

## Burkitt's lymphoma

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**Burkitt's lymphoma is a highly aggressive B-cell non-Hodgkin lymphoma and is the fastest growing human tumour. The disease is associated with Epstein-Barr virus and was one of the first tumours shown to have a chromosomal translocation that activates an oncogene (*c-MYC*). Burkitt's lymphoma is the most common childhood cancer in areas where malaria is holoendemic. The incidence is very high in immunosuppressed patients in non-endemic areas, especially when associated with HIV infection. Outcome with intensive chemotherapy has improved and is now excellent in children, but the prognosis is poor in elderly adults. The success of intensive treatment relies on good supportive care. The therapy offered in oncology units in low-income countries is not as aggressive as in centres in high-income countries and outcomes are less successful. Adjuvant monoclonal antibody therapy with rituximab shows promise for improved outcomes and reduced toxic effects in the future.**

### Introduction and history

Burkitt's lymphoma has had an important role in the understanding of tumorigenesis. It was the first human tumour to be associated with a virus,<sup>1</sup> one of the first tumours shown to have a chromosomal translocation that activates an oncogene,<sup>2,3</sup> and the first lymphoma reported to be associated with HIV infection.<sup>4</sup> Burkitt's lymphoma is the fastest growing human tumour, with a cell doubling time of 24–48 h, and was the first childhood tumour to respond to chemotherapy alone.<sup>5</sup> It is the most common childhood cancer in areas where malaria is holoendemic—eg, equatorial Africa, Brazil, and Papua New Guinea.<sup>6</sup> The so-called Burkitt's lymphoma belt stretches across central Africa 15° either side of the equator where the climate is hot and wet (more than 50 cm annual rainfall). The epidemiological maps of malaria and Burkitt's lymphoma overlap.<sup>5–7</sup>

Early in the 20th century, Sir Albert Cook, a missionary doctor in Uganda, and other medical staff working in west, east, and central Africa noted the high frequency of jaw tumours and childhood lymphomas.<sup>8–10</sup> In 1958, Denis Burkitt, an Irish surgeon working in Uganda, reported cases of children presenting with rapidly growing jaw or abdominal tumours.<sup>11</sup> Burkitt suggested that these tumours were round-cell sarcoma. However, in 1960 George O'Connor, a pathologist, concluded that the cancer was of lymphoma lineage.<sup>12</sup> In 1964, three virologists, Michael Anthony Epstein, Yvonne Barr, and Bert Achong identified viral particles in the tumour tissue; this virus became known as Epstein-Barr virus (EBV).<sup>1</sup> Meanwhile, Burkitt travelled through eastern and central Africa to map the tumour spread and found records of affected children in all the malarial areas of the region.<sup>13</sup> These associations with malaria and EBV have inspired research throughout the world (figure 1).

### Classification

The WHO classification of Burkitt's lymphoma describes three clinical variants: endemic, sporadic (the predominant type found in non-malarial areas), and immunodeficiency-related.<sup>20</sup> These types are similar in morphology, immunophenotype, and genetic features.

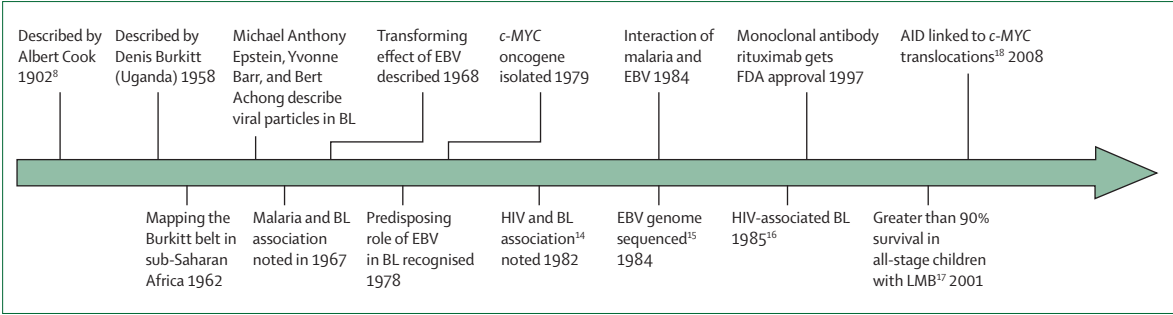
The endemic variant is associated with malaria endemicity and EBV is found in almost all cases. The sporadic type occurs mainly throughout the rest of the world (predominantly North America and Europe), with no special climatic or geographical links, and is rarely associated with EBV infection. 1–2% of adult lymphomas and 30–40% of childhood non-Hodgkin lymphomas in Europe and North America are sporadic-type Burkitt's lymphoma.<sup>21</sup> The immunodeficiency-related type is seen most often in patients with HIV infection and less than 40% of US and European cases are associated with EBV. Before the advent of antiretroviral therapy in North America the disorder was 1000 times more common in HIV-positive people than in uninfected individuals.<sup>22,23</sup> Immunodeficiency-related Burkitt's lymphoma is more common when the CD4 T-cell count is greater than 200 per  $\mu$ L (early in the progression of HIV infection). The association of HIV with Burkitt's lymphoma is not as clear in the endemic form.<sup>24</sup> The risk of BL increases 4 to 5 years after organ transplantation, but this risk is much less than that associated with HIV infection.<sup>25</sup>

### Epidemiology

The distribution of endemic Burkitt's lymphoma across Africa and Papua New Guinea corresponds to areas of holoendemic malaria and the early acquisition of EBV.<sup>13,26–32</sup> The annual incidence has been estimated at 40–50 per million children younger than 18 years.<sup>33</sup> In these high-risk areas endemic Burkitt's lymphoma comprises about half of all childhood cancer diagnoses and up to 90% of

#### Search strategy and selection criteria

We searched for articles in English on Medline and Embase with the search terms "Burkitt lymphoma" and "Burkitt's lymphoma", together with the terms "paediatric", "pediatric", "children", "adult", "sporadic", "epidemiology", "co factor", "HIV", "malaria", "EBV", "pathology", "immunology", "treatment", and "outcome". We also searched the reference lists of articles identified by this strategy. We did not limit ourselves by date so as to provide historical context.



**Figure 1: Milestones in understanding of Burkitt's lymphoma**  
 Modified from Rochford and colleagues.<sup>19</sup> BL=Burkitt's lymphoma. EBV=Epstein-Barr virus. FDA=Food and Drug Administration. AID=activation-induced deaminase. LMB=lymphoma malign B.

lymphoma diagnoses. Incidence peaks at age 6 years and the disease is twice as common in boys as in girls. Sporadic Burkitt's lymphoma occurs most commonly in children aged 3–12 years (median 6–8 years) and is 3·5 times more common in boys than in girls.<sup>34,35</sup>

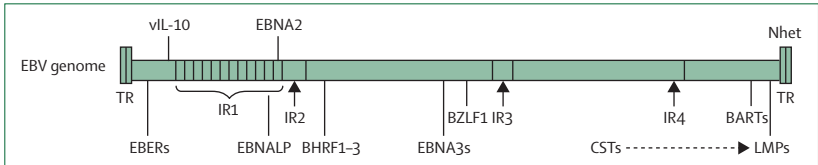
Sporadic Burkitt's lymphoma is found in low-risk areas such as North America, northern and eastern Europe, and east Asia at an annual incidence of 2 per million children younger than 18 years. Parts of South America, southern Europe, north Africa, and the Middle East are areas of intermediate risk.<sup>30</sup> Immunodeficiency-associated Burkitt's lymphoma occurs at an incidence of 22 per 100 000 person-years in the USA.<sup>36</sup>

**Cofactors**

**Epstein-Barr virus**

Several observations suggest a direct causative role for EBV in endemic Burkitt's lymphoma. For example, EBV is consistently present in these tumours;<sup>37</sup> infection of malignant B cells precedes tumorigenesis;<sup>38</sup> EBV induces immortalisation of B cells in culture; and very high EBV antibody titres are recorded in children before development of the disease.<sup>39</sup> However, the underlying mechanism linking EBV infection of B cells to the emergence of malignancy remains undiscovered.

Although EBV encodes several latent proteins essential for viral immortalisation of B cells,<sup>40–42</sup> EBNA1 protein is the only EBV latent protein consistently expressed in endemic Burkitt's lymphoma tumours. Other EBV latent and lytic transcripts are also detected in some tumours (figure 2),<sup>37,44</sup> but only in a subset of cells. Tumours containing a deletion of the EBNA2 gene have been identified, which leads to expression of EBNA3A, EBNA3B, and EBNA3C genes.<sup>46</sup> Cell lines derived from these lymphomas are resistant to apoptosis, which suggests that loss of EBNA2 provides a survival advantage to the tumour.<sup>47</sup> One function of EBV in endemic Burkitt's lymphoma might be to block apoptosis in B cells with an MYC translocation through either the EBNA1 protein, the BHRF1 protein, EBER transcripts, or epigenetic modification and subsequent repression of the pro-apoptotic BIM protein by the latent transcript LMP1.<sup>48,49</sup>

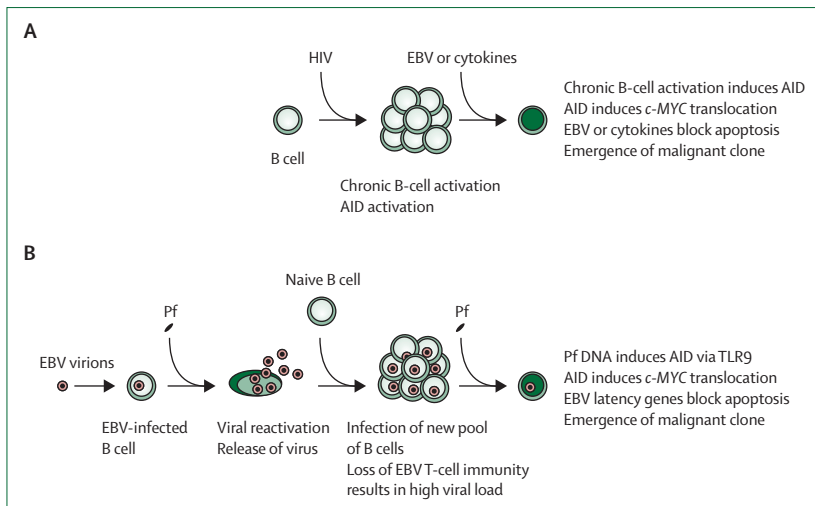


**Figure 2: Expression of Epstein-Barr virus transcripts in endemic Burkitt's lymphoma**  
 Shown is a schematic illustration of the EBV genome and the various EBV transcripts that have been detected in endemic Burkitt's lymphoma. All EBV-positive tumours express EBNA1. The repeat regions within the genome (eg, TR, IR1–4) are also indicated. In a subset of tumours, detection of other EBV transcripts has also been reported. These include the lytic immediate early transcript, BZLF1, the cellular homologues vBCL2 (eg, BHRF1), and vIL-10 and the latent transcripts LMP1 and LMP2.<sup>15,18,43</sup> In a subset of tumours, a unique variant of EBV has been described that has a deletion of EBNA2 and expresses the EBNA3A–C and EBNA1P transcripts. Most endemic Burkitt's lymphomas express the RNA polymerase III transcripts, EBER1, and EBER2.<sup>44</sup> More recently, viral microRNAs have been identified within the BamHI-A rightward transcript (BART) introns.<sup>45</sup> EBV=Epstein-Barr virus.

EBV can also promote genomic instability, dysregulate telomere functions, and induce DNA damage to infected cells.<sup>50</sup> Viral microRNAs have been identified in EBV-positive endemic and AIDS-associated Burkitt's lymphomas,<sup>45</sup> and are thus also potential candidates for driving tumorigenesis.

The cell type of origin of the Burkitt's lymphoma cell is controversial; some have argued that the tumour arises from a germinal centre B cell,<sup>51</sup> whereas others believe that it originates from a memory B cell.<sup>52</sup> This question is also relevant to the role of EBV in endemic disease. EBV persists for the lifetime of the healthy host as a latent infection in peripheral memory B cells. If the malignant cell arises from a latently infected cell and cycling memory B cells express only EBNA1 (similar to endemic Burkitt's lymphoma),<sup>53</sup> the latently infected memory B cell could be the source of the malignancy.

EBV can be identified in almost all endemic Burkitt's lymphomas, but is reported less frequently in the other types, which raises the question of whether EBV is a requirement for pathogenesis. The absence of EBV in other types of Burkitt's lymphoma might result from loss of viral episomes from tumour cells after cell division. EBV-positive Burkitt's lymphoma has a higher frequency than EBV-negative disease of somatic mutations in the immunoglobulin variable heavy chain with evidence of antigen selection. A possible explanation for this finding



**Figure 3: Model for the cause of Burkitt's lymphoma**

(A) During HIV infection, B cells are chronically stimulated, which results in activation of the enzyme AID. Aberrant expression of AID can result in a *c-MYC* translocation that is the hallmark of BL. EBV infection or cytokines can block apoptosis and rescue the *c-MYC* overexpressing B cell, leading to the emergence of a malignant clone. (B) In regions where malaria transmission is stable, *Plasmodium falciparum* (Pf) can drive reactivation of EBV from latently infected B cells leading to release of virus and infection of naive B cells. This process ultimately expands the pool of latently infected B cells, which increases the peripheral viral load as well as lessening T-cell immunity. *P. falciparum* DNA and haemozoin function as a toll-like receptor 9 ligand and can interact directly with EBV-infected B cells to induce the enzyme AID. Aberrant expression of AID can result in a *c-MYC* translocation and EBV latency genes can block apoptosis and rescue the *c-MYC* overexpressing B cell leading to the emergence of a malignant clone. EBV=Epstein-Barr virus. AID=activation-induced cytidine deaminase. Pf=*Plasmodium falciparum*. TLR9=toll-like receptor 9.

is that EBV-positive Burkitt's lymphoma arises from memory cells whereas EBV-negative disease originates from an earlier germinal centre counterpart.<sup>54</sup>

### Malaria

In Africa, pronounced seasonal, temporal, and spatial variations in the incidence of Burkitt's lymphoma have long been linked to the prevalence of malaria,<sup>31,55,56</sup> and in 2008, direct evidence of a link between malaria, EBV, and endemic Burkitt's lymphoma emerged.<sup>57,58</sup> Two epidemiological studies showed that the risk of Burkitt's lymphoma was greatest in people with the highest titres of antibodies against both EBV and *Plasmodium falciparum*.<sup>19,59</sup>

Several studies have shown that malaria can cause a profound dysregulation of EBV persistence and immunity in children.<sup>60–65</sup> These results suggest that malaria increases the risk of endemic Burkitt's lymphoma through interactions with EBV-infected B cells. For example, the cysteine-rich interdomain 1α of the *P. falciparum* erythrocyte membrane protein induces reactivation of EBV.<sup>66</sup> Additionally, *P. falciparum* has a ligand for toll-like receptor 9.<sup>67</sup> Signalling through toll-like receptor 9 was shown to induce the enzyme activation-induced cytidine deaminase in human B cells.<sup>68,69</sup> Overexpression of this enzyme induces the immunoglobulin-*MYC* translocations<sup>70</sup> characteristic of Burkitt's lymphoma. Normal B cells undergo apoptosis if *MYC* is overexpressed after an activation-induced cytidine deaminase-mediated translocation. However,

EBV latent proteins are antiapoptotic, which might allow the B cells to tolerate the translocation and ultimately give rise to a malignant clone. In malaria-endemic regions, diminished EBV-specific cytotoxic T-cell responses were observed in children at peak age of Burkitt's lymphoma incidence.<sup>61</sup> Children with acute malaria also have transient loss of EBV-specific T-cell control.<sup>71</sup> Malaria probably increases the risk of endemic Burkitt's lymphoma by increasing the number of latently infected B cells through viral reactivation and reseeding of the latent pool; by causing loss of immune control of latently infected B cells; and by inducing *MYC* translocation through a mechanism mediated by activation-induced cytidine deaminase.

### HIV infection

Burkitt's lymphoma occurs in HIV-infected patients with high CD4 T-cell numbers, which suggests that immunosuppression is not in itself the cause of the malignancy. Chronic antigenic stimulation of B cells, as in sustained *P. falciparum* infection or chronic HIV infection, might be a common pathogenetic mechanism of endemic and HIV-associated Burkitt's lymphoma. HIV-infected patients with Burkitt's lymphoma have high serum concentrations of soluble CD30 and CD23—markers of B-cell activation—before emergence of lymphoma.<sup>72–74</sup> Patients with chronic HIV viraemia, even if on antiretroviral therapy, have a higher risk of developing HIV-associated lymphomas than those with unmeasurable viral loads.<sup>75,76</sup> The virus might affect B cells through dysregulation of activation-induced cytidine deaminase and chronic B-cell activation. The enzyme has been detected in peripheral lymphocytes in HIV-infected patients with lymphoma, but not in HIV-positive patients without the malignancy, nor in healthy controls.<sup>77</sup> Impaired immune surveillance and deregulated cytokine release could promote survival of B cells with chromosomal rearrangements induced by overexpression of the activation-induced cytidine deaminase (figure 3).

The effect of HIV infection on the risk of endemic Burkitt's lymphoma is unclear. Different clinical presentations and tumour behaviour have been noted between HIV-infected and uninfected people.<sup>78,79</sup> An association was first reported from a Ugandan study,<sup>24</sup> but neither work in Côte d'Ivoire<sup>80</sup> nor in Zambia<sup>81</sup> confirmed this link. Preliminary data from Malawi identified an increased risk of endemic Burkitt's lymphoma in HIV-infected patients,<sup>58</sup> but updated analyses found no significant association.<sup>82</sup>

### Other possible cofactors

Arboviruses and schistosome parasites have both been suggested as causative cofactors of endemic Burkitt's lymphoma, although evidence is sparse.<sup>30</sup> The plants *Euphorbia tirucalli* and *Jatropha curcas* are common in areas where the endemic type of the disease occurs. The

milky sap of these plants contains dipterene esters that can activate latent EBV and induce rearrangements of chromosomes in about 10% of exposed EBV-infected B cells.<sup>83–85</sup>

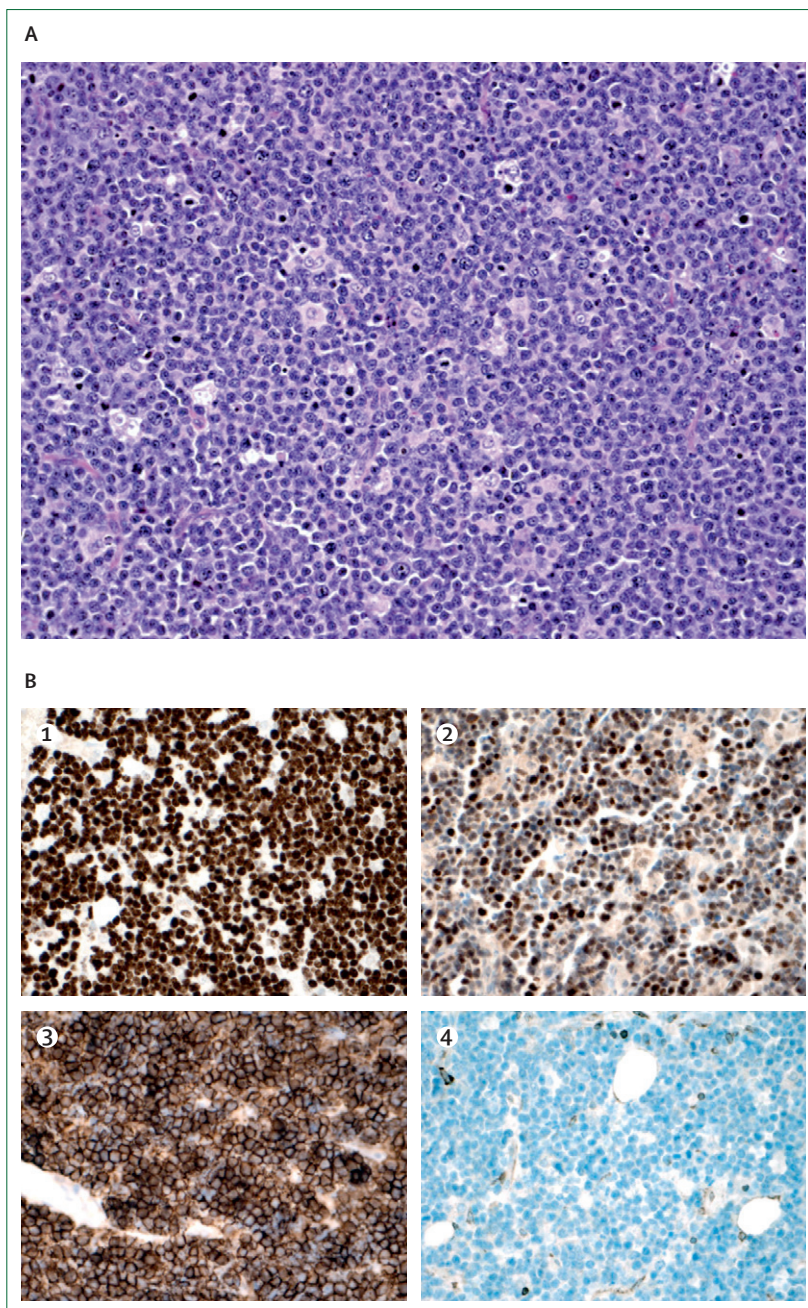
### Clinical presentation

The most common site of presentation in sporadic Burkitt's lymphoma is the abdomen (60–80%).<sup>21</sup> Presenting symptoms include abdominal pain (25% of patients have ileocaecal disease—either a right lower quadrant mass or pain from intussusception), distension, nausea and vomiting, and gastrointestinal bleeding.<sup>86,87</sup> The next most common site is the head and neck, including lymphadenopathy and involvement of the nasal or oropharynx, tonsils, or sinuses. The jaw is infrequently implicated. Bone marrow is infiltrated in roughly 20% of patients. Some cases are classified as Burkitt's leukaemia and are characterised by extensive marrow infiltration (more than 25% blasts), with possible bone pain as a presenting feature. Rare presenting sites include the mediastinum, CNS, skin, testes, breasts, and thyroid gland.

Patients with endemic Burkitt's lymphoma most frequently present with jaw or periorbital swellings, or abdominal involvement (of retroperitoneal tissue, gut, ovary, or kidney).<sup>88</sup> 15% present with sudden paraplegia and incontinence. Infiltration of bone marrow is rare. Jaw involvement is common in young children (peak ages of incidence 3–7 years).<sup>89</sup> In low-income countries, such as in sub-Saharan Africa, many children present with advanced disease. In a study of 84 Malawian children with Burkitt's lymphoma, 26 (31%) presented with facial disease only and 52 (62%) with abdominal disease; 58 (69%) had St Jude stage III or IV disease.<sup>88</sup> Patients are commonly malnourished at diagnosis.<sup>90</sup>

### Histopathology and immunocytochemistry

Burkitt's lymphoma is a highly aggressive B-cell non-Hodgkin lymphoma characterised by monomorphic medium-sized cells with a very high proliferation rate (figure 4). The cells are intermediate in size and contain coarse chromatin and prominent basophilic nucleoli. Some plasmacytoid and atypical variants show more nuclear pleiomorphism. In tissue sections, typically the cells seem to be moulded and the cytoplasm is deeply basophilic with squared-off cytoplasmic margins. The proliferation index is almost 100%, with a high turnover shown by increased apoptosis. A “starry sky” appearance is due to scattered tingible-body-laden macrophages that contain apoptotic tumour cells.<sup>43</sup> The cells are always of B-cell lineage (CD20 positive and CD79a positive). CD10 and Bcl-6 are commonly coexpressed, but the cells are generally negative for Bcl-2. There is a scarcity of T cells in the background.<sup>91</sup> Epstein-Barr-encoded RNA can be identified by fluorescence in-situ hybridisation. Classification is difficult when the cells have the morphology of



**Figure 4: Burkitt's lymphoma**

(A) Classic Burkitt's lymphoma (haematoxylin and eosin stain) with starry sky appearance under microscope. (B) Immunocytochemistry of Burkitt's lymphoma showing Ki-67 (proliferation index) positivity (1), Bcl-6 positivity (2), CD20 positivity (3), and Bcl-2 negativity (4).

diffuse large B-cell lymphoma but the genetic and immunophenotypic features of Burkitt's lymphoma. Some of these cases are now classified as “B-cell lymphoma, unclassifiable, with features between diffuse large B-cell lymphoma and BL [Burkitt's lymphoma]”.<sup>92</sup> However, distinct molecular changes in Burkitt's lymphoma could provide a more reliable diagnosis.

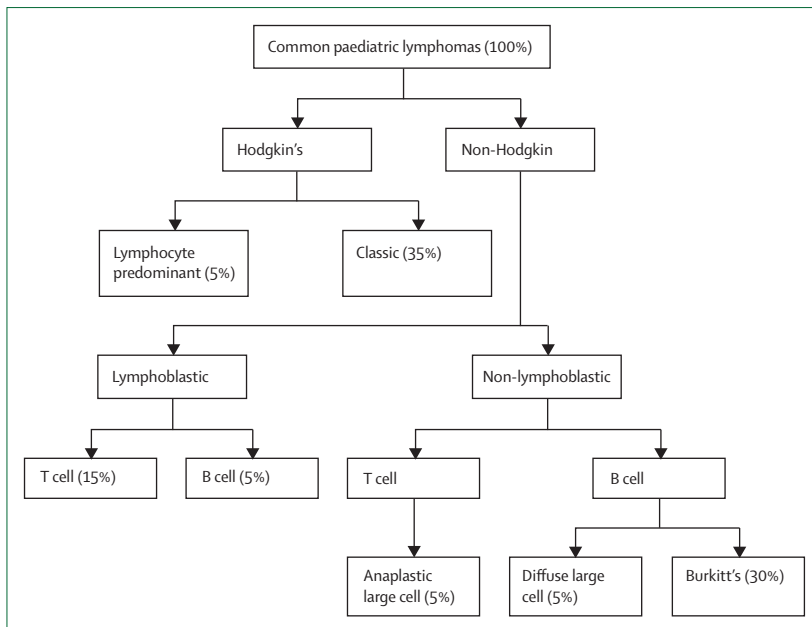


Figure 5: Common paediatric lymphoma subtypes<sup>105</sup>

### Cytogenetics and molecular studies

The translocation t(8;14)(q24;q32) is the hallmark of Burkitt's lymphoma and occurs in 70–80% of patients. The variant translocations, t(2;8)(p12;q24) and t(8;22)(q24;q11), occur in 10–15% of patients.<sup>93–95</sup> The molecular consequence of the three translocations is deregulated expression of the *MYC* oncogene, which has an essential role in cell cycle control. Deregulated expression arises as a result of juxtaposition of *MYC* to the enhancer elements of one of the immunoglobulin genes: the heavy chain at 14q32; the kappa light chain at 2p12; or the lambda light chain at 22q11. The three translocations have different breakpoints; activation of *MYC* occurs on the derived chromosome 14 in t(8;14), with breakpoints centromeric of *MYC*, whereas it occurs on the derived chromosome 8 in cases with t(2;8) and t(8;22), with breakpoints telomeric of *MYC*. In addition to this variation in breakpoint location based on the type of translocation, the breakpoints themselves are dispersed over several hundred kilobases. Although endemic, sporadic, and immunodeficiency-associated forms of Burkitt's lymphoma show different clustering of breakpoints of both chromosome partners, some overlap occurs between disease types. Generally, the endemic form has breakpoints upstream of *MYC* and originates from aberrant somatic hypermutation within the immunoglobulin gene loci, whereas the sporadic type breakpoints are closer to *MYC* and involve mostly the switch regions of the loci.<sup>96,97</sup> The differences in *MYC* breakpoint are probably due to the differences in EBV positivity between the endemic and sporadic forms.<sup>54</sup> These findings suggest that different pathogenetic mechanisms give rise to the translocations in the

different disease types. Accurate diagnosis depends on the presence of one of the three translocations.

Specificity is supported by a characteristic gene expression signature that includes a high level of *MYC* expression, which defines Burkitt's lymphoma as a homogeneous disease.<sup>91,98,99</sup> As well as the translocations involving the immunoglobulin gene loci, both the heavy and light chain genes are clonally rearranged in all cases. This feature can be exploited to monitor disease after treatment. *MYC* translocations are not completely specific for Burkitt's lymphoma and have been reported in other B-cell lymphomas. In up to 10% of Burkitt's lymphomas fluorescence in-situ hybridisation or other molecular techniques detect no evidence of chromosomal translocations involving *MYC*. Thus, *MYC* might be deregulated in these cases by other mechanisms.<sup>100,101</sup> Since these mechanisms are unknown, all other features should be completely typical for a diagnosis of Burkitt's lymphoma to be made.

Typically, Burkitt's lymphoma has a simple karyotype with increasing genetic complexity linked to disease progression.<sup>102</sup> In the CCG 9561 trial, patients who had an associated deletion of the long arm of chromosome 13 had significantly lower 5-year overall survival than those lacking that deletion (77% vs 95%).<sup>103</sup>

Overexpression of *MYC* has been shown to induce apoptosis through a p53-dependent pathway in normal B cells. Many Burkitt's lymphomas have mutations of the tumour suppressor gene, *TP53*, which could override the cellular apoptotic machinery. A p53-independent pathway can be circumvented via the downregulation of the cellular protein, BIM, which is an antagonist of the antiapoptotic protein, Bcl-2.<sup>104</sup>

### Diagnosis

#### High-income countries

Diagnosis of Burkitt's lymphoma should be confirmed by microscopy and immunocytological analysis (figure 5). The recommended approach is to remove and examine the most accessible disease-containing tissue. This sample could be a superficial lymph node or malignant pleural fluid. Excision biopsy of a lymph node is preferable to fine-needle aspiration, which does not provide sufficient tissue for all the investigations required. In some cases a laparotomy or laparoscopy is necessary to obtain tissue.

Several essential investigations should be done in patients with suspected Burkitt's lymphoma: full blood count, differential and film, ESR and urea and electrolyte measurements, liver function tests, a clotting screen (prothrombin time, partial thromboplastin time, D-dimers) to assess renal and hepatic involvement or dysfunction, serum lactate dehydrogenase and urate measurements (to assess tumour turnover), EBV status, and chest radiography. The radiograph should be done before any anaesthetic is given, to look for mediastinal lymph nodes with or without pleural effusions. CTs of chest and

abdomen show disease extent and can be done after tissue diagnosis unless airway obstruction is suspected. PET scanning is recommended, but is not essential. After confirmation of the diagnosis, bilateral bone-marrow aspirates, trephine cores, and cerebrospinal fluid should be examined for the presence of malignant cells.<sup>105</sup>

#### Low-income countries

Diagnostic facilities in low-income countries are likely to be restricted. The most common diagnostic test is cytological examination of a fine-needle aspirate. Results are commonly not available at the time of clinical decision making. Ultrasonography is useful to detect intraabdominal masses. Examination of cerebrospinal fluid and bone-marrow aspirates will detect CNS and bone-marrow involvement. If possible radiography should be done, as well as basic blood tests (such as full blood count, urea and electrolyte measurements, and liver function tests).

Common coinfections (eg, malaria, helminth infections) should be identified and treated before chemotherapy begins. HIV infection should be noted so that antiretroviral therapy can be given after chemotherapy for Burkitt's lymphoma. Tuberculosis and Kaposi's sarcoma should be ruled out either clinically or histologically.

#### Prognostic markers

Therapy is guided partly by clinical and histopathological staging with biological features beginning to inform therapeutic strategies. Clinically, prognosis is determined by staging, which includes extent of disease.<sup>106</sup> The St Jude/Murphy classification for Burkitt's lymphoma is the most common staging system used (panel).<sup>107</sup> Cytogenetic analysis is important in diagnosis to identify *MYC* deregulation and the presence of additional cytogenetic abnormalities, some of which have been shown to have prognostic significance.<sup>103</sup> PET is helpful to assess residual or recurrent disease. Burkitt's lymphoma produces a very strong signal with fluorodeoxyglucose-PET. Disease can be monitored regularly throughout treatment. Because of the high fluorodeoxyglucose avidity of the lymphoma, a single scan can provide valuable confirmation of recurrent disease.<sup>108</sup>

The role of minimal residual disease monitoring in Burkitt's lymphoma is not yet established. Some clinicians routinely monitor for it, although findings are not generally used to guide treatment. The presence of minimal residual disease in bone marrow (which is also a measure of minimal disseminated disease) is better applied to the prediction of high risk of treatment failure.<sup>102</sup> The construction of primers for use in monitoring of minimal residual disease is generally based on the original tumour material: 5VH and 7DH family primers in combination with one JH consensus primer for immunoglobulin heavy chain rearrangements,<sup>109</sup> BIOMED 1 primer set for kappa light chain deletions; and BIOMED 2 primer set for immunoglobulin kappa v-J.<sup>110</sup> Other strategies have been used such as patient-specific long-range PCR with

#### Panel: St Jude/Murphy staging system for non-Hodgkin lymphoma in children

##### Stage I

- A single tumour (extranodal) or single anatomical area (nodal), excluding mediastinum or abdomen
- A single tumour (extranodal) with regional node involvement, on same side of the diaphragm

##### Stage II

- A single tumour (extranodal) with regional node involvement
- On same side of the diaphragm:
  - Two or more nodal areas
  - Two single extranodal tumours, with or without regional node involvement
- A primary gastrointestinal tract tumour (usually ileocaecal) with or without associated mesenteric node involvement, grossly completely resected

##### Stage III

- On both sides of the diaphragm:
  - Two or more nodal areas
  - Two single extranodal tumours
- All primary intrathoracic tumours (eg, mediastinal or pleural thymic)
- All extensive primary intraabdominal disease; unresectable abdominal disease, even if only in one area
- All primary paraspinous or epidural tumours, irrespective of other sites

##### Stage IV

- Any of the above with initial CNS or bone-marrow involvement (only if <25% of the marrow is composed of Burkitt's cells)

primers related to the t(8:14) translocation and primer pools from the immunoglobulin V<sub>H11-117</sub>.<sup>111</sup> However, the most accurate analysis uses primers determined by the original tumour material. Assessment of prognosis by retrospective molecular profiling (eg, array-based comparative genomic hybridisation and gene-expression profiling) does not seem to offer any advantages over standard morphology and immunocytochemistry.<sup>112</sup>

In low-income countries, disease staging and response to treatment (including ultrasonography of the abdomen) might be the only prognostic guides available.

#### Management

##### High-income countries

Treatment of Burkitt's lymphoma in most centres is guided by the FAB LMB study (cooperative study between the Children's Cancer Group, the Société Française d'Oncologie Pédiatrique, and the UK Children's Cancer Study Group)<sup>86,87</sup> or Berlin–Frankfurt–Münster protocols. The former consists of initial cytoreduction with cyclophosphamide, prednisolone, and vincristine, followed by more intensive chemotherapy in varying combinations. The risk of pronounced tumour lysis is high in the first few days of therapy, but the use of urate oxidase has reduced this danger substantially. Because of the toxic effects of these protocols, sophisticated supportive care is needed, which is not possible for most low-income countries.

Management of Burkitt's lymphoma can be divided into three broad groups of patients. Children with localised

disease that has been completely removed surgically need only two cycles of moderately intensive chemotherapy such as cyclophosphamide, vincristine, prednisolone, and doxorubicin. Children with residual or stage III disease need at least four cycles of dose-intensive chemotherapy, such as two cycles of cyclophosphamide, vincristine, prednisolone, doxorubicin, and high-dose methotrexate, followed by two cycles of cytarabine and high-dose methotrexate with concurrent intrathecal treatment. Children with CNS or bone-marrow involvement are given similar treatment to the second group, but receive up to eight courses of dose-intensive treatment. This therapy typically involves two courses of cyclophosphamide, vincristine, prednisolone, doxorubicin, and high-dose methotrexate followed by two courses of high and low doses of cytarabine, and etoposide) and four courses of maintenance with varying combinations of vincristine, prednisolone, high-dose methotrexate, cyclophosphamide, doxorubicin, cytarabine, and etoposide. Intrathecal therapy is given alongside systemic chemotherapy.

The use of rituximab (anti-CD20) in primary therapy has been assessed, and some small single-centre studies report encouraging results.<sup>113</sup> Data are awaited from a Children's Oncology Group pilot study on toxic effects (ANHL01P1) in which rituximab was given to patients with stage III and IV Burkitt's lymphoma. The next UK trial will randomise the use of rituximab for stage III and IV patients.

#### Low-income countries

Therapy needs to be modified in accordance with local conditions to avoid unacceptable treatment-related mortality (table). The intensity of treatment is determined by the amount of available supportive care, a child's tolerance of chemotherapy, and the extent of comorbidities. In Malawi, for example, the treatment for Burkitt's lymphoma of all stages is intravenous cyclophosphamide (40 mg/kg on day 1 and oral cyclophosphamide 60 mg/kg on days 8, 18, and 28). Intrathecal hydrocortisone (12·5 mg) and methotrexate (12·5 mg) are given with each treatment cycle. The cost of this 28-day treatment is less than US\$50.<sup>88</sup> Previous attempts to use intensive treatments with high-dose methotrexate resulted in unacceptably high treatment-related mortality (11 of 42 participants).<sup>119</sup>

In a French-African Paediatric Oncology Group study, two moderately intensive modified LMB 89 protocols (including high-dose methotrexate and cytarabine) were used in several French-speaking African countries.<sup>114</sup> Of 306 patients, 71 (23·2%) died during treatments; 40 (13·1%) deaths were attributed to infection.<sup>114</sup>

Adequate and timely supportive care, even if not as intensive as in high-income countries, is essential, and should include measures to prevent and manage tumour lysis syndrome, nutritional support (malnutrition is associated with chemotherapy-related neutropenia<sup>90</sup>), antiemetics, transfusion support, and a local fever protocol. In low-income countries, many patients do not

complete the full course of treatment.<sup>120,121</sup> Travel distances and expense, treatment costs, and poor knowledge of the disease all contribute to non-completion.<sup>121,122</sup> Ideally, medical treatment would be free to the patient and appropriate social support would be provided to enable treatment to be completed.

#### Outcome

The outcome for sporadic Burkitt's lymphoma in high-income countries is excellent with an overall cure rate of roughly 90%. In most studies all B-cell non-Hodgkin lymphomas and B-cell leukaemias are treated similarly. Separate subanalyses of children with Burkitt's lymphoma are not always published. Children with resected stage I and II disease have event-free survival and overall survival above 98%.<sup>17</sup> Those with stage III and IV disease do less well if lactose dehydrogenase concentrations are more than twice normal values, if response to induction with cyclophosphamide, prednisolone, and vincristine is poor, or if CNS disease is detected at presentation (5-year event-free survival is 84%).<sup>17</sup> Without these adverse prognostic features, the 5-year event-free survival is greater than 92%.<sup>17</sup>

Treatment has pronounced acute toxic effects. Extended periods of inpatient chemotherapy are necessary, with long periods of haematological toxic effects and mucositis, as well as a risk of severe infection. Initial tumour lysis is another possible adverse event, although the use of urate oxidase has reduced greatly the need for dialysis. Improved supportive care has contributed to better outcomes.

Relapse of Burkitt's lymphoma, which most commonly occurs within 6 months of end of treatment, has a poor prognosis, probably because the most intensive chemotherapy regimens have already been used, and thus few drug choices remain. In low-income countries, where treatment is less aggressive, more children can be rescued at relapse.<sup>123</sup> Use of more intensive chemotherapy regimens, such as ifosfamide, carboplatin, and etoposide or ifosfamide, etoposide, and high-dose cytarabine, often with allogeneic bone-marrow transplantation and adjuvant rituximab, has achieved salvage rates of up to 25%.<sup>113,124</sup>

	Study site	Year	EFS%	TRM%
Hesseling et al <sup>88</sup>	Malawi	2009	48	5
Harif et al <sup>114</sup>	Africa	2008	61	23
El Kababri et al <sup>115</sup>	North Africa	2009	60	19
Klumb et al <sup>116</sup>	Brazil	2009	80	1
Chantada et al <sup>117</sup>	Argentina	2009	83	5
Patte et al <sup>118*</sup>	Europe	2001	93 (all stages)	..
Gerrard et al <sup>117*</sup>	Europe	2001	99 (localised)	..

Intensity of treatment and gross domestic product increase from top to bottom of the table. EFS=event-free survival. TRM=treatment-related mortality. \*The European studies cover all B-cell non-Hodgkin lymphoma and not Burkitt's lymphoma in isolation.

Table: Treatment regimens and outcomes in paediatric Burkitt's lymphoma

In low-income countries, treatment failure can be caused by incomplete treatment, treatment-related mortality, late presentation, or relapse or progression of disease. Malawian patients treated with a simple regimen of four cycles of cyclophosphamide had a 1-year event-free survival of about 50%.<sup>119</sup> Treatment-related mortality was roughly 5%.<sup>88,119</sup> 1-year event-free survival is a reasonable indicator of long-term survival in patients with endemic Burkitt's lymphoma because the risk of relapse is 5% or less after 1 year.<sup>125</sup>

### Adult Burkitt's lymphoma

Burkitt's lymphoma in adults is uncommon with an annual incidence of about 1200 patients in the USA. The disease occurs at any age, although 59% of patients are older than 40 years. As in children, in adults the disease can be associated with HIV infection or other immunodeficiencies.<sup>126</sup> Outcome in adult patients has been poor, but is improving. No randomised therapeutic trials have been done for adult Burkitt's lymphoma.

Adults present with rapidly developing disease, commonly in the abdomen, and symptoms such as weight loss, night sweats, and unexplained fever. Extranodal disease is common, especially in bone marrow (70%) and the CNS (40%).<sup>126</sup> Diagnosis and staging are urgent because treatment should be started as soon as possible. Staging should always include sampling of bone marrow and lumbar puncture. Tumour lysis syndrome can occur even before treatment, and incidence usually increases with therapy. Aggressive prophylaxis for and treatment of tumour lysis syndrome must be started immediately after diagnosis is confirmed.

Aggressive high-dose therapy is needed for adult Burkitt's lymphoma. However, interpretation of response is difficult because most studies of this approach have been done with a single protocol in mainly young adults. The regimen generally used in the UK and USA is cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and high-dose cytarabine. In a study of 54 patients (median age 24 years), 2-year survival was 89%.<sup>127</sup> 2 year survival of about 70% has been reported in patients older than 65 years treated with modified regimens.<sup>128,129</sup> Other approaches have used paediatric regimens for acute lymphoblastic leukaemia, which led to survival of roughly 71%.<sup>130</sup> A Dutch study used intensive chemotherapy and consolidation with high dose carmustine, etoposide, cytarabine, and melphalan and autologous stem-cell rescue (73% event-free survival at 5 years).<sup>131</sup>

Older patients have poorer outcomes than young patients on most therapies. The MD Anderson Cancer Center has trialled hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternated with methotrexate and cytarabine.<sup>132</sup> Although initial results were poor in patients older than 65 years, modification of the protocol by adding rituximab resulted in overall survival of 89% (29% in patients older than 60 years of age).<sup>133</sup>

Highly active antiretroviral therapy has allowed the use of high-dose chemotherapy regimens in HIV-positive patients with Burkitt's lymphoma. When 63 HIV-infected patients (median age 40 years) with advanced-stage disease were treated with the LMB 86 regimen (escalated cyclophosphamide, doxorubicin, vincristine, and prednisolone and consolidation with cytarabine and etoposide), the rate of complete remission was 70%, whereas 2-year overall survival was 47%; seven patients died from treatment-related causes. A high CD4-cell count and progression-free disease were predictors of improved survival.<sup>134</sup> Other intensive regimens with initial high response rates in HIV-positive patients with Burkitt's lymphoma have also been used.

Very elderly patients (older than 75 years) who are unfit for intensive therapy are generally treated with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab combined with intrathecal chemotherapy. Treatment is given with palliative rather than curative intent. Overall results for adults with Burkitt's lymphoma are improving, although older and HIV-infected patients remain a difficult challenge.

### Future

In low-income countries better diagnostic testing is needed. When only morphology is available, tumours are probably incorrectly classified as Burkitt's lymphoma. Additionally, a high standard of supportive care and medical infrastructure is necessary to deliver the most effective therapy. New, effective, and inexpensive therapies are needed for low-income countries. One possibility is to use compounds with histone deacetylase inhibitor activity as adjuvant therapy.<sup>135</sup> These agents stimulate tumour cells to differentiate and undergo apoptosis, and also induce virus lytic replication in EBV-positive tumours. Tumours with some viral replication have been shown to be more sensitive to chemotherapy than those without any replication.<sup>136,137</sup> For example, sodium phenylbutyrate induces EBV lytic replication in susceptible B-lymphocyte cultures.<sup>138</sup>

With improved molecular profiling and understanding of the cause of Burkitt's lymphoma, targeted therapy will be developed that still has excellent cure rates but has reduced toxic effects. Potential targets could include the *MYC* oncogene, DNA methyltransferase inhibitors, cyclin-dependent kinase inhibitors, and proteasome inhibitors. As further biological factors are identified, more targeted therapies will probably be developed.

In the 1980s Guy de Thé described Burkitt's lymphoma as "the Rosetta stone of cancer".<sup>139</sup> This description remains true now. In attempting to understand Burkitt's lymphoma, much is still to be learnt about how all cancers develop, grow, and are treated.

### Contributors

All the authors contributed to the writing of this paper and have seen and approved the final submitted version.



**Conflicts of interest**

We declare that we have no conflicts of interest.

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