute		
Denburg, et al (Better indicated by lower values)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[1]	122	-	-	MD 0.55 higher (0.45 to 0.64 higher)	ÅÅÅÅ HIGH	
Hesseling et al (Better indicated by lower values)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	44	-	-	MD 0.57 higher (0.43 to 0.73 higher)	ÅÅÅO MODERATE	

[1] No explanation was provided

Should cost of treatment and the overall survival rate be used in pediatric Burkitt's lymphoma for its inclusion in the National Insurance Program?

Patient or population: Pediatric Burkitt's Lymphoma patients
Settings: Low Middle Income Countries
Intervention: National and/Private Insurance Company

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk National and/Private Insurance Company				
Denburg, et al	The mean Denburg, et al in the control groups was **1401 US Dollars**	The mean Denburg, et al in the intervention groups was **0.55 higher** (0.45 to 0.64 higher)		122 (2 studies)	⊕⊕⊕⊕ **high**[1]	
Hesseling et al	The mean Hesseling et al in the control groups was **217 US Dollars**	The mean Hesseling et al in the intervention groups was **0.57 higher** (0.43 to 0.73 higher)		44 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	

*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;

Question: Should System of Social Protection vs Overall survival rates be used for Children with Non-Hodgkin Lymphoma?
Settings: Developing Countries
Bibliography: Ricardo Perez Cuevas et al

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	System of Social Protection	Overall survival rates	Relative (95% CI)	Absolute		
Fund for Protection against Catastrophic Expenditures (measured with: Fund for Protection Against Catastrophic Expenditures; Better indicated by higher values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1]	179[2]	-	-	MD 40.1 higher (25.1 to 54.6 higher)	ÅÅÅO MODERATE	IMPORTANT

[1] Non-Hodgkin Lymphoma had a survival rate of 40.1% at 36 months.

[2] Number of Children with Cancer covered by Fund for the Protection Against Catastrophic Expenditures

System of Social Protection compared to Overall survival rates for Children with Non-Hodgkin Lymphoma

Patient or population: patients with Children with Non-Hodgkin Lymphoma
Settings: Developing Countries
Intervention: System of Social Protection
Comparison: Overall survival rates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Overall survival rates	System of Social Protection				
Fund for Protection against Catastrophic Expenditures Fund for Protection Against Catastrophic Expenditures		The mean fund for protection against catastrophic expenditures in the intervention groups was **40.1 higher** (25.1 to 54.6 higher)		179 (1 study)	⨁⨁⨁⊖ **moderate**[1]	Non-Hodgkin Lymphoma has a survival rate of 40.1% at 36 months. It is difficult to make comparisons with this type of malignancy as various treatment are available, and a minimum of three histological types exists: BURKITT, ANAPLASTIC and LYMPHOBLASTIC lymphomas. However, a report that included all histological types estimated a 76.2% survival rates in adolescence and 81 % survival rates in children.

*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).

Question: Should supportive care expenses such as chemotherapeutic drugs, antibiotics and other incidental expenses get coverage from National Health Insurance and other private insurance company be used in treatment of pediatric Burkitt Lymphoma?

Settings: Low Income Middle Countries

Bibliography: Bhakta, N et al., 2012

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supportive care expenses such as chemotherapeutic drugs, antibiotics and other incidental expenses get coverage from National Health Insurance and other private insurance company	Control	Relative (95% CI)	Absolute		
447 children with BL enrolled in the Treatment Study (assessed with: standard methods from the WHO Global Burden of Disease)												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	strong association[2] dose response gradient[2]	447/978 (45.7%)	-	-	-	⨁⨁⨁⨁ HIGH	CRITICAL
Cost effectiveness of pediatric BL treatment												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[3] dose response gradient[4]	447/978 (45.7%)	-	-	-	⨁⨁⨁⨁ HIGH	

[1] case reports

[2] Using a short-course (30 days) regimen in Blantyre, Malawi, however, 48% of children with BL were cured. The cost of chemotherapeutic and supportive care drugs was reported as less than US$50 per child, representing less than 1% of the calculated US$14 243 threshold for very cost-effective BL treatment in Malawi.

[3] BL in Malawi yielded with 1:1 ratio of cost per DALY averted to per capita GDP making it very cost effective.

[4] The cost of chemotherapeutic and supportive care drugs was reported as less than US$50 per child, representing less than 1% of the calculated US$14243 threshold for very cost-effective BL treatment in Malawi

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Bhakta, N et al. Nov. 2012						
Observational Study – (Case Report)	4	0	0	0	0	4

supportive care expenses such as chemotherapeutic drugs, antibiotics and other incidental expenses get coverage from National Health Insurance and other private insurance company for treatment of pediatric Burkitt Lymphoma

Patient or population: treatment of pediatric Burkitt Lymphoma
Settings: Low Income Middle Countries
Intervention: supportive care expenses such as chemotherapeutic drugs, antibiotics and other incidental expenses get coverage from National Health Insurance and other private insurance company

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Supportive care expenses such as chemotherapeutic drugs, antibiotics and other incidental expenses get coverage from National Health Insurance and other private insurance company				
447 children with BL enrolled in the Treatment Study standard methods from the WHO Global Burden of Disease	See comment	See comment	Not estimable	978 (1 study[1])	⊕⊕⊕⊕ **high**[2]	single case report; 447 events in 0 subjects
Cost effectiveness of pediatric BL treatment	See comment	See comment	Not estimable	978 (1 study[1])	⊕⊕⊕⊕ **high**[3,4]	single case report; mean 14243 higher (0 to 0 higher)

*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).

Question: Should cost effectiveness in supportive care and other incidental expenses be used in pediatric Burkitt lymphoma?
Settings: Low Middle Income Countries
Bibliography: Denburg, AE et al. 2019

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cost effectiveness in supportive care and other incidental expenses	Control	Relative (95% CI)	Absolute		
Annual per patient costs of UCI BL treatment program (measured with: WHO-CHOICE methodology; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association dose response gradient	122	-	-	MD 0 higher (0 to 0 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Cumulative estimates of National DALYs (measured with: WHO-CHOICE methodology; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[1] dose response gradient[1]	122	-	-	MD 0 higher (0 to 0 higher)	⨁⨁⨁⨁ HIGH	CRITICAL

[1] This study demonstrates that treating BL with locally tailored protocol is very cost-effective by international standards.

[2] Studies of this kind will furnish crucial evidence to help policymakers prioritize the allocation of LMIC health system resources among non-communicable diseases, including childhood cancer

cost effectiveness in supportive care and other incidental expenses for pediatric Burkitt lymphoma

Patient or population: pediatric Burkitt lymphoma
Settings: Low Middle Income Countries
Intervention: cost effectiveness in supportive care and other incidental expenses

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Cost effectiveness in supportive care and other incidental expenses**				
Annual per patient costs of UCI BL treatment program WHO-CHOICE methodology	The mean annual per patient costs of uci bl treatment program in the control groups was **1351.72 US Dollar**	The mean annual per patient costs of uci bl treatment program in the intervention groups was **0 higher** (0 to 0 higher)		122 (1 study)	⨁⨁⨁⨁ **high**	
Cumulative estimates of National DALYs WHO-CHOICE methodology	The mean cumulative estimates of national Daly's in the control groups were **834879 US Dollar**	The mean cumulative estimates of national Daly's in the intervention groups were **0 higher** (0 to 0 higher)		122 (1 study)	⨁⨁⨁⨁ **high**[1]	

*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;

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] This study demonstrates that treating BL with locally tailored protocol is very cost-effective by international standards.

[2] Studies of this kind will furnish crucial evidence to help policymakers prioritize the allocation of LMIC health system resources among non-communicable diseases, including childhood cancer

Question: Should insurance status be used for improvement in survival for children with ALL?
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		
Risk of death Hodgkin's (assessed with: relative risk)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	-	- 0%	RR 2.17 (1.06 to 4.47)	- -	⨁⨁⨁◯ LOW	CRITICAL
Risk of death nonhodgkins (assessed with: relative risk)												
1	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	strong association[2]	-	- 0%	RR 2.36 (1.26 to 4.41)	- -	⨁⨁⨁◯ LOW	

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

Social Issues

Question: Should socioeconomic factors be used in affects access to treatment with childhood cancer. ?
Settings:
Bibliography: Meremikwu, M.M et al 2005

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Socioeconomic factors	Control	Relative (95% CI)	Absolute		
Father's occupation: Farming												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	15/41 (36.6%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
Father's education: No school education												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	9/41 (22%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
Mother's occupation: Farming												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	18/41 (43.9%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
Mother's education: No school education												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	18/41 (43.9%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
Consulted a traditional healer or spiritual												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	11/41 (26.8%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		

Cont.

Consulted unorthodox practitioner/drug seller												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	13/41 (31.7%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
Sought help from a health center/clinic/general hospital												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	17/41 (41.5%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
left against medical advice												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	7/41 (17.1%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
Absconded from hospital												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	6/41 (14.6%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		
lost to follow-up												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	12/41 (29.3%)	-	-	-	⨁⨁⨁⨁ MODERATE	CRITICAL
								0%		-		

Meremikwu, M.M et al 2005

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cross-sectional	4	0	0	0	0	4

Question: Should guardians' perspective influence to affect adherence treatment be used in pediatric patient with Burkitt Lymphoma?
Bibliography: Israels, T., Chirambo et al. 2008

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guardians' perspective influence to affect adherence treatment	Control	Relative (95% CI)	Absolute		
Consulted traditional healer												
1	observational studies	serious	no serious inconsistency	serious[1]	no serious imprecision	none	27/32 (84.4%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Decision Making: Asked advice from other relatives												
1	observational studies	serious	no serious inconsistency	serious	no serious imprecision	none	2/32 (6.3%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Concept Concerning Disease: Fear of recurrence or death												
1	observational studies	serious	no serious inconsistency	serious	no serious imprecision	none	6/32 (18.8%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Absence from home: Mother concern about not being take care of other children												
1	observational studies	serious	no serious inconsistency	serious	no serious imprecision	none	6/32 (18.8%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Perception of Hospital Care: Reluctant to ask the health personnel questions												
1	observational studies	serious	no serious inconsistency	serious	no serious imprecision	none	7/32 (21.9%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		

[1] With other cancer case included

Israels, T., Chirambo et al. 2008

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cross-sectional	4	-1	0	-1	0	2

Question: Should abandonment of treatment be used in to affect treatment of childhood cancer?

Bibliography: F. Njuguna et al. 2014

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abandonment of treament	Control	Relative (95% CI)	Absolute		
Financial difficulties												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious	no serious imprecision	strong association	7/26 (26.9%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Inadequate access to health insurance												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious	no serious imprecision	strong association	7/26 (27%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
								0%		-		
Transportation difficulties												
1	observational studies	no serious risk of bias	no serious inconsistency	very serious	no serious imprecision	strong association	6/26 (23%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL

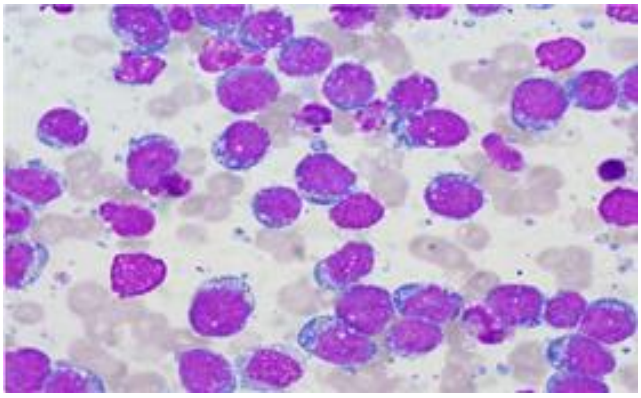
F. Njuguna et al. 2014

	Design Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality Score
Cross-sectional	4	0	0	-1	0	3

2016 WHO Classification of Tumors of Hematologic and Lymphoid Tissues

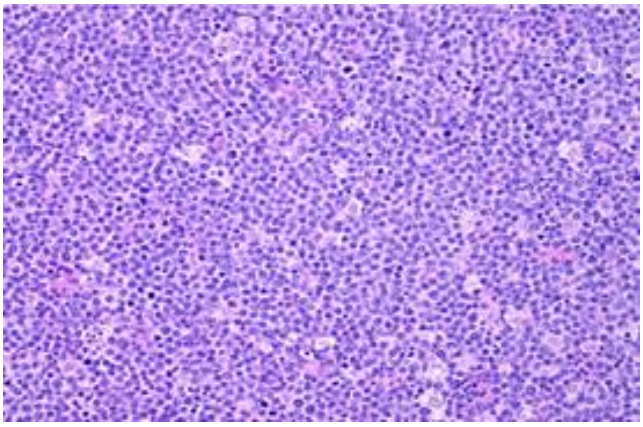
Burkitt lymphoma (BL) is a highly aggressive but curable lymphoma that often presents in extranodal sites or as an acute leukemia. No single parameter, such as morphology, genetic analysis, or immunophenotyping, can be used as the gold standard for diagnosis of BL; a combination of several diagnostic techniques is necessary.

Morphologic

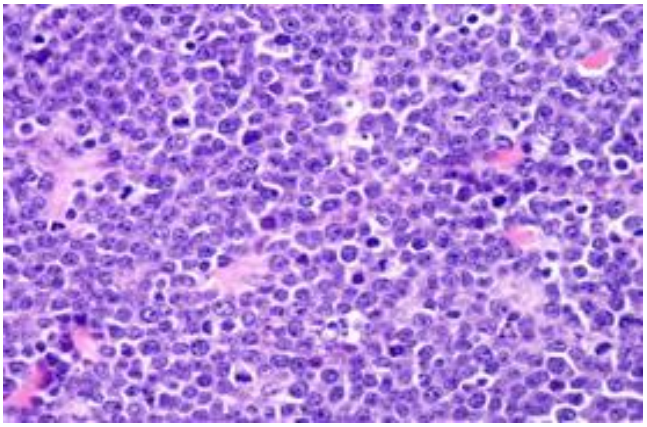


Nuclei of tumor cells are round, with finely clumped chromatin, and contain multiple basophilic medium-sized, paracentrally located nucleoli.

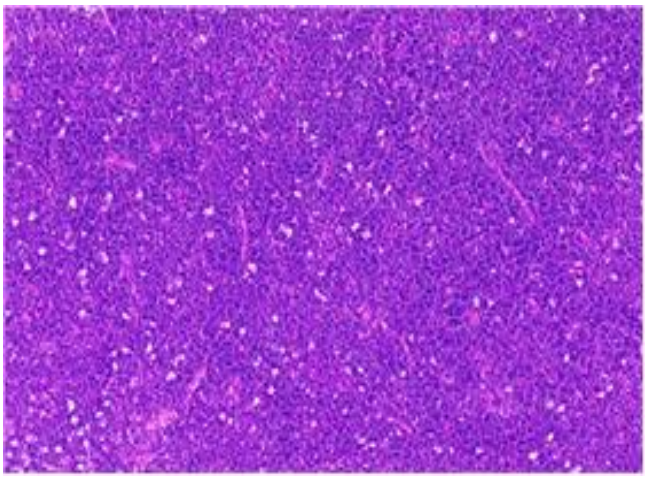
Cytoplasm is deeply basophilic and usually contains lipid vacuoles, which are better seen in imprint preparations or fine-needle aspiration cytology



Medium sized tumor cells with diffuse monotonous pattern of growth.

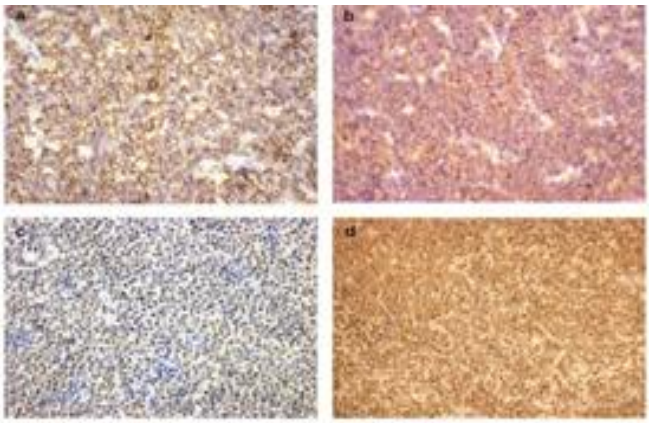


Has an extremely high proliferation rate, with many mitotic figures, as well as a high rate of spontaneous cell death (apoptosis).

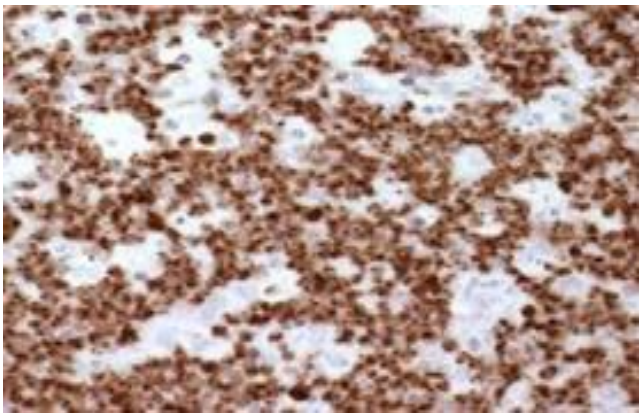


A so-called starry sky pattern is usually present, which is due to the presence of numerous tingible body macrophages

Immunophenotypic

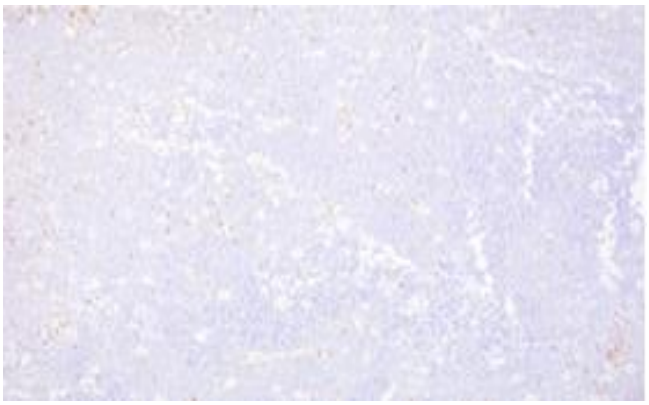


Typically express moderate to strong membrane IgM with light chain restriction, B-cell antigens (CD19, CD20, CD22, CD79a, and PAX5), and germinal center markers (CD10 and BCL6) CD38, CD77, and CD43 are also frequently positive



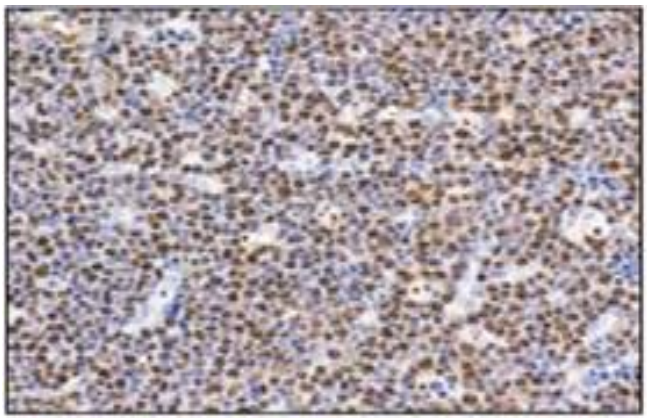
Almost all BLs have strong expression of MYC protein in most cells

(Formalin-fixed, paraffin embedded BL stained with Anti-c-MYC antibody using peroxidase-conjugate and DAB chromogen. Note nuclear staining of cells.)



The neoplastic cells are usually negative for CD5, CD23, CD138, BCL2, and TdT

BCL2 negative



TCL1 is strongly expressed in most pediatric BLs

TCL1 oncoprotein: strong immunoreactivity (brown stain) in the nucleus of Burkitt lymphoma cells

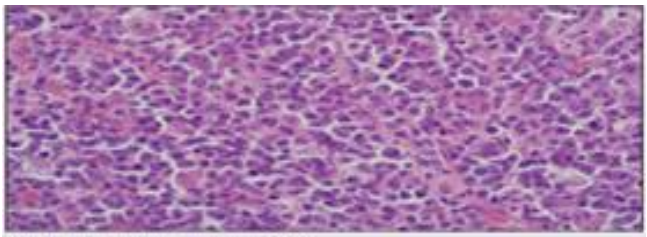


Fig. 1. H&E of Burkitt lymphoma (400X)

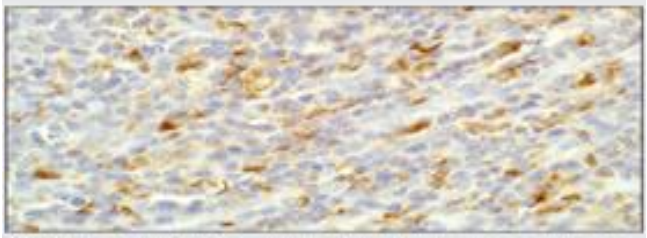
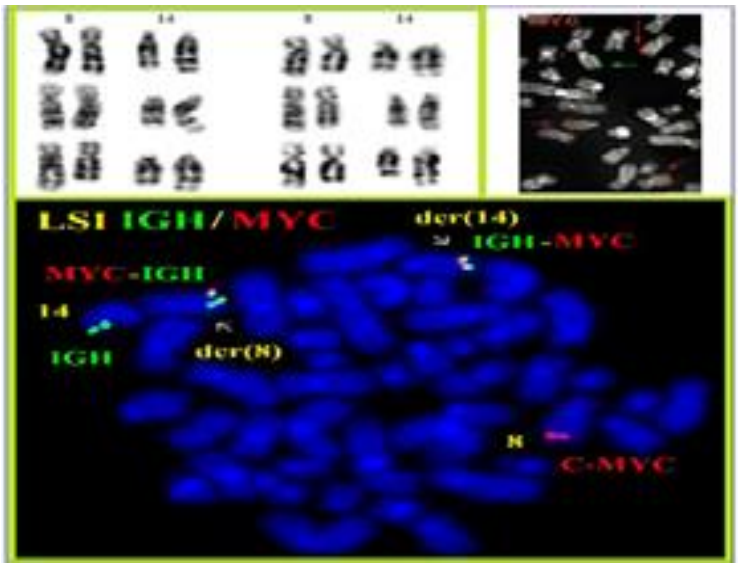


Fig. 2. The lipid droplets in the cytoplasm of Burkitt lymphoma cells are positive for anti-adipophilin. (400X)

Adipophilin may be used in paraffin-embedded tissue sections to demonstrate cytoplasmic lipid vesicles

Cytogenetics / Molecular



The molecular hallmark of BL is the translocation of MYC at band 8q24 to the IGH region on chromosome 14q32, t(8;14) (q24;q32), or less commonly to the IGK locus on 2p12 [t(2;8)] or the IGL locus on 22q11 [t(8;22)].

Note: MYC translocations are not specific for BL, and may occur in other types of lymphoma

Additional chromosomal abnormalities may also occur in BL: (a) gains of 1 q, 7, and 12; (b) losses of 6q, 13q32-34, and 17p . In addition, molecularly defined BLs do include some cases that are best not diagnosed as BL, and some cases of BL may have a gene expression profile intermediate between those of BL and DLBCL.

Burkitt Lymphoma Admitted Patients at Southern Philippines Medical Center – Davao City from 2013 – 2020 Billing Statement Table

Patient No.	Year of Diagnosis	Initial Admission Date	Hospital Days	Insurance	Actual Charges	Discount	Amount Due
1	2013	01/25/2013	10 days	PHIC	P21,837.00	P1,600.00	P17, 837.00
2	2015	09/17/2015	44 days	PHIC	P51,506.00	P21,180.00	P30,326.00
3	2015	12/30/2015	46 days	PHIC	P302,389.98	P21,480.00	P280,909.98
4	2017	03/16/2017	3 days at ER 5 days at PICU	PHIC	P106,648.19	P32,000.00	P74,648.19
5	2017	07/26/2017	1 day at PICU 17 days at WARD	PHIC	P86,127.20	P32,000.00	P54,127.20
6	2017	07/26/2017	9 days	No PHIC	P24,212.00	P7,200.00	P17,012.00
7	2017	08/24/2017	49 days	PHIC	P233,628.50	P60,680.00	P172,948.50
8	2017	08/30/2017	48 days	PHIC	P167,937.00	P21,180.00	P146,757.00
9	2018	03/15/2018	23 days	PHIC	P74,775.50	P39,280.00	P35,495.50
10	2018	04/16/2018	27 days at PICU 37 days at WARD	PHIC	P416,830.00	P39,280.00	P377,550.40
11	2018	04/19/2018	1 day at PICU 22 days at WARD	PHIC	P86,524.00	P21,180.00	P65,344.00
12	2018	05/14/2018	27 days at WARD 16 days at PICU	PHIC	P456,749.75	P32,000.00	P424,749.75
13	2019	10/18/2019	85 days	PHIC	P243,787.80	P22,400.00	P221,387.80
14	2019	12/28/2019	25 days	PHIC	P61,004.00	P21,180.00	P39,824.00
15	2020	02/13/2020	17 days	PHIC	P75,327.00	P21,180.00	P54,147.00