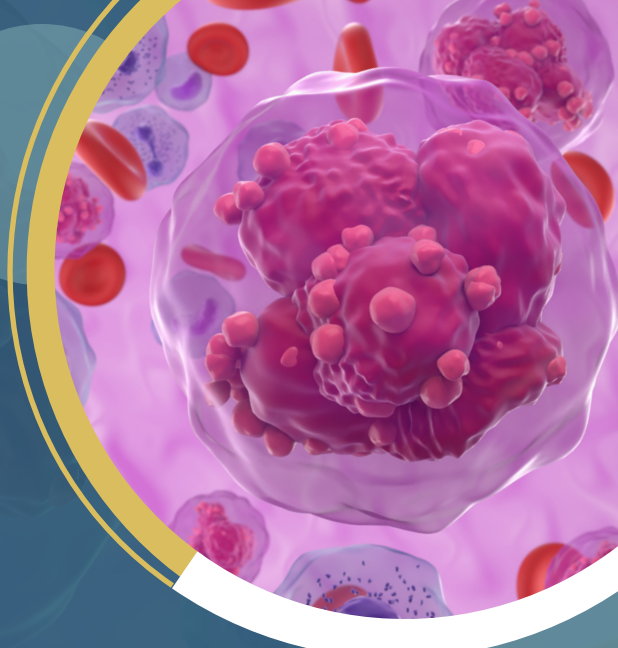


# Guidelines for the Management of B-cell ALL



## Objective

To develop evidence-based practical consensus recommendations for the management of B cell ALL in Indian settings

## Methodology

The Delphi Method: A robust method to collect real-world knowledge from a small panel of experts to form a consensus

### Panel selection

- 15 members including a chairperson
- Based on academic and clinical track record

### Evidence review

- Based on literature review (Jan 2001–Sept 2022)
- Panel surveyed on diagnosis and risk assessment
- Frontline therapy
- Choice of therapy in r/r setting

### Delphi consensus (round 1)

- Consensus categorized as
  - High ( $\geq 80\%$ )
  - Moderate (60–79%)
  - No consensus ( $< 60\%$ )

### Discussion rounds 2 & 3

- Any gaps or revisions to recommendations were addressed

### Finalization of recommendations

## Diagnosis

### High consensus

- CBC, peripheral blood morphology, flow cytometric immunophenotyping
- Markers must include CD19 and CD22
- Hepatitis B/C screening, HIV testing
- Males to be screened for testicular health
- CT/MRI in case neurological symptoms present
- Lumbar puncture with intrathecal chemotherapy
- Tumor lysis syndrome screening
- Cytogenetics
- CT of chest with intravenous contrast (not for routine practice)



### Moderate consensus

- Screening for opportunistic infections
- Early evaluation for transplant and search for donors
- Cardiac screening for patients with prior history of cardiac disease
- Pregnancy testing
- Fertility counselling



### No consensus

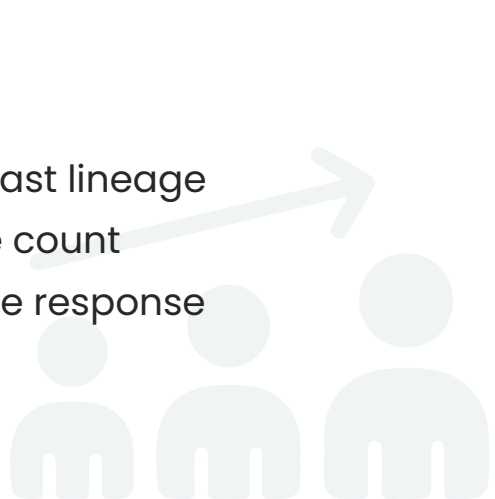
- Genetic tests such as next-generation sequencing and gene expression profiling
- Disseminated intravascular coagulation panel



## Risk stratification factors

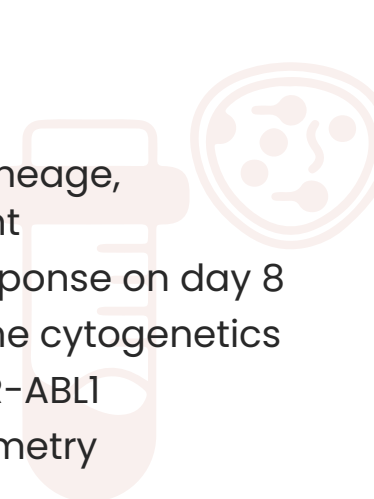
### Level 1

- Age
- Lymphoblast lineage
- Leukocyte count
- Prednisone response on day 8



### Level 2

- Age
- Lymphoblast lineage, leukocyte count
- Prednisone response on day 8
- Ph chromosome cytogenetics
- RT-PCR for BCR-ABL1
- MRD Flow cytometry



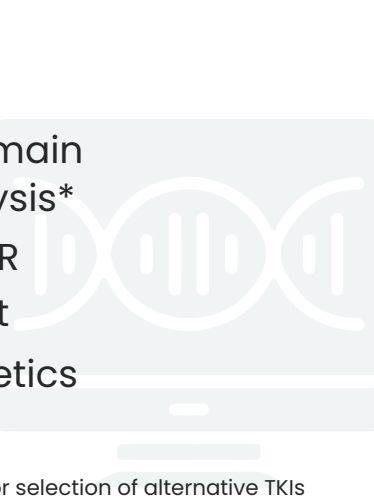
### Level 3

- RT-PCR for BCR-ABL1 and MLL-AFF1
- Cytogenetics for hyperdiploid  $> 50$
- BCR-ABL1 FISH
- Flow cytometry evaluation for MRD



### Level 4

- ABL-kinase domain mutation analysis\*
- NGS for IgH/TCR rearrangement
- Pharmacogenetics



\*especially the T315I mutation for selection of alternative TKIs

## Frontline treatment

- Modified Berlin-Frankfurt-Munster protocol: Preferred frontline therapy for pediatric and AYA B-cell ALL patients
- BFM/GMALL (German Multicenter Study Group for Adult Acute Lymphoblastic leukemia) protocol recommended for adults with B-cell ALL
- Flow cytometry to evaluate MRD status (table 1)
- Intrathecal methotrexate and systemic therapy preferred for CNS prophylaxis in pediatric and AYA patients.
- NCCN guidelines strongly recommend the use of MRD monitoring during patient evaluation over the course of sequential treatment

Table 1. MRD assessment methods

Technique	Sensitivity	Application
Flow Cytometry	$10^{-4}$	Ph-/+ B-Cell ALL
RT-PCR of Ig/T-cell receptor rearrangement	$10^{-4}$ to $10^{-5}$	Ph-/+ B-Cell ALL
RT-qPCR of BCR-ABL1 transcript	$10^{-4}$ to $10^{-5}$	Ph+ B-Cell ALL
NGS of Ig T-cell receptor rearrangement	$10^{-6}$	Ph-/+ B-Cell ALL

## Key takeaways

- Use of advanced molecular and genetic testing are crucial for the accurate diagnosis of B-cell ALL.
- A Modified version of the Berlin-Frankfurt Munster protocol has been shown to be an effective frontline treatment option for pediatric and AYA B-cell ALL patients.

### Abbreviations:

ABL1: Tyrosine-protein kinase ABL1; ALL: Acute lymphoblastic leukemia; Allo-HCT: Allogeneic hematopoietic cell transplantation AYA: Adolescent and young adult; BCR: breakpoint cluster region; BiIna: Blinatumomab; CBC: Complete blood count; CNS: Central nervous system; CT: Computed tomography; Ig: Immunoglobulin; InO: Inotuzumab; MRD: Minimal residual disease; MRI: Magnetic resonance imaging; Ph+: Philadelphia chromosome positive; Ph-: Philadelphia chromosome negative; RT-PCR: Reverse transcription polymerase chain reaction; RT-qPCR: Quantitative reverse transcription polymerase chain reaction; TKI: Tyrosine kinase inhibitor

### Reference:

Mathews V et al, Frontiers in Oncology, 2023 Apr 24;13:1171568.

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