ABSTRACT
Non-Hodgkin lymphoma (NHL) is the fourth most common malignancy in children, has an even higher incidence in adolescents, and is primarily represented by only a few histologic subtypes. Dramatic progress has been achieved, with survival rates exceeding 80%, in large part because of a better understanding of the biology of the different subtypes and national and international collaborations. Most patients with Burkitt lymphoma and diffuse large B-cell lymphoma are cured with short intensive pulse chemotherapy containing cyclophosphamide, cytarabine, and high-dose methotrexate. The benefit of the addition of rituximab has not been established except in the case of primary mediastinal B-cell lymphoma. Lymphoblastic lymphoma is treated with intensive, semi-continuous, longer leukemia-derived protocols. Relapses in B-cell and lymphoblastic lymphomas are rare and infrequently curable, even with intensive approaches. Event-free survival rates of approximately 75% have been achieved in anaplastic large-cell lymphomas with various regimens that generally include a short intensive B-like regimen. Immunity seems to play an important role in prognosis and needs further exploration to determine its therapeutic application. ALK inhibitor therapeutic approaches are currently under investigation. For all pediatric lymphomas, the intensity of induction/consolidation therapy correlates with acute toxicities, but because of low cumulative doses of anthracyclines and alkylating agents, minimal or no long-term toxicity is expected. Challenges that remain include defining the value of prognostic factors, such as early response on positron emission tomography/computed tomography and minimal disseminated and residual disease, using new biologic technologies to improve risk stratification, and developing innovative therapies, both in the first-line setting and for relapse.

INTRODUCTION
Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies. The histologic classification of these diseases has changed many times over the years as a result of better understanding of lymphomagenesis and development of new diagnostic tools. The 2008 WHO classification of lymphoma is now widely used, providing clinicians with a common language and valuable comparisons. NHL is the fourth most common malignancy across the pediatric age spectrum. Pediatric NHL exhibits significant differences in the distribution of histologic subtypes to NHL observed in adults with clinical features characterized by almost exclusively diffuse high-grade lymphomas and frequent extranodal involvement. Dramatic progress has been achieved in developing curative therapy for pediatric NHL, with an overall survival rate now exceeding 80%. Because of the relatively small numbers of each subtype, such progress could not have been achieved without national and international collaborations especially through the European Intergroup for Childhood NHL (EICNHL), which comprises most European countries, Japan and Hong Kong, and the North American Children’s Oncology Group (COG). This review will present current knowledge on pediatric NHL and identify future research directions, especially in terms of biology and new therapies.

GENERALITIES
Epidemiology and Histopathology
The overall incidence and frequency of the different histologic subgroups of NHL vary according...
to age at diagnosis. Data from the US National Cancer Institute’s Surveillance, Epidemiology, and End Results program have demonstrated a steady increase in NHL with age. The annual incidence per million inhabitants ranges from 5.9 in children younger than 5 years of age to about 10 in children between 5 and 14 years old, and 15 in adolescents (approximately 150 in adults). The increased incidence in adolescents is related to the higher incidence of large-cell lymphomas at that age. The vast majority of childhood NHL is high-grade lymphoma, mostly of B-cell origin (Table 1). Other subtypes, such as peripheral T-cell lymphoma, extranodal natural killer/T-cell lymphoma, and follicular lymphoma, represent less than 5% of all pediatric NHL.

It is well known that immunodeficiency, either primary (such as ataxia telangiectasia or Nijmegen breakage syndrome) or secondary (induced by HIV or immunosuppressive drugs), increases the risk of NHL. Less known and more recently described are the association of interleukin (IL) -10 receptor deficiency with childhood B-cell NHL (B-NHL) and the increased risk of NHL in the constitutional mismatch repair deficiency syndrome. The latter is characterized by biallelic germline mutations of mismatch repair genes and multiple cancers including NHL, brain tumors, and colorectal cancers in children with café au lait spots.

### Staging

The Ann Arbor classification is not adapted to childhood NHL because of its predominant involvement in extranodal primary sites. The commonly used St Jude staging classification designates mediastinal and extensive abdominal lesions as stage III and restricts stage IV assignment to bone marrow (BM) and CNS involvement regardless of involvement of other visceral sites. The International Prognostic Index is not used in childhood NHL because of the difference in staging and because the performance status index does not reflect quality-of-life deterioration but rather rapidity of tumor growth and tumor volume. The role of fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in the management of childhood NHL has yet to be established. PET-FDG may be more accurate than conventional imaging to assess disease involvement because high FDG uptake has been shown in most subtypes (Abbou et al, submitted for publication), but its impact on therapeutic stratification has not been evaluated. The role of FDG-PET in remission assessment has only been investigated in small series. Most reports indicate high rates of false-positive results, requiring histologic examination of residual masses before treatment modification (Abbou et al, submitted for publication). Lastly, the prognostic value of early (after one to three cycles of chemotherapy) FDG-PET/CT response assessment has

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**Table 1. Immunophenotypic, Cytogenetic, and Molecular Markers of Pediatric NHL**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Histology and Frequency</th>
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<tbody>
<tr>
<td></td>
<td>BL (50%-60%)</td>
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<tr>
<td>Immunohistochemistry*</td>
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<tr>
<td>MIB1</td>
<td>~100%</td>
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<tr>
<td>CD10</td>
<td>+</td>
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<tr>
<td>CD19</td>
<td>+</td>
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<tr>
<td>CD20</td>
<td>+</td>
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<tr>
<td>CD79a</td>
<td>+</td>
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<tr>
<td>sIg</td>
<td>+</td>
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<tr>
<td>Bc6</td>
<td>+</td>
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<tr>
<td>MUM1</td>
<td>–</td>
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<tr>
<td>MAL</td>
<td>–</td>
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<tr>
<td>TdT</td>
<td>–</td>
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<tr>
<td>cCD3</td>
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<tr>
<td>CD4</td>
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<td>CD8</td>
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<td>CD7</td>
<td>–</td>
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<tr>
<td>CD5</td>
<td>–</td>
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<tr>
<td>CD30</td>
<td>–</td>
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<tr>
<td>ALK</td>
<td>–</td>
</tr>
</tbody>
</table>

| Cytogenetic | | | |
| 11q14(2(q22) | Rbq24 (~30%) | Few data |

| Molecular biology | | | |
| MYC/IGH | Nuclear factor-kB pathway dysregulation |
| IGK/MYC | IGH/TCR rearrangements |
| MYC/IGL | NOTCH/FBXW7, PTEF |

**NOTE.** Other NHLs, such as peripheral T-cell lymphoma, extranodal natural killer/T-cell lymphoma, nasal type, and pediatric follicular lymphoma, represent less than 5% of pediatric NHLs and are not indicated in the table.

Abbreviations: ALCL, anaplastic large-cell lymphoma, ALK positive; BL, Burkitt lymphoma; B-LL, B-cell lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; LBL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PMBL, primary mediastinal (thymic) large B-cell lymphoma; T-LL, T-cell lymphoblastic lymphoma.

*+, > 90% of patients; +/-, > 50% of patients; –/-, < 50% of patients; –, < 10% of patients.

*Positive especially in the rare anaplastic variant.

*Positive in the ALK-positive LBCL.
also not been established. A prospective study is ongoing in France since 2011 for B-NHL, lymphoblastic lymphoma (LL), and anaplastic large-cell lymphoma (ALCL) to evaluate the role of FDG-PET/CT in pediatric NHL (ID-RCB: 2010-A01154-35).

Several groups have investigated the prognostic impact of minimal disseminated disease (MDD) at diagnosis identified by molecular techniques or flow cytometry in the blood, BM, and/or CNS.9,11 Recently, a multidisciplinary multinational group proposed a Revised International Pediatric NHL Staging System Classification and International Pediatric Non-Hodgkin Lymphoma Response Criteria for improved staging and response assessments.11a,11b

Treatment

At the beginning of the 1980s, investigators contended that the type of multagent chemotherapy should differ according to the NHL histology based on clinical experiences. A Children’s Cancer Group randomized study showing that LL benefited from a 10-drug leukemia-like LSA-L2 protocol and that non-LL had better outcomes with a four-drug cyclophosphamide, vincristine, methotrexate (MTX), and prednison regimen confirmed these perceptions.12 Since 1981, national groups have conducted prospective trials with different strategies, including essential CNS prophylaxis, for B-NHL and LL that significantly advanced cure rates in these diseases.

Burkitt lymphoma (BL) accounts for more than 80% of childhood B-NHL. It generally arises in the abdomen and/or head and neck region and presents as an advanced-stage disease involving the BM and/or CNS in approximately 20% to 25% of patients. Outcomes have improved dramatically as a result of several consecutive prospective trials, such as the French Society of Pediatric Oncology and French-American-British (FAB) Lymphomes Malins L (LB) and the oligo-national Berlin-Frankfurt-Munster (BFM) studies (Table 2).4,13-20 Treatment of BL is based on 2 to 6 months of intensive pulse polychemotherapy. Relapses occur early, typically within the first year. The LMB studies,13,14 including the international FAB/LMB96 trial,15-17,21 sequentially demonstrated that high-dose (HD) MTX is an effective drug for CNS prophylaxis; patients with mature B-cell acute leukemia and CNS-positive disease benefit from a higher dose of HDMTX and the addition of HD cytarabine (Ara-C [in cytarabine/etoposide (CYVE) courses]); treatment intensity should be based on tumor resectability, stage, and response to chemotherapy (at day 7 and after three courses); early dose-intensity is essential as evident by a 10% lower event-free survival (EFS) in the intermediate-risk group of the FAB/LMB96 trial when the second induction course started later than 21 days after the first one; and the total dose of cyclophosphamide and doxorubicin could be reduced to 3.3 g/m² and 120 mg/m², respectively, for more than 70% of patients, substantially reducing the risk of gonadal and cardiac toxicity. The BFM studies4,18,19 showed that treatment intensity can be adapted to the lactate dehydrogenase (LDH) level; HDMTX is an effective systemic drug; and advanced disease benefits from more prolonged HDMTX exposure and HD Ara-C. Although stratification and the therapy intensity are not exactly comparable in the LMB and BFM strategies, the results are quite similar. Other studies also showed the value of short-duration therapy and confirmed that cyclophosphamide, HDMTX, and Ara-C are the major drugs in BL, in addition to vincristine, doxorubicin, etoposide, and corticosteroids.20 Collectively, all studies established the effectiveness of CNS prophylaxis with HD MTX ± HD Ara-C and intrathecal (IT) injections of MTX ± Ara-C, eliminating the need for cranial irradiation. In higher income countries, the EFS of BL reaches 80% to 90% using these strategies; however, acute treatment-related toxicities necessitate adequate supportive care and protocol management experience (Table 2).15,17,19-21

BL frequently occurs in countries with fewer resources, especially in sub-Saharan countries. Treatment should be adapted to find a compromise between sufficient effectiveness, tolerable toxicity, and socioeconomic constraints. Several groups have published results demonstrating cure in about half of the children with resource-adapted protocols.22,23 These cure rates should improve with experience, better resources, and less family abandonment of treatment.

Diffuse large B-cell lymphoma (DLBCL) accounts for 10% to 20% of B-cell lymphoma in children and occurs more frequently in adolescents.24 DLBCL in children is more homogeneous than in adults, with the majority originating from germinal centers (germinal center B-cell–like [GCB]), possibly representing a distinct biologic subgroup of GCB devoid of BCL6/3q27 and BCL2/18q21 translocations.25-26 MYC/8q24 is frequently rearranged (20% to 30%), in contrast to adult DLBCL (5% to 10%).27 Outcomes in children and adolescents are similar to those of BL with the same protocols except that relapses have been reported up to 3 years after diagnosis.14,18,20

The subgroup of primary mediastinal large B-cell lymphoma (PMBL) has to be distinguished from other DLBCL.19,27,28 Using BL pediatric protocols, EFS is lower than in DLBCL (70%), but similar to that obtained with adult protocols. PMBL biology is similar in both age groups (although gray zone lymphoma with features intermediate between DLBCL and classical Hodgkin lymphoma is infrequently seen in children),29 suggesting that rituximab-containing treatment regimens may improve outcomes as seen in adults.

The use of rituximab in pediatric B-NHL remains a relevant clinical question. Pilot studies have yielded responses for single-drug use in newly diagnosed BL30 and immediate good tolerance when combined with induction chemotherapy.21,31 However, considering the high cure rates obtained in children and adolescents with anticipated no or minimal long-term toxicity, the benefit of adding rituximab to conventional chemotherapy in BL has yet to be established. The ongoing Inter-B-NHL Ritux 2010 international trial combines a randomized phase III study testing the impact of adding rituximab to the LMB regimen for advanced-stage B-cell lymphoma and a phase II study of the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab regimen for PMBL (ClinicalTrials.gov identifier: NCT01516580; Table 2).

Clinical prognostic factors observed in previous B-NHL studies include stage; LDH level; CNS involvement, especially the presence of blasts in the cerebrospinal fluid; and treatment-related factors such as early response, initial dose-intensity, and complete response (CR). Biologic characteristics also seem to have prognostic value, including the presence of 13q abnormalities, MYC/8q24 rearrangement in DLBCL, and MDD and minimal residual disease (MRD) in BL.19,27,34 These results require confirmation in larger prospective studies, as planned in the Inter-B-NHL Ritux 2010 study.

Relapses in B-NHL are rare, but their outcome is dismal, with a cure rate of less than 30%.35-37 CYVE26 and rituximab, ifosfamide,
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Groups</th>
<th>Randomization</th>
<th>Criteria for Stratification and Risk Groups</th>
<th>No. of Patients (%)</th>
<th>3- or 5-Year EFS (%)</th>
<th>No. of Courses</th>
<th>CNS Prophylaxis</th>
<th>MTX (g/m²) and Infusion Duration</th>
<th>Cyclophosphamide (g/m²)</th>
<th>Idarubicin (mg/m²)</th>
<th>Etoposide (g/m²)</th>
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<tr>
<td>LMB89[14]</td>
<td>SFOP No</td>
<td>Stage, resection, CNS, response at day 7 A: stage I and II resected 52 (9%) 98% 2 No 5 MTX = 3 g/m² (3 hours), 10 DIT 5.3 180 0</td>
<td>56 91%</td>
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<td>FAB/LMB89[15-17] SFOP Yes</td>
<td>Idem LMB89 1,111 88%</td>
<td>A: idem LMB89 132 (12%) 99% 2 No 3 HDMTX 5 g/m² (24 hours), 5 TIT 6.8 240 2.5</td>
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<td>UKCCSG</td>
<td>Yes</td>
<td>B: not A and C 744 (67%) 89% 4 Idem LMB89 3.3</td>
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<tr>
<td>CCG</td>
<td>Yes</td>
<td>C: CNS involvement and BM 235 (21%) 79% 8 Idem LMB89 6.8</td>
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<tr>
<td>BFM90[18]</td>
<td>BFM No</td>
<td>Resection, site, LDH (&lt;500 IU/L), BM, CNS R1: complete resection 71 (17%) 100% 2 2 MTX 0.5 g/m² (24 hours), 3 TIT 2 4 50 0.2</td>
<td>413 88%</td>
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<td>R2: extra-abdominal only or abdominal and LDH &lt; 500 IU/L 167 (40%) 90% 4 4 HDMTX 5 g/m² (24 hours), 5 TIT 3 8 100 0.4</td>
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<td>R3: abdominal and LDH &gt; 500 IU/L and/or CNS involvement, and/or BM positive, and/or multifocal bone 175 (43%) 79% 6 6 HDMTX 5 g/m² (24 hours), 7 TIT 4 12 150 0.6</td>
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<tr>
<td>BF195[19]</td>
<td>BFM Yes</td>
<td>Resection, stage, CNS, LDH (&lt;500, 500-1000, &gt;1000 IU/L) R: Random: HDMTX 4 h v 24 h</td>
<td>505 89%</td>
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<td>Yes</td>
<td>G1: stage I and II resected 48 (10%) 94% 2 2 HDMTX 1 g/m² (4 hours), 2 MTX 0.5 g/m² (24 hours), 3 TIT 2 4 50 0.2</td>
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<tr>
<td>Yes</td>
<td>G2: stage I and II nonresected, stage III and LDH &lt; 500 IU/L 233 (46%) 94% 4 4 HDMTX 1 g/m² (24 hours), 5 TIT 2.4 8 100 0.4</td>
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<tr>
<td>Yes</td>
<td>G3: stage III and LDH &gt; 1000 IU/L 82 (16%) 85% 5 4 HDMTX 5 g/m² (24 hours), 1 HD Ara-C (Cytosine), 6 TIT 2.4 8 100 0.9</td>
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<tr>
<td>Yes</td>
<td>G4: LDH &gt; 1000 IU/L, CNS involvement 142 (28%) 81% 6 4 HDMTX 5 g/m² (24 hours), 2 HD Ara-C, 7 TIT 2.4 8 100 1.4</td>
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<tr>
<td>B-NHL03[20] JPLSG No</td>
<td>Stage, resection, BM, CNS G1: stage I and II resected 32 (17) 87% 2 2 DIT</td>
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<tr>
<td>G2: stage I and II nonresected 103 99% 4 2 MTX, 2 DIT, 2 HDMTX 3 g/m² (24 hours), 2 MTX 0.5 g/m² (6 hours) 1.5 120t 0</td>
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<tr>
<td>G3: stage III and IV, no CNS involvement 111 84% 6 4 DIT, 2 TIT, 4 HDMTX 3 g/m² (24 hours), 2 MTX 0.5 g/m² (6 hours) 3 240t 0.6</td>
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<tr>
<td>G4: stage IV, CNS involvement, and B-AL 90 78% 6 6 TIT, 2 DIT, 4 HDMTX 5 (24 hours), 2 HD Ara-C 5.5 240t 0.9</td>
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</tbody>
</table>

(continued on following page)
Table 2. Characteristics and Results of Main Studies in Childhood (< 18 years of age) B-Cell Lymphoma (continued)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Groups Randomization</th>
<th>Criteria for Stratification and Risk Groups</th>
<th>No. of Patients (%)</th>
<th>3- or 5-Year EFS (%)</th>
<th>No. of Courses</th>
<th>CNS Prophylaxis MTX (g/m²) and Infusion Duration</th>
<th>TD</th>
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<tbody>
<tr>
<td>Inter-B-NHL Ritux 2010 Part of EICNHL and COG</td>
<td>Yes</td>
<td>Stage, LDH &gt; 2N, CNS, CSF; random assignment: with or without rituximab</td>
<td>600 planned Study ongoing (NCT01516580)</td>
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<tr>
<td>NCT01516580</td>
<td>Yes</td>
<td>B-high: stage III and LDH &gt; 2N, stage IV and no CNS involvement</td>
<td>4</td>
<td>5 HDMTX = 3 g/m² (3 hours), 10 DIT</td>
<td>3.3</td>
<td>120</td>
<td>0</td>
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<tr>
<td></td>
<td>Yes</td>
<td>C1: stage IV and CNS involvement, B-AL, and CSF negative</td>
<td>6</td>
<td>3-4 HDMTX = 8 g/m² (4 hours), 2 HD Ara-C (CYVE), 10-12 TIT</td>
<td>5.8</td>
<td>180</td>
<td>1.6</td>
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<td></td>
<td>Yes</td>
<td>C3: CSF positive</td>
<td>6</td>
<td>4 HDMTX = 8 g/m² (24 hours), 2 HD Ara-C (CYVE), 12 TIT</td>
<td>5.8</td>
<td>180</td>
<td>1.6</td>
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<tr>
<td>No PMBL: PMBL, no CNS involvement, DA-EPOCH-R regimen</td>
<td>No</td>
<td>40 planned</td>
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</table>

Abbreviations: B-AL, mature B-cell acute leukemia; BFM, Berlin-Frankfurt-Munster; BM, bone marrow; BM > 70%, bone marrow involvement with more than 70% blasts; CC, combination of HD Ara-C with etoposide and vindesine; CCG, Children’s Cancer Group; COG, Children’s Oncology Group; CSF, cerebrospinal fluid; CYVE, combination of cytarabine in continuous infusion and HD Ara-C with etoposide; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab; DIT, double intrathecal injection (two drugs injected, either MTX or cytarabine with corticosteroid); EFS, event-free survival; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB French-American-British; HD Ara-C, high-dose cytarabine; HDMTX, high-dose methotrexate (with folinic rescue); JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; LDH, lactate dehydrogenase; LDH > 2N, LDH level more than twice the institutional normal value; LMB, Lymphoma Malin B; MTX, methotrexate; PMBL, primary mediastinal B-cell lymphoma; SFOP, Société Française d’Oncologie Pédiatrique; TD, total cumulative dose; TIT, triple intrathecal injection (corticosteroids, MTX, cytarabine); UKCCSG, United Kingdom Children’s Cancer Study Group.

*As results of the random assignments, these are the doses and the MTX infusion durations that are the standards in the current protocols.
†Pirarubicin instead of doxorubicin.
carboplatin, and etoposide\(^39\) regimens are effective reinduction chemotherapy in achieving a second CR, with CR rates of 45\%\(^37,38\) and 35\%,\(^39\) respectively. HD chemotherapy and hematopoietic cell support are needed to consolidate the second CR. An allograft does not afford more benefit than an autograft,\(^40\) but the former could be considered to maintain dose-intensity and/or in case of leukemic involvement. Adverse prognostic factors at relapse include early relapse (within 6 months), multiple sites of recurrence, BL histology, and initial presentation features (eg, elevated LDH and advanced-stage disease).\(^35-37\)

Innovative therapies are difficult to explore in childhood B-NHL because of the small number of patients with refractory/relapsed disease. The most promising therapies include new antibody therapies along with immunomodulatory agents that improve antibody-coated tumor cell killing and Bruton’s tyrosine kinase inhibitors. New monoclonal antibodies targeting B-cell markers such as next-generation humanized anti-CD20, obinutuzumab (GA101), or veltuzumab (IMMU-106) may be active, but none have been investigated in relapsed/refractory childhood B-NHL. Other new agents include the bi-specific CD20/CD22 or CD20/CD74 antibodies and the bi-specific CD19/CD3 T-cell engager blinatumomab (AMG103), with a reported response rate of approximately 55\% among adults with relapsed aggressive B-NHL.\(^41\) Another promising agent is ibrutinib, a potent oral inhibitor of Bruton’s tyrosine kinase, which has a direct effect on malignant B cells and may also regulate the tumor B-cell microenvironment. Ibrutinib has demonstrated single-drug activity in relapsed/refractory B-cell malignancies in adults and has recently been reported to have a favorable tolerance profile and efficacy when combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in a nonrandomized study of newly diagnosed adult DLBCL (mostly post–germinal center disease).\(^42\) Thus, ibrutinib could be a novel targeted therapy for relapsed/refractory childhood B-NHL in combination with a chemo-immunotherapy backbone.

Technologies such as next-generation sequencing, microRNA and gene expression profiling, and single nucleotide polymorphism array analysis may identify novel therapeutic targets. In BL, genetic alterations other than the 8q24/MYC translocation participate in the deregulation of the MYC pathway and may be essential for disease initiation and progression. Recurrent mutations in the PI3K pathway suggest a cooperative role between MYC overexpression and deregulation of PI3K signaling.\(^43\) Other studies highlight the pathogenic and clinical relevance of mutations affecting the transcription factor TCFC3 (E2A) or its negative regulator ID3, a novel tumor suppressor gene, with TCFC3 or ID3 mutations affecting nearly 70\% of sporadic BL.\(^44-46\) In addition, mutations in genes including CCND3, GNA13, TP53, and SMARCA4 have been described. Interestingly, a comparison between the frequency of mutations in BL and adult GCB DLBCL revealed a stronger overlap, further supporting the notion that BL and GCB DLBCL both originate from germinal center B cells.\(^47\) Altogether, these findings support the development of drugs targeting the PI3K kinase pathway, antigen-independent BCR signaling, and cyclin D3/CDK6 pathways in relapsed/refractory childhood B-NHL.

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**LL**

LL includes both precursor T-cell (T-LL) and B-cell (B-LL) NHL. Unlike acute lymphoblastic leukemia (ALL), with predominant B-cell diseases, most LL is of T-cell origin, rather than B-cell origin (80\% to 90\% v 10\% to 20\%, respectively). T-LL generally presents with mediastinal and advanced-stage disease (stage III or IV in > 90\% of patients) and may involve BM (approximately 30\%) and less often CNS (approximately 5\%) at diagnosis. B-LL is more likely to involve the skin, soft tissue, bone, and peripheral lymph nodes and represents the majority of the localized stages.\(^48\)

Both precursor B- and T-lymphoid blasts usually express terminal deoxynucleotidyl transferase (TdT). TdT expression is the best immunohistochemical marker for determining the precursor origin of the neoplasm.\(^49\) This is useful for differentiating B-LL from mature B-NHL, because they can express other similar markers (CD79a, CD10, and CD19 and/or CD20; **Table 1**).

The best treatment approaches for childhood advanced LL are ALL-based therapeutic regimens (eg, LSA1-L2\(^50\) and BFM\(^44,51,52\) regimens). These protocols were modified by adding HDMTX to the original LSA1-L2 protocol to promote CNS prophylaxis\(^53\) and by gradually excluding local and CNS radiotherapy.\(^52,54\) Regimens are based on semi-continuous intensive polychemotherapy followed by maintenance therapy for a total duration of 2 years (**Table 3**).\(^4,11b,52,53,55-63\)

Numerous drugs are given including corticosteroids, vincristine, anthracyclines, cyclophosphamide, Ara-C, asparaginase, and MTX. Several studies have demonstrated significance of asparaginase and its dose-intensity in LL outcomes.\(^52,66\) CNS prophylaxis, another important component of treatment, generally involves HDMTX and/or IT injections. The randomized Pediatric Oncology Group\(^56\) and COG\(^60\) studies investigated the importance of HDMTX in LL. CNS prophylaxis with either sufficient number of IT injections or HDMTX prevented CNS relapse. In contrast to BL, these studies suggested that HDMTX may not have as profound a systemic effect in LL. Other protocols introduced early intensification to BFM-like regimens to produce more rapid disease response, but this approach did not improve long-term outcome.\(^60,62\)

Of note, outcomes for pediatric LL have not changed significantly since the 1980s, with most clinical trials achieving EFS rates of 75\% to 85\% (**Table 3**). The BFM90 study, which attained a 90\% EFS rate, represents the only exception, but this result was not reproduced in the subsequent BFM95 study.\(^52\) Despite minimal differences between the two protocols, the divergent results obtained may be explained by a different dose and type of asparaginase. To date, except for stage (localized v advanced), no clinical prognostic factors have been identified.\(^51,64\) A trend toward a better prognosis was shown in patients with a very good response after the 7-day prephase of corticosteroids\(^54\) or with a radiologic response at 2 weeks.\(^60\) The EICNHL group designed the Euro-LB02 trial to compare dexamethasone (known to better penetrate the CNS) to prednisone in the induction phase and evaluate the possibility of decreasing the duration of treatment from 24 to 18 months (second random assignment). The reference arm was the NHL-BFM90 regimen without cranial irradiation, and only patients with T-LL were randomly assigned. The study had to be closed prematurely because of excess toxic deaths. Preliminary results\(^54\) showed an EFS rate of 81\% ± 2\% for the 319 eligible patients (75\% T-LL) with a median follow-up of 4.8 years. Although no CNS relapses occurred in the dexamethasone arm, survival was not better.

Because of relevant acute and long-term toxicity and poor prognosis at relapse, identifying prognostic factors is an important challenge in LL. This has been hampered by the rarity of the disease and,
Table 3. Characteristics and Results of Main Series of Pediatric Lymphoblastic Lymphoma (series of localized diseases or B-LL are not presented)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Group and Period of Study</th>
<th>Study Patients</th>
<th>Treatment Strategy</th>
<th>Treatment Duration (months)</th>
<th>RT</th>
<th>CNS Prophylaxis</th>
<th>No. of Patients With LL</th>
<th>3- to 5-Year EFS (%)</th>
<th>3- to 5-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG-5512 (COMP v LSA2L2)</td>
<td>CCG, 1977-1982</td>
<td>NHL</td>
<td>LSA2L2</td>
<td>18</td>
<td>Local</td>
<td>IT</td>
<td>124 (stages III and IV)</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>LSA2L2</td>
<td>MSKCC, 1980</td>
<td>LL, all stages</td>
<td>LSA2L2</td>
<td>24-36</td>
<td>Local</td>
<td>IT</td>
<td>95 (80% T-LL)</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>LMT8153</td>
<td>IGR, 1981-1989</td>
<td>LL, all stages</td>
<td>LSA2L2 +</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>HDMTX, IT</td>
<td>84</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>CCG50255 (LSA2L2 v ADCOMP)</td>
<td>CCG, 1983-1990</td>
<td>LL</td>
<td>LSA2L2</td>
<td>24</td>
<td>Local Craniospinal if CNS involvement</td>
<td>IT</td>
<td>143</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>POG940456 (HDMTX, yes v no)</td>
<td>POG, 1996-2000</td>
<td>T-ALL and T-LL</td>
<td>Dana-Farber backbone</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>IT ± HDMTX, cranial RT</td>
<td>137</td>
<td>85</td>
<td>NA</td>
</tr>
<tr>
<td>COG59411</td>
<td>COG, 1994-1997</td>
<td>LL, advanced stages</td>
<td>Condensed</td>
<td>12</td>
<td>Cranial if CNS involvement</td>
<td>IT, HDMTX</td>
<td>85 (91% T-LL)</td>
<td>78</td>
<td>85</td>
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<tr>
<td>BFM86</td>
<td>BFM, 1986-1990</td>
<td>LL, all stages</td>
<td>NHL-BFM-</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>IT, HDMTX, cranial RT (stage IIIV)</td>
<td>63 (91% T-LL)</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>BFM90</td>
<td>BFM, 1990-1995</td>
<td>LL, all stages</td>
<td>NHL-BFM-</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>IT, HDMTX, cranial RTX (stage IIIV)</td>
<td>136 (81% T-LL)</td>
<td>90</td>
<td>92</td>
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<tr>
<td>BFM95</td>
<td>BFM, 1995-2001</td>
<td>LL, all stages</td>
<td>NHL-BFM-</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>IT, HDMTX</td>
<td>198 (73% T-LL)</td>
<td>80</td>
<td>86</td>
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<td>CLG5888154</td>
<td>EORTC, 1989-1998</td>
<td>T-LL</td>
<td>NHL-BFM-</td>
<td>24</td>
<td>No</td>
<td>IT, HDMTX</td>
<td>119</td>
<td>77.5</td>
<td>86</td>
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<tr>
<td>LMT96</td>
<td>SFOP, 1997-2002</td>
<td>T-LL</td>
<td>Modified BFM</td>
<td>18-24</td>
<td>Cranial if CNS involvement</td>
<td>IT, HDMTX</td>
<td>79</td>
<td>85</td>
<td>89</td>
</tr>
<tr>
<td>AIEOP92</td>
<td>AEIOP, 1992-1997</td>
<td>LL, all stages</td>
<td>LSA2L2</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>IT, HDMTX</td>
<td>55 (85% T-LL)</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>COG597160 (CCG/ALL v NHL/BFM95; intensified: yes v no)</td>
<td>COG, 2000-2005</td>
<td>LL, advanced stages</td>
<td>Modified BFM</td>
<td>24</td>
<td>Cranial if CNS involvement</td>
<td>IT ± HDMTX</td>
<td>266 (86% T-LL)</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>EuroLb802</td>
<td>EICNHL, 2003-2008</td>
<td>LL, all stages</td>
<td>NHL-BFM90</td>
<td>24 v 18</td>
<td>Local</td>
<td>IT, HDMTX</td>
<td>319 (78%)</td>
<td>81</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ADCOMP, cyclophosphamide, vincristine, methotrexate, prednisone, daunorubicin, asparaginase, cytarabine; AEIOP, Italian Association of Pediatric Hematology and Oncology; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; B-LL, B-cell lymphoblastic lymphoma; CCG, Children’s Cancer Group; COG, Children’s Oncology Group; COMP, cyclophosphamide, vincristine, methotrexate, and prednisone; EFS, event-free survival; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; EORTC, European Organisation for Research and Treatment of Cancer; HDMTX, high-dose methotrexate; IGR, Institut Gustave Roussy; IT, intrathecal injection; LL, lymphoblastic lymphoma; LMT, Lymphomes Malins T; LSA2L2, protocol of MSKCC; MSKCC, New York Memorial Sloan-Kettering Cancer Center; NA, not available; NHL, non-Hodgkin lymphoma; OS, overall survival; POG, Pediatric Oncology Group; RT, radiation therapy; SFOP, Société Française d’Oncologie Pédiatrique; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma.
series studying 30%. In LL, there is a clear indication for an allograft if a second T-LL. The outcome is dismal, with a cure rate of generally less than 10% to 20% of patients. Relapse is mostly local in mediastinal lymph nodes. With intensive first-line treatment, refractory disease or relapse occurs in 10% to 20% of patients. Relapse is mostly local in mediastinal T-LL. The outcome is dismal, with a cure rate of generally less than 10% to 20%. In LL, there is a clear indication for an allograft if a second CR is achieved. However, the difficulty of obtaining a second CR emphasizes the need for new treatments. So far, new agents for T-LL such as nelarabine or cladribine have demonstrated limited effectiveness. Blinatumomab, a bi-specific CD19/CD3 antibody, may be promising for B-LL.

ALCL

Two forms of ALCL have been described—systemic and cutaneous ALCL. Systemic ALCL is characterized by peripheral, mediastinal, or intra-abdominal lymph node involvement, frequently associated with "B" symptoms and extranodal disease. A translocation resulting in the fusion of the anaplastic lymphoma kinase (ALK) gene to one of several partners can be detected in more than 90% of patients.

Primary cutaneous ALCLs usually lack ALK translocations and belong to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders, a group that also includes lymphomatoid papulosis. These entities remain confined to skin and usually carry an excellent prognosis after surgical resection without systemic therapy.

ALCLs express CD30 and, in most cases, EMA and cytotoxic molecules such as TIA-1, granzyme B, or perforin. Most patients express at least one T-cell antigen and exhibit clonal rearrangement of JAK/STAT3, AKT/PI3K, and RAS/ERK, leading to growth factor–independent cell proliferation and inhibition of apoptosis.

In previous therapeutic studies with diverse first-line chemotherapy regimens in terms of duration of treatment and the number and cumulative doses of drugs, similar EFS rates of approximately 65% to 75% have been achieved in children and adolescents (Table 4). Several pediatric groups now treat patients according to the ALCL99 protocol, a chemotherapy regimen derived from the NHL-BFM-B regimen, with MTX 3 g/m² in a 3-hour infusion and without IT therapy.

One of the unique features of ALCL compared with other pediatric NHL is its sensitivity to chemotherapy after recurrence, leading to a survival rate of more than 90% in the recent ALCL99 study. Several strategies, including reinduction chemotherapy followed by autologous or allogeneic hematopoietic stem-cell transplantation or weekly vinblastine, have been successful. The efficacy of vinblastine, initially shown in a small series of patients with multiple relapses, was confirmed in the European ALCL relapse study. An interim analysis in August 2011 showed an 87% 2-year EFS rate in a small series of

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study Group and Period of Study</th>
<th>Treatment Strategy</th>
<th>Treatment Duration (months)</th>
<th>No. of Patients</th>
<th>3- to 5-Year EFS (%)</th>
<th>3- to 5-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM99-91</td>
<td>SFOP, 1989-1997</td>
<td>B-cell regimen (COPADM + maintenance)</td>
<td>7-8</td>
<td>82</td>
<td>68</td>
<td>83</td>
</tr>
<tr>
<td>NHL-BFM90</td>
<td>BFM, 1990-1995</td>
<td>B-cell regimen (BFM-B)</td>
<td>2-5</td>
<td>89</td>
<td>76</td>
<td>—</td>
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<tr>
<td>NHL 9000 and 9602</td>
<td>UKCCSG, 1990-1998</td>
<td>B-cell regimen (LMB)</td>
<td>4-5</td>
<td>72</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>LH92</td>
<td>AEIOP, 1993-1997</td>
<td>T-cell regimen</td>
<td>24</td>
<td>34</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>PO9315</td>
<td>POG, 1994-2000</td>
<td>APO + randomization of HDMTX and HDARA-C</td>
<td>12</td>
<td>86</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>CCG5941</td>
<td>CCG, 1996-2001</td>
<td>Compressed T-cell regimen</td>
<td>11</td>
<td>86</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>ALCL99</td>
<td>EICNHL, 1999-2006</td>
<td>B-cell regimen (BFM-B) + randomization of vinblastine</td>
<td>4-12</td>
<td>352</td>
<td>73</td>
<td>92</td>
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<tr>
<td>ANL1013</td>
<td>COG, 2004-2008</td>
<td>APO + randomization of vinblastine</td>
<td>12</td>
<td>125</td>
<td>74</td>
<td>84</td>
</tr>
</tbody>
</table>

Abbreviations: AEIOP, Italian Association of Pediatric Hematology and Oncology; ALCL, anaplastic large-cell lymphoma; APO, doxorubicin, prednisone, and vincristine; BFM, Berlin-Frankfurt-Munster; CCG, Children’s Cancer Group; COG, Children’s Oncology Group; COPADM, vincristine, methotrexate, doxorubicin, cyclophosphamide, prednisone, bleomycin, and interferon; CCG5941, Children’s Cancer Group 5941; COG, Children’s Oncology Group; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; HDARA-C, high-dose methotrexate, dexamethasone, cytarabine, cytosine arabinoside, and cyclophosphamide; HDARA-C, high-dose methotrexate; LMB, Lymphomas Malins B; NHL, non-Hodgkin lymphoma; OS, overall survival; POG, Pediatric Oncology Group; SFOP, Société Française d’Oncoologie Pédiatrique; UKCCSG, United Kingdom Children’s Cancer Study Group.

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patients with a late relapse (median follow-up, 34 months) treated with vinblastine. The role of weekly vinblastine maintenance in first-line treatment has also been investigated in the ALC199 trial (addition of vinblastine to each course and as maintenance for a total treatment duration of 12 months) and in the COG ANHL0131 trial (vincristine replaced by weekly vinblastine in the doxorubicin, prednisone, and vincristine regimen), but no reduction in risk of relapse could be demonstrated with this duration of treatment.

Several prognostic factors associated with an increased risk of failure have been identified in ALCL, including the presence of mediastinal or visceral involvement and skin lesions, histologic lymphohistiocytic and small-cell variant patterns, and the detection of MDD by reverse transcriptase PCR for NPM-ALK in blood or BM (positive in approximately 50% of patients, whereas <15% of patients exhibit cytologically detectable BM disease). More recently, new parameters such as the persistence of positive MRD after 4 weeks of treatment and low production of anti-ALK titers were also identified. In a series of 128 patients, MDD and antibody titer allowed stratification into the following three biologic risk groups: high risk with MDD-positive status and low antibody titer (20% of patients; 5-year PFS, 28%), low risk with MDD-negative status and a high antibody titer (31% of patients; 5-year PFS, 93%), and intermediate risk including the remaining patients (48% of patients; 5-year PFS, 68%). Validation of this prognostic classification is planned in the future EICNHL clinical study.

Accumulating evidence indicates that the immune system plays a major role in both the pathogenesis and final control of ALK-positive ALCL. Antibodies against ALK and cytotoxic T-cell and CD4 T-helper responses to ALK have been detected in patients with ALK-positive ALCL both at diagnosis and during remission, with a significant inverse correlation between ALK antibody titers and incidence of relapse. The presence of germline monoallelic mutations of the perforin gene has been demonstrated in ALCL, suggesting that impairment of cytototoxic lymphocyte function may predispose to ALCL.

Interestingly, vinblastine is a potent immunomodulator that enhances anticancer immune response by stimulating dendritic cell (DC) function. In vitro, vinblastine induces the production of IL-1α, IL-6, and IL-12; increases surface expression of CD40, CD80, CD86, and major histocompatibility complex class II; and enhances T-cell stimulatory capacity of DCs. Vinblastine is speculated to release the high mobility group box 1 protein, a major molecule involved in DC stimulation and immunogenic cell death.

Several new drugs have recently been implemented in the treatment of ALCL. Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody conjugated to the antimicrotubule cytotoxic monomethyl auristatin-E. A study of 58 patients with relapsed/refractory ALCL (ALK positive, n = 16) treated with BV reported an objective response rate of 86% with a median duration of 12.6 months. After these results, BV was approved by the US Food and Drug Administration and European Medical Agency for the treatment of systemic ALCL after failure of at least one chemotherapy regimen in adults.

ALK inhibitors such as crizotinib, an ALK/MET inhibitor, are also promising drugs. Crizotinib is now approved by the US Food and Drug Administration and European Medical Agency for the treatment of ALK-positive lung cancers. The results in ALCL are also encouraging with seven CRs in nine patients with relapsed/refractory ALCL included in a pediatric phase I trial of crizotinib. The same results were obtained with a response rate of 91% in 11 patients with ALK-positive resistant/refractory adult lymphoma.

Given these results, the COG is currently investigating the feasibility of combining BV or crizotinib with ALC199 chemotherapy in children with newly diagnosed stage II to IV ALCL (ClinicalTrials.gov identifier: NCT01979536), whereas the EICNHL is planning a randomized trial with risk stratification based on MDD and antibody levels, aimed at evaluating the efficacy of adding crizotinib to ALC199 in first-line therapy for intermediate- and high-risk ALCL and comparing weekly vinblastine to ALC199 in low- and intermediate-risk disease.

**CONCLUSION**

Thanks to better recognition of the diseases and to national and international collaborations, the vast majority of children and adolescents with NHL will be cured using chemotherapy adapted to specific lymphoma subtype and disease extent. However, contemporary treatments are often associated with acute myelosuppressive and GI toxicities that not only hamper quality of life, but can also be life threatening. However, for many children, few long-term toxicities are anticipated because of low cumulative chemotherapy doses and elimination of radiation therapy.

The therapeutic strategies and treatment intensity vary considerably between pediatric and adult approaches for similar NHL subtypes. The lack of uniform criteria for staging and the limited data concerning age-related biologic characteristics of each subtype preclude understanding of the impact of these differences on patient outcomes. Defining new prognostic factors will facilitate the development of better risk-adapted strategies. New treatments including antibodies and/or targeted therapies hold promise for advancing outcomes in children with refractory/relapsed lymphoma. It is improbable that they will cure NHL on their own, but their combination with chemotherapy may allow reduction in treatment intensity and chemotherapy-related toxicities. Except for high-risk patients who require further therapeutic improvements, the challenge over the coming years will be to maintain already high cure rates while minimizing acute and long-term toxicity. This effort will require further pediatric international collaboration as well as partnerships with adult lymphoma groups.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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**AUTHOR CONTRIBUTIONS**

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REFERENCES


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Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead

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