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1. Introduction

Follicular lymphoma (FL) is the most common form of indolent lymphoma and second most common form of non Hodgkin’s lymphoma presenting in 5/10,000 population/year with a median age of onset of around 60 years.

It shows a slight male preponderance and the majority (~80–90%) have advanced (stage 3 or 4) disease at presentation, with at least half demonstrating bone marrow involvement.

A proportion of limited stage FL cases may be considered cured after targeted radiotherapy but, for the vast majority of advanced stage cases, this remains an incurable disease.

While advanced stage disease may often be managed by observation alone at least initially, and some cases never need treatment, most will require systemic treatment and follow a pattern of relapsing and remitting disease over several years.

Moreover, therapy resistant disease progression and transformation to aggressive lymphoma are common causes of death. However, overall survival has improved in recent years in tandem with advances in both treatment and supportive care and median survival is now over a decade.

2. Early Diagnosis and Prevention

While certain environmental factors, lifestyle influences and genetic loci are associated with development of FL, no clear causative factor(s) exist for which screening or prevention of disease could be pursued.

However, stage and other measures reflecting disease extent/bulk are associated with survival so early presentation might contribute favourably to patient outcome by limiting these adverse parameters in cases of FL.

Local community engagement exercises to emphasise and raise awareness in the primary care setting regarding the potential presentation of lymphoma and when to refer for specialist review are encouraged.
3. Referral Pathways from Primary Care

3.1. Presentation

Patients typically present with persistent lymph node enlargement that may be accompanied by B symptoms (otherwise unexplained: temperature >38°C, drenching night sweats, loss of >10% body weight over 6 months). Less common presentations may include the sequelae of bone marrow suppression; skin lesions, bowel involvement; and other extra-nodal/organ site involvement.

3.2. Referral

The typical trigger for referral is a persistent (>4–6 weeks) suspected enlarged lymph node. In work-up to referral it is recommended that the following blood tests are performed as a minimum in primary care:

- FBC
- LDH
- renal profile
- LFTs
- calcium/bone profile
- HIV.

The urgent/2 week wait referral pathway should be utilised if lymphoma is suspected and early direct contact is encouraged between the primary care referring team and the receiving lymphoma managing centre as appropriate, particularly in systemically unwell or complex cases.

Similarly, specialist centres may receive internal referrals from other hospital teams (such as head and neck/ENT, breast surgeons, general surgeons, HIV/infectious disease teams regarding suspected or proven lymphoma) and organisation specific pathways should be followed.
4. Investigations/Diagnosis

4.1. Diagnosis

Definitive diagnosis requires examination of a tissue biopsy sample from an index lesion (most often an enlarged lymph node).

If a tissue/excision biopsy is not possible, then needle core biopsy can be performed acknowledging the limits this may impose on assessment of tissue architecture. Adequate material is essential and re-biopsy must be considered if samples are deemed insufficient.

Biopsies should be transferred promptly for initial macroscopic examination and slicing by a histopathologist and immersed in formalin for fixation; where possible, separate fresh frozen storage of part of the biopsy is recommended. For details of SIHMDS please see Annex 2.

A diagnosis can typically be made through histological examination of adequate tissue samples stained with haematoxylin and eosin (H&E) supported by immuno-staining for:

- CD20
- CD10
- Bcl-2
- CD5
- CD3
- (+/- Bcl-6, cyclin D1, CD43, κ and λ light chains).

Fluorescent in-situ hybridisation (FISH) or cytogenetic analyses may reveal evidence of the t(14;18)(q32;q21) that is present in the majority of FL; while molecular analysis using the polymerase chain reaction (PCR) may identify the corresponding IgH/Bcl-2 rearrangement.

Occasionally, flow cytometry analysis of cellular samples may aid diagnosis while rarely a frozen section panel may be required.

The diagnosis should be reported as per current WHO requirements.

4.2. Staging

A fundamental aspect of disease assessment is determining the anatomical extent (stage) of disease as this has direct implication on treatment selection and prognosis.

Staging can be performed by computed tomography (CT) imaging of the neck/chest/abdomen/pelvis ideally with both oral and intravenous contrast. Positron emission tomography (PET) with low dose CT (PET/CT) should be considered as an alternative.

Staging has routinely been documented according to the Ann Arbor system (with Cotswolds Revision) as indicated in Table 1 and it is recommended that recent updates to this approach detailed in the Revised Staging System for Primary Nodal Lymphomas are recorded.
Table 1. Summary of revised Ann Arbor staging classification for staging of lymphoma

Staging is according to the modified Ann Arbor staging.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prognostic groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of two or more lymph node regions (number to be stated) on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by localised involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (III_S) or both (III_SE)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. Organ should be identified by symbols</td>
</tr>
</tbody>
</table>

A – No symptoms
B – Fever, drenching night sweats, loss of more than 10% of body weight over 6 months
X: Bulky disease: >1/3 mediastinum at the widest point; >10cm maximum diameter of nodal mass
E: Involvement of single, contiguous or proximal, extra nodal site

4.3. Baseline investigations

Recommended as mandatory:

- Blood tests
  - FBC, blood film and consider PB immunophenotyping if lymphocytosis
  - Renal profile
  - LFTs
  - Bone profile/calcium
  - LDH
  - ESR
  - Immunoglobulins
  - Serum protein electrophoresis
  - Beta-2-microglobulin
  - Virology: HIV/HCV/HBV sAg + cAb (+/- HBV DNA)
- Bone marrow aspirate and trephine biopsy
- ECG
- CXR.

Consider in specific cases:

- Left ventricular ejection fraction determination (for example in older patients +/- cardiac risk factors under consideration for anthracycline treatment and patients planned for myeloablative treatment)
- Targeted further organ assessment if indicated by patient review/past medical history/results of other investigations
- Fertility team review, counselling and preservation measures
• Formal ENT assessment
• Pleural fluid/ascitic fluid/CSF for flow cytometry
• In young cases (aged 16 to 25 years old): Teenage and Young Adult (TYA) review.

### 4.3.1. Imaging

Standard is contrast enhanced CT scan NCAP

Positron emission tomography (PET) with low dose CT (PET/CT) has an emerging role in FL with its potential to even more rigorously determine stage 1 disease and identify sites of potential transformation suitable for biopsy as well as end of treatment response prediction of long-term survival.

Recently, revised international consensus guidelines\textsuperscript{3, 4} for response assessment in lymphoma support the role for PET/CT in FL disease staging and response assessment and it is a valid alternative to CT.

### 4.4. Prognosis

While the overall prognosis of FL has improved over recent years, it is also possible to risk stratify affected patients. Multiple clinical, radiological, haematological and biochemical aspects of FL correlate with outcome and these have been incorporated in various clinical risk models.

The follicular lymphoma international prognostic index (FLIPI and FLIPI2) each include five parameters, the presence or absence of which contribute to a score that can used to determine risk categories for progression free and overall survival (Table 2).

While these cannot yet prospectively determine management decisions, it is recommended that they are recorded at diagnosis as they may inform patient discussion.

Molecular aspects of both FL tumour cells and the surrounding micro-environment correlate with outcome but at present have no role in routine clinical management.

### Table 2. FLIPI and FLIPI2 prognostic systems

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FLIPI</th>
<th></th>
<th></th>
<th>FLIPI2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score = 1</td>
<td>Total score</td>
<td>Risk</td>
<td>OS (%)</td>
<td>Score = 1</td>
<td>Total score</td>
</tr>
<tr>
<td>Age</td>
<td>≥60</td>
<td></td>
<td></td>
<td></td>
<td>Age</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Stage</td>
<td>3 or 4</td>
<td>0–1</td>
<td>low</td>
<td>90.6</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>&gt;ULN</td>
<td>2</td>
<td>int</td>
<td>77.6</td>
<td>50.9</td>
<td>BM</td>
</tr>
<tr>
<td>Hb</td>
<td>&lt;120g/dL</td>
<td>3–5</td>
<td>high</td>
<td>52.5</td>
<td>35.5</td>
<td>Hb</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt;4</td>
<td></td>
<td></td>
<td>Max node</td>
<td>&gt;6cm</td>
<td></td>
</tr>
</tbody>
</table>

OS, overall survival; ULN, upper limit of normal range; LDH, lactate dehydrogenase; Hb, haemoglobin; Nodal sites, number of lymph node sites involved by lymphoma; int, intermediate; BM, bone marrow; B2M, beta-2-microglobulin; Max node, maximum diameter of largest involved lymph node.
5. Service Configuration across the LCA

All new diagnoses and cases under consideration for treatment should be reviewed and discussed in the local multidisciplinary team meeting (see Annex 1). It is recommended that cases requiring 2nd line treatment or greater are similarly discussed in the MDT particularly in view of the wide range of potential management options in this context.

The MDT referral form should include full patient identifier details including NHS number, relevant presenting history, associated symptoms including presence or absence of B symptoms, performance status (such as ECOG or Karnowsky score) and co-morbidities.

The recorded MDT outcome should include histological confirmation of diagnosis including grade (1/2, 3a or 3b as per WHO classification), stage and the relevant ICD code with recording of FLIPI(2) risk stratification recommended. A designated key-worker and the agreed management approach, expectant or treatment with specific modality and regimen indicated, should conclude the MDT outcome.

The completed MDT outcome form should be authorised by the MDT lead and distributed to the patient’s GP within 24 hours.

5.1. Levels of care

The systemic immuno-chemotherapy typically used to treat FL can be managed through BCSH level 1 or 2a facilities. In the less common scenarios when more intensive or complex regimens are administered (for example, such as when disease transformation occurs after anthracycline treatment in fitter patients) an appropriate higher level of care will be required.

Those cases proceeding to consolidation of response through high-dose therapy and autologous stem cell transplantation or allogeneic transplantation will be managed through a JACIE accredited transplantation service. See Annex 3 for JACIE-accredited centres in the LCA.
6. Patient Information and Support

If the diagnosis of follicular lymphoma is certain, patients should be informed that follicular lymphoma is a cancer of the blood, bone marrow and immune system. Their prognosis should be discussed including reference to co-morbidities that may influence management approach and to prognostic indices (FLIPI/FLIPI2) as appropriate. The risk of transformation to high-grade lymphoma should also be discussed. It is particularly important this process is done sensitively, in a timely manner and with consideration of any specific needs and feelings of the patient. Possible management options including appropriate treatment options, clinical trials and research studies should be discussed.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist. The LCA has produced a key worker policy (see Appendix 4: LCA Key Worker Policy) which sets out the definition of a key worker and provides an overview of their role and responsibilities.

The key worker/clinical nurse specialist should ensure that all patients are offered a holistic needs assessment (HNA) (see Appendix 5: LCA Holistic Needs Assessment Tool) at key pathway points, including within 31 days of diagnosis; at the end of each treatment regimen; and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

The Leukaemia & Lymphoma Research Fund (LLR) or Macmillan Cancer Support information booklets and the NHS Information Prescription are good sources of patient information at diagnosis. Patient leaflets are available for all treatment options and are also available for download on the following websites:

- [https://bloodwise.org.uk/](https://bloodwise.org.uk/)
- [www.lymphomas.org.uk/](http://www.lymphomas.org.uk/)
- [www.nhs.uk/conditions/non-hodgkins-lymphoma/Pages/Definition.aspx](http://www.nhs.uk/conditions/non-hodgkins-lymphoma/Pages/Definition.aspx)

Particularly important aspects of communication and patient information may include:

- the typically incurable nature of this disease
- the concept of watch and wait
- the inability to definitively predict when or even if treatment may be appropriate in such cases
- treatment intent when it is needed
- the range and types of therapy (including novel treatments and SCT)
- clinical trials
- the fact that follow-up will be long-term for a chronic typically incurable disease
- fertility
- treatment toxicity and late effects.
7. Treatment Recommendations

All patients with FL should be considered for entry to clinical trials appropriate to their aspect of disease management.

If not available at the managing centre then patients should be offered the opportunity to attend other centres within the LCA where relevant trials may be open for accrual. For clinical trials in FL currently open to recruitment across the LCA go to www.londoncanceralliance.nhs.uk/trials.

Ahead of any treatment the informed consenting process, including completion of local consent forms, should be completed and documented in the patient’s case-notes and communicated to their GP.

Management is critically dependent on FL histological subtype and disease stage.

National and international consensus recommendations for management should be consulted.5, 6

Consideration of fertility preservation should be made for those of reproductive age (NHS funding applies to men below the age of 55 and women below the age of 40). Please see the LCA Guidance and recommendations for referral to fertility services for more information on referral criteria and contact details for services.

7.1. Follicular lymphoma, grades 1, 2 and 3a

7.1.1. First line management

a) Limited stage disease (Stage 1A +/- 2A non-bulky)

FL is highly radiosensitive and the minority of cases presenting with limited stage 1 or 2 disease and no adverse factors may be considered for local radiotherapy utilising 24Gy over 12 fractions with curative potential.

A lower radiation dose of 4Gy split over 2 fractions may be appropriate in cases where a palliative approach is pursued or radiation toxicity requires particular consideration.

b) Advanced stage disease

The fundamental aspect of managing advanced disease is determining whether treatment is indicated. There is no overall survival benefit to initiation of anti-lymphoma therapy in advanced stage disease based solely on the presence of FL in the absence of other adverse factors.

Such indications for treatment include:

- rapidly progressive disease
- B symptoms
- pruritus
- vital organ compression/compromise
- significant bone marrow infiltration/haematopoietic suppression
- bone lesions
- renal infiltration
• ascites
• pleural effusion
• splenomegaly
• bulky disease including multiple (>3LNs each >3cm in diameter or single sites >7cm in diameter).

In the absence of these aspects then the expectant management (“watch and wait”/“watchful waiting”) approach may be undertaken.

However, some patients with bulky disease may be managed by watch and wait but are likely to have a shorter duration until progression that requires treatment.

Moreover, patients without any clear indication for treatment may prefer to be treated. Such cases should be counselled carefully regarding the lack of evidence for an overall survival benefit to initiation of treatment in this situation and their, understandable, concerns or worries regarding the watch and wait approach addressed as far as possible.

Similarly, patients with indications to recommend treatment may opt not to have treatment. They should be counselled and supported following their decision and closely monitored for evidence of disease progression.

c) Systemic treatment regimens

• Combination immuno-chemotherapy (rituximab + chemotherapy).
• Bendamustine + rituximab\(^7\) (BR; currently requires nCDF application\(^8\)) should be considered as front-line therapy.
• The rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (oncovin), prednisolone\(^9,10\) (R-CHOP) regimen is an option and should particularly be considered for FL that demonstrates clinically aggressive behaviour.
• Rituximab, cyclophosphamide, vincristine, prednisolone\(^10\) (R-CVP) is also an option for front-line therapy.
• In frail patients, single agent rituximab or rituximab + chlorambucil\(^10\) are options.

d) Consolidation of response

Maintenance rituximab given once every 2 months for 2 years is recommended if a complete or partial response is received following first-line systemic therapy.\(^11,12\)

e) Toxicity/co-morbidities/dose adjustments

Although these regimens are typically well tolerated, particular attention should be paid to the potential for therapy related toxicity regarding this or other regimens in this patient population who frequently have additional medical issues. Careful clinical and organ function assessment should be undertaken, dose modifications applied to the treatment regimen as necessary and appropriate supportive therapy (such as primary prophylactic G-CSF in selected cases) administered.
7.1.2. Second (and subsequent) line management

FL may relapse/progress and require (further) treatment. At progression or relapse, biopsy of index lesions is strongly recommended particularly to assess the possibility of disease transformation. If there is no evidence for transformation, there are multiple possible management approaches in FL in the second (or subsequent) line setting. Important aspects to consider include:

- patient preference
- initial response duration
- evidence of aggressive disease transformation
- previous treatment regimens
- toxicities
- patient fitness and co-morbidities
- emerging evidence supporting novel management approaches.

Again, the stage of disease helps guide management. In selected, patients (particularly the less fit) with limited stage disease a palliative approach with local radiotherapy as 4Gy split in 2 fractions may be appropriate.

In advanced disease, particularly if low bulk and in absence of other indications for treatment, selected patients may again be appropriate for watch and wait with close disease monitoring.

However, if systemic treatment is indicated at relapse/progression following initial management an important consideration is whether a patient is a candidate for consolidation of response to second line treatment by either high-dose chemotherapy with autologous haematopoietic stem cell transplantation (HDT + Auto-HSCT) or allogeneic haematopoietic stem cell transplantation (Allo-HSCT).

In fitter patients demonstrating a sufficient response to second line therapy then Auto-HSCT should be considered. Rarely, particularly in young, otherwise fit patients with rapidly progressive/early refractory disease then Allo-HSCT should be considered. Early liaison with the local transplantation centre is recommended.

a) Systemic treatment regimens

The optimal systemic regimen at second (or subsequent) line treatment is unknown. Determining the approach is particularly dependent on the preceding treatment regimen(s), response duration and patient fitness.

At second line, an alternative regimen should be considered (particularly if remission duration was less than 12-24 months). Re-treatment with a previous regimen may be appropriate in selected cases who experienced good response duration and lack of significant toxicity with appropriate consideration of fitness, co-morbidities and patient preference.

Rituximab-chemotherapy options at second or subsequent line treatment include:

- BR (currently requires nCDF application)
- R-CHOP
- R-CVP
The purine analogue fludarabine and rituximab are efficacious in combination with cyclophosphamide (FCR), mitoxantrone (R-FM), and cyclophosphamide + mitoxantrone (R-FCM). These might be considered as possible alternative second-line regimens but may have significant toxicity (full courses are not recommended)\(^5\) and should be avoided where possible in Auto-HSCT candidates due to the potential adverse effect on haematopoietic stem cell harvesting.

- Rituximab monotherapy\(^{13}\) or rituximab + chlorambucil may be appropriate in less fit cases.
- Other options to consider include early patient access schemes for emerging novel therapies. These typically require direct liaison with a pharmaceutical company and details of currently available schemes for such treatment options are available on the LCA website at [www.londoncanceralliance.nhs.uk/trials](http://www.londoncanceralliance.nhs.uk/trials).

**b) Consolidation of response**

Maintenance rituximab\(^{13}\) given once every 3 months for 2 years if a complete or partial response is received following second-line systemic therapy.

### 7.2. Follicular lymphoma, grade 3b

This should be managed as per [diffuse large B cell lymphoma (DLBCL) guidelines](#).

### 7.3. Transformation

FL has a risk of undergoing histological high-grade disease transformation\(^{14}\) to aggressive lymphoma (typically DLBCL) at a rate of around 3% of cases per year.\(^{15}\) If transformation is suspected, biopsy is recommended. Clinical indicators suggestive of possible transformation include:

- sudden rise in LDH to ≥twice upper limit of normal
- rapid discordant localised nodal growth (detected clinically or by imaging)
- new involvement of unusual extra-nodal sites (e.g. liver, bone, muscle, brain)
- new B symptoms
- new hypercalcaemia.

Transformation to DLBCL should be managed as per *de novo* DLBCL with the anthracycline containing R-CHOP regimen and consideration of consolidation of response by HDT + Auto-HSCT in patients fit enough for this approach. Early liaison with the local transplantation centre is recommended.

Previous treatment regimens represent a complicating issue and if transformation develops after anthracycline exposure then alternative regimens to R-CHOP (such as rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-DHAP) should be considered in patients fit enough for this approach.

In patients who are chemo-naïve at the time of transformation or those in whom the disease is localised/limited stage, outcomes are usually better and consolidation with high-dose therapy may not be indicated.

If FL cases in which transformation is the first indication for treatment are not HDT + Auto-HSCT candidates then rituximab maintenance should be considered if an adequate response to treatment is achieved.

In the rare cases in which FL undergoes transformation to a different high-grade histology, treatment should be specific to the respective aggressive lymphoma as appropriate.
8. Management of Common Disease and Treatment-related Complications

Patient review should include specific attention to screening for, prevention of where possible and management of treatment related complications both those developing acutely during treatment and longer-term issues/late effects.

8.1. Disease-related complications

These are rare but usually due to marrow involvement e.g. anaemia or symptomatic lymphadenopathy/hepatosplenomegaly.

Autoimmune cytopenia can occur rarely with follicular lymphoma or treatment of follicular lymphoma where drugs like fludarabine are used. The management is as per the CLL guidelines.

8.1.1. Hypogammaglobulinaemia\textsuperscript{17}

Refer to the CLL guidelines.
8.2. Treatment related complications

8.2.1. Hepatitis B infection

**Patient to receive chemotherapy or immunosuppressive therapy (this includes high-dose steroids, fludaribine, bendamustine, rituximab, ofatumumab or alemtuzumab)**

**Screen for HBV infection (HBsAg & HBcAb)**

**Past exposure**
(HBsAg -ve, HBcAb +ve)

- **Test for HBV DNA**
  - HBV DNA detectable
    - No
    - **Patient undergoing SCT or intensive immunosuppression**
      - No
      - Monitor LFTs, HBsAg & HBV DNA monthly
      - Or lamivudine prophylaxis
    - **HBsAg or HBV DNA becomes positive**
    - Yes
    - **Commence antiviral prophylaxis**
      - Commence lamivudine 1 week prior to start of chemotherapy and continue for 6 months after chemotherapy, post autologous SCT, following discontinuation of immunosuppression in allogeneic SCT or immune reconstitution. While the patient is on lamivudine, check HBV DNA titres monthly – this could be reduced to 3-monthly depending on clinical status. Monitor LFTs & HBV DNA monthly for up to 6 months after discontinuation of lamivudine prophylaxis. If there is an increase or non-response in HBV DNA levels on lamivudine then this should be switched to tenofovir.

**Current infection**
(HBsAg +ve, HBcAb +ve)

- **Assess for treatment or prophylaxis**
  - This should include:
    - Referral to a hepatologist in a specialist centre
    - Clinical assessment (acute hepatitis, cirrhosis)
    - Test for HBeAg, HBeAb and quantitative HBV DNA
    - LFTs
    - Consider a liver biopsy
  - **Evidence of hepatic inflammation/fibrosis**
    - (elevated ALT, HBV DNA >2000IU/ml, significant fibrosis with detectable HBV DNA)
    - No
    - Yes
    - **Commence antiviral therapy**
      - (tenofovir)

**No previous exposure**
(HBsAg -ve, HBcAb -ve)

- **Start therapy**
8.2.2. Cardiac complications

Cardiac risk factor assessment, cardiological investigations including cardiac function assessment (e.g. echocardiography) with cardiology review and follow-up cardiac function assessment if appropriate. Ensure surveillance, national screening programmes, health education and risk factor modification, late-effects clinics.

8.2.3. Nausea and vomiting

The LCA Acute Oncology Clinical Guidelines contain guidance for the acute management of patients with uncontrolled nausea and vomiting. They are not guidelines for prophylactic anti-emetic use in patients about to receive anticancer treatment. Do not assume that nausea and vomiting are chemotherapy related. Many chemotherapies have no significant emetic potential, while chemotherapy will seldom causes nausea and vomiting more than 1 week after administration. Therefore identify the cause before starting regular anti-emetics. Reflecting their mechanism of action, certain anti-emetics are indicated in specific situation.

8.2.4. Febrile neutropenia

Suspected or proven infection in a neutropenic patient is a medical emergency and is an indication for immediate assessment and prompt treatment with intravenous (IV) antibiotics within 1 hour of presentation to anywhere within the hospital. Patients who are neutropenic following anti-cancer treatment may initially appear well. However, infections may progress within hours to shock or death, especially when due to gram-negative bacilli. The LCA Acute Oncology Clinical Guidelines provide guidance to admitting clinicians when faced with a case of suspected infection and neutropenia in both solid tumour oncology and haematology-oncology. If there is clinical suspicion of neutropenic sepsis in existing inpatients, they should be treated within 1 hour of clinical onset, as defined by baseline observations, Early Warning Score (EWS) or clinical suspicion. Local policy should be followed for antibiotic cover.

Patients with neutropenic pyrexia or sepsis should be treated according to local protocols for neutropenic sepsis (and following National Institute for Health and Care Excellence (NICE) guidance). Refer to the LCA Acute Oncology Clinical Guidelines.

In addition, for haematology oncology patients the following are mandatory:

- urinalysis
- midstream specimen of urine
- chest X-ray
- swabs: throat (bacterial and viral), CVAD site if present and any other focal lesions as appropriate
- sputum and stool culture
- CMV, EBV, Adeno PCR if indicated.

Such patients should ideally be cared for by specially-trained nurses on a BCSH Level 2b-3 unit. The use of G-CSF is highly dependent upon the context of the disease and the chemotherapy protocol in which it is being used. G-CSF is used to hasten recovery of the neutrophil count, decrease risk of infection and reduce hospital stay. However, evidence supporting improved survival with G-CSF is lacking.


8.2.5. Tumour lysis syndrome (TLS) and hyperuricaemia

TLS is not a typical feature of FL as cases are generally low risk for this complication. Some cases, such as those with concurrent co-morbidities (such as renal impairment) or large disease bulk or those with aggressive transformation will be at increased risk. TLS should be managed according to published guidelines (see Annex 4 and Annex 5).\textsuperscript{16}

8.2.6. Second malignancies

Ensure surveillance, national screening programmes, health education and risk factor modification, late-effects clinics.
9. Supportive Care

Supportive care is very important for all patients with haematological malignancies. There are many aspects to consider and they are carefully documented in current clinical trial protocols. These protocols are available for download and should be consulted for precise details of appropriate supportive care, even if patients are not entering the clinical trial.

9.1. Infection prophylaxis

Hepatitis B: see 8.2.1 Hepatitis B infection.

Prophylactic G-CSF may be used in cases where the risk of febrile neutropenia is greater than 20%.

Patients receiving intensive chemotherapy should ideally be nursed in isolation rooms with appropriate protocols to prevent infections. Clean, neutropenic diets should be instituted and appropriate infection control measures should be undertaken. Prophylaxis and treatment of infection from presentation should be instituted based on local protocols with antibiotic choice largely dependent on local microbiological flora. For patients who will undergo intensive treatment schedules, a central venous access device should be inserted as soon as is safely possible.

9.2. Weight loss and dietetics

Referral for specialist dietetic input should be made in the following instances:

- Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
- If artificial feeding is being considered, a referral to the specialist dietitian should be made.
- Any patient with mucocitis should be referred for dietetic assessment, as well as for specialist speech and language assessment.
- Weight loss/malnutrition should be identified through the regular outpatient assessment of patients who a) are on treatment or b) are deemed at risk through other co-morbid or c) have post-treatment (including radiotherapy) complications as well as the weekly screening of those who may be inpatients.

9.3. Complex symptom management

Discuss with Specialist Palliative Care team for advice on symptom management e.g. pain, mucositis when there is no/poor response to standard interventions. If appropriate, referral can be made to the specialist palliative care team using the LCA referral form (see Appendix 7).
10. End of Treatment Information

An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA (see Appendix 5) and associated written care plan and should also include the discussion and provision of a comprehensive treatment summary. On successful completion of treatment, both the patient and their GP should be made aware of follow-up plans and potential future disease or treatment related issues.

10.1. Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of their treatment:

- **A treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information. The treatment summary should be completed by the named CNS/key worker with the patient and a copy sent to the GP and the patient (see Appendix 6: NCSI Treatment Summary).

- **A care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

**Recommendation:** An end of treatment consultation should be offered to every patient. This should include an end of treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

People should be offered access to a health and wellbeing clinic at the end of treatment. This should provide information to enable person to self-manage any expected consequences of their cancer and its treatment, as well as general health promotion information, including diet and physical activity.

The MDT outcome form and clinic letters will serve to communicate diagnosis, treatment initiation and new lines of treatment with the GP.

Lymphoma team, key worker and patient support group contact details should be reiterated and details of future follow-up arrangements provided.

Patients should be educated regarding the potential symptoms and signs that might indicate disease progression or recurrence and counselled on the need to re-present to the unit should these occur.
11. Follow-up Arrangements

The nature and frequency of follow-up review and investigations for patients will be somewhat tailored by their disease presentation, treatment type, treatment toxicities, disease related effects, co-morbidities and psycho-social factors.

However, an outline for clinic follow-up visits following completion of treatment includes:

- 3–4 monthly in year 1 and 2
- 6 monthly in year 3
- 6–12 monthly in years 4 and 5.

Further follow-up should be agreed with the patient after year 5. This may continue at 6–12 monthly intervals and (annual) late effects clinic attendances are encouraged particularly for assessment and follow-up of patients with long-term disease responses while remote (telephone) clinics may be appropriate in certain cases.

If a satisfactory interim imaging response was achieved, then subsequent imaging can be performed at ~1–3 months following end-of-treatment. A final CT scan can be performed one year after completion of therapy. Further surveillance imaging is not recommended.

Follow-up clinical reviews should include history taking and physical examination with particular reference to eliciting any evidence of progression/recurrence of disease or development of treatment related toxicities. Blood tests performed at review visits should include FBC and LDH as a minimum with renal, liver and bone profile tests advised.

All patients should be made aware of the risks of secondary cancers and participate in national cancer screening programmes, and of the increased risk of cardiovascular disease with the need for periodic monitoring of risk factors in general practice.
12. Rehabilitation and Survivorship

Issues in relation to rehabilitation and the long-term consequences of treatment should be monitored throughout the patient pathway and highlighted to the appropriate allied health professionals if required. Survivorship issues can relate to the effects of the disease process and/or management of long-term adverse effects of treatment. Please refer to LCA Survivorship Guidelines for more information. It may be particularly difficult for patients to reconcile and accept the typically incurable nature of follicular lymphoma. Particular individualised approaches may be necessary to address and manage patients’ concerns with involvement of dedicated oncology counselling and psychotherapy services.

Any patient experiencing or reporting reduced mobility and/or ability to perform activities of daily living should be referred for occupational therapy and physiotherapy assessment.

People reporting ongoing consequences such as fatigue, anxiety, pain should have a detailed assessment as to potential underlying causes (which should be treated as appropriate). Otherwise, they may be considered for non-pharmacological intervention, including but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

Onward referrals may include:

- physiotherapist/occupational therapist (fatigue management, rehabilitation)
- dietitian if symptoms impacting on intake/nutritional status especially in cases of GI disturbances and mucositis, weight loss
- speech and language therapist (weight loss, dysphagia or concerns regarding aspiration).

13. Research and Clinical Trials

Where possible, biobanking of all patient blood and tissue samples is encouraged in a certified facility within the context of an ethically approved research framework and in compliance with the Human Tissue Act.

Eligible patients should always be offered the opportunity to consider clinical trials for any stage of disease management. This may be either at the treating centre or within the LCA in another lymphoma centre. For an up-to-date list of all clinical trials which are currently recruiting patients with follicular lymphoma, please see the LCA website.

Occasionally, it may be appropriate to refer patients to centres outside the LCA for clinical trials open elsewhere and, in a reciprocal manner, centres within the LCA may occasionally receive referrals of patients from other integrated cancer systems. Such collaboration within and across cancer systems should be supported.
14. End-of-life Care

Common causes of death include lymphoma (treatment resistant disease progression or transformation), therapy related complications and infections.

Although predicting when death may occur is often inaccurate, it is important to consider and offer discussions with patients, and partners/relatives/carers/friends as appropriate, when it is apparent that disease or its complications are progressing and further treatment is futile.

Such matters require sensitivity and consideration of patients’ culture, beliefs, wishes and communications as well as those of their next of kin, in particular.

Where appropriate, patients should be asked as to their preferred place of death and local and national guidance on resuscitation decisions should be followed.

The best interests of the patient must be at the forefront of discussions and decision making regarding end-of-life care while early involvement of local palliative care teams (hospital and/or community) will optimally facilitate the formation of individualised end-of-life care. Input may be required from specialist palliative care teams which are available in the cancer units and centres affiliated to the LCA. See Appendix 7: LCA Specialist Palliative Care Referral Form for the LCA form for referral to specialist palliative care.
15. Specific or Miscellaneous Considerations

15.1. Fertility
See section 7: Treatment (page 11).

15.2. Follicular lymphoma in situ (FLIS)
This may be identified in excised lymph nodes. While progression to FL is uncommon, it is recommended that patients with FLIS are assessed for evidence elsewhere of overt FL.

15.3. Primary cutaneous follicular cell lymphoma (PCFCL)
PCFCL is a particularly indolent form of lymphoma that has excellent long-term survival and rarely disseminates from the skin.

Localised disease can typically be managed by excision or radiotherapy with curative intent.

For more extensive disease observation may be appropriate particularly given the slow progression of this entity while radiation, intra-lesional steroids or topical agents may control disease; only rarely is systemic therapy indicated.

15.4. Primary intestinal follicular lymphoma
This most commonly occurs in the small intestine and its clinical course mirrors that of nodal FL. It may be managed similarly, often with the watch and wait expectant management approach initially and treated only if disease is symptomatic or progresses; survival is very good even without any treatment.

15.5. Irradiated cellular blood products
Patients treated with bendamustine and purine analogues (such as fludarabine) have a life-long requirement to receive irradiated cellular blood products if such transfusions are ever required.

The proportion of patients this applies to will increase given the current role of bendamustine in first-line treatment of FL.

Patients should be counselled and empowered to “check and challenge” regarding blood products if required and be provided with the NHSBT information booklet and wallet card while the sticker is placed on their case-notes.

Local and national policies and procedures regarding the notification, need for and administration of irradiated blood products should be followed when patients have received these agents or haematopoietic stem cell transplantation.
References


2. IARC Lyon Eds Swerdlow et al. WHO Classification Tumours of Haematopoietic and Lymphoid Tissues. 2008.


8. www.blueteq.com/cdf/


10. NICE technology appraisal guidance 243. 2012; NICE.


12. NICE technology appraisal guidance 226. 2011; NICE.

13. NICE technology appraisal guidance 137. 2008; NICE.


### Annex 1: Multidisciplinary Teams (MDTs) and Constituent Hospital Trusts

<table>
<thead>
<tr>
<th>South East London MDT 1</th>
<th>Guy’s &amp; St Thomas’ NHS Foundation Trust/Lewisham and Greenwich NHS Trust (Lewisham Hospital and Queen Elizabeth Hospital)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South East London MDT 2</td>
<td>King’s College Hospital NHS Foundation Trust (including Princess Royal University Hospital)</td>
</tr>
<tr>
<td>South West London MDT 1</td>
<td>Kingston Hospital NHS Foundation Trust/St George’s University Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>South West London MDT 2</td>
<td>Epsom and St Helier University Hospitals NHS Trust/Croydon Health Services NHS Trust</td>
</tr>
<tr>
<td>South West London MDT 3</td>
<td>The Royal Marsden NHS Foundation Trust</td>
</tr>
<tr>
<td>North West London MDT 1</td>
<td>Imperial College Healthcare NHS Trust/The Hillingdon Hospitals NHS Foundation Trust/Chelsea and Westminster Hospital NHS Foundation Trust/West Middlesex University Hospital NHS Trust/Ealing Hospital</td>
</tr>
<tr>
<td>North West London MDT 2</td>
<td>London North West Healthcare NHS Trust (Northwick Park Hospital and Central Middlesex Hospital)</td>
</tr>
</tbody>
</table>
Annex 2: SIHMDS or Current Diagnostic Services and Contacts

**Guy’s & St Thomas’ NHS Foundation Trust**
Cytogenetics/Flow Lab
ViaPath Pathology
4th Floor, Southwark Wing
Guy’s Hospital
Great Maze Street
London, SE1 9RT

**Imperial College Healthcare NHS Trust**
Imperial Molecular Pathology Laboratory
G Block, North Corridor
Hammersmith Hospital
Du Cane Road
London, W12 0HS

**London North West Healthcare NHS Trust**
Processed centrally in TDL laboratories on-site for SIHMDS (in progress), cytogenetics/molecular to:
North West Thames Regional Genetics Service, Haematology Section
Northwick Park Hospital
Watford Road
Harrow, HA1 3UJ

**The Royal Marsden Hospital NHS Foundation Trust**
The Centre for Molecular Pathology
Downs Road
Sutton, SM2 5PT
Tel: 020 8915 6570
Immunophenotyping Tel: 020 8915 6517 or 020 8915 6518
Cytogenetics Tel: 020 8722 4232
Molecular Genetics Tel: 020 8915 6565

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**For APML diagnostic and MRD**
Dr Yvonne Morgan
Molecular Oncology Diagnostics Unit
GSTT Pathology, 4th Floor, Southwark Wing
Guy’s Hospital
Great Maze Street
London, SE1 9RT

**King’s College Hospital NHS Foundation Trust**
KingsPath: Clinical Diagnostic Pathology Service
Haematological Medicine
King’s College Hospital
Denmark Hill
London, SE5 9RS
Annex 3: JACIE-accredited Transplant Centres in the LCA

**Imperial College Healthcare NHS Trust**
Dr Eduardo Olavarria  
Consultant Haematologist  
BMT Programme Director  
Haematology Department  
ICHNT  
Hammersmith Hospital  
Du Cane Road  
London, W12 0HS  
Tel: 020 8383 3237  
Fax: 020 8742 9335  
Email: eduardo.olavarria@imperial.nhs.uk

**The Royal Marsden NHS Foundation Trust**
Dr Mike Potter via 020 8661 3670  
katrina.sharpe@rmh.nhs.uk  
Dr Chloe Anthias, contact details as above.  
Dr Mark Ethell, via 020 8661 3794,  
PA: janet.bromell@rmh.nhs.uk

**Department of Haemato-Oncology**
**The Royal Marsden NHS Foundation Trust**
RS11, 2nd Floor, Orchard House,  
Downs Road, Sutton,  
Surrey, SM2 5PT  
Tel: 020 8661 3670  
Fax: 020 8642 9634 (safe haven)  
Alternative email: katrina.sharpe@nhs.net

**St George’s University Hospitals NHS Foundation Trust**
Dr Mickey Koh  
Director: Stem Cell Transplantation  
Consultant Haematologist  
St George’s Hospital and Medical School  
Jenner Wing Corridor 6  
Blackshaw Road  
London, SW17 0QT  
Tel: 020 8725 3545  
Fax: 020 8725 2859  
Email: mickey.koh@stgeorges.nhs.uk

**King’s College Hospital NHS Foundation Trust**
Bone Marrow Transplant Team  
4th Floor, Hambleden Wing  
King’s College Hospital  
Denmark Hill  
London, SE5 9RS  
Tel: 020 3299 4694, 020 3299 5268
Annex 4: Guideline for the Management of Tumour Lysis Syndrome (TLS)

To be read in conjunction with Annex 5: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients.

TLS is life-threatening. Rapid lysis of tumour cells leads to the release of cellular contents into circulation resulting in hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia which may lead to acute oliguric renal failure and cardiac arrhythmias. TLS can occur spontaneously in tumours with a very high proliferative rate, and/or during induction treatment. It can be classified as laboratory TLS (no clinical manifestations) or clinical TLS (life-threatening clinical abnormalities). Symptoms during TLS/rasburicase include fever, haemolysis, headaches, vomiting, diarrhoea, rash and hypersensitivity reactions.

Prevention of TLS

1. Standard care is hydration and allopurinol and these help prevent TLS
2. Check urate, renal function and LDH prior to starting chemotherapy and hydrate with 3L/m² over 24 hours
3. For high risk patients rasburicase should be considered

Management (see separate rasburicase protocol): Rasburicase is to be used immediately prior to and during treatment-induction for the indications below and when authorised by a consultant haematologist.

TLS Screen is to be ordered 1–4 times per day according to patient’s clinical condition until resolves: urea, creatinine, uric acid, phosphate, potassium, corrected calcium and LDH (FBC if AML/ALL/CML/MPN).

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Diagnosis</th>
<th>Preventative Strategies</th>
</tr>
</thead>
</table>
| **High**   | Burkitt lymphoma  
Burkitt-type ALL  
AML or ALL with WBC >100 x 10⁹/L | 1. IVF (~3L/m²/day, to maintain UOP >100ml/m²/hr) or aggressive hydration as per chemotherapy protocols.  
2. Rasburicase* as per rasburicase protocol |
| **Moderate** | AML with WBC > 50 x 10⁹/L  
Other ALL  
High-grade NHL with bulky disease  
CML accelerated/blast phase, or where rapid response to therapy expected | 1. IVF (~3L/m²/day, to maintain UOP >100ml/m²/hr) or aggressive hydration as per chemotherapy protocols.  
2. Rasburicase* as per rasburicase protocol |
| **Minor**   | Other AML  
Myeloma  
Other lymphoma/CLL  
Other CML and MPN | Use allopurinol.  
Use rasburicase* where clinically indicated (high risk):  
High LDH (>ULN)  
Renal failure  
High proliferation index  
High uric acid (>420 umol/L or 7mg/ml) |

* No dose adjustment in renal/hepatic impairment. Ensure normal G6PD level prior to rasburicase (if low, use aggressive hydration & allopurinol).
References:


Annex 5: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients

Criteria for use

Rasburicase may be used only for the following indications, when authorised by a consultant haematologist or oncologist:

Urate oxidase (rasburicase) is an enzyme which catalyses the oxidation of uric acid to allantoin, which is more easily excreted in the urine.

**Used in the treatment of:**

- hyperuricaemia associated with high grade haematological malignancies
- prevention of complications of tumour lysis syndrome

**Indications (see also separate guideline):**

- Induction or salvage therapy of AML, ALL, high grade lymphoma, high grade multiple myeloma with
  - High LDH (>ULN)
  - Renal failure
  - High proliferation index (Ki67>80%; consider if Ki67>50%)
  - High uric acid (>420 umol/L or 7mg/ml)

Further to the above, consider using rasburicase in those patients unable to tolerate aggressive hydration.

**Protocol for use:**

1. Ensure patient (male or female) is G6PD negative prior to use (if positive, use aggressive hydration with allopurinol – consider higher doses based on risk of TLS and creat level).
2. Ensure aggressive hydration as per chemotherapy protocols.
3. At initiation of treatment, for uric acid levels of:
   a) < 420 umol/L (7mg/L), give a single 3mg dose of rasburicase.
   b) >420 umol/L (7mg/L), give a single 6mg dose of rasburicase.
4. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
5. Start allopurinol as per protocols the morning after rasburicase given.
6. Measure uric acid levels as per tumour lysis (TLS) protocols and at least daily until TLS resolved.
7. During TLS monitoring, if uric acid levels >20 umol/L (>0.3 mg/L), or renal failure worsens, give another 1.5–6 mg rasburicase, as indicated by level and clinical parameters of TLS.

**References:**


Special warnings and precautions for use

Allergic reactions may occur with this product, patients should be closely monitored and full resuscitation facilities should be at hand. Should any serious allergic or anaphylactic reaction occur treatment should be immediately discontinued and appropriate resuscitation given.

Caution should be exercised in patients with a history of atopic allergies.

Administration of rasburicase decreases serum uric acid to below normal levels, but has no direct effect in reversing hyperphosphataemia, hyperkalaemia and hypocalcaemia. If severe these abnormalities should be corrected following standard treatment guidelines.

There are limited data available to recommend the sequential use of rasburicase and allopurinol.

To ensure accurate measurement of uric acid plasma level during treatment with rasburicase, a strict sample handling procedure must be followed to minimise ex vivo degradation of the analyte. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
Appendices

Appendix 1: 2 Week Wait Referral Forms
- North West London
- South East London
- South West London

Appendix 2: Treatment of Children

Appendix 3: Treatment of Teenagers and Young Adults
- Teenagers and Young Adults PTC Referrals
- Teenagers and Young Adults MDT Proforma

Appendix 4: LCA Key Worker Policy

Appendix 5: LCA Holistic Needs Assessment Tool

Appendix 6: NCSI Treatment Summary

Appendix 7: LCA Specialist Palliative Care Referral Form

Appendix 8: LCA Referral Criteria to Specialist Palliative Care