

Burkitt Lymphoma PI Burkitt-1

MODIFIED LMB PROTOCOL

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on behalf of the

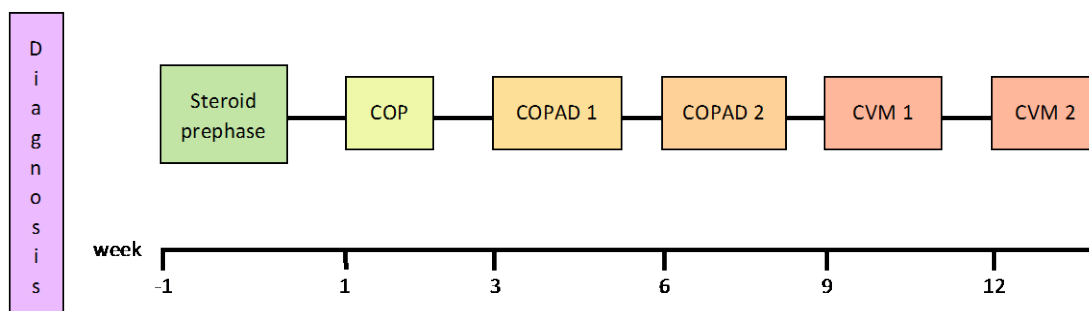
NCCN Pacific Island Working Group

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Treatment Schema



Week Phase

-1	Steroid pre-phase with hyper hydration and allopurinol
1	COP
3	COPAD 1
6	COPAD 2
9	CVM 1
12	CVM 2

Initial Diagnostic investigations

1. FBC, differential count and blood film, and ESR
2. Coagulation
3. Electrolytes and liver function tests, including Phosphate and Calcium
4. Creatinine, urea and urate
5. CXR – do before any invasive procedures to exclude a mediastinal mass.
6. US Scan of abdomen
7. CT Scan of neck, chest, abdomen and pelvis
8. Bilateral bone marrow aspirates and trephine biopsy
9. LP for CSF cytology
10. Biopsy – excision biopsy preferred. Request histology and immunohistochemistry
11. Cytogenetics – optional or can be done where there is doubt about the diagnosis (Fiji to arrange with Christchurch)

Chemotherapy courses

Course 1	COP: cyclophosphamide, vincristine, prednisone and IT MTX
Course 2	COPAD 1: cyclophosphamide, vincristine, prednisone, doxorubicin and IT MTX
Course 3	COPAD 2: cyclophosphamide, vincristine, prednisone, doxorubicin and IT MTX
Course 4	CVM 1: cyclophosphamide, vincristine, methotrexate and IT MTX
Course 5	CVM 1: cyclophosphamide, vincristine, methotrexate and IT MTX

(These Background sections are reproduced, with permission, from Molyneax *et al* Lancet 2012)

Background

The WHO classification of Burkitt's lymphoma describes three clinical variants: endemic, sporadic (the predominant type found in non-malarial areas), and immunodeficiency-related. 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. This sporadic-type Burkitt's lymphoma accounts for 1–2% of adult lymphomas and 30–40% of childhood non-Hodgkin lymphomas in Europe and North America. 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.

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. The annual incidence has been estimated at 40–50 per million children younger than 18 years. In these high-risk areas endemic Burkitt's lymphoma comprises about half of all childhood cancer diagnoses and up to 90% of 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. 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. Immunodeficiency-associated Burkitt's lymphoma occurs at an incidence of 22 per 100 000 person-years in the USA.

Clinical presentation:

The most common site of presentation in sporadic Burkitt's lymphoma is the abdomen (60–80%). 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. 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). Approximately 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).

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. Patients are commonly malnourished at diagnosis.

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. The cells are intermediate in size and contain coarse chromatin and prominent basophilic nucleoli. Some plasmacytoid and atypical variants show more nuclear pleomorphic. 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. 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. Epstein-Barr-encoded RNA can be identified by fluorescence in-situ hybridisation.

Classification is difficult when the cells have the morphology of 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]”. However, distinct molecular changes in Burkitt's lymphoma could provide a more reliable diagnosis.

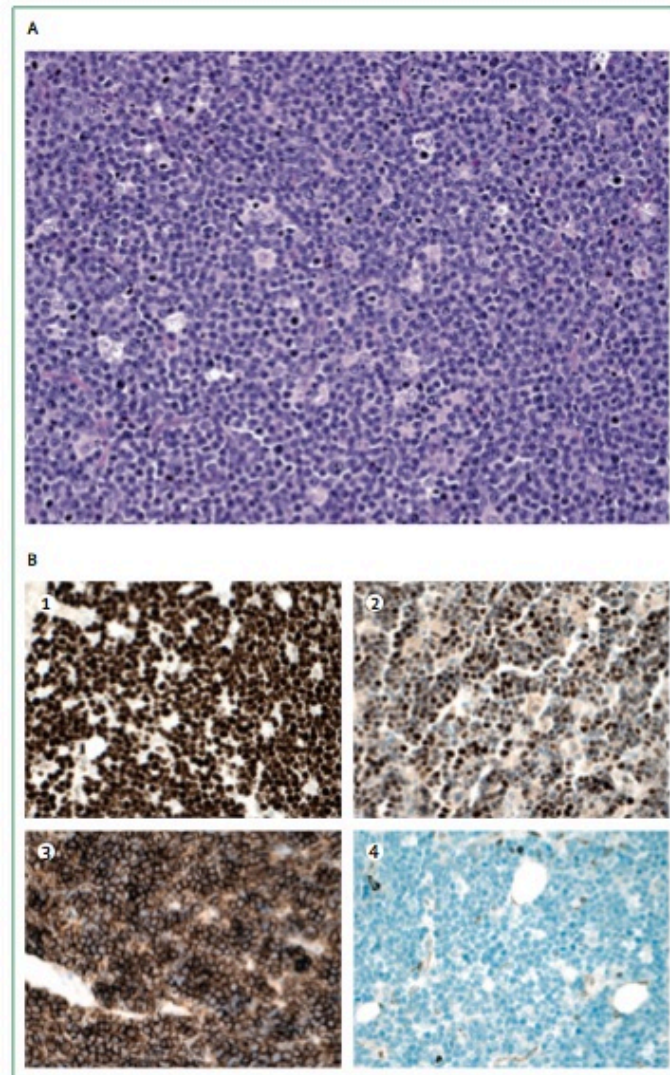


Figure 4: Burkitt's lymphoma
 (A) Classic Burkitt's lymphoma (haematoxylin and eosin stain) with starry sky appearance under microscope.
 (B) Immunocytochemistry of Burkitt's lymphoma showing Ki-67 (proliferation index) positivity (1), Bcl-6 positivity (2), CD20 positivity (3), and Bcl-2 negativity (4).

(Figure 4 from Molyneux et al Lancet 2012)

Cytogenetics and molecular studies:

Typically, Burkitt's lymphoma has a simple karyotype with increasing genetic complexity linked to disease progression. 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. 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*.

While cytogenetic studies are a routine part of the diagnostic assessment of children presenting to Child Cancer Centres such as Starship, Auckland and CHOC, Christchurch, these do not inform current management and do not inform treatment planning. However, where there is doubt about the diagnosis, a FISH analysis of the diagnostic biopsy to detect the t(8;14) translocation may be helpful.

Diagnosis

Diagnosis of Burkitt's lymphoma should be confirmed by microscopy and immunocytological analysis (figure 5) if available. 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.

Clinical examination:

Thorough general examination; examine all nodal regions, ENT, orbits and fundi, CVS, Respiratory exam. Abdominal exam, document liver and spleen size, examine testes. CNS – cranial nerves and routine peripheral nerve examination. Establish nutritional status and consider clinical signs of concurrent infections such as TB and HIV (if at risk).

Investigations:

Essential investigations are:

1. FBC, differential count and blood film, and ESR
2. Coagulation
3. Electrolytes and liver function tests, including Phosphate and Calcium
4. Creatinine, urea and urate
5. CXR – do before any invasive procedures to exclude a mediastinal mass.
6. US Scan of abdomen
7. CT Scan of neck, chest, abdomen and pelvis
8. Bilateral bone marrow aspirates and trephine biopsy
9. LP for CSF cytology
10. Biopsy – excision biopsy is preferred. Request histology and immunohistochemistry
11. Cytogenetics – optional or can be done where there is doubt about the diagnosis (Fiji to arrange with Christchurch)

Staging:

Several different staging systems are in use – but the St Jude/Murphy Staging is most commonly used for the assessment of lymphoma in childhood. While disease stage is needed for using a risk adapted approach to the treatment of Burkitt Lymphoma in Child Cancer Centres, most cases of Burkitt Lymphoma presenting in the Pacific will be advanced stage

and will benefit from treatment according to the LMB based strategy described below; no risk based stratification will be used.

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 paraspinal 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)

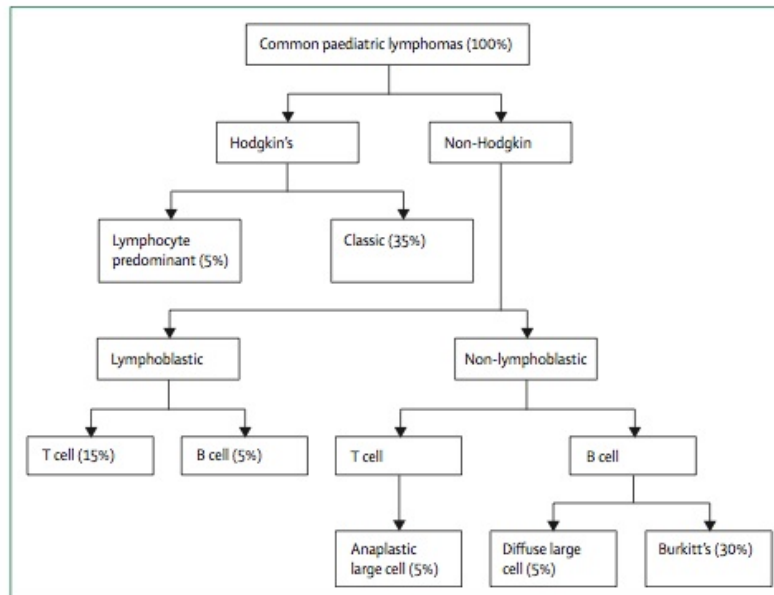


Figure 5: Common paediatric lymphoma subtypes³⁹⁵

Treatment

This Pacific Island Burkitt Lymphoma guideline is based on the French LMB Burkitt Lymphoma protocol with several modifications to provide children a very good chance of cure within the resources available.

Initial Supportive Care

The major clinical problems at diagnosis or immediately following the start of treatment are;

- Tumour Lysis Syndrome (with the potential for acute renal failure), - spontaneous TLS may be present before the start of any treatment
- Infection – at diagnosis and during therapy
- Complicated disease-related malnutrition
- Other potential problems at diagnosis include, mediastinal mass with airway or SVC obstruction, pericardial effusion, pleural effusion, and CNS disease

1. Admit to ward with barrier isolation
2. Treat fever with broad spectrum antibiotics – avoid aminoglycosides in the initial phase due to the risk of renal impairment
3. Fluconazole and Cotrimoxazole prophylaxis as per ALL protocol
4. Transfuse if necessary
5. Nasogastric tube for early commencement of NG feeding.
6. Allopurinol – start 24 hrs before commencing corticosteroids and continue for 7 days
7. Hyper hydration at 125 ml/m²/hr (3L m²/day) to maintain a urine output >3ml/kg/hr as per ALL induction protocol (½ Normal saline or 1/5th Saline – no KCL). If satisfactory urine output is not achieved, increase fluid rate to 150 ml/m²/hr

Steroid Prephase;

Once pre-hydrated with adequate urine output start a steroid pre-phase with Prednisone 20mg/m²/day (Day 1-2), increase to 40mg/m²/day (Day 3-4) and 60mg/m²/day (Day 5-7) – give in 2 divided doses.

1. Diagnostic LP – give first Intrathecal Methotrexate in age related doses (see below)
2. Check Electrolytes, K⁺, PO₄, Ca, Cr, urea, urate, twice daily – monitor for hyperkalaemia, hyperphosphataemia, hypocalcaemia and hyperuricaemia; treat metabolic disturbance as per Tumour Lysis Syndrome protocol
3. Hyper hydration should continue until clinical resolution of lymph nodes, resolution of any metabolic evidence of tumour lysis syndrome and return of normal renal function.
4. Burkitt lymphoma usually responds to steroids with the rapid resolution of lymph nodes
5. If the child has significant co-morbidity such as a very poor nutritional state or concurrent infection, complete the 7-day steroid pre-phase and reassess.
6. If there is control of disease as evidenced by resolving lymph nodes, consider a 1 week period of nutritional support and treatment for infection before commencing chemotherapy Course 1 (COP) – But continue prednisone at 60mg/m²/day. This approach should reduce the risk of treatment related mortality from infection and malnutrition.
7. Continue NG feeding support throughout treatment if malnourished
8. Omeprazole or ranitidine concurrently with steroids

Intrathecal Methotrexate: Age related dosing: Day 1 of steroid pre-phase or Course 1

Age years	Intrathecal Methotrexate dose mg
< 1	8
1 – 2	10
2 - 3	12
> 3	15

Chemotherapy Course 1: COP

COP is a cytoreductive phase of chemotherapy. Day 1 of COP commences on Day 8 from the start of the steroid pre-phase, or when patient has recovered from steroid pre-phase and is clinically stable. Delay the start of COP if there is ongoing severe infection, or renal impairment.

DAY	1	2	3	4	5	6	7
Vincristine 1.5 mg/m ²	↓						
Cyclophosphamide 300 mg/m ²	↓						
Prednisone 60 mg/m ² /day	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓
IT Methotrexate (age related doses) if not given in pre-phase	↓						

Chemotherapy administration:

- Vincristine 1.5 mg/m² IV push, Day 1
- Cyclophosphamide 300 mg/m² IV push, in Normal saline, Day 1
- Prednisone 60 mg/m²/day, PO in 2 divided doses, Days 1-7
- IT Methotrexate Age relate doses, Day 1 of steroid prephase or Day 1 of COP

Intrathecal Methotrexate: Age related dosing: intrathecal day 1 or steroid pre-phase or Course 1

Age years	Intrathecal Methotrexate dose mg
< 1	8
1 – 2	10
2 - 3	12
> 3	15

Chemotherapy Course 2: COPAD 1

Start COPAD 1 from Day 8 of the start of COP regardless of blood count so long as the patient is fit for ongoing treatment. If not continue with supportive care as required, but endeavour to start COPAD 1 by Day 12 from the start of COP

DAY	1	2	3	4	5	6	7
Vincristine 1.5 mg/m ²	↓						
Cyclophosphamide 250 mg/m ²		↓ ↓	↓ ↓	↓ ↓			
Doxorubicin 60 mg/m ²		↓					
Prednisone 60 mg/m ² /day	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓		
IT Methotrexate (age related doses)	↓						

Chemotherapy administration: COPAD 1

1. Vincristine 1.5 mg/m²/dose IV push, Day 1
2. Cyclophosphamide 250 mg/m² /dose IV push, in Normal saline, q12hrly, Day 2-4
3. Doxorubicin 60 mg/m²/dose, IV push, Day 2
4. Prednisone 60 mg/m²/day, PO, in 2 divided doses, Days 1-5
5. IT Methotrexate Age relate doses, Day 1
6. Hyper hydration Hyper hydrate during cyclophosphamide D2-4, monitor urine for haematuria with dipstix, if present increase fluid hydration rate.

Intrathecal Methotrexate: Age related dosing: COPAD 1

Age years	Intrathecal Methotrexate dose mg
< 1	8
1 - 2	10
2 - 3	12
> 3	15

Chemotherapy Course 3: COPAD 2

COPAD 2 is the same as COPAD 1.

Commence COPAD 2 with count recovery from COPAD 1 (neutrophils >1 x 10⁹/L and platelets > 100 x 10⁹/L). Expect to commence COPAD 2 between 14-21 days from the start of COPAD 1. Continue supportive care.

DAY	1	2	3	4	5	6	7
Vincristine 1.5 mg/m ²	↓						
Cyclophosphamide 250 mg/m ²		↓ ↓	↓ ↓	↓ ↓			
Doxorubicin 60 mg/m ²		↓					
Prednisone 60 mg/m ² /day	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓		
IT Methotrexate (age related doses)	↓						

Chemotherapy administration: COPAD 2

1. Vincristine 1.5 mg/m²/dose IV push, Day 1
2. Cyclophosphamide 250 mg/m² /dose IV push, in Normal saline, q12hrly, Day 2-4
3. Doxorubicin 60 mg/m²/dose, IV push, Day 2
4. Prednisone 60 mg/m²/day PO, in 2 divided doses, Days 1-5
5. IT Methotrexate Age relate doses, Day 1
6. Hyper hydration Hyper hydrate during cyclophosphamide D2-4, monitor urine for haematuria with dipstix, if present increase fluid hydration rate.

Intrathecal Methotrexate: Age related dosing: COPAD 2

Age years	Intrathecal Methotrexate dose mg
< 1	8
1 - 2	10
2 - 3	12
> 3	15

Chemotherapy Course 4: CVM 1

Commence CVM 1 with count recovery from COPAD 2 (neutrophils $>1 \times 10^9/L$ and platelets $> 100 \times 10^9/L$). Expect to commence CVM1 between 14-21 days from the start of COPAD 2. Continue supportive care.

DAY	1	2	3	4	5	6	7
Vincristine 1.5 mg/m ²	↓						
Cytarabine 100 mg/m ²		↓	↓	↓	↓	↓	
Methotrexate 30 mg/m ² /day	↓						
IT Methotrexate (age related doses)	↓						

Chemotherapy administration CVM 1

1. Vincristine 1.5 mg/m²/dose IV push, Day 1
2. Cytarabine 100 mg/m²/dose IV push, in Normal saline, daily Day 2-6
3. Methotrexate 30 mg/m²/day PO as a single dose, D1
4. IT Methotrexate Age relate doses, Day 1

Intrathecal methotrexate: Age related dosing: CVM1

Age years	Intrathecal Methotrexate dose mg
< 1	8
1 - 2	10
2 - 3	12
> 3	15

Chemotherapy Course 5: CVM 2

CVM 2 is the same as CVM 1. Commence CVM 2 with count recovery from CVM 1 (neutrophils $>1 \times 10^9/L$ and platelets $> 100 \times 10^9/L$). Expect to commence CVM2 between 14-21 days from the start of CVM1. Continue supportive care.

DAY	1	2	3	4	5	6	7
Vincristine 1.5 mg/m ²	↓						
Cytarabine 100 mg/m ²		↓	↓	↓	↓	↓	
Methotrexate 30 mg/m ² /day	↓						
IT Methotrexate (age related doses)	↓						

Chemotherapy administration CVM 2

1. Vincristine 1.5 mg/m²/dose IV push, Day 1
2. Cytarabine 100 mg/m² /dose IV push, in Normal saline, daily Day 2-6
3. Methotrexate 30 mg/m²/day PO as a single dose, D1
4. IT Methotrexate Age relate doses, Day 1

Intrathecal methotrexate; age related dosing: CVM2

Age years	Intrathecal Methotrexate dose mg
< 1	8
1 – 2	10
2 - 3	12
> 3	15

Follow-up

Compared to the outcomes reported for less intense protocols used in other resource challenged countries, we anticipate this protocol will have a 60-75% chance of cure. If Burkitt lymphoma relapses it tends to do so in the first 18-24 months from completion of treatment. Most relapses can be detected by routine history, clinical examination and blood counts. There is no need for routine radiological surveillance, but if clinical indicated a CXR, abdominal US scan and CT scan would be valuable to confirm clinical relapse. If CNS signs develop, an LP would confirm a CNS relapse.

Year 1 and 2 off therapy: Clinical review, physical examination and FBC 1-2 monthly

	Study site	Year	EFS%	TRM%
Hesseling et al ¹¹⁸	Malawi	2009	48	5
Harif et al ¹¹⁴	Africa	2008	61	23
El Kababri et al ¹¹⁵	North Africa	2009	60	19
Klumb et al ¹¹⁶	Brazil	2009	80	1
Chantada et al ¹¹⁷	Argentina	2009	83	5
Patte et al ^{119*}	Europe	2001	93 (all stages)	..
Gerrard et al ^{117*}	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