doi.org/10.58931/cht.2024.3147

About the Author

Adam J. Olszewski, MD

Dr. Adam Olszewski is Associate Professor of Medicine at The Warren Alpert Medical School of Brown University, and an oncologist specializing in the management of lymphoma. He is a faculty member at the Lifespan Cancer Institute at Rhode Island Hospital, Providence, RI, a Research Scholar of the American Cancer Society and a Scholar in Clinical Research of the Leukemia and Lymphoma Society. His research has also been supported by the American Society of Hematology and the National Institutes of Health. His focus is on clinical trials and observational studies, particularly developing immunotherapies and molecularly targeted approaches for the treatment of non-Hodgkin lymphoma, as well as molecular correlates of responsiveness to these therapies.

Affiliations: Department of Medicine, Alpert Medical School of Brown University, Providence, RI
Division of Hematology-Oncology, Rhode Island Hospital, Providence, RI

Burkitt Lymphoma: The Curable Challenge

Adam J. Olszewski, MD

Introduction

Among the multiple subtypes of non-Hodgkin lymphoma, Burkitt lymphoma (BL) holds a unique position as the most aggressive mature B-cell malignancy. Named after the British physician who first described rapidly growing jaw and abdominal tumours in Ugandan children in 1958, BL is now understood to be a highly proliferative lymphoma arising from B-cells in the dark-zone germinal centre. BL is driven by the hallmark genomic lesion (*IG::MYC* rearrangement) and occurs in specific epidemiologic and clinical contexts.[1-4]

Historically, BL was classified as follows: "endemic" (common in the equatorial strip, associated with Epstein-Barr virus [EBV] and malaria infections, and predominantly pediatric), "immunodeficiency-associated" (in individuals with HIV infection or a history of solid organ transplantation), or "sporadic"—which includes 80% of cases observed in Canada and the United States (US). However, the current World Health Organization classification of lymphomas has discounted those descriptive terms and instead it recommends describing BL according to the presence or absence of EBV in the tumour, which provides more biological relevance.[5]

BL has an age-standardized incidence of 4 per million person-years, with a median age at diagnosis of 40 years, and an incidence three times higher in men than in women.[6] The incidence shows one peak in childhood, another around the age of 40 for men (partly due to the association with HIV), then it steadily increases after the age of 60 years, reflecting immune senescence.

BL often presents with clinical emergencies, which highlights the importance of promptly recognizing its symptoms for a rapid diagnostic workup and therapy. Patients with BL present with rapidly growing nodal disease, often disseminated to extranodal organs. Approximately 20% of BL cases may resemble acute lymphoblastic leukemia, with extensive bone marrow, blood, and frequent central nervous system (CNS) involvement. Serum lactate dehydrogenase (LDH) is typically elevated, and some patients may develop spontaneous tumour lysis syndrome (TLS) with life-threatening hyperkalemia, hyperuricemia, and renal failure, even before therapy starts. In a recent study that

included 641 US adults with BL, 78% had stage 3 or 4 disease, 43% had ≥2 extranodal sites of involvement, 35% had disease in the bone marrow, and 19% showed infiltration of the CNS (**Fig. 1A**).[7] Curiously, approximately 15% of patients present with only a single, large tumour arising from the ileocecal intestine that may involve regional lymph nodes, which raises a suspicion of colon cancer. In these patients, initial surgery may be performed due to emergent bowel obstruction or perforation, with an occasional complete resection of the BL tumour. The ileocecal location, together with the other known primary tumour locations in the jaw or the breasts of lactating women, hypothetically reflect genomic errors occurring when B-cells undergo immunoglobulin class switching to IgA in those organs.[2]

The initial medical workup of a patient with suspected BL is often undertaken in the inpatient setting owing to the rapid and relentless increase in the lymphoma burden. Early use of corticosteroids after or even before a diagnostic biopsy can be life-saving; however, this treatment requires close clinical and laboratory monitoring due to the risk of TLS. Diagnostic procedures typically involve a biopsy of the nodal or extranodal mass, although examination of the bone marrow or even peripheral blood or cerebrospinal fluid (by flow cytometry) may yield the diagnosis. The presence of vacuolated lymphoma cells with a characteristic immunophenotype and confirmatory *MYC* rearrangement suggests BL. An additional laboratory workup should include an assessment of blood counts, kidney and liver function, LDH, and serologies for hepatitis B, C, and HIV. Radiologic staging often relies on imaging with computed tomography or, when feasible, positron emission tomography (PET), with further evaluation of possible involvement of the blood/bone marrow, and mandatory sampling of the cerebrospinal fluid to rule out CNS invasion.

The histopathology of BL is distinct, revealing a dense, monotonous "blue cell" infiltrate consisting of medium-sized B-cells with extensive mitotic activity, and scattered tingible body macrophages that create the characteristic "starry sky" appearance on a low magnification view. BL cells strongly express CD10, CD19, CD20, and B-cell lymphoma 6 (BCL6), affirming their germinal centre B-cell origin. Conversely, they should not exhibit B-cell lymphoma 2 (BCL2), CD5, or terminal deoxynucleotidyl transferase (TdT), which facilitates rapid differentiation from B-lymphoblastic lymphoma/leukemia, or blastoid mantle cell lymphoma. Considering the morphologic and immunophenotypic overlaps between BL and other high-grade B-cell lymphomas (HGBL), diagnostic confirmation of the *MYC* rearrangement through chromosome analysis or fluorescent *in situ* hybridization (FISH) is important. Approximately 80% of BL tumours show the typical t(8;14)(q24;q32) *IGH::MYC* rearrangement, while most others involve translocations to light-chain immunoglobulin loci.[3] A lack of other karyotypic abnormalities, especially the absence of concurrent *BCL2* or *BCL6* translocations or copy number alterations, differentiates BL from HGBL with *MYC* and *BCL2* rearrangements or HGBL, not otherwise specified. Some cases of BL may test negative for *MYC* translocation, requiring additional workup to rule out rare entities such as HGBL with 11q aberration. Sequencing studies have identified recurrent somatic mutations in BL, including *TCF3, ID3, TP53, DDX41, CCND3,* or *FOXO1,* which contribute to our understanding of the highly proliferative nature of BL, its dependence on specific intracellular signals, and the role of EBV infection in lymphomagenesis.[2,3,8]

Unfortunately, the advances in molecular biology have not yet been translated to prognostic assessments or treatment decisions, which continue to rely on clinical features. A comprehensive international analysis identified four prognostic factors at diagnosis of BL (age >40 years, poor performance status, CNS involvement, and LDH >3x upper limit of normal). These factors provide clinical prognostic stratification for adults with BL. For instance, long-term progression-free survival ranges from 92% for those with no risk factors to only 53% for those with two or more factors.[9] Importantly, HIV infection does not appear to significantly compromise outcomes, possibly due to BL occurring in patients with less advanced immunodeficiency (median CD4 T-cell count of approximately 200 per mm^3). Many patients require initial stabilization due to TLS or organ impairment, including a cautious "debulking" pre-phase using corticosteroids (e.g., dexamethasone 20 mg daily for 5 days) with or without fractionated cyclophosphamide (e.g., 200 mg/m^2 for 5 days) to facilitate the diagnostic workup and therapy preparation.

Pediatric hematologists typically treat children and adolescents with BL using short-duration, dose-intensive chemotherapy regimens that are designed for aggressive mature

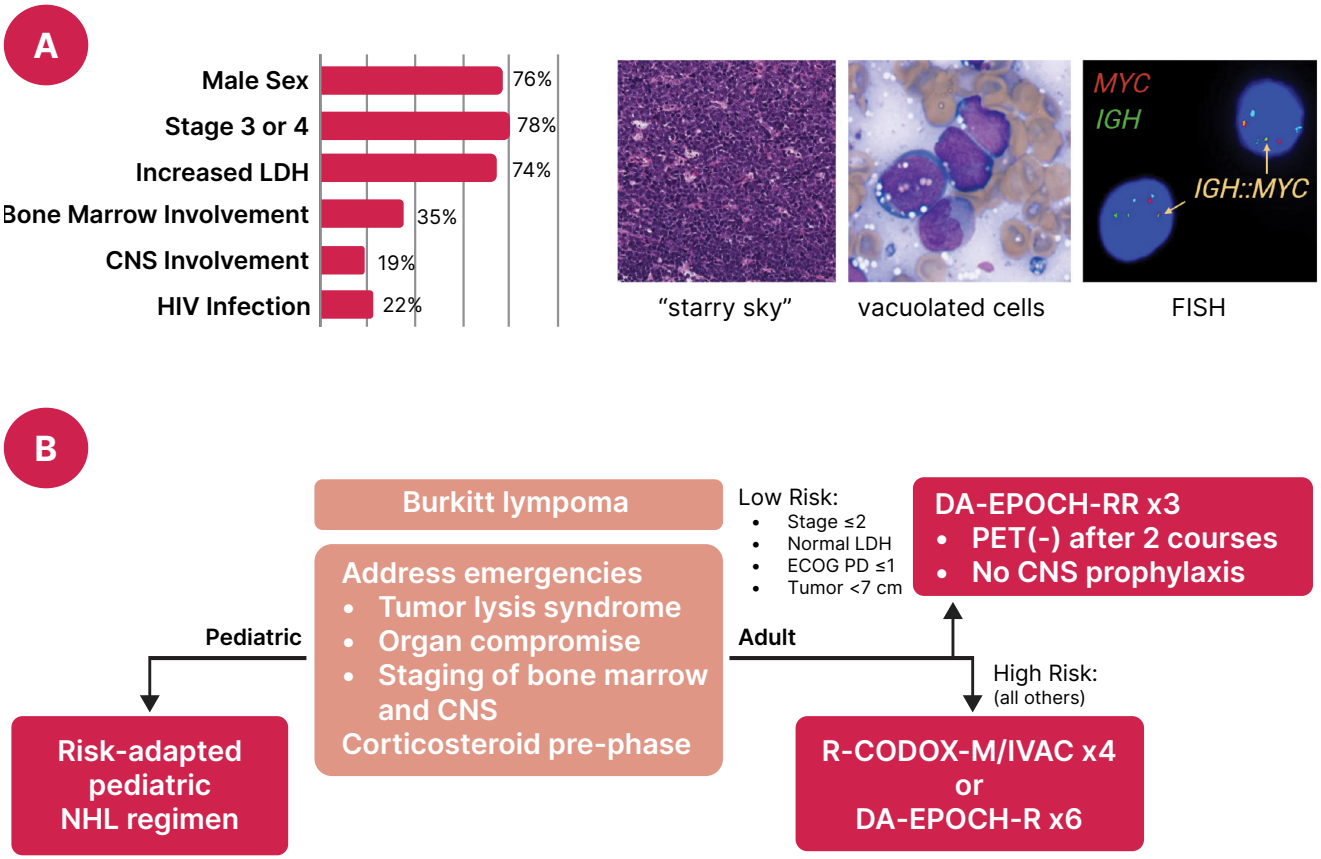

Figure 1. Clinico-pathologic characteristics **(A)** and treatment algorithm **(B)** for Burkitt lymphoma; *figure created with BioRender.com.*

Abbreviations: CNS: central nervous system; **DA-EPOCH R:** dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; **ECOG PS:** Eastern Cooperative Oncology Group; **FISH:** fluorescent in situ hybridization; **LDH:** lactate dehydrogenase; **NHL:** non-Hodgkin lymphomas; **PET:** positron emission tomography; **R-CODOX-M/IVAC:** rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with ifosfamide, etoposide, and cytarabine

B-cell lymphomas, regardless of histologic subtype.[10] These regimens, incorporating rituximab and CNS-penetrant agents, are risk-adapted, are based on disease burden (stage, resection status, bone marrow and CNS involvement) and result in long-term event-free survival for 94% of children, even with high-risk disease.[11] For adult patients, curative therapy also involves short, dose-intense regimens. However, these regimens are associated with higher toxicity and less favourable outcomes in adults than in children with BL (**Fig. 1B**).[3,4,12] Standard-intensity protocols such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) may be inadequate and often lead to chemoresistance and early progression of BL. In North America, 3 immunochemotherapy regimens are commonly used, with the choice depending on local expertise. These regimens include R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with ifosfamide, etoposide, and cytarabine),[13-15] R-hyperCVAD/MA (rituximab, hyper-fractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone, alternating with methotrexate and cytarabine),[16] and DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab).[15,17,18] Different but conceptually similar protocols are used in other

countries, sharing the overall plan of dose intensity and include rituximab and CNS-directed intrathecal and/or systemic therapy, and no maintenance therapy. Treatment can be stratified according to disease burden, being significantly shortened for patients with low-risk features, which are variably defined as a single or localized stage 1 or 2 tumour <7 cm in size, with normal LDH levels and a good performance status. The R-CODOX-M schema allows for the treatment of low-risk BL with 3 courses of R-CODOX-M (omitting the IVAC modules),[13] while the low-risk DA-EPOCH-R schema (applicable if a complete response is confirmed by a PET scan after the initial 2 courses) includes a total of 3 courses of chemotherapy with double-dosing of rituximab and without any intrathecal CNS prophylaxis.[17,18] Prospective comparative data between various protocols are limited; however, observational studies suggest no difference in outcomes,[7] and one randomized trial showed no survival difference between the R-CODOX-M/IVAC and DA-EPOCH-R protocols for high-risk BL, with 2-year progression-free survival of 76% and 70%, respectively. However, the trial was underpowered due to incomplete accrual.[15] Some observational studies show higher treatment-related mortality with the R-hyperCVAD/MA protocol, which requires prolonged, intensive therapy.[7] The DA-EPOCH-R protocol offers significant practical advantages due to its outpatient administration and lower toxicity, thus providing effective curative therapy for patients aged over 60 years, and those who are unable to tolerate more intensive regimens. However, this protocol lacks high-dose CNS-penetrant agents, thus requiring meticulous and intensive CNS prophylaxis. However, this protocol may be insufficient in a setting of CNS involvement, in which many clinicians favour regimens that contain high-dose methotrexate and cytarabine.

Patients with BL undergoing dose-intense therapy require expert supportive care to ensure safe and uninterrupted treatment delivery. The initial cycle of chemotherapy is critical due to frequent organ compromise at diagnosis, the risk of tumour lysis, bowel perforation, profound cytopenia when the bone marrow is involved, and a high risk of potentially fatal sepsis. Supportive measures for patients with BL should always include the use of granulocyte growth factor (regardless of age), antibacterial, antiviral, and *Pneumocystis jirovecii* pneumonia prophylaxis. HIV-positive patients can receive standard intensive protocols such as R-CODOX-M/IVAC or DA-EPOCH-R; however, they require attention regarding the risk of opportunistic infections and interactions between chemotherapy and antiviral agents. BL is best treated in centres providing expertise in management, including familiarity with chemotherapy protocols, established procedures for timely intrathecal chemotherapy delivery, and resources for transfusions and other medical and psychosocial support during intensive and partly inpatient therapy. Successful initial therapy delivery is essential owing to the "all or nothing" effect. Most patients completing treatment without major complications or interruptions are cured of BL, and recurrences beyond 1 year after therapy are rare. In contrast, patients not achieving a complete response or experiencing a recurrence, often soon after the end of initial therapy, frequently have chemoresistant disease, which may not respond to salvage therapy. The traditional pathway of reinduction using non-cross-resistant chemotherapy followed by consolidative (autologous or allogeneic) stem cell transplantation rarely leads to long-term survival, either in the pediatric or adult setting. Although several novel strategies have recently been developed for diffuse large B-cell lymphoma (DLBCL), including antibody-drug conjugates such as polatuzumab vedotin or loncastuximab tesirine, chimeric antigen receptor T-cells (CAR T-cells), and CD20xCD3-targeting bispecific antibodies, their efficacy in BL remains to be evaluated. One observational study suggests that autologous CAR T-cells are associated with less favourable outcomes in BL than in DLBCL, with only 31% of patients sustaining a complete response after 6 months of therapy, with a median progression-free survival of 4 months.[19]

Conclusion

Current research on BL is focused on incorporating novel immunotherapies into first-line treatment. Major areas of need include developing treatments applicable to older patients with comorbidities or designing management strategies for countries with limited medical resources, in which delivery of multiagent chemotherapy is challenging. The recently established BL Network (**https://www.burkitt-lymphoma.org/**) aims to bring together international researchers dedicated to improving outcomes of patients with this rare cancer.

Correspondence

Dr Adam J Olszewski
Email: adam.olszewski@gmail.com

Financial Disclosures :

Consulting or advisory role: Genmab, Schrodinger, ADC Therapeutics, Bristol-Myers Squibb, and BeiGene;
Research funding: Schordinger, Genmab, Beigene, Bristol-Myers Squibb, and received research funding from Genentech/Roche, the Leukemia & Lymphoma Society, the Institute for Follicular Lymphoma Innovation, Genmab, Artiva Biotherapeutics, Precision BioSciences, and Kymera Therapeutics.

References

1. Burkitt D. A sarcoma involving the jaws in African children. Br J Surg. 1958;46(197):218-223. doi:10.1002/bjs.18004619704
2. López C, Burkhardt B, Chan JKC, Leoncini L, Mbulaiteye SM, Ogwang MD, et al. Burkitt lymphoma. Nat Rev Dis Primers. 2022;8(1):78. doi:10.1038/s41572-022-00404-3
3. Zayac AS, Olszewski AJ. Burkitt lymphoma: bridging the gap between advances in molecular biology and therapy. Leuk Lymphoma. 2020;61(8):1784-1796. doi:10.1080/10428194.2020.1747068
4. Roschewski M, Staudt LM, Wilson WH. Burkitt's Lymphoma. N Engl J Med. 2022;387(12):1111-1122. doi:10.1056/NEJMra2025746
5. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748. doi:10.1038/s41375-022-01620-2
6. Mburu W, Devesa SS, Check D, Shiels MS, Mbulaiteye SM. Incidence of Burkitt lymphoma in the United States during 2000 to 2019. Int J Cancer. 2023;153(6):1182-1191. doi:10.1002/ijc.34618
7. Evens AM, Danilov A, Jagadeesh D, Sperling A, Kim SH, Vaca R, et al. Burkitt lymphoma in the modern era: real-world outcomes and prognostication across 30 US cancer centers. Blood. 2021;137(3):374-386. doi:10.1182/blood.2020006926
8. Thomas N, Dreval K, Gerhard DS, Hilton LK, Abramson JS, Ambinder RF, et al. Genetic subgroups inform on pathobiology in adult and pediatric Burkitt lymphoma. Blood. 2023;141(8):904-916. doi:10.1182/blood.2022016534
9. Olszewski AJ, Jakobsen LH, Collins GP, Cwynarski K, Bachanova V, Blum KA, et al. Burkitt Lymphoma International Prognostic Index. J Clin Oncol. 2021;39(10):1129-1138. doi:10.1200/jco.20.03288
10. Dunleavy K, Gross TG. Management of aggressive B-cell NHLs in the AYA population: an adult vs pediatric perspective. Blood. 2018;132(4):369-375. doi:10.1182/blood-2018-02-778480
11. Minard-Colin V, Aupérin A, Pillon M, Burke GAA, Barkauskas DA, Wheatley K, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. N Engl J Med. 2020;382(23):2207-2219. doi:10.1056/NEJMoa1915315
12. Crombie J, LaCasce A. The treatment of Burkitt lymphoma in adults. Blood. 2021;137(6):743-750. doi:10.1182/blood.2019004099
13. Mead GM, Barrans SL, Qian W, Walewski J, Radford JA, Wolf M, et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood. 2008;112(6):2248-2260. doi:10.1182/blood-2008-03-145128
14. Noy A, Lee JY, Cesarman E, Ambinder R, Baiocchi R, Reid E, et al. AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma. Blood. 2015;126(2):160-166. doi:10.1182/blood-2015-01-623900
15. Chamuleau MED, Stenner F, Chitu DA, Novak U, Minnema MC, Geerts P, et al. R-CODOX-M/R-IVAC versus DA-EPOCH-R in patients with newly diagnosed Burkitt lymphoma (HOVON/SAKK): final results of a multicentre, phase 3, open-label, randomised trial. Lancet Haematol. 2023;10(12):e966-e975. doi:10.1016/s2352-3026(23)00279-x
16. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569-1580. doi:10.1002/cncr.21776
17. Dunleavy K, Pittaluga S, Shovlin M, Steinberg SM, Cole D, Grant C, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med. 2013;369(20):1915-1925. doi:10.1056/NEJMoa1308392
18. Roschewski M, Dunleavy K, Abramson JS, Powell BL, Link BK, Patel P, et al. Multicenter study of risk-adapted therapy with dose-adjusted EPOCH-R in adults with untreated Burkitt lymphoma. J Clin Oncol. 2020;38(22):2519-2529. doi:10.1200/jco.20.00303
19. Samples LS, Sadrzadeh H, Frigault MJ, Jacobson CA, Hamadani M, Gurumurthi A, et al. Outcomes among adult recipients of CD19 CAR T-cell therapy for Burkitt lymphoma. Journal of Clinical Oncology. 2023;41(16_suppl):7571-7571. doi:10.1200/JCO.2023.41.16_suppl.7571