Guidelines for the diagnosis and management of adult acute leukaemia within the East of England Cancer Alliance

Contents

1 Introduction

These guidelines outline the current management of acute leukaemia in the hospitals of the East of England Cancer Alliance.
These guidelines do not replace national guidelines but are a condensed summary of agreed local practice in line with them. In case of a discrepancy e.g. if a national guideline is updated, national guidelines should be followed.

2 Background

Acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) are relatively rare haematological malignancies.

The incidence of AML is 4.4 per 100,000. It is more common in the elderly, with two-thirds occurring in those over 60 years. The prognosis is influenced by age and cytogenetics: these factors may inform treatment strategies.

ALL is predominantly a disease of childhood. Adult ALL has an incidence of 1.2 per 100,000 with approximately 75% of B-cell and 25% of T-cell lineage.

3 Clinical presentation

Acute leukaemia usually presents with signs of bone marrow failure and is a medical emergency. Many cases will be identified by full blood count (FBC) and blood film analysis in the laboratory. Patients should be seen urgently by a haematology team.

4 Investigations

4.1 Establishing the diagnosis

Morphological examination of the blood film and bone marrow should be performed. Bone marrow, ideally accompanied by a blood film, should be sent to the Haematopathology and Oncology Diagnostic Service (HODS) to confirm the diagnosis. For details see HODS http://www.cambridgehods.com. Exceptions to this include the very elderly where diagnosis can be confirmed on peripheral blood morphology and immunophenotyping alone.

It is particularly important to establish the diagnosis of acute promyelocytic leukaemia (APML) in order that all-*trans* retinoic acid (ATRA) therapy and correction of clotting abnormalities and transfusion support, can be commenced promptly. If the diagnosis is suspected, urgent FISH for t(15;17) should be performed and ATRA should be started whilst awaiting results (see section 9).

Acute leukaemia should be classified according to the most up-to-date WHO criteria (2022) see appendix 1. The 2022 classification for AML has some important changes, such as the ability to diagnose AML with ≥10% blasts if certain genetic abnormalities are present (rather than the usual figure of ≥20% blasts).
Once all results are available, these should be reviewed at the appropriate MDT to confirm risk stratification and therapeutic strategy.

4.2 Baseline investigations

The following should be carried out and documented at diagnosis:

- Full history, with particular reference to infection, bleeding, neurological symptoms and co-morbidities,
- Family history, to identify patients who have an inherited predisposition to leukaemia (and potential donors if the patient is a transplant candidate).
- Full clinical examination,
- FBC and film,
- Coagulation screen including fibrinogen and D-dimer,
- Blood group and antibody screen,
- U&E, LFTs, calcium, phosphate, urate, LDH and glucose,
- Bone marrow aspirate for morphology, immunophenotyping, cytogenetics and molecular studies (bedside slides, 2 x EDTA tubes and cytogenetic sample).**If the patient is a trial candidate additional samples should be obtained as indicated by the trial protocol.**
- Bone marrow trephine if the aspirate is inadequate,
  NB. If an adequate aspirate cannot be obtained, consider obtaining a second trephine and placing in sterile saline (for immunophenotyping).
- Blood for HLA-typing (tissue typing) if the patient is a transplant candidate,
- Viral serology for Hepatitis B & C, HIV & CMV **IgG** *prior to receiving transfusion*. **Taking samples before transfusion is particularly important in potential transplant candidates as equivocal results can lead to difficulties with donor identification.**
  HSV, VZV, measles, Hepatitis A and toxoplasma serology may also be carried out.
- If febrile/infection suspected: MSU, nose and throat swab, culture of potential infected areas and blood cultures,
- CXR and ECG; echo or MUGA, if appropriate,
- Whole genome sequencing (WGS) e.g. skin biopsy, if patient eligible (more information at: https://www.eastgenomics.nhs.uk/). *This includes TYA patients and patients with ≥2 1st- / 2nd- degree relatives with a haematological malignancy/bone marrow failure, or with features suggestive of an inherited predisposition (e.g. longstanding cytopenias/familial platelet disorder) after discussion with Genomic Laboratory Hub (GLH),*
- Lumbar puncture (LP), on those patients where there is clinical suspicion of CNS involvement, and/or according to the ALL treatment protocol.
  NB. LP may need to be deferred in patients with high WBC or coagulopathy.

- *In addition to the above tests, certain patients will have germline testing recommend by the Genomics Tumour Advisory Board (GTAB) because of mutations (e.g. DDX41, RUNX1, CEBPA, GATA2, ETV6 and ANKRD26) identified at a variant allele frequency (VAF) of >30%. Referral to GTAB is often made by HODS and the requesting clinician is informed by email. Alternatively, referral to the Haem/Onc GTAB can be made via cuh.genomics-mdtgtab@nhs.net.*

5 Risk stratification

5.1 Risk Stratification in AML

Patients on national trials will be risk-stratified according to the trial risk score.

The European Leukaemia Network (ELN) AML risk stratification is used for adult patients having intensive chemotherapy (Döhner H et al. Blood 2022)

Risk category	Genetic abnormality
Favourable	t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*‡,‡ inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB*::*MYH11*‡,‡ Mutated *NPM1*‡,§ without *FLT3*-ITD bZIP in-frame mutated *CEBPA*‖
Intermediate	Mutated *NPM1*‡,§ with *FLT3*-ITD Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*‡,¶ Cytogenetic and/or molecular abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* t(v;11q23.3)/*KMT2A*-rearranged# t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1)* t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged −5 or del(5q); −7; −17/abn(17p) Complex karyotype,** monosomal karyotype†† Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ Mutated *TP53*[a]

‡Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.
§AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
‖Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favourable outcome.
¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
#Excluding *KMT2A* partial tandem duplication (PTD).
**Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favourable-risk AML subtypes.
a *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

For patients receiving less intensive therapies, the ELN 2024 Less-intensive risk classification should be used (Döhner H et al. Blood 2024)

Risk category	Genetic abnormality
Favourable	Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH1*∗ (*TP53*^{wt}) Mutated *DDX41*† Other cytogenetic and/or molecular abnormalities‡ (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	Other cytogenetic and molecular abnormalities‡ (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	Mutated *TP53*

This classification does not apply to patients who have received prior treatment with a hypomethylating agent.
∗ Favourable risk applies specifically to patients treated with AZA + IVO, irrespective of the presence of activating signalling gene mutations.
† Identification of a *DDX41* mutation at near-heterozygous frequency should prompt consideration of germ line *DDX41* mutation.
‡ For many cytogenetic and molecular abnormalities, single or as co-aberrations, no data are currently available; they are tentatively categorized as favourable and intermediate-risk depending on the absence or presence of activating signalling gene mutations.

In addition to the above:
Patients with secondary AML i.e. transformed from another myeloid disorder (MDS or MPN), or AML post cytotoxic therapy (AML-pCT), also have adverse-risk disease.

NUP98 is adverse risk, but not incorporated into the current classifications.

Positive *NPM1* molecular MRD in peripheral blood post course 2 of intensive chemotherapy (or in blood or marrow at any time point thereafter) confers an adverse risk (see section 8.4 for more detail about MRD).
The time at which ongoing NPM1 MRD positivity should be a cause for concern in patients treated with venetoclax-containing therapies is not known. Consideration should be given to offering intensive chemotherapy if a confirmed rise in MRD occurs in patients initially treated with venetoclax-containing regimens and transplant in patients where there is a failure to achieve MRD negativity following 2 cycles of subsequent intensive chemotherapy.

Positive flow MRD (>0.1%) in bone marrow post course 2 (or at any time point thereafter) confers an adverse risk to intermediate-risk AML with NPM1wt (see section 8.4 for more detail about MRD).

Positive molecular MRD may confer an adverse risk to core binding factor AML i.e. t(8;21), t(16;16) or inv(16), at specific timepoints (see section 8.4 for more detail about MRD).

5.2 Prognostic classification for ALL (taken from UKALL14 protocol)

ALL risk category	Risk Factors
Poor risk	High presenting WBC (B>30x10^9/L, T>100x10^9/L) Age>40 years t(4;11)(q21;q23)/MLL-AF4 Philadelphia chromosome t(9;22) Low hypodiploidy/near triploidy (30-39 or 60-78 chromosomes) Complex karyotype (5 or more chromosomal abnormalities) MRD positive at end of induction phase 2
Standard risk	None of the above

6 Teenage and young adults (TYA)

All patients aged between 16 and 24 years must be notified to the TYA MDT.

Patients aged 16 to 18 must be referred for treatment to the TYA principal treatment centre (PTC) at Addenbrooke's Hospital.

Those aged 19 to 24 must be offered referral to the PTC as well as treatment locally at a designated shared care facility in Norwich, Ipswich or Peterborough. If such a patient chooses to continue treatment locally, this will be discussed and agreed at the appropriate haematology MDT and ratified by the TYA MDT, allowing patients choice as well as access to TYA support services.

7 Supportive care

7.1 Prevention of tumour lysis syndrome (TLS)

At presentation, all patients should commence allopurinol and hydration. Fluid balance should be monitored and biochemistry (U&E, calcium, phosphate) reviewed twice daily for at least 48 hours after the start of intensive chemotherapy.

Rasburicase prophylaxis prior to the first course of chemotherapy should be given in the following situations which increase the risk of TLS:

- Burkitt or Burkitt-like lymphoma/leukaemia,
- WBC>100x10^9/L,
- ALL with WBC<100x10^9/L ***but with*** LDH≥2x upper limit of normal (ULN),
- Urate>450 µmol/L (0.45 mmol/L) ***plus*** any of:
    - Phosphate>2.0 mmol/L
    - Abnormal renal function

Renal dialysis should be available.

7.2 Blood product support

Red cell and platelet transfusion support should be provided according to local guidelines. Irradiated products should be given if recommended by BSH guidelines. Communication between hospitals regarding special blood product requirements is essential and should be done using the national NHSBT form.

7.3 Infection prophylaxis and treatment

See local policies for prophylaxis and treatment of infection in neutropenic patients.

To reduce the risk of perianal infection, the use of medicated sitz baths is recommended (see appendix 2 for patient information leaflet).

7.4 Use of growth factors

See local policies. The routine use of growth factors in AML is not recommended.

7.5 Patient Information

All patients will be offered clear and comprehensive written information including:

- Nature of the disease
- Diagnostic procedures being undertaken
- Treatment options available
- Likely outcomes in terms of benefits, risks, side effects and alternatives
- Contact details for the specialist team
- Psychological support
- Financial support
- Management of fever and infection
- Blood product support
- Long term risks – e.g. infertility, second malignancy

7.6 Palliative care team

Where necessary, the local palliative care team should be involved at the outset of treatment to provide symptom control and psychological support.

8 Treatment of Acute Myeloid Leukaemia (AML)

TYA patients should be transferred to the TYA PTC if necessary (see section 6).

The effects of chemotherapy on fertility should be discussed and referral to reproductive medicine for counselling and male fertility preservation i.e. semen storage offered. This should be done at the earliest opportunity but should not significantly delay treatment.
The management of complex cases e.g. APML, Burkitt lymphoma/leukaemia, WBC>100x10^9/L, should be discussed with a tertiary centre and consideration should be given to transferring these patients from centres treating only small numbers of these types of patient per year.

The decision to treat intensively should be based on clinical assessment including, amongst other factors, patient age, performance status, co-morbidities and AML prognosis. The risks, benefits and alternatives should be discussed with the patient. Consideration should be given to tissue typing all patients who are transplant candidates along with their siblings at diagnosis to avoid delays if a decision to transplant is made.

8.1 Induction therapy for AML - patients fit for intensive therapy

For treatment of APML see section 9.

This is a constantly changing landscape and clinicians are advised to discuss all cases at the appropriate MDT.
Clinicians should refer to the protocol for each regimen for the supportive medication (antimicrobials etc.) to be administered alongside the chemotherapy.

Below is an outline of a currently acceptable treatment algorithm (summarised in Figure 1).

- The option of receiving less intensive chemotherapy with venetoclax-containing regimens should be discussed with patients, taking into consideration their performance status and preference.

- **All patients who are eligible should be offered entry into a clinical trial** e.g. patients aged ≥60 years, *NPM1* mut and *FLT3* wt should be offered entry into the VICTOR trial (rapid screening is available to establish eligibility), patients who are *FLT3*-mutated should be offered entry into the OPTIMISE FLT3 trial.

- **For patients with secondary AML**; AML post cytotoxic therapy (AML-pCT), AML myelodysplasia-related (AML-MR), or AML transformed from MDS (or CMML), the options are liposomal cytarabine-daunorubicin, Flag-Ida or venetoclax-azacitidine.

- **If no trial is available**, or the patient declines entry, and treatment **cannot be deferred**, treatment should be with DAGO or venetoclax-based therapy.

- **If no trial is available**, or the patient declines entry, and treatment **can be safely deferred** by 5 working days (the current turnaround time), the treatment should be directed by the results of molecular analysis (of *NPM1*, *FLT3* (ITD and TKD)) and AML FISH (panel able to detect: *KMT2A, PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11*, del(5q31), del(7q31) and monosomy of chromosomes 5 or 7).

    - Patients diagnosed with AML-MR (by virtue of cytogenetic changes characteristic of MDS) should be offered venetoclax-azacitidine or liposomal cytarabine-daunorubicin. Flag-Ida may also be considered.
    - Patients diagnosed with AML with *RUNX1::RUNX1T1* or *CBFB::MYH11* (also referred to as core binding factor AML), should be offered DAGO.
    - Patients with a *FLT3* mutation should be offered DA + midostaurin/ quizartinib.
    - Patients with *MECOM* have a particularly poor outcome regardless of the therapy used. Flag-Ida with the addition of venetoclax may be

considered (the venetoclax is not currently funded on the NHS), but consideration should also be given to less intensive chemotherapy and a focus on quality of life following frank discussion with patients and their families about the likely outcome.

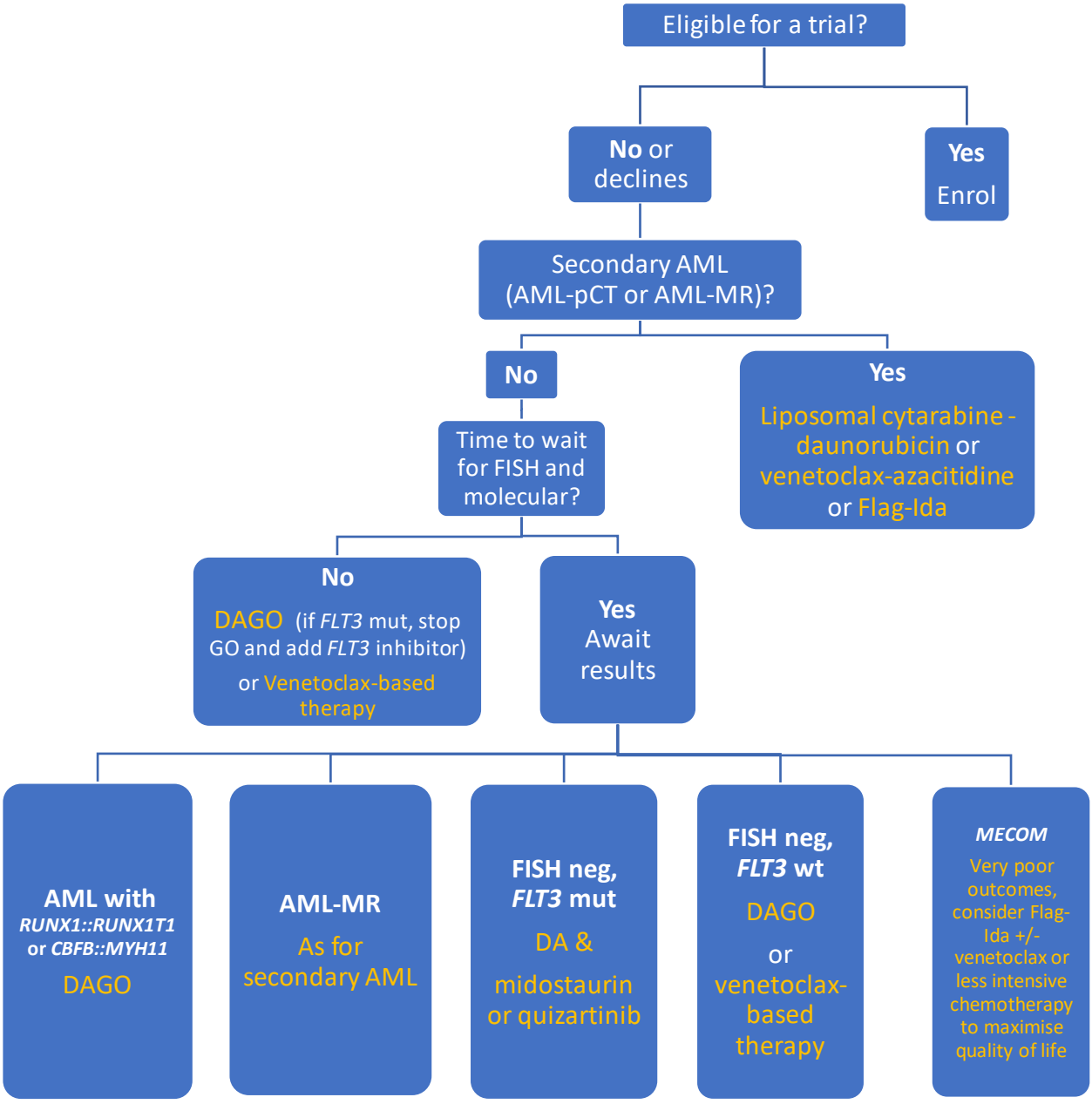

Figure 1 – decision tree for induction therapy

8.1.1 Daunorubicin and cytarabine (DA) +/- gemtuzumab ozogamicin (GO) +/- midostaurin/quizartinib induction

Patients with *de novo* AML who do not enter a trial, should be offered induction therapy with daunorubicin and cytarabine (**DA**, since cytarabine is also called Ara-C) 3+10. This is usually followed by DA 3+8 if the patient responds (see section 8.3). Daunorubicin 60mg/m^2 is given with course 1 and 50mg/m^2 with course 2.

Patients with **CD33 positive** AML and favourable or intermediate risk cytogenetics or where the cytogenetic result is unknown, are eligible to receive gemtuzumab ozogamicin (**GO**) alongside DA induction course 1. The GO dose is 3mg/m^2 (up to a maximum of 5mg) on days 1, 4 and 7 (*NICE TA545 2018)*, however, in patients with core binding factor (CBF) leukaemia i.e. t(8;21), t(16;16) or inv(16), there is evidence to support the use of a single dose of GO with induction. In other leukaemias, standard practice is to give only 2 doses of GO (based on the outcomes of AML19).

Patients who are ***FLT3*** mutation positive (ITD or TKD) are eligible to receive the *FLT3* inhibitor **midostaurin** in combination with DA. The dose is 50mg bd for 14 days with each cycle after administration of IV chemotherapy is complete (*NICE TA523 2018).* If the patient has been started on GO, this should be discontinued when the *FLT3* mutation is discovered.

An alternative for patients who are ***FLT3 ITD*** (but not TKD) mutation positive is the *FLT3* inhibitor **quizartinib**. The dose is 35.4mg od for 14 days after completion of IV chemotherapy is complete *(NICE TA1013 2024).* When prescribed alongside posaconazole or voriconazole the dose is 17.7mg od. Quizartinib can also be given following allogeneic stem cell transplant and may be preferable in patients where a transplant is planned, although it is associated with a greater degree of cytopenias.

8.1.2 Liposomal cytarabine-daunorubicin induction

Liposomal cytarabine–daunorubicin is an option for patients with secondary AML(AML-pCT or AML-MR)**.** For induction, the dose is daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 given on days 1, 3 and 5 for the first course and days 1 and 3 for subsequent courses, if needed *(NICE TA552 2018).*
In most cases, especially where there is a TP53 mutation/deletion or the patient is older (age >65), venetoclax and azacitidine is preferable as it is better tolerated.

Other small molecules are being considered by NICE and their use may be approved between updates of this guideline. Clinicians are directed to the NICE website for the most up-to-date information on these: http://www.nice.org.uk/guidance/conditions-and-diseases/blood-and-immune-system-conditions/blood-and-bone-marrow-cancers

8.2 Induction therapy for AML - patients not fit for intensive therapy / choosing less intensive option

Patients not fit for intensive treatment should be offered entry into clinical trials where available.

Frail patients may be offered **hydroxycarbamide** or **low-dose cytarabine.** Patients with adverse cytogenetics may not benefit from low-dose cytarabine.

8.2.1 Single-agent azacitidine

Azacitidine may be used in patients with bone marrow blasts of 20-30% and multilineage dysplasia (*NICE TA218 2011)*. It is given for at least 4 cycles, as responses can be slow, and is continued until relapse/loss of response.

8.2.2 Azacitidine and ivosidenib

Ivosidenib may be added to azacitidine in patients with an ***IDH1*** mutation *(NICE TA979 2024)*. The dose is 500mg od, but can be reduced to 250mg od by co-administration of posaconazole or voriconazole.

8.2.3 Venetoclax with azacitidine or low dose cytarabine

Venetoclax was approved for use in combination with azacitidine (Ven-Aza) or low-dose cytarabine (Ven-LDAC) for front-line treatment of AML to minimise the need for admission during the Covid-19 pandemic (*NICE NG161 2020)*.

Ven-LDAC (*NICE TA787* 2022 – only if marrow blasts are >30%) and Ven-Aza *(NICE TA765 2022)* remain available for patients who are unsuitable for treatment with intensive chemotherapy.

Therapy should follow the NCRI AML working group guidance, incorporating a dose escalation phase on days 1-4, with the addition of posaconazole or voriconazole on day 4. Venetoclax is associated with a risk of tumour lysis syndrome. Monitoring may be needed during the first 5 days of therapy if the starting white cell count is >25x10^9/L or there is renal impairment.

Patients should undergo assessment after each cycle and may require G-CSF to promote neutrophil recovery if complete remission with incomplete count recovery (CRi) is confirmed. Those achieving a partial remission (PR) should proceed to cycle 2 without awaiting count recovery. Treatment failure should not be determined until 2 cycles have been completed. In patients who achieve complete remission (CR) and who are not proceeding to allogeneic stem cell transplantation, a minimum of 12 cycles should be administered.

8.3 Post-remission therapy for AML - patients fit for intensive therapy

Patients on trial should continue treatment according to the trial protocol.

8.3.1 Patients who received daunorubicin and cytarabine (DA) +/- gemtuzumab ozogamicin (GO) +/- midostaurin in course 1

Patients who enter remission after course 1 of DA will be given a second induction, usually DA 3+8, followed by consolidation with 2 cycles of high-dose cytarabine (Ara-C) 3g/m^2 bd on days 1, 3 and 5. Consideration can be given to reducing the dose to 1.5g/m^2 bd on days 1, 3 and 5 for older patients or those with co-morbidities.

Patients with intermediate or poor risk disease (see section 5) should be considered for allogeneic stem cell transplant and be discussed with the transplant centre.

CD33 positive AML with favourable or intermediate risk or unknown cytogenetics who received gemtuzumab ozogamicin (**GO**) in course 1 induction, are eligible to receive a single dose of GO (3 mg/m^2 up to a maximum of 5mg) on day 1 of each of up to 2 cycles of consolidation (*NICE TA545 2018).*

Patients with a ***FLT3*** mutation treated with DA and **midostaurin** induction, can continue to receive midostaurin, with second induction and high-dose Ara-C

consolidation (50mg bd for 14 days each cycle after completion of IV chemotherapy), followed by midostaurin maintenance (50mg bd for 28 days) for up to 12 cycles if they do not have an allogeneic stem cell transplant (*NICE TA523 2018).*

Patients with a ***FLT3 ITD*** mutation treated with DA and **quizartinib** induction, can continue to receive quizartinib, with second induction and high-dose Ara-C consolidation (35.4mg od for 14 days of each cycle after completion of IV chemotherapy), followed by maintenance (35.4mg od for 28 days) for up to 36 cycles if they do not have an allogeneic stem cell transplant *(NICE TA1013 2024).* When prescribed alongside posaconazole or voriconazole the dose is reduced to 17.7mg od.

8.3.2 Patients who received liposomal cytarabine-daunorubicin in course 1

Patients who receive liposomal cytarabine–daunorubicin as induction course 1, are eligible to receive a second course of induction (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2 on days 1 and 3) if they are not in CR with negative MRD post cycle 1. Induction should be followed by up to 2 cycles of consolidation (daunorubicin 29 mg/m2 and cytarabine 65 mg/m2 on days 1 and 3) (*NICE TA552 2018).*

8.3.3 Patients who are MRD positive after induction chemotherapy who cannot or do not want a stem cell transplant (oral azacitidine)

Patients in CR of CRi after induction therapy with or without consolidation treatment who cannot have or do not want an allogeneic stem cell transplant are eligible to receive oral Azacitidine maintenance treatment (*NICETA827 2022)*.

8.4 Minimal residual disease (MRD) in AML

Measurement of MRD in AML can be performed via 1 of 2 modalities:

1. Monitoring of mutations/gene fusions by RNA-based polymerase chain reaction (RT-qPCR).
2. Multiparameter flow cytometry using a leukaemia associated immunophenotype (LAIP), or a change in flow characteristics in relapse/progressive disease samples ‘different-from-normal’.

Please send a separate sample of aspirate in EDTA, labelled “first pull” for MRD assessment.

RT-qPCR MRD is available (for patients with NPM1 mutations and the fusion genes RUNX::RUNX1T1, CBFB::MYH11, PML::RARA, KMT2A::x and NUP98::NSD1) from the molecular laboratory at Guy’s and St Thomas’ Hospital, London. **Samples can be sent directly to the molecular laboratory or via HODS (email notification to HODS is essential if the latter approach is followed so that the sample is processed correctly and urgently).**
RNA sequencing may also be possible to monitor other, rare gene fusions. The MRD strategy can be discussed at MDT once full cytogenetic/molecular information is available.

Flow cytometry for MRD in AML has a limit of detection of 0.1%.

Time points for sequential analysis of MRD are more clearly defined for molecular (RT-qPCR) than flow cytometry. Molecular MRD sampling is recommended by the ELN in blood and marrow at diagnosis (to establish the marker), then as a minimum after 2 cycles of standard induction/consolidation chemotherapy and after the end of treatment. The ELN Guideline also recommends MRD assessment should continue thereafter on a 3-monthly basis for at least 2 years. *Data from AML17 and AML19, suggests no overall survival benefit to monitoring of MRD in remission, and this should be discussed with patients who are in remission and they should be offered the option of not monitoring MRD with 3-monthly bone marrows.*

For patients undergoing allogeneic stem cell transplant, MRD should be assessed in blood and marrow not earlier than 4 weeks before transplant conditioning begins. MRD assessment should continue thereafter in marrow on a 3-monthly basis for at least 2 years.

See ELN working party recommendations on sampling requirements, time points and markers to follow (Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 update measurable residual disease in acute myeloid leukemia: European LeukemiaNet Working Party consensus document. Blood. 2021; 138(26): 2753- 2767).

8.5 Extramedullary disease in AML

This refers to the gum and skin infiltration often seen in acute monoblastic type AML or to solid tissue masses, also called chloromas or granulocytic sarcomas. Such patients should receive standard AML therapy as described above irrespective of marrow involvement.

8.6 CNS disease in AML

Leptomeningeal disease with blasts in the CSF is rare (0.5% of patients). Post-remission relapses include CNS disease in 5% of cases, either isolated or as part of systemic relapse. The use of high-dose cytarabine during treatment is thought to reduce the incidence of CNS relapse in AML.

Routine CSF examination is not indicated in AML. However, there are data which suggest that selected patients may have an increased risk of CNS involvement (which can be asymptomatic).

Risk factors include:

- Monocytic/monoblastic AML
- High LDH at diagnosis e.g. >700 iU/L (in one study)
- African/Afro-Caribbean ethnic origin
- Younger age
- Abnormalities of chromosome 11
- Inv(16)
- FLT3-ITD mutation
- CD56 expression on blasts
- Presence of other extramedullary disease

In the TYA patients <18 years, consideration should be given to following the Myechild recommendations for CNS prophylaxis which are two doses of IT cytarabine 50mg with course 1 and course 2.

It is not possible to give firm recommendations regarding screening for CNS disease in the remaining asymptomatic patients due to the limitations of the reported (mainly retrospective) data. However, a diagnostic LP once remission is achieved or prior to reduced intensity conditioning (RIC) allogeneic stem cell transplant, should be considered in patients exhibiting 2 or more of the risk factors above in order to exclude the presence of clinically silent CNS disease.

Patients with neurological symptoms and/or signs e.g. headaches, altered mental status, paraesthesia/numbness, localizing neurological signs or seizures, should be investigated by appropriate imaging (CT/MRI) and LP (once the circulating blast count has been reduced).

CSF should be sent for a cell count, assessment of morphology (on cytospin of CSF) and immunophenotyping to confirm the presence of AML.

Intrathecal (IT) chemotherapy should only be given if there is proven CNS disease.

If detected, treatment should be with IT cytarabine 50mg two to three times weekly until CSF is clear, then every 2 weeks until consolidation treatment is complete.

CNS relapse should be treated with systemic re-induction chemotherapy using a high dose cytarabine-based regime, with concurrent IT cytarabine as above.

Patients with relapsed APML should have an LP to exclude CNS disease.

8.7 Relapsed AML

Relapse will occur in >50% patients overall**.** Fewer than 50% of these will achieve a second complete remission (CR2) and median survival varies from 3-12 months. This is predicted by duration of first remission and karyotype. Up to 90% with favourable cytogenetic who relapse will achieve CR2 and greater responses are achieved if the duration of CR1 was > 6 months.

A pre-treatment bone marrow aspirate (and trephine if the aspirate is inadequate) should be performed where possible. In cases of morphological AML relapse, *FLT3*-testing should be repeated as 10-30% of AML cases may gain/lose mutations at relapse. Where molecular relapse is detected (e.g. *NPM1* transcripts), current NGS testing strategies are not sensitive enough to detect *FLT3* mutations and it should be assumed that the relapse clone harbours the original diagnostic mutations.

In the absence of a *FLT3* mutation, if the patient is fit enough for re-induction therapy, patients should be offered entry into trials where available. If not on trial, a high-dose cytarabine containing regimen e.g. FLAG-Ida, is appropriate. In older patients, the dose of cytarabine can be reduced to 1g/m^2.

If CR2 is obtained and the patient is fit enough, allogeneic stem cell transplant should be considered – refer to the transplant team early after relapse if this is the case.

Compassionate access for small molecules can be explored depending on availability of drugs.

8.7.1 Gilteritnib

Gilteritinib is approved as monotherapy for patients aged over 18 years with relapsed/refractory AML with a *FLT3* (ITD or TDK) mutation and a performance status 0-2 (*NICE TA642 2020)*.

Prior therapy with some *FLT3* inhibitors makes the patient ineligible for gilteritinib. This excludes first line use of sorafenib, midostaurin, quizartinib or a *FLT3* inhibitor used first-line in a clinical trial.
Patients who respond to gilteritinib and go on to receive a stem cell transplant may not resume treatment with gilteritinib after the transplant.
Gilteritinib has notable drug interactions (please consult SPC for more information) and patients require ECG monitoring for QTc prolongation weekly during cycle 1, alternate weeks during cycle 2 and monthly thereafter (if ECG features are stable). If no response is observed after 4 weeks, the gilteritinib dose may be increased to 200mg od if tolerated.
Treatment continues until disease progression/unacceptable toxicity/patient considered to be cured/proceeds to stem cell transplant (whichever occurs first).

8.8 Management of AML in patients who are pregnant

AML in pregnancy should be jointly managed between the Haematologist, Obstetrician and mother.

Chemotherapy in the first trimester is associated with a high risk of foetal malformation and should be avoided; the opportunity to terminate the pregnancy should be discussed with the mother. If termination is refused and the mother's life is at risk, chemotherapy should be started.

Chemotherapy in the second and third trimester is associated with an increased risk of miscarriage as well as small-for-dates babies. Consideration should be given to early induced labour between cycles of chemotherapy once count recovery has occurred.

ATRA can be used in pregnancy in the second and third trimester.

9 Treatment of acute promyelocytic leukaemia (APML)

It is essential to establish the diagnosis of APML as quickly as possible. Once morphology suggests the diagnosis, treatment with ATRA should be initiated whilst awaiting the results of rapid confirmatory testing by FISH analysis for t(15;17).

Baseline molecular analysis of blood or marrow is essential for future MRD monitoring by PCR and should be sent to Guy's and St Thomas' molecular laboratory (as should subsequent molecular monitoring samples).

9.1 Management of APML

This is a **medical emergency** due to the high risk of coagulopathy-associated death. FBC and coagulation screen including fibrinogen must be performed at least twice daily until resolution of the coagulopathy.

ATRA (tretinoin capsules) 45mg/m^2 in two divided doses rounded to the nearest 10mg should be started as soon as the diagnosis is suspected.

Low to intermediate risk APML (WBC ≤10x10^9/L) patients should receive arsenic trioxide in addition to ATRA according to the AML 17 schedule (*NICE TA526 2018).*

High-risk APML (WBC>10x10^9/L) should be given ATRA and arsenic trioxide alongside idarubicin or hydroxycarbamide to control the white cell count (off-label use - NHS England Clinical Commissioning Policy 2320).

Patients should be monitored for **differentiation syndrome** (a life-threatening condition with fluid retention and capillary leak manifesting as cough, breathlessness, fever, weight gain, pleural and pericardial effusions and pulmonary infiltrates). This is more likely to occur in those with elevated WBC > 10 x 10^9/L. It should be treated promptly with dexamethasone 10mg bd IV for a minimum of 3 days until the symptoms resolve.

During induction the platelet count should be kept above >30x10^9/L. FFP should be given to normalize the APTT and cryoprecipitate to keep fibrinogen>1.5-2g/L.

Leukapheresis is associated with increased coagulopathy and should NOT be performed in APML.

Patients should undergo MRD monitoring throughout therapy (see section 8.4).
If they are MRD negative at the end of therapy and have received arsenic, MRD monitoring following completion of treatment is no longer required.

9.2 Relapsed/refractory APML

Patients treated with ATRA and idarubicin (AIDA), who relapse or are refractory, should be treated with arsenic trioxide (*NICE TA526 2018)*.
Patients who received arsenic and ATRA as primary therapy and later relapse should be treated with AIDA.
Patients with relapsed APML should have an LP to exclude CNS disease.
Transplant should be considered in CR2 although if the APML is in a good molecular remission following re-induction, then a monitoring strategy may be considered.

10 Treatment of acute lymphoblastic leukaemia (ALL)

Treatment of adult ALL includes induction, consolidation, intensification and maintenance chemotherapy with CNS prophylaxis and, in some cases, stem cell transplantation.

In addition to supportive care, all patients will be offered entry into trials where available. If not on trial, UKALL14, standard arm will be the treatment regimen for adults aged 25 or over (if fit enough), and the standard arm of the current paediatric trial (ALLTogether1 at the time of writing) or UKALL 2019 interim guidelines for those under 25.

10.1 Rituximab for CD20 positive B-ALL

Rituximab should be given alongside UKALL14 chemotherapy for patients aged over 18 years with CD20 positive B-ALL (regardless of Philadelphia chromosome status). Patients on paediatric-style treatment and those receiving less intensive induction regimens are excluded from this recommendation.

Along with the UKALL14 backbone, rituximab 375mg/m^2 IV is given at the following timepoints:

- Induction Phase 1: Days 3, 10, 17 and 24
- Induction Phase 2: Days 2 and 9
- CNS Intensification: Days 3 and 17
- Consolidation 1: Day 1
- Consolidation 2: Day 1
- Consolidation 3: Days 2 and 9
- Maintenance: Year 1 only (Months 1,4,7 and 10)

Patients who receive an allogeneic stem cell transplant will not receive any further rituximab from the point at which they receive their transplant.

10.2 Pegylated asparaginase

Two doses of peg-asparginase are given during UKALL14 induction to Ph-negative patients aged <40 years. One dose appears in the UKALL14 protocol for Ph-negative patients aged >41 years. This dose-reduction is a result of serious toxicities, especially hepatotoxicity, identified during an interim analysis in patients >40 years in the UKALL14 trial (Patel et al Leukemia 2017). Consideration should be given to omitting peg-asparginase completely for patients >40 years old.

10.3 Philadelphia positive ALL

At diagnosis, the presence of the Philadelphia (Ph) translocation, t(9;22), *BCR-ABL1* should be established using FISH.
If the patient is not on trial and found to be Ph +ve, imatinib (400mg initially increased to 600mg) should be added to UKALL14 therapy as soon as this is known. Ph-positive patients should NOT receive peg-asparaginase regardless of patient age.

10.4 ABL-class gene fusions

FISH probes to detect tyrosine kinase sensitive Ph-like (ABL-class) ALL are used where no other defining cytogenetic changes are present.
All patients with an ABL-class gene fusion will need to be identified so that treatment with imatinib can be started by day 15 of induction.

10.5 ALL in TYA population

In view of the superior outcomes of **young adults** treated with paediatric protocols compared to patients in the same age-range treated with adult protocols, it is strongly recommended that young adults (up to their 30th birthday at present) be treated according on the current paediatric and adolescent ALL trial (ALLTogether1 at the time of writing) if available. If the trial is not available, or the patient declines entry, treatment should follow the standard arm of the ALLTogether1 trial protocol (up to their 25th birthday) or UKALL 2019 interim guidelines.

Consideration should be given to transferring adolescents and young adults on paediatric protocols to the TYA unit (ward C9) at Addenbrooke's – see section 6.

10.6 Infection prophylaxis in ALL

There is a high risk of infections during the prolonged period of cytopenia and exposure to corticosteroids experienced during intensive treatment of ALL. Notable organisms include pneumocystis and aspergillus.

10.6.1 Pneumocystis pneumonia (PCP) prophylaxis

Patients should receive co-trimoxazole prophylaxis or, if the WBC does not tolerate this, then inhaled pentamidine (at a dose of either 300 mg every 4 weeks or 150 mg every 2 weeks), oral dapsone or oral atovaquone are acceptable alternatives.

10.6.2 Prevention of Fungal Infection

Patients with prolonged neutropenia and/or receiving high dose steroid therapy are at risk of invasive fungal infections. The use of prophylaxis against fungal infections and early institution of anti-fungal therapy e.g. anti-fungal therapy within 72 hours of a fever not resolving with first-line antibiotic therapy, is recommended.

Clinicians should be aware that there is a serious interaction between the azole antifungals (fluconazole, itraconazole, voriconazole, posaconazole) and vincristine. The metabolism of vincristine is inhibited by azoles and neurotoxicity can be potentiated. These drugs must therefore not be given together (i.e. during induction phase 1). The alternative suggested prophylaxis regime is AmBisome 7mg/kg weekly in divided doses.

10.7 CNS disease

10.7.1 CNS disease - UKALL 14 (adults > 25)

The first lumbar puncture is scheduled at day 14. For confirmed CNS leukaemia or a traumatic LP (>10rbc/µl) obtained at a time when the patient has circulating blasts, intrathecal (IT) methotrexate 12.5mg (or 10mg via Ommaya reservoir) should be given twice weekly until blasts are no longer present in the CSF.

10.7.2 CNS disease - ALLTogether1 (TYA)

In TYA protocols, the first IT MTX is administered on day 1 to coincide with bone marrow examination being performed under general anaesthetic for paediatric

patients. Where anaesthetic is not an issue and in patients not on trial, consideration should be given to deferring the initial lumbar puncture until WBC is low following initial chemotherapy to reduce the risk of contaminating the CNS with blasts.
IT MTX should always be given at the time of the first lumbar puncture, irrespective of whether there is known CNS disease.

Frequency of IT MTX should follow the relevant protocol (ALLTogether1) dependent on the extent of CNS disease.

10.8 MRD in ALL

In ALL, MRD estimation using DNA PCR of Ig-/TCR-rearrangements or RNA PCR of BCR-ABL transcripts is the current standard of care.

MRD using Ig-/TCR-rearrangements is available from specialised ALL MRD laboratories at St Bartholomew's Hospital (for patients aged 25 or over) and Bristol (for patients aged under 25). Measurement of BCR-ABL transcripts can be carried out by HODS (or sent to Birmingham if the patient has one of the less common transcript types).

Bone marrow for MRD assessment should be sent at baseline, to establish a marker, and following recovery from each subsequent course of chemotherapy. Samples sent to HODS will be sent urgently on to Bart's or Bristol for this purpose.
Email notification to HODS is essential if the sample is to be sent via HODS so that the sample is processed correctly and urgently. Please provide a separate EDTA sample for this purpose at diagnosis, and a separate sample in EDTA labelled "first pull" for MRD assessment at each time point.

MRD positivity, especially post induction phase 2 and prior to transplant, is a strong independent risk factor for relapse and mortality; in TYA patients being treated according to paediatric protocols, MRD is an essential part of risk stratification to determine therapy.

For patients undergoing allogeneic stem cell transplant, MRD should be assessed in blood and marrow after the last conventional chemotherapy, but not earlier than 4 weeks before transplant conditioning begins.

10.8.1 Blinatumomab

In patients with CD19 positive B-ALL:

Blinatumomab is recommended as part of consolidation in Philadelphia negative patients, who are in CR1 and are MRD negative (<0.01%) following induction chemotherapy (*NICE TA11571 2025)*.
Patients can receive a maximum of 4 cycles of blinatumomab given as cycles 1, 2, 6 and 8 of consolidation treatment with chemotherapy given in cycles 3, 4, 5 and 7.

Blinatumomab is available as monotherapy for Philadelphia negative patients in CR with MRD ≥ 0.01% (*NICE TA589 2019).*

Blinatumomab is also available as monotherapy for Philadelphia positive patients in CR with MRD ≥ 0.01% via the Cancer Drugs Fund despite not being available via NICE (https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list).

Note that the levels of MRD positivity required to be eligible have changed since the previous iteration of this guideline (from 0.1% to 0.01%).
For the most up to date information, clinicians are encouraged to check the Blueteq approval criteria before prescribing.

10.9 Relapsed ALL

Therapeutic strategy will depend upon time of relapse in relation to previous therapy, age and performance status.

Treatment options for relapsed ALL are rapidly increasing. This guideline should be used in conjunction with other sources to ensure that the best currently available treatment is offered. Current options are outlined here; MDT discussion is recommended to guide treatment decisions. The national ALL advisory panel (which also functions as the national CART panel) can be used to discuss especially complicated patients. Patients can be added by completing the appropriate referral form and emailing it to:
the-christie.adultallpanel@nhs.net.

TYA patients should be discussed at the national Paediatric and TYA leukaemia MDT which can be accessed by completing the appropriate referral form and emailing it to: haemmdt@gosh.nhs.uk.

FLAG-Ida may be useful in primary refractory disease to 'de-bulk' patients with high volume disease.

Young and fit patients with T-ALL that is refractory to induction therapy may benefit from nelarabine-based chemotherapy, such as the NECTAR protocol or NOPHO high risk protocol blocks A, B +/- C, to obtain remission and bridge to allogeneic stem cell transplantation.

Blinatumomab is available for treatment of relapsed or refractory Philadelphia negative B-ALL (*NICE TA450 2017).*
Blinatumomab is most effective when the disease burden is low, and in patients with significant marrow infiltration (>10% blasts) 'debulking' with FLAG-Ida, re-induction, phase 2 induction or augmented BFM consolidation chemotherapy is recommended before using blinatumomab.

Inotuzumab ozogamicin is available for relapsed or refractory CD22-positive B-ALL. Patients with Ph+ve disease are eligible providing they have received at least one TKI (*NICE TA541 2018)*

Chimeric antigen receptor T-cells (CART) are becoming more widely available for use in ALL.
Kymriah® (tisagenlecleucel) is available for treating patients aged < 26 years with B-ALL that is refractory, relapsed post-transplant or in second relapse or later (*NICE TA554 2018).*

Tecartus® (brexucabtagene autoleucel) is available for treating patients aged 26 years and over with B-ALL that is refractory or relapsed *(NICE TA893 2023).*

Obecabtagene autoleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia is being assessed by NICE – a decision is expected in August 2025.

Patients who have an isolated extramedullary relapse are not currently eligible for CART. Clinicians are directed to the CDF criteria/CART panel for the most up to date detail on eligibility of patients for available CART products as this is a rapidly evolving field.

For patients relapsing off treatment after achieving a long remission, re-induction with UKALL14-type regimen (being mindful of cumulative anthracycline dose) may be appropriate if there is an option to perform an allogeneic transplant if CR2 is achieved.

Weekly vincristine and prednisolone may be used for palliation of patients not fit for more intensive treatment and can restore a reasonable quality of life in patients who respond.

11 Stem cell transplantation

Addenbrooke's Hospital provides the regional allogeneic stem cell transplant service.

Donor searches are a time-consuming process.
In order to avoid delays, patients who may be transplant candidates should have tissue typing sent at diagnosis for the patient and any full siblings, at the earliest opportunity.
The patient should be asked to sign a consent form for a volunteer unrelated donor (VUD) search and this should be sent to the transplant team, so that they can initiate a donor search.
It is not necessary to wait for confirmation of remission post course 1 before performing these steps, in fact early completion of the above is encouraged by the transplant team.
VUD search consent forms can be obtained by contacting the transplant team in Addenbrooke's.

11.1 Transplant for patients with AML in CR1

Indications for consideration of allogeneic stem cell transplant in CR1 are:

- adverse-risk cytogenetics or molecular genetics (see section 5),
- primary refractory disease (defined as>15% blasts **and** <50% reduction in blasts after course 1),
- not in CR/CRi after course 2,
- high-risk by AML trial risk score,
- NPM1 mut patients who are MRD positive in blood post course 2,
- high level flow MRD (>0.1%) in marrow post course 2,
- standard risk patients aged>40 years with an HLA-matched sibling,
- patients unable to receive further intensive chemotherapy e.g. because of marrow aplasia.

Emerging data about other MRD markers and co-mutations may also be incorporated into local decision making.

Patients with favourable risk AML should not routinely be offered a transplant in CR1.

Current recommendations are that patient Core Binding Factor Leukaemia patients should be referred for a **transplant opinion** if:

RUNX1::RUNX1T1 - t(8;21) leukaemia	
Timepoint	**Molecular MRD level**
After cycle 2	Less than 3 log reduction with a *KIT* mutation present
After cycle 4	MRD persistently above 500 copies regardless of *KIT* mutation status
At any time	Log increase in transcripts on two consecutive samples

CBFB::MYH11 - t(16;16) or inv(16) leukaemia	
Timepoint	**Molecular MRD level**
After cycle 2	Less than 3 log reduction with a *KIT* mutation present
After cycle 4	MRD persistently above 100 copies regardless of *KIT* mutation status
At any time	Log increase in transcripts on two consecutive samples

11.2 Transplant for patients with AML in CR2 or beyond

Patients achieving a second remission (CR2) should be considered for transplant.
Older patients may be offered reduced intensity conditioning (RIC) transplants - in the context of a clinical trial if available.
Younger patients (under 55) should be offered myeloablative transplants if fit enough.

Autologous transplantation may be appropriate in APML in molecular CR2.

Patients with APML who achieve a second good molecular remission may be suitable for a monitoring strategy rather than transplantation.

11.3 Transplant for patients with ALL

For patients treated on trial, the decision regarding transplant may be recommended by the trial protocol. Patients aged < 25 being treated on an age-appropriate protocol, such as ALLTogether1, are not conventionally transplanted unless they are taken off protocol for poor disease response.
For those patients aged ≥ 25 and ≤70 years who are not on a trial, allogeneic stem cell transplant is recommended, fitness permitting, for:

- Patients with standard risk ALL not achieving MRD negativity at the end of induction phase 2

- Patients with high-risk ALL, deemed fit for allogeneic stem cell transplant, in CR1, for whom HLA matched and mismatched unrelated donors, and cord blood transplants may be considered
- Patients with relapsed ALL achieving CR2

For risk stratification and definition of high risk disease see section 5.

The conditioning used for the stem cell transplant will be decided by the transplant team after taking into consideration the patient's age and fitness.

12 Patient support

- Big C - www.big-c.co.uk. Provides cancer information and support - centres in Norwich, King's Lynn and Great Yarmouth.

- Blood Cancer UK – www.bloodcancer.org.uk. UK charity funding research into blood cancer including leukaemia. Also offers patient information and support.

- Macmillan Cancer Support – www.macmillan.org.uk. Cancer support and information. Centre in Peterborough.

- Maggie's – www.maggies.org. Provides physical, psychological and emotional support for patient, family and friends. Centre in Cambridge.

For young adults

- Young Lives Vs Cancer https://www.younglivesvscancer.org.uk/

- Teenage Cancer Trust www.teenagecancertrust.org

- CCLG Living Beyond Cancer www.cclg.org.uk/living-beyond-cancer.

13 References

Alaggio R et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022; 36(7):1720-48.

Ali S et al. Guidelines for the diagnosis and management of acute myeloid leukaemia in pregnancy. Br J Haematol 2015; 170: 487-495.

Döhner H et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022; 140(12):1345-1377.

Döhner H et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024; 144(21):2169-2173.
Heuser M, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021; 138(26):2753-67.

Khoury JD, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022; 36(7):1703-19.

Patel B, et al. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: toxicity data from the UKALL14 trial. Leukemia 2017; 31: 58–64.

Potter N, et al. UK AML Research Network. Molecular monitoring versus standard clinical care in younger adults with acute myeloid leukaemia: results from the UK NCRI AML17 and AML19 randomised, controlled, phase 3 trials. Lancet Haematol. 2025; 12(5):e346-e356.

Sanz MA, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood. 2019; 133(15):1630-43.

Foukaneli T, et al. Guidelines on the use of irradiated blood components. Br. J. Haematol. 2020; 191: 704-724.

14 Monitoring the effectiveness of the process

Process for monitoring compliance and effectiveness: Determined by local audits for which each hospital is responsible.

Disclaimer
It is your responsibility to check that any printed copy is the most recent version of this document. Please notify any changes required to the document owner.

Development
This guideline has been developed by the Haematology Departments of the Hospitals of the East of England Cancer Alliance. During its development it has been circulated to the Haematology Consultants and its final content has been agreed by them.

Quality Management
This document will be kept on the Quality Management System of the Norfolk and Norwich University Hospital to ensure regular review. It is made available to the region via the Knowledge Now website.

Document ratification and history				
Approved by:	Haematology			
Date approved:	15th July 2025	Date placed on QPulse:		15th July 2025
Review period:	3 years (or earlier in the light of new evidence)			
Authors:	East of England Cancer Alliance Haematology Consultants		Document Owner: Dr Angela Collins, Haematology Consultant NNUH	East of England Cancer Alliance https://www.canceralliance.co.uk/
Version number:	5		Unique identifier:	H.MA.193

Appendix 1
WHO Classification of Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia (2022)

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with PML::RARA fusion
Acute myeloid leukaemia with RUNX1::RUNX1T1 fusion
Acute myeloid leukaemia with CBFB::MYH11 fusion
Acute myeloid leukaemia with DEK::NUP214 fusion
Acute myeloid leukaemia with RBM15::MRTFA fusion
Acute myeloid leukaemia with BCR::ABL1 fusion
Acute myeloid leukaemia with KMT2A rearrangement
Acute myeloid leukaemia with MECOM rearrangement
Acute myeloid leukaemia with NUP98 rearrangement
Acute myeloid leukaemia with NPM1 mutation
Acute myeloid leukaemia with CEBPA mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Myeloid sarcoma

Acute leukaemia of ambiguous lineage with defining genetic abnormalities
Mixed-phenotype acute leukaemia with BCR::ABL1 fusion
Mixed-phenotype acute leukaemia with KMT2A rearrangement
Acute leukaemia of ambiguous lineage with other defined genetic alterations
Mixed-phenotype acute leukaemia with ZNF384 rearrangement
Acute leukaemia of ambiguous lineage with BCL11B rearrangement
Acute leukaemia of ambiguous lineage, immunophenotypically defined
Mixed-phenotype acute leukaemia, B/myeloid
Mixed-phenotype acute leukaemia, T/myeloid
Mixed-phenotype acute leukaemia, rare types
Acute leukaemia of ambiguous lineage, not otherwise specified
Acute undifferentiated leukaemia

B-cell lymphoblastic leukaemias/lymphomas
B-lymphoblastic leukaemia/lymphoma, NOS
B-lymphoblastic leukaemia/lymphoma with high hyperdiploid
B-lymphoblastic leukaemia/lymphoma with hypodiploid
B-lymphoblastic leukaemia/lymphoma with iAMP2
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion
B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features
B-lymphoblastic leukaemia/lymphoma with KMT2A rearrangement
B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); KMT2A-rearranged
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion
B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1-like features
B-lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion
B-lymphoblastic leukaemia/lymphoma with IGH::IL3 fusion
B-lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities

T-lymphoblastic leukaemia/lymphoma
T-lymphoblastic leukaemia / lymphoma, NOS
Early T-precursor lymphoblastic leukaemia / lymphoma

Appendix 2

Prevention of Perianal Infection in Neutropenic Patients – Patient information

What is a perianal infection?

A perianal infection is an infection of the area surrounding or involving a person's anus. Perianal infection may result in pain and inflammation and in severe cases an abscess (collection of pus) may form.

Who is at risk of perianal infections?

Patients who experience more than 2 weeks of neutropenia (where they have low numbers of a type of white blood cell called the neutrophil) are most at risk. For example, patients with acute leukaemia who undergo treatment with high-dose chemotherapy or a stem cell transplant.

Perianal infection can have a negative effect on a patients' quality of life and may lead to interruptions in their treatment and increase their time spent in hospital.

How can perianal infections be prevented with a sitz bath?

A sitz bath is a warm shallow bath for a patient to sit in. 10mL of 10% iodine (or similar antiseptic) should be added for every 1L of water.

A sitz bath is used to keep the perianal area clean.

It should be used for 10 minutes twice a day (morning and evening).

After each bath the perianal region should be dried and kept clean.

It is advised to do this from the start of treatment until the neutrophil count recovers after the final cycle of chemotherapy or for 3 months after an allogeneic stem cell transplant (a transplant from a stem cell donor).

What are some potential benefits of using a sitz bath?

Use of a sitz bath with iodine reduces the chances of developing perianal infection. The warm water from the sitz bath also reduced discomfort in the perianal area.

Should I buy a sitz bath?

If you are an inpatient in hospital, the nurses will provide you with a basin to use for your sitz baths. When you leave the hospital, we would recommend buying a sitz bath if you do not have a suitable basin you can use for this purpose at home. Simple, over the toilet sitz baths can be bought cheaply online from sites such as Temu, Etsy or Amazon. Reusable sitz baths should be cleaned with soapy and water after each use.

What are the potential side effects of using a sitz bath?

Burns may occur if the water is too hot. To avoid burns, the water should be warm, but not hot, aiming for about 37 to 39 degrees Celsius.

Rarely, patients can have allergic reactions to the iodine in the sitz bath. If you develop any new lesions in your perianal region you should inform the medical team. If you are allergic to iodine, please let the medical team know so that they can advise on a different antiseptic to use in your sitz bath.

What else can I do to reduce risk of a perianal infection?

In between sitz baths, make sure to keep the skin around the anus clean and dry. Avoid constipation – foods which can help are those with soluble fibre (fruit, vegetables, oats and pulses) and insoluble fibre (wholemeal bread, white pasta, white rice, nuts, crackers, cereals and linseed). Foods to avoid are bran, wholewheat pasta and brown rice, as these can slow the gut down by absorbing water and causing bloating. Drinking plenty of water, gentle exercise and use of laxatives when needed can also help to avoid or treat constipation.

Whilst neutropenic do not use suppositories or have anal sex, as passing anything through the anus can lead to small tears in the skin which may become infected.