A. Introduction

Non-Hodgkin lymphomas (NHL), clonal disorders of the immune system, are caused by the transformation of lymphoid progenitor cells at a particular stage of differentiation.

The significant variations in the clinical and biological characteristics of lymphoid malignancies among young patients reflect the fact that the lymphoid system is functionally diverse, has a wide anatomic distribution, interacts with other cellular systems, and undergoes continuous remodeling during childhood and adolescence.

NHL is classified according to the lymphoid lineage involved. B-lineage NHL (Burkitt, lymphoblastic, and large B-cell lymphomas) represents about 50% of cases; T-lineage accounts for the remaining half (lymphoblastic and anaplastic large-cell lymphomas).
B. Epidemiology and Risk Factors

In the U.S., 800 (6.5%) of the 12,400 new cases of cancer diagnosed annually in children, adolescents, and adults younger than 20 years are NHL.\(^1\) NHL represents 3% of all cases of pediatric cancer affecting children younger than 5 years of age and 9% of the cases of those 15 to 19 years of age (B.Figure 1).

B. Figure 1
Age-specific rates, for all races and both sexes, of NHL. Data from the Surveillance Epidemiology End Results (SEER; used with permission)\(^1\)

During the past 20 years, the incidence of NHL appears to have increased in the U.S, while the incidence of NHL in children younger than 15 years remained stable from 1975 through 1995, that of adolescents increased for
unknown reasons from 10.7 per million (1975-1979) to 16.3 per million (1990-1995). The incidence of NHL is higher among boys, and the rate of NHL in all age groups is markedly higher for white American children than for black American children.

International variation in the incidence of NHL has been reported that Burkitt lymphoma is more common in tropical areas such as Equatorial Africa. In this part of the world, endemic Burkitt lymphoma usually affects the jaw and its geographical distribution is similar to malaria.

The incidence of pediatric NHL is likely to be affected by the environment since the disease typically originates in immune-system structures that come in contact with the environment, such as the Peyer follicles in the bowel and the lymphoid nodules at airway branch points. Such a relation has already been observed between Epstein-Barr virus (EBV) infection (with malaria as a co-factor) and the incidence of Burkitt lymphoma. Moreover, AIDS (acquired immunodeficiency syndrome), which is cause by human immunodeficiency virus (HIV) infection, has been associated with an increased risk of NHL. However, in developing countries, the lack of population registries makes estimation of this incidence very difficult.

Causes of childhood lymphoid malignancies are largely unknown; and most children with NHL do not appear to have predisposing factors. However, certain factors and specific constitutional syndromes have been associated with an increased predisposition to lymphoid malignancies. For example, increased risk of NHL has been associated with congenital immunodeficiencies such as Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, ataxia telangiectasia and other chromosomal breakage syndromes and severe combined immunodeficiency.
B. References


C. Diagnosis and Classification

A definitive diagnosis of NHL requires examination of the tumor mass (nodal or extranodal). When NHL is suspected, it is best to sample the most accessible, representative nodal or extranodal tumor. When patients have a large mediastinal mass and they are at very high risk of complications during anesthesia, pleural effusion can provide an adequate number of tumor cells for diagnosis. Alternatively, fine needle aspiration of regional lymph nodes or mediastinal masses, which can be performed without general anesthesia, may also yield adequate material for diagnosis if a complete immunocytological panel can be done. However, in most cases, an open biopsy procedure is needed to yield sufficient material for an accurate diagnosis.

Cytologic diagnosis of pediatric lymphoma is justified only in emergency cases, and results should be confirmed at least by immunophenotyping. Although the classification of NHL in general is very complex and the process is still evolving, the classification of pediatric NHL is considered to be simpler.
than that of its adult counterpart. The classification developed by the WHO is the current standard classification in use.

Virtually all childhood NHL can be classified into one of three types: Burkitt, lymphoblastic, and large-cell. Each type exhibits diffuse histologic characteristics. In a study of 1,336 children and adolescents, histologic examination indicated that only 17 cases (1.3%) were follicular (nodular) NHL. \(^1\) Rarely, other subtypes of NHL are seen in children, and many can cause a diagnostic dilemma (see section on uncommon forms of pediatric NHL).

Burkitt lymphoma is characterized by sheets of monomorphic lymphoid cells. Commonly, macrophages dispersed throughout the tumor give it the classic “starry sky” appearance. In the bone marrow or blood, the Burkitt cells (in FAB L3 subtype ALL, C. Figure 1) are relatively uniform in shape, and have a moderate amount of deeply basophilic cytoplasm containing sharply defined, clear vacuoles, and round nuclei containing coarsely reticular chromatin.

The cells express monotypic surface immunoglobulin (either IgM k or l light chains) and harbor specific chromosomal translocations involving the \(C-MYC\) oncogene. The most common of these cytogenetic abnormalities, present in 80% of cases, is the t(8;14)(q24;q32) translocation. In the remaining cases, t(2;8)(p12;q24) and t(8;22)(q24;q11) translocations are observed. \(^2\)

Even though cytogenetic abnormalities are a hallmark of Burkitt lymphoma, it is not always possible to do a complete study. In such cases, fluorescence in situ hybridization (FISH) analysis performed in paraffin embedded tissue, may give additional important information.

Lymphoblastic NHL arises from transformed, immature T or B cells. Lymphoblastic NHL that arises from T cells, which accounts for more than 80% of all cases of the disease, expresses an immunophenotypic profile similar to that of normal thymocytes at an intermediate or late stage of differentiation. As with Burkitt NHL, T-cell malignancy is characterized by several cytogenetic abnormalities that cause activation of transcription factors due to specific translocations in the T-cell receptor genes. Typically, these translocations are
juxtaposed with a small number of developmentally important transcription factor genes, including \textit{HOX11 (TLX1), TAL1 (SCL), TAL2, LYL1, BHLHB1, LMO1, and LMO2}.\textsuperscript{3} Recent studies suggest that loss of heterocigocity of 6q14-q24 may have a negative impact in prognosis of lymphoblastic lymphoma\textsuperscript{4} and the pattern of this aberration is different in cases of T-ALL from those seen in T-cell lymphoblastic lymphoma.\textsuperscript{5} B-cell precursor lymphoblastic lymphoma occasionally represents a diagnostic dilemma. It is important to identify accurately this entity since it may be confused with a mature B cell malignancy that would need a different treatment.\textsuperscript{6} Usually, B-cell precursor lymphoblastic lymphoma express tdt as well as a more immature B cell precursor phenotype and they usually don’t express surface immunoglobulins.

\textbf{C. Figure 1}
FAB L3 cells showing basophilic cytoplasm containing sharply defined, clear vacuoles (May-Grunwald-Giemsa staining X 100).
Large-cell NHL is the most heterogeneous pediatric NHL subtype. Immunophenotypic analysis of large-cell NHL shows that the neoplastic cells can be of T-cell or B-cell lineage or occasionally, they have no lineage-specific markers (null cells). However, anaplastic large cell lymphoma and B cell diffuse large cell lymphoma are the most common subtypes. According to the classification system adopted by the WHO, most pediatric large-cell lymphomas can be classified as diffuse B-cell or anaplastic large-cell lymphoma (ALCL).

Classification as ALCL requires the co-expression of CD30, the expression of anaplastic lymphoma kinase (ALK) and the membrane epithelial antigen in lymphoma cells expressing usually T-cell markers. Anaplastic lymphomas with B cell phenotype and ALK expression have been reported infrequently. Approximately 80% of ALCL cases identified on the basis of this criterion harbor the t(2;5)(p23;q35) chromosomal rearrangement. This translocation juxtaposes the gene encoding anaplastic lymphoma kinase (ALK) with regulatory elements of the gene encoding nucleophosmin (NPM), a nonribosomal nucleolar phosphoprotein. Rarely, the ALK gene is involved in other translocations, including t(1;2), t(2;3), inv(2), and t(2;22). Importantly, ALK protein expression can be detected by immunohistochemical study. The use of polyclonal and monoclonal antibodies to detect these proteins aids in diagnosis. Children with ALK-positive ALCL appear to have a better prognosis than do those with other forms of large cell NHL.

C.1 Clinical Manifestations

Childhood NHL manifests in extremely diverse ways. The dominant clinical manifestations depend on the tumor’s location and the extent of the disease. Virtually any lymphoid tissue can be affected, including peripheral lymph nodes, tonsils, thymus, spleen, and intestinal lymphoid aggregates (Peyer’s patches). In addition, pediatric NHL commonly extends to the bone marrow, CNS, bone, and skin.
Generally, the primary tumor site is associated with a particular histologic subtype. In patients with Burkitt NHL, an abdominal mass is most common; in lymphoblastic or diffuse, large B-cell NHL, mediastinal and peripheral lymph node tumors are most common; in ALCL, skin, bone, and soft tissue tumors are most common. When disease is disseminated, it is often impossible to determine the tumor’s primary site. Less-common presentations of NHL include subcutaneous lesions, thyroid and parotid enlargement, proptosis, and spinal cord compression. Although rare, spinal cord compression should be considered a medical emergency, and it should be treated urgently to prevent permanent neurologic deficits. Painless enlargement of the cervical lymph nodes is the most common clinical presentation. In a retrospective chart review conducted at St. Jude Children’s Research Hospital\textsuperscript{16}, one-third of children with NHL had palpable lymph nodes in the head and neck region. Another third presented with primary mediastinum involvement, which is commonly associated with supraclavicular and axillary adenopathy (**Figure 2**).
The clinical presentation of patients with a large mediastinal mass and anterior vena cava syndrome can be seen in https://www.cure4kids.org/ums/oncopedia/case_detail/?id=240.

Abdominal presentation of childhood NHL is associated with a palpable mass. Tumors in the gastrointestinal tract usually affect the distal ileum, cecum, and mesenteric nodes (C. Figure 3).
C. Figure 3
Massive intraperitoneal invasion by Burkitt lymphoma.

C. Figure 4
Retroperitoneal and renal extension is also common

Patients with a large abdominal mass complain of intermittent pain in the periumbilical region or right iliac fossa. Nausea, vomiting, and weight loss are also common features. Occasionally, signs of an acute abdomen due to intussusception are the dominant feature.

See case in: https://www.cure4kids.org/ums/oncopedia/case_detail/?id=310

Burkitt lymphoma should always be considered in the differential diagnosis of intussusception in children older than 2 years.
Occasionally, Burkitt lymphoma may present with bowel perforation, or it may develop after the initiation of chemotherapy. See case in: https://www.cure4kids.org/ums/oncopedia/case_detail/?id=86

Less frequently, rectal prolapse was described. See https://www.cure4kids.org/ums/oncopedia/case_detail/?id=314

The histologic, immunophenotypic, and cytogenetic characteristics of childhood NHL are listed in **C. Table 1**.

### C. Table 1
**Clinically Relevant Histologic Types, Immunophenotype, and Cytogenetic Features of NHL in Children**

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Immunophenotype</th>
<th>Cytogenetic abnormality</th>
<th>Fusion gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt B-cell (mature)</td>
<td>t(8;14)(q24;q32)</td>
<td>MYC-IgH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(8;22)(q24;q11)</td>
<td>MYC-IgL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;8)(p12;q24)</td>
<td>MYC-IgK</td>
<td></td>
</tr>
<tr>
<td>Lymphoblastic T-cell</td>
<td>Same as T-cell ALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-B–cell</td>
<td>Same as pre-B–cell ALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large-cell B-cell</td>
<td>t(2;5)(p23;q32)</td>
<td>NPM-ALK</td>
<td></td>
</tr>
<tr>
<td>Anaplastic large-cell T-cell</td>
<td>t(1;2)(q21;p23)</td>
<td>TPM3-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;3)(p23;q21)</td>
<td>TFG-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lnv(2)(p23q35)</td>
<td>ATIC-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;22)(p23;q11)</td>
<td>CTCL-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(X;2)(q11;p23)</td>
<td>MOESIN-ALK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(2;19)(p23;13)</td>
<td>TPM4-ALK</td>
<td></td>
</tr>
</tbody>
</table>

*World Health Organization classification*
C.2 Laboratory Findings

In patients with NHL, blood counts are usually normal. In those with bone marrow involvement, anemia and thrombocytopenia are common, and circulating lymphomatous cells may be present, but hyperleukocytosis is infrequent. As in patients with ALL, serum concentrations of uric acid and lactate dehydrogenase activity (LDH) can be elevated. Although CNS involvement is rare at presentation of NHL, particularly in those with large-cell lymphoma, all patients should undergo lumbar puncture and CSF examination. A prompt radiologic investigation is required to demonstrate areas of tumor involvement and is used to monitor the tumor’s response to therapy.

Whole-body computed tomography (CT) is the imaging modality of choice to determine tumor extent. The roles of magnetic resonance imaging, photon emission CT, and thallium scanning in childhood NHL have not yet been defined. However, in the initial evaluation, bilateral bone marrow examination is mandatory. Occasionally bone marrow involvement is unilateral. Bone marrow biopsy may reveal tumor involvement that is not clear from examination of the bone marrow aspirate; therefore, to determine disease stage, most investigators recommend bone marrow biopsy as part of the work-up. However, children with massive mediastinal involvement may not tolerate the anesthetic procedure needed to perform bilateral bone marrow aspirations, and biopsies and a single aspirate may be sufficient. Suspected cases of pediatric lymphoma should be diagnosed promptly, and treatment should begin without delay.

C.3 Differential Diagnosis

Because of its varied clinical and laboratory manifestations, childhood NHL can mimic several nonmalignant and malignant diseases. Differentiating between a reactive lymphoproliferative process and NHL is rarely difficult.
However, diagnosis of NHL is occasionally delayed in patients with localized, painless adenopathy when results of histologic studies of the lymph nodes are inconclusive for the presence of malignancy. Patients with persistent, painless enlargement of the lymph nodes after a 10- to 14-day trial of antibiotic therapy should undergo a lymph node biopsy, preferably surgically, to provide adequate tissue for immunophenotyping and for molecular and conventional studies.

Persistently enlarged lymph nodes in patients with acquired or congenital immunodeficiency represent a substantial diagnostic dilemma. Collectively, these abnormalities have been classified as lymphoproliferative disorders, and they range from reactive polyclonal hyperplasia to true monoclonal malignant lymphomas. Children presenting with an isolated mediastinal mass present a diagnostic challenge because a mediastinal mass can be present at diagnosis of several malignant and nonmalignant conditions, including histoplasmosis, sarcoidosis, Hodgkin disease, germ cell tumor, thymic carcinoma, neuroblastoma, and myeloblastoma. Results of serologic studies can provide evidence of some of these diseases, but a CT-guided needle biopsy procedure is usually necessary to provide tissue for diagnosis.

Primary lymphoma of the bone is commonly misdiagnosed.\textsuperscript{10,11} Indeed, in one St. Jude study, 10 of the 11 patients with biopsy-confirmed primary lymphoma of the bone had previously received an alternative initial diagnosis.\textsuperscript{11} To differentiate between primary lymphoma of the bone and other small blue cell tumors, immunohistochemical studies with an extensive panel of markers are required to supplement histologic studies.

\textbf{C.4 Prognostic Factors}

In NHL, staging systems have been used to identify groups of patients with diverse prognoses. The most commonly used, a system introduced by St. Jude Children’s Research Hospital, applies to all subtypes of NHL (\textbf{C. Table 2})\textsuperscript{12}
However, in recent years, a review an update of such classification is being discussed.

To view a poll on this topic visit:
https://www.cure4kids.org/ums/oncopedia/polls/

C. Table 2
The St. Jude Staging System for NHL in Children.¹²

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A single tumor (extranodal) or single anatomic area (nodal), excluding mediastinum or abdomen</td>
</tr>
<tr>
<td>II</td>
<td>A single tumor (extranodal) with regional node involvement,</td>
</tr>
<tr>
<td></td>
<td>On same side of the diaphragm:</td>
</tr>
<tr>
<td></td>
<td>(a) Two or more nodal areas</td>
</tr>
<tr>
<td></td>
<td>(b) Two single extranodal tumors, with or without regional node involvement</td>
</tr>
<tr>
<td></td>
<td>A primary gastrointestinal tract tumor (usually ileocecal) with or without associated mesenteric node involvement, grossly completely resected</td>
</tr>
<tr>
<td>III</td>
<td>On both sides of the diaphragm:</td>
</tr>
<tr>
<td></td>
<td>(a) Two or more nodal areas</td>
</tr>
<tr>
<td></td>
<td>(b) Two single extranodal tumors</td>
</tr>
<tr>
<td></td>
<td>All primary intrathoracic tumors (mediastinal, pleural thymic)</td>
</tr>
<tr>
<td></td>
<td>All extensive primary intra-abdominal disease; unresectable</td>
</tr>
<tr>
<td></td>
<td>All primary paraspinal or epidural tumors, regardless of other sites</td>
</tr>
<tr>
<td>IV</td>
<td>Any of the above with initial CNS or bone marrow involvement (&lt; 25%)</td>
</tr>
</tbody>
</table>

Its main value is in separating patients with localized disease from those with advanced disease. More recently, information on immunophenotype and molecular findings has been incorporated into classification schemes. This approach has established a foundation on which investigators can develop treatment regimens specific to immunophenotype and disease stage.
Recently many groups of investigators have used LDH level as a surrogate value for tumor burden in making treatment decisions regarding B-cell NHL.\textsuperscript{13} Response to therapy has been used similarly. In patients with B-cell lymphoma, French investigators have proposed the use of imaging studies to estimate the reduction in tumor mass after one week of cyclophosphamide, vincristine, and prednisone treatment. Patients whose primary tumor was reduced by less than 20% received more intensive treatment.\textsuperscript{14} Recently, more attention has been paid to the molecular kinetics of response to chemotherapy detecting minimal residual disease by molecular techniques or flow cytometry.\textsuperscript{15,16}

The most important prognostic factor in pediatric NHL is an accurate diagnosis and evaluation of the extent of disease, so every effort should be made to correctly characterize disease biology before treatment.

C. References


D. Treatment

Progress in the treatment of children and adolescents with NHL parallels that of childhood acute lymphoblastic leukemia. Investigators of most contemporary clinical trials report survival estimates approaching 90% in more developed countries. Moreover, the relevance of clinical and biologic prognostic factors has been practically eliminated by the use of risk-adapted strategies specific to disease stage and immunophenotype in conjunction with a wide range of effective agents, which are largely responsible for the improved survival estimates.

Adequate treatment has emerged as the single most important determinant of successful outcome of NHL. Clinical and biologic features that guide the therapeutic strategy include the extent of the disease at the time of diagnosis, sites of involvement, immunophenotype, morphology and immunohistochemistry of tumor cells, and early response to therapy. The BFM group evaluated the impact of age and gender in the prognosis of pediatric and adolescent lymphomas. In their study of 2084 patients the probability of event-free survival was significantly superior for males with T lymphoblastic lymphomas and diffuse B large cell lymphomas. When age-groups were compared dividing in groups between 0-4, 5-9, 10-14 and 15-18 years, the
outcome was poorer for the youngest patients only in the precursor B-
lymphoblastic lymphomas and anaplastic large cell lymphomas.
Adolescent females with T lymphoblastic lymphomas and diffuse large cell B
cell lymphomas had worse outcome than younger girls while age had no impact
on pEFS for boys.\(^5\)

Most groups developed different strategies for treatment of patients
according to biological subgroups, that encompass about 90% of the cases.
These include:

1) Lymphoblastic lymphoma
2) Mature B-cell malignancies
3) Anaplastic large cell lymphoma

D.1 *Lymphoblastic lymphoma*

Investigators developing treatment for lymphoblastic NHL have assumed
that this form of the disease behaves the same as does T-cell ALL. Their
assumption is based on results of the seminal Children’s Cancer Group study,
reported more than 20 years ago, showing that the LSA\(_2\)L\(_2\) regimen, an ALL-type
therapy, was significantly more effective than pulse chemotherapy (COMP) in
the treatment of lymphoblastic NHL.\(^6\) However, because most lymphoblastic
NHL is of T-cell immunophenotype, ALL regimens that have not been
particularly successful in the treatment of T-cell ALL are expected to yield poor
results in the treatment of lymphoblastic NHL. So, most of the groups use BFM-
based protocols that have been highly effective in ALL.\(^1\) The BFM-90 protocol for
NHL incorporates treatment components found to be effective in T-cell ALL.\(^7\)
These regimens include an induction phase with steroids, vincristine, L-
asparaginase and anthracyclines followed by cyclophosphamide, cytarabine and
mercaptopurine. The original BFM study included a consolidation phase
including high dose methotrexate (5 g/m\(^2\) in 24 hour infusion) and 6-
mercaptopurine.\(^7\) However, a recently completed study from the COG and yet
unpublished, failed to show any benefit from high dose methotrexate for patients with lymphoblastic lymphoma treated with a modified BFM-based protocol. A re-induction phase should be prescribed for these patients followed by maintenance therapy to complete 2 years of therapy. However, children with limited disease (stages I and II) might not need it.

See case in: https://www.cure4kids.org/ums/oncopedia/case_detail/?id=221

Cranial radiotherapy for patients with no initial CNS involvement is probably not necessary if an intensive intrathecal chemotherapy is used. The NHL-BFM-90 protocol was associated with a 5-year event-free survival (EFS) estimate of 92% in more than 100 patients with lymphoblastic lymphoma—a truly remarkable achievement. However, results from other groups using a similar strategy were not as remarkable.

D.2 Mature B-cell malignancies

The highly successful protocol (LMB89) developed by French investigators and the BFM studies developed by the German-Austrian groups to treat mature B-cell NHL (Burkitt, Burkitt-like, and large B-cell lymphomas) have become the benchmark for other protocols. For such subtypes, intensive, high-dose treatment of short total duration (5 to 8 months) and a reduced interval between treatment cycles are the hallmark of all effective types of combination therapy. CNS-directed therapy is mandatory, and patients with evidence of CNS involvement or those in the high-risk category should receive intensive therapy.
D.2.1 Treatment of localized disease

The results of the treatment of localized mature B cell malignancies are excellent and current efforts are directed to use the less intensive therapy possible that could preserve these excellent results while reducing the acute and late side effects associated with therapy. Even though, it can be generalized that patients with stage I and II disease constitute those with localized disease, most groups have used their own risk groups based in other prognostic factors such as the completeness of resection. Thus, based on the classification used by the French LMB group, the FAB (French, American, British consortium) they defined lower risk patients as those with completely resected Stage I disease and also those abdominal stage II that underwent complete resection of their tumor manifestations. The definition used by the BFM group was similar. The results of the FAB group for the treatment of Group A disease showed that a survival rate of 99% can be achieved with the use of only 2 cycles of COPAD chemotherapy (Cyclophosphamide, Prednisone, Doxorubicin and Vincristine) and no intrathecal chemotherapy. These results were obtained in a large cohort in a multicentric study, involving many institutions from developed countries.

Similar results were obtained by the BFM group in their protocol 95 in a smaller cohort and using a slightly more intense protocol with intermediate dose methotrexate and prophylactic intrathecal chemotherapy. The results from less developed countries are also encouraging with survival rates over 90%, but most results from mid income countries came from single institutions with few patients included. It is essential that patients should be meticulously staged in order to give them a reduced-dose regimen. This is important to be emphasized, especially in less developed countries, where staging procedures might be not accurate in all institutions and patients with more advanced disease might be missed.
A typical example is the case with intussusception, operated in a local hospital with reportedly completely resected disease. Since it is often impossible to be completely sure about the completeness of the resection in some of these cases, and they might benefit from a more intense regimen if the tumor was not completely resected. Reduced dose chemotherapy should be used only when there is absolute certainty of the completeness of the resection.

D.2.2 Treatment of advanced disease

Patients who are not classified as having limited or low-risk disease are collectively grouped as high-risk patients. Naturally, patients placed in this category have a wide range of tumor burdens and are likely to have diverse prognoses. Due to this diversity, treatments vary greatly on the basis of the staging system used. For example, a patient with Burkitt lymphoma without CNS involvement and < 25% blast cells in the bone marrow is considered to have stage IV disease according to the St. Jude system; but the patient is placed in group B in the French Society of Pediatric Oncology (SFOP) staging system, which stipulates 70% or more of bone marrow involvement for group C. Treatment of group C disease is much more intensive than that of group B.\textsuperscript{16}

Other investigators define risk categories associated with advanced-stage disease on the basis of serum LDH concentrations.\textsuperscript{2} Berlin-Frankfurt-Munster (BFM) protocols also stratify patient groups according to their LDH values. Those whose values exceed 1,000 U/L are at highest risk and receive a more intensive therapy.\textsuperscript{2} However, because what is considered a normal range of LDH values may vary by institution, relative, rather than absolute values of LDH should be considered as a basis for making treatment decisions. Therefore, other investigators in cooperative groups used an elevation of LDH greater than 2 times the institutional normal values as a basis for stratification of patient groups.
Therefore, regardless of the definition used, these patients need intensive chemotherapy to achieve a high cure rate. The results of the FAB and BFM series of studies were excellent with the use of high intensity chemotherapy.\textsuperscript{2,3,16} There does not seem to be a significant difference between the effectiveness of each of these strategies and different treatment groups or institutions should use the strategy with which they are familiar with. With these regimens, it is expected that over 85% of the patients could be cured with tailored intensive therapy. Only CNS invasion and poor response to chemotherapy remain as significant risk factors.\textsuperscript{11,16} In recent years, children with primary mediastinal (thymic) B cell lymphoma have been identified as an independent subtype with poorer prognosis. Therefore, they are analyzed separately in most current series.\textsuperscript{17}

The BFM series of studies classified patients according to stage, tumor burden based on serum LDH levels and the presence of CNS invasion. In the study BFM 95, the use of a higher dose of methotrexate (5g/m2) in a prolonged infusion (24 hours) for patients with abdominal primaries and high tumor burden obtained better results.\textsuperscript{18} With that classification patients of Risk group R3 (stage III abdominal primary with LDH greater than 500 IU/L but lower than 1000 IU/L and those of stage IV and B-ALL with the same LDH values but with negative CNS involvement) and those with Risk group 4 (those with stage III or IV and LDH >1000 IU/L or CNS involvement) achieved an overall survival rate greater than 85%.\textsuperscript{2} So, the major conclusion of that study was that the dose and the duration of Methotrexate infusion are important in advanced B-cell lymphomas. Therefore, higher dose and prolonged infusions of Methotrexate were associated to a reduced relapse rate, but at the same time, they were less toxic. This information is important for less developed countries where induction mortality is still a problem. So, each institution should analyze their own results, so that if toxic mortality is a greater problem, they might benefit from shorter infusions, associated to lower toxicity.
D.3 Anaplastic large cell lymphoma

The third largest group of childhood NHL (ALCL) comprises approximately 15% of all cases of pediatric NHL, and it includes tumors mostly with T-cell markers. Because the clinical and biologic characterization of this NHL subtype is still evolving, treatment programs for this disease have differed vastly. Only a few pediatric cooperative treatment groups have reported results of studies in which patients were selected by using the contemporary definition of ALCL. Remarkably, the results, albeit inferior to those noted in pediatric B-cell or lymphoblastic NHL, have shown that approximately survival rates from 60% to 80% can be achieved with either treatment strategy.

The French Society of Pediatric Oncology used a protocol based on the treatment of B-cell NHL that prescribes 2 cycles of COPDAM (methotrexate, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by 5 to 7 months of maintenance chemotherapy. Complete responses were achieved in 95% of the patients; 21/82 patients experienced an adverse event. By using a strategy developed for B-cell NHL, BFM investigators also reported improved results. The 5-year EFS estimate for 55 patients with stage III disease was 76%; for 6 patients with stage IV NHL, 50%. In the BFM study, treatment lasted only 5 months; in the others, 10 to 24 months.

A recently completed study from multinational European and Japanese investigators showed in a randomized fashion that the BFM treatment strategy was reproducible in a larger cohort of patients. That study was designed to test in a randomized factorial design the effectiveness and toxicity of two different doses and schedules of methotrexate and the impact of maintenance with Vinblastin. Vinblastin was identified as a candidate active drug based upon the observations of French investigators in relapsed patients where single drug Vinblastine was associated to a high response rate. The results of that study showed that the preferred methotrexate schedule was 3 g/m2 in a 3 hour infusion followed by leucovorin rescue.
The alternative schedule of 1 g/m2 in 24 hour infusion was equally effective but more toxic. With the use of the 3g/m2 schedule, no intrathecal prophylaxis was necessary. The preliminary results of the randomized question of the effectiveness of vinblastin for maintenance failed to show any benefit, but final results have not been published at the time of this report. In that study, 2-year event-free survival for the whole cohort was around 70-75%, but many patients could be rescued after relapse. Most tumor failures occur in the first year of diagnosis.

That seminal study also contributed to shed light on prognostic factors for this subtype. Prognostic factors are related to treatment, so the conclusions of that study are valid only for treatment with a similar strategy. Mediastinal, visceral (including lung, liver and spleen) and skin involvement were identified as poor prognostic factors in that study.25

Other groups also reported encouraging results. The POG reported the effectiveness of the APO regimen and the impact of methothrexate and cytarabine was inconclusive in that population. However, that regimen has a high cumulative dose of anthracyclines.27 Similar results were reported by Italian investigators with a leukemia-based therapy.28 In these cases where a lower intensity regimen is used, occasional late relapses may be seen.28

D.4 Salvage Therapy (Partial Responses or Relapse)

Persistent or relapsed NHL presents serious management problems. Because contemporary, risk-directed therapies are usually very intensive, the overall prognosis for such cases is dismal.

In patients with a residual mass after induction and consolidation therapy, persistent disease should be confirmed by biopsy, as imaging studies commonly detect nonviable tumor. The use of PET scans is under evaluation for this situation.
When persistent disease during therapy or relapse is documented, the options for salvage therapy depend on the intensity and types of agents used in the primary therapy, histologic disease type, and timing of the relapse. Because primary therapy for Burkitt lymphoma or large B-cell lymphoma includes most of the known effective agents, salvage therapy is usually based on regimens containing cisplatin or carboplatin, such as the widely used combination of ifosfamide, carboplatin, and etoposide. Monoclonal antibodies to B-cell antigens, successfully used to treat B-cell lymphomas, have been combined with conventional chemotherapy or conjugated to radioisotopes. The monoclonal anti-CD20 (rituximab), for example, has been widely used in combination with standard chemotherapy. A report of the combination of Rituximab and the ICE (Ifosfamide, Carboplatin and Etoposide) combination showed encouraging results with a response rate of 60%. The response of relapsed B cell malignancies to second line chemotherapy is usually short lived, and patients showing at least a partial response to second line chemotherapy should undergo intensification with high dose chemotherapy and stem cell rescue. The results of autologous stem cell rescue seem to parallel those of allogeneic transplantation and it is usually feasible in a shorter period of time in patients without bone marrow involvement. However, even in the favorable situations where a response to second line chemotherapy occurred and the patient could undergo a stem cell transplant, relapse usually occurs and the survival rate is usually below 30%. Preparative regimens usually include chemotherapy only regimens since B-cell malignancies are usually not sensitive to radiotherapy.

The principles of management of relapsed lymphoblastic NHL are similar to those of relapsed ALL. When a second remission is achieved, HSCT is also indicated. However, the results of rescue therapy for lymphoblastic lymphoma are poor, even with high dose chemotherapy and stem cell rescue. The outcome of residual disease after salvage therapy is very poor. Allogeneic transplantation is usually preferred for relapsed lymphoblastic lymphoma, however registry data from adults report a comparable result after autologous
transplantation. Preparative regimens usually contain total body irradiation along with chemotherapy.

Contrary to what is observed in Burkitt and lymphoblastic NHL, in ALCL, second remission is usually possible. Salvage treatment has included intensive chemotherapy with stem cell rescue. In a recent SFOP study, a second remission was achieved in 36 of 41 cases of relapsed ALCL.\textsuperscript{26} Eight of 13 patients receiving a single agent, (vinblastine administered weekly) experienced prolonged remission, which suggests that several relapses of ALCL do not preclude a long period of disease-free survival. BFM investigators have reported the use of allogeneic BMT for 20 patients with relapsed/resistant ALCL\textsuperscript{30}. Event-free survival 3 years after BMT was 75%; and outcome was not influenced by donor type or conditioning regimens.

D.5 Supportive Care

Patients with lymphoid malignancies often present with respiratory, cardiovascular, neurologic, renal, hemorrhagic, infectious, and metabolic complications. Intense tissue remodeling—cell proliferation and cell death—results in a large tumor burden and rapid turnover of nucleoproteins, both of which are responsible for the dysfunction of these organ systems. The rate of mortality due to these complications has been reduced to less than 1\% by prompt recognition of signs and symptoms, careful clinical and laboratory evaluation to determine the presence of these complications, and early intervention. However, in less developed countries, it is still a significant problem. Mortality resulting from these complications is defined as death not due directly to the leukemia or lymphoma. Respiratory distress from compression of mediastinal structures is common in lymphoblastic NHL.\textsuperscript{35}
Compression of the vessels of the mediastinum can lead to intraluminal thrombosis and sudden death.\textsuperscript{35} In cases of severe compression, general anesthesia is not recommended because of an increased risk of complete, irreversible airway block. In an emergency it is sometimes necessary, before diagnosis is made, to reduce the risk of airway compression by administration of corticosteroids or local radiotherapy (or both). Massive ascites and intra-abdominal involvement in Burkitt lymphoma can cause compression of the bowel and ureter.\textsuperscript{16} In addition, abdominal blood and lymphatic vessels can become compressed, which results in reduced blood flow and lymphatic return and in edema of the lower extremities.

Patients with NHL are at particularly high risk of biochemical complications because of the high rate of cell turnover and the high sensitivity of the malignant cells to chemotherapy.\textsuperscript{37} Biochemical abnormalities, often present before chemotherapy begins, are induced by fever, processes associated with infection, dehydration, and even spontaneous cell lysis. These metabolic abnormalities, which include hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and azotemia, characterize tumor lysis syndrome (TLS). The pathogenetic consequences of this syndrome result from the release of cellular breakdown products that exceed the hepatic and renal anabolic and catabolic capacities. The deposition of phosphorus, uric acid, and its precursors (hypoxanthine and especially xanthine or both) in the lumina of the renal tubules is believed to be central to the development of renal insufficiency. If these metabolic abnormalities become severe, renal failure, cardiac arrhythmia, respiratory distress, and death can follow.

Features associated with increased risk of TLS include hyperleukocytosis, massive organomegaly, renal enlargement, extrinsic compression of the genitourinary tract, and elevated serum LDH activity.
Patients with established TLS or those at high risk for TLS should be monitored carefully. Preferably, they should be admitted to an intensive care unit and cared for by a multidisciplinary team. The team must ensure adequate urinary flow before chemotherapy is started. To determine the adequacy of renal function, a slightly hypotonic solution without potassium should be administered intravenously at a rate of 2 to 5 L/m² per day. Administration of fluids dilutes intravascular solutes such as urates and phosphates, increases renal blood flow and glomerular filtration, and flushes precipitated solutes from the renal tubules. The availability of recombinant urate oxidase (rasburicase) has greatly facilitated the prevention and management of hyperuricemia.  

It is important to consider the outcome of tumor lysis and the presence of renal failure at the time of initiating chemotherapy especially in children with B cell lymphomas. Since renal failure leads to disturbances in the pharmacokinetics of many drugs used in these malignancies, it may be prudent to consider delaying the chemotherapy or giving a prolonged pre-phase in children with renal abnormalities. Occasionally, renal failure is caused by tumor invasion of the renal parenchyma or obstruction of the urinary tract, so a careful evaluation is needed in these cases.

D. References

16. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not...


### E. Uncommon Forms of Pediatric Non-Hodgkin Lymphoma

Although the overwhelming majority of patients with pediatric lymphoma fall into the three categories, (Burkitt, lymphoblastic and large cell), some patients occasionally present with less common disease subtypes that pose diagnostic and treatment challenges. Many times, pathologists in children’s hospitals do not have the experience or reagents needed to precisely characterize these uncommon forms of lymphomas. It is crucial for pediatric oncologists to have a high index of suspicion for these rare lymphomas, and collaboration among pediatric and adult pathologists is often necessary to reach the correct diagnosis.

#### E.1 Follicular lymphoma

Follicular pediatric NHL, which occurs in about 3% of all pediatric cases, differs substantially from its adult counterpart. In adults, follicular NHL is disseminated, has a low histologic grade, and is incurable with current therapies. Conversely, pediatric NHL is typically localized with intermediate or high histologic grade (grade 2 or 3), and highly curable. Pediatric cases are more common in males. Head and neck lymph nodes or tonsils are the most common primary sites. Extranodal sites include the gastrointestinal tract, parotid, kidney, epididymis, and testes, but the BFM series failed to show any
case of testicular location.\textsuperscript{1,2} Approximately 70\% of the pediatric cases have localized (Stage I or II) disease. CD10 is expressed in most tumor cells; in a minority, CD34 is expressed.\textsuperscript{2} The Bcl-6 protein is occasionally present, as the Bcl-2 protein, but the typical t(14;18) translocation seen in adults is not.\textsuperscript{1} Furthermore, in contrast to the adult counterpart, in the most cases of pediatric follicular NHL, the t(14;18) rearrangement is not present.\textsuperscript{1}

NHL involvement of the testes is rare; most involvement is present at diagnosis in patients with disseminated lymphoblastic or Burkitt NHL. Primary testicular lymphoma is usually of follicular histiotype. Of the approximately 12 cases reported,\textsuperscript{1} the median age at diagnosis was 5 years; tumors were small (2-4 cm), and the histologic grade was III. CD10 was expressed in 6 of 9 cases tested, and the Bcl-6 protein was expressed in 10 of 11 cases tested. In that series, the Bcl-2 protein was not expressed in any of the cases tested, and the t(14;18) rearrangement was not evident in 8 cases tested.\textsuperscript{3}

The treatment of pediatric follicular NHL is controversial. Investigators from the United Kingdom Children Cancer Study Group (UKCCSG) have even suggested that children with localized and completely resected tumors do not need further therapy.\textsuperscript{4} Their recommendation is based on a very small number of patients. Patients with more advanced disease or those who had incomplete resections received a short course of chemotherapy in accordance with the UKCCSG protocol 10.\textsuperscript{4} At St. Jude, patients with follicular NHL are treated according to disease stage. Patients with Murphy disease stage I or II receive chemotherapy. Those children with the rare diagnosis of advanced-stage follicular NHL usually receive more intensive treatment. A recent report from the BFM group also showed excellent results with B-cell based chemotherapy. It seems that, as opposed to the clinical behavior in adults, follicular lymphoma in children does not follow an indolent clinical course with multiple relapses and behaves more like a B-cell diffuse large cell lymphoma.\textsuperscript{1}
E.2 Marginal Zone B-cell Lymphomas

Marginal zone lymphomas are relatively rare forms of B-cell malignancies derived from post-germinal B-cells. They are much more common in older patients (median age, 60 years) than in children or in young adults. Pediatric cases are very rare and have been associated with autoimmune disorders such as Sjögren syndrome, Hashimoto thyroiditis, and systemic lupus erythematosus. The primary site varies considerably and includes nodal and extranodal regions.

Approximately 8% to 10% of adult cases of NHL are classified as extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type (MALT). The stomach is the most commonly affected among the extranodal sites. Other extranodal sites include the salivary glands, orbit, and lungs. In the etiology of MALT-associated gastric lymphoma, infection with the bacterium *Helicobacter pylori* has been implicated. Isolated cases of MALT lymphoma have been reported in pediatric patients who are HIV-infected. Only four patients (<0.1%) of the 2,703 admitted on NHL BFM studies between 1986 and 2004 received a diagnosis of MALT lymphoma. All four cases had extranodal sites: lower lid, breast, conjunctiva, and stomach. In another, 32 of 48 children and young adults with marginal zone B-cell lymphoma (67%) had nodal presentation. They ranged in age from 2 to 27 years (median, 16 years); 21 patients (66%) were 18 years of age or younger and the disease predominated in males.

Most patients (88%) presented with isolated, painless, peripheral adenopathy in the head and neck region that lasted from a few weeks to 2 years. None of these patients were HIV positive or showed signs of autoimmune disorder. In 19 of these patients, examination of bone marrow did not indicate the presence of tumor. Only one patient had stage III disease, with cervical, supraclavicular, and mesenteric nodes involvement.
Treatment approaches varied among 28 patients. Surgery only, with completely excised tumors, was reported in 19 patients; 5 received local radiotherapy; 3 received systemic chemotherapy; and 1 patient received a combination of radiotherapy and chemotherapy.

Only one disease recurrence was reported, and that was in a patient who underwent surgery and received no other treatment. At the time of the report (four years of follow-up), the patient was free of disease.

Sixteen of the 48 patients (33%) had extranodal marginal zone lymphoma. The median age was 24.5 years, 4 of 16 cases were pediatric, and there was no gender preponderance. The most common disease sites at presentation were the ocular adnexa (5 of 16, 31%), the salivary glands (4 of 16, 25%), and skin (3 of 16, 19%). Only one patient had gastric involvement. Three patients with salivary gland involvement (two females) had a history of autoimmune disease. Two had Sjögren syndrome, and one had systemic lupus erythematosus. In addition, the single patient with gastric involvement had a history of *Helicobacter pylori* gastritis and gastric ulcers.

More than 70% of evaluable patients had stage I disease. Concomitant regional lymph node involvement was evident in two cases, but dissemination to other nodal or extranodal sites was not observed. In all five cases in which bone marrow was examined, involvement was not present.

Information on treatment and outcome was available for nine patients. Five were treated with local radiotherapy, two with excision alone, and two with chemotherapy. Follow-up ranged from 1 to 24 months. Only one patient experienced a local relapse of disease. He had a large conjunctival mass at presentation, and had been treated with excision only. The accurate diagnosis of these conditions requires experienced pathologists and sophisticated immunologic and molecular diagnostic tools often not available in developing countries. In this setting, the treating physician should also consider that other more common types of lymphoma may extend to the stomach, orbit, and
tonsils. Therefore, every effort should be made to biologically characterize these lymphomas to ensure adequate treatment.

**E.3 Cutaneous lymphoma**

The skin may be involved in patients with systemic lymphomas [8] but occasionally, primary cutaneous occur in children. There is little published about their outcome in children and most of the knowledge of these entities comes from the adult experience. The most frequently seen entities include primary cutaneous CD30+ anaplastic large T-cell (ALTC) lymphoma and lymphomatoid papulosis are rarely seen in children. In recent years, they have been recognized as different expressions of a distinct clinicopathological entity different from other lymphoproliferative disorders such as mycosis fungoides (E. Figure 1), and subcutaneous panniculitis-like T-cell lymphoma (E. Figure 2) (E.Table 1). Primary cutaneous lymphomas have been recently re-classified including these new entities by the EORTC. Most patients with CD30+ ALCT present with isolated or multifocal nodules, papules, or tumors that are frequently ulcerated. Multifocal lesions are seen in approximately 20% of the patients. The skin lesions may regress spontaneously, but they do not wax and wane as do those in lymphomatoid papulosis. Disease extension to other organs is rare (10%) and typically involves the lymph nodes.

The prognosis of CD30+ ALTC is favorable (E. Figure 3). Conversely, children with systemic CD30+ large cell lymphoma with secondary skin involvement have much worse prognosis and require intensive systemic chemotherapy.
E. Figure 1
Child with typical plaques of mycosis fungoides
E. Figure 2
Skin nodules of panniculitis like T-cell lymphoma. These nodules underwent a wax and wane presentation.
Lymphomatoid papulosis is a chronic condition characterized by recurrent papulonecrotic skin lesions that wax and wane. Its malignant nature has not been definitively proved. However, progression to cutaneous ALTC has been documented. Lymphomatoid papulosis has also been associated with other types of malignancy, including Hodgkin disease. The typical lesions, which can be localized or generalized, are red-brown papules and nodules in different stages of evolution. The lesions evolve with central hemorrhage, necrosis, and crusting, and wax and wane (the hallmark of this condition). The pathologic distinction between lymphoid papulosis and cutaneous CD30+ ALTC
is often difficult to see; therefore, the dermatologic features and natural history have usually been used to make that distinction.

No uniform guidelines have been developed for the management of these interrelated disorders. The correct diagnosis and classification are crucial to treatment planning. Being able to distinguish between primary cutaneous CD30+ ALTC and systemic large cell lymphoma with secondary cutaneous involvement requires careful disease staging. For primary cutaneous ALTC, the type of treatment depends on the extent of the disease. A solitary or a few regional lesions can be treated with local radiotherapy. If a solitary lesion has been completely excised, no further treatment is recommended, unless it recurs. Some of these cases of primary cutaneous ALTC and those involving residual disease can be treated with a short course of chemotherapy such as that used for low-stage NHL.

Management of multifocal primary cutaneous ALTC is controversial. Intensive chemotherapy has been used, but it appears to be ineffective. In some cases, low-dose methotrexate has been successfully used. A treatment regimen for lymphomatoid papulosis has not been defined. Intensive chemotherapy or radiotherapy is not indicated because the lesions will reappear after a period of “remission.” When the lesions regress without scarring, specific treatment is not necessary. When scarring occurs, low-dose methotrexate can be administered orally. Other less common primary cutaneous lymphomas in children include subcutaneous panniculitis-like lymphoma, mycosis fungoides, CD4-CD56 hematodermic neoplasm, which has recently been characterized as a dendritic cell neoplasm.
For more information and pictures or videos on cutaneous lymphoma, please follow these links:

https://www.cure4kids.org/ums/oncopedia/case_detail/?id=245
https://www.cure4kids.org/ums/oncopedia/case_detail/?id=206
https://www.cure4kids.org/ums/oncopedia/case_detail/?id=202
https://www.cure4kids.org/ums/oncopedia/case_detail/?id=187
https://www.cure4kids.org/ums/oncopedia/case_detail/?id=156

E. 4 Mature T- and Natural Killer-cell non-Hodgkin Lymphomas

E.4.1 Extranodal NK/T-cell Lymphoma, Nasal Type

Nasal extranodal NK/T-cell lymphoma, a distinct clinicopathologic entity, is characterized by chronic midfacial processes.\(^{15-17}\) It most commonly presents clinically as a destructive nasal or midline facial tumor within one year of evolution.

The lesion usually develops in the nasal cavity, causing nasal obstruction, rhinorrhea, epistaxis, and facial edema. Palatal destruction and orbital swelling may also occur. Less commonly, extranodal NK/T-cell lymphomas involve cervical nodes, skin, soft tissues, testicles, and the gastrointestinal and respiratory tracts. Other names by which this entity is known include Stewart granuloma, lethal midline granuloma, angiocentric lymphoma, idiopathic midline destructive disease, pseudolymphoma, malignant midline granuloma, non-healing midline granuloma, polymorphic reticulosis, and lymphomatoid granulomatosis. It occurs more often in male patients in Asian and Central American countries and Native Americans. This disease is highly associated with EBV and distinctly more common in Southeast Asia and some areas in Latin America.\(^{18,19}\) In the early stages, extranodal NK/T-cell lymphoma is difficult to characterize histologically. The lesion is composed of an atypical polymorphic
infiltrate with a broad spectrum ranging from small cells to large transformed cells with a propensity to invade and destroy blood vessels. *In situ* hybridization studies with probes to EBV-encoded small nuclear RNA can detect even small numbers of neoplastic cells; such studies are invaluable in diagnosis and follow up. Analysis of immunohistochemistry usually reveals T cell-associated antigens, including CD2, the intracytoplasmic CD3-ε chain, and the NK-associated antigen CD56. Results of molecular studies do not indicate the presence of the T-cell gene rearrangement in malignant cells.

This malignancy may also appear at extra-nasal sites. This entity shares biological features with the nasal counterpart. Treatment of extranodal NK/T-cell lymphoma is still evolving. Anthracycline and asparaginase-based therapy plus local radiotherapy is typically used. Because the disease is rare in children and adolescents outside endemic areas, prognostic factors have not been established in this age group. In adults treated with chemotherapy and radiotherapy, predictors of poor outcome include constitutional “B” symptoms, high lactated dehydrogenase levels, and regional nodal involvement. Patients without any of the risk factors (localized disease) had an approximately 50% probability of survival, whereas patients with disseminated disease had a dismal outcome.

E.4.2 *Aggressive NK-Cell Leukemia*

Aggressive NK-cell leukemia is characterized by a fulminant clinical course. Immunophenotype and molecular genetic findings are similar to those of nasal-type NK/T-cell lymphoma. Patients are typically from Asian countries who present with fever, hepatosplenomegaly, leukopenia, and coagulopathy. This may lead to multiple organ failure followed by death within weeks of the initial signs and symptoms. As was the case with extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia is highly associated with EBV.
A closely related condition also seen in children and adolescents has been designated EBV+ fulminant T-cell lymphoproliferative disorder (fatal mononucleosis). It can occur after acute EBV infection, or more commonly after chronic EBV infection.\textsuperscript{19,23} However in this case, the malignant cells express true T-cell immunophenotype, including expression of clonality by rearranged T-cell receptor studies. In a manner similar to that of aggressive NK-cell leukemia, fatal mononucleosis is also characterized by severe hemophagocytic syndrome, from which the patient usually dies.

E.4.3 \textit{Hepatosplenic T-cell Lymphoma}

Hepatosplenic T-cell lymphoma is a rare, extranodal, and usually fatal, disorder resulting from the malignant transformation of cytotoxic T-cells, usually of $\gamma\delta$ T-cell receptor type. It occurs very rarely in children and most often affects young adults.\textsuperscript{24} Typically, patients with hepatosplenic T-cell lymphoma present with marked hepatosplenomegaly and various degrees of cytopenia. Adenopathy and circulating blasts are usually absent. Bone marrow involvement is frequent. The neoplastic cells, typically $\gamma\delta$ T-cells, are present in the sinusoids of the bone marrow. In most cases, CD4 and CD8 are not expressed in neoplastic cells, while CD56 is. Also, TIA-1, a cytoxic T-cell marker, is usually expressed. T-cell variants with an $\alpha\beta$ phenotype have been described as well. Isochromosome 7q and trisomy 8 are consistent cytogenetic abnormalities.\textsuperscript{25} Although a few cases have been successfully treated with chemotherapy alone, the overall prognosis of this disease is dismal. Hematopoietic stem cell transplantation (HSCT) has been effective in a small number of patients.
E.4.4 Primary Mediastinal (thymic) Large B-cell Lymphoma

Primary mediastinal (thymic) large B-cell lymphoma (PMLBCL) has been recently recognized as a distinct clinicopathologic entity with a molecular gene-expression signature reminiscent of nodular sclerosis subtype of classical Hodgkin disease. Although it develops more commonly in adults, it can develop in children, predominantly adolescent girls.

Tumor cells arise from the medullary thymic B cells and often express CD79a, CD19, CD20, and CD22, but not surface immunoglobulin. CD30 may also be expressed by these tumors, but it is not as frequent as in ALCL. Patients often present with a rapidly growing mediastinal (thymic) mass, usually without involvement of other areas; the kidney, the adrenal glands and the ovaries may also be involved.

Limited information is available on this disorder in children. In adults, regimens with polychemotherapy combined with local radiotherapy were used. Other adult studies suggest a benefit from therapy intensification and autologous stem cell rescue. The BFM group reported its experience in successive trials (30 patients) in which results were relatively poorer than those of studies of other types of B-cell malignancy. The group reported a probability of event-free survival of 0.7 for the whole group, and elevated LDH values were correlated with prognosis. Therefore, the most effective treatment of this condition in children it is not currently known, and the utility of radiotherapy in children is debatable.

E.4.5 Treatment of Non-Hodgkin Lymphoma in Developing Countries

Pediatric NHL in developing countries is associated with some peculiarities. In an INCTR study, Naresh et al. evaluated the distribution of lymphomas in several developing countries and found regional variation of
subtypes. The archetypical example is Burkitt lymphoma, which is endemic to Equatorial Africa, and which typically involves the jaw or the orbit in younger children. In Africa, Burkitt lymphoma accounts for 45% of all cases of childhood malignancy. In Africa and other developing areas of the world treatment is still inadequate. For example, in Malawi, only approximately 50% of children with localized Burkitt lymphoma survive disease free, in sharp contrast with the greater than 90% survival estimates of comparable groups of patients in the more developed countries.

To improve the outcome in Malawi, the International Society of Pediatric Oncology (SIOP) launched a series of studies in which attempts to use a modification of the high-dose regimens proposed by the SFOP caused unacceptable number of deaths due to toxicity and had to be discontinued. A low-intensity regimen is prescribed in this setting because of poor patient tolerance caused by malnutrition, malaria, parasitosis, and lack of compliance for longer therapies.

Although many African children with NHL have no access to chemotherapy, encouraging results have been reported in South Africa. In other emerging nations, non-Hodgkin lymphoma also represents a challenge. In some Latin American countries, such as Brazil and Argentina, encouraging results have been reported by those using adapted BFM therapies. In Turkey and Venezuela, SFOP protocols have been used with success. However, death due to toxicity is higher than that reported in developed nations. Physicians working in developing countries should also consider that B-cell lymphoma might behave differently in their areas and that treatment tailored to these differences should be developed.

In developing countries, only tertiary-care centers can provide the quality of care needed for patients with B-cell lymphoma when they receive high intensity therapy. In the developed nations, uncommon subtypes might be more prevalent than in developing countries. In some Latin American countries, hydroa vacciniforme such as skin lymphoma has long been recognized and has
recently been included in the WHO-EORTC classification for skin lymphomas.\textsuperscript{12} 
In Asia, NK-cell malignancies are more frequent.\textsuperscript{19}

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\textbf{E. References}


