This review will cover the key elements of modern acute lymphoblastic leukemia treatment regimens, focusing primarily on front-line treatment and concluding with a brief discussion of the management of relapsed disease.

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood, accounting for approximately 25% of childhood cancer and approximately 4,900 cases per year in the United States. A second peak in incidence occurs after 50 years of age, and although ALL accounts for a smaller proportion of adult than of pediatric malignancies, the absolute number of adult cases is ten times greater. Survival in childhood ALL has improved dramatically over the past 50 years; once a nearly incurable disease, pediatric ALL now has overall survival rates of over 80%. Survival in adults has also improved over time but remains considerably poorer at approximately 40%. Some of the key principles responsible for the improvement in outcomes include the use of combination chemotherapy to prevent the emergence of resistant clones, preventive CNS-directed therapy, the introduction of a delayed intensification phase of treatment, and risk stratification based on cytogenetic features and early response to treatment. Nevertheless, significant challenges remain. Survival in certain subgroups, such as infants and cases with adverse genetic features (eg, hypodiploidy), has improved very little over time. In addition, salvage rates are dismal for most patients who relapse. This review will cover the key elements of modern ALL treatment regimens, focusing primarily on front-line treatment and concluding with a brief discussion of the management of relapsed disease. Childhood ALL will be the primary focus, since children constitute over 60% of ALL cases and the majority are enrolled in clinical research trials. Significant contrasts with adult ALL will be highlighted.

Risk Stratification

One of the key factors responsible for survival gains in ALL is the recognition that, rather than being treated as a single entity, ALL should be treated as a set of heterogeneous disease subgroups that each require tailored therapy. Table 1 lists the key risk factors that affect prognosis on current regimens. It should be noted that risk factors are not absolute; rather, they differ in significance depending on the treatment regimen. Host factors include age, gender, and race and ethnicity. Disease characteristics include initial white blood cell (WBC) count at diagnosis, immunophenotype, genetic features, extramedullary involvement, and treatment response. Both age (with the exception of infants under one year of age) and initial WBC count behave as continuous variables; increasing values are associated with increasingly poor prognostic impact. However, in most pediatric risk stratification schemas they are treated as categorical variables, and cut-off values known as the
National Cancer Institute (NCI)/Rome criteria are used; in the NCI/Rome criteria, age <1 year and > 10 years, and initial WBC count > 50,000/µl are considered high risk.[5] Increasing age and initial WBC are both significant prognostic factors in adults as well, with the age cutoffs for high risk on different protocols ranging anywhere from 35 to 65 years, and initial WBC counts from 5,000 to 30,000/µl.[4] Males historically have had slightly worse survival, although this difference has diminished recently.[3] Race and ethnicity also affect outcome, with Asians having the best outcomes, followed by Caucasians, blacks, and Hispanics.[6] Racial and ethnic differences in outcome have multifactorial causes, including socioeconomic factors and biologic differences in disease features and host pharmacogenetics.[6,7] Indeed, a gene expression signature significantly associated with Hispanic ethnicity was recently identified, which may partially explain the survival disadvantage in Hispanics[8]; also, a component of genomic variation cosegregating with Native American ancestry was recently reported to be associated with increased risk of relapse.[9]

Immunophenotype is used to stratify patients to distinct treatment regimens for T-cell, B-precursor, or mature B-cell leukemia. Other immunophenotypic differences (eg, the adverse effects of CD10 negativity in B-precursor ALL, and a recently identified early T-cell precursor immunophenotype) affect prognosis but do not at present alter treatment.[10] The genetic features of ALL have been intensively researched for decades, and new insights have been generated by each successive methodological advance that emerged, including karyotype, fluorescence in situ hybridization (FISH), gene expression and single nucleotide polymorphism (SNP) array profiling, conventional and next-generation sequencing, and other techniques.[11] However, only a few features fulfill the criteria for incorporation into risk stratification schemas on a widespread basis:

- Occurrence in a clinically relevant proportion of patients.
- Contribution of independent prognostic information beyond that of other established risk factors.
- Ready availability in everyday clinical practice.

Significant favorable features used for risk stratification for most modern regimens include the ETV6-RUNX1 fusion gene generated by the t(12;21) translocation, and high hyperdiploidy (particularly trisomies 4, 10, and 17).[12] Adverse features include the BCR-ABL1 fusion gene generated by the t(9;22) translocation, hypodiploidy, and MLL rearrangements.[12] Recent studies have identified additional novel adverse prognostic factors that are beginning to be incorporated in risk stratification schemas: Ikaros (IKZF1) deletions or mutations,[13] Janus kinase 2 (JAK2) activating mutations and/or cytokine receptor–like factor 2 (CRLF2) overexpression,[14] and chromosome 21 intrachromosomal amplification (iAMP21).[15] Genetically defined subtypes have specific drug sensitivity patterns; enhanced sensitivity to asparaginase is seen in ETV6-RUNX1-positive ALL, and to methotrexate in hyperdiploid ALL, whereas ETV6-RUNX1-positive, TCF3-PBX1-positive, and T-cell ALL require higher methotrexate doses to yield equivalent intracellular concentrations of the active methotrexate polyglutamate metabolites.[16]

Event-Free Survival (EFS) of All Patients Enrolled in the Pediatric Oncology Group 9900 Series of Trials Who Had Satisfactory End-Induction Minimal Residual Disease (MRD)

Treatment response has assumed importance relatively recently, as technologic advances have made detection of minimal residual disease (MRD) possible on a routine clinical basis. MRD assays are based either on flow cytometric detection of an aberrant combination of surface markers characteristic of the leukemic clone, or on polymerase chain reaction (PCR) detection of a fusion transcript, gene mutation, or clonal immunoglobulin or T-cell receptor rearrangement.[17] Many current regimens include measurements of MRD during and at the end of induction, and sometimes at later time points as well. MRD positivity generally necessitates intensification of therapy (see Figure 1), and MRD negativity in some cases may warrant consideration of decreased treatment intensity—eg, for selected favorable-risk patients with low MRD at days 8 and 29, a recent series reported 5-year event-free survival (EFS) of 97% ± 1%.[18] Bone marrow morphology following one or two weeks of induction therapy was previously used as a measure of early response, but this is
generally being replaced by measures of either bone marrow or peripheral blood MRD due to the superior sensitivity of these tests. The Berlin-Frankfurt-Münster (BFM) Study Group continues to employ another measure of early response as well, namely, response to an initial seven-day prednisone window.[19]

**Induction**

Traditionally, the goal of induction has been to achieve morphologic remission (<5% blasts in the bone marrow). However, it is now recognized that achieving a molecular remission, generally defined as below a threshold of 0.01% blasts by MRD assay, substantially improves the chance of long-term cure.[18] Complete remission is achieved in approximately 98% of children and 85% of adults.[20] Generally, induction regimens consist of vincristine, asparaginase (Elispam), a glucocorticoid, and in some cases an anthracycline, for a period of 4 to 6 weeks. While this general framework has been employed for decades, some modifications have been made as new drug formulations have become available. Whether dexamethasone or prednisone is used during induction varies across cooperative groups because each of these glucocorticoids has its pros and cons.[21] Dexamethasone has the advantages of more potent cytotoxicity and superior CNS penetration. However, it also carries an increased risk of infection, avascular necrosis (AVN), and other toxicities. Most cooperative groups currently use prednisone in patients over 10 years of age, because of the significant risk of AVN in this age group, while they use dexamethasone in children younger than 10 years. The asparaginase formulation used in most regimens has shifted from *Escherichia coli* (or native) asparaginase to a pegylated form, pegaspargase (Oncaspar), which has the advantages of a longer half-life and lower immunogenicity.[22] The lower immunogenicity has dual benefits: a lower frequency of both hypersensitivity reactions and neutralizing antibodies that reduce drug efficacy. An anthracycline, most often daunorubicin, is generally included in induction only for a subset of high-risk patients. A recent meta-analysis has questioned the benefit of anthracyclines altogether, suggesting that antileukemic efficacy is counterbalanced by increased cardiotoxicity and treatment-related deaths.[23]

Asparaginase is less well tolerated in adults; thus, another common regimen employed in this population is hyper-CVAD, which consists of courses of cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine for a total of eight courses.[24] However, more recent studies have demonstrated that the survival in adolescents and young adults treated in pediatric cooperative trials is superior to the survival of those treated in adult trials.[25] It is unclear whether the survival differences are attributable to differences in treatment regimen and dose intensity of the regimens, to protocol adherence by the physicians, or to demographic differences between patients enrolled in adult studies and patients in pediatric studies. Nevertheless, several recent studies have begun studying pediatric-style regimens in adult patients.

**Post-Induction Intensification**

It is well established that further intensification of therapy to consolidate remission status following induction improves outcomes in ALL.[26,27] This phase is generally termed consolidation or intensification. A wide variety of systemic chemotherapy regimens have been successfully utilized for consolidation—eg, methotrexate (ranging from 20 mg/m² to 5 g/m²) with or without mercaptopurine[28]; prolonged asparaginase[29,30]; and cyclophosphamide, cytarabine, and thioguanine.[31] Consolidation is usually followed by an interim maintenance phase, and then by a reinduction or delayed intensification (DI) phase that includes many of the same chemotherapy agents used in induction and consolidation. A key Children's Cancer Group (CCG) study demonstrated that augmentation of post-induction therapy improved outcomes for high-risk ALL patients with a slow early response to therapy.[32] The augmented regimen included two rather than one interim maintenance and DI phase; these phases incorporated additional vincristine, asparaginase, dexamethasone, and escalating-dose intravenous methotrexate with asparaginase (the “Capizzi” methotrexate regimen) instead of the standard post-induction intensification.[32] A subsequent CCG study demonstrated that high-risk ALL patients with a rapid early response benefited from augmented intensity of postinduction therapy but not from double versus single DI.[33] More recently, a CCG study of standard-risk ALL patients confirmed the benefit of Capizzi methotrexate during interim maintenance[34] but again showed no benefit of double versus single DI.[35] Although a wide variety of agents and dose schedules have demonstrated efficacy, the general principle that significant post-induction intensification improves outcomes appears to hold.
true across treatment studies and ALL subgroups, with increasingly high-risk subgroups benefiting from correspondingly greater increases in treatment intensity and duration.

**CNS-Directed Therapy**

In addition to reduction of systemic disease burden, another key goal of post-induction therapy is the prevention of CNS disease. Introduction of prophylactic cranial radiation was a historic milestone in averting CNS relapse, which otherwise occurred in over half of patients following induction of remission. However, it has been largely replaced by alternative approaches in recent decades because of the substantial associated morbidity of acute neurotoxicity, long-term neurocognitive deficits, growth impairment, second malignancies, endocrinopathies, and obesity.[36]

### Definition of Central Nervous System Involvement

The St. Jude Children's Research Hospital group recently reported that a regimen omitting cranial radiation for all patients with newly diagnosed ALL (of whom 9 of 498 had overt CNS disease) produced 5-year event-free and overall survival figures that did not differ significantly between cases and historical controls.[37] However, most cooperative groups currently use cranial radiation for between 2% and 20% of patients who have significant risk factors for CNS relapse—eg, CNS2 and CNS3 involvement at diagnosis (see Table 2 for definitions), hyperleukocytosis, T-cell immunophenotype, BCR-ABL1 positivity, MLL rearrangement, or hypodiploidy. Typically, radiation doses of 12 to 18 Gy are used for prevention, and doses of 18 to 24 Gy are used for treatment of CNS3 disease. Recently, the Dana-Farber Cancer Institute Consortium reported that hyperfractionated (twice-daily) delivery of cranial radiation does not improve late neuropsychologic function and may actually decrease antileukemic efficacy, compared to conventionally fractionated (daily) radiation.[38]

Other effective approaches to the control and/or prevention of CNS disease include intensive intrathecal therapy and the use of systemic chemotherapy regimens with CNS penetration, such as dexamethasone, high-dose methotrexate, high-dose cytarabine, and intensive asparaginase. The relative benefit of triple intrathecal therapy (methotrexate, cytarabine, and hydrocortisone) versus single-agent intrathecal methotrexate in ALL remains unclear. A recent CCG study reported that triple intrathecal therapy decreased CNS relapses but unexpectedly led to inferior overall survival due to increased bone marrow and testicular relapses.[39] However, the systemic therapy used in this protocol, administered from 1996 to 2000, was substantially less intensive than most current regimens. When triple intrathecal therapy is combined with a backbone of intensive systemic therapy, the outcomes appear to be excellent.[37]

### Reference Guide

**Therapeutic Agents**

- Alemtuxumab (Campath)
- Asparaginase (Elspar)
- Bortezomib (Velcade)
- Clofarabine (Clolar)
Pegaspargase (Oncaspar)
Prednisone
Rituximab (Rituxan)
RO4929007
Thioguanine
Vincristine
Vorinostat (Zolinza)

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

Maintenance Therapy

Maintenance or continuation therapy, which consists of approximately 2 to 3 years of primarily oral antimitabolites, is a unique feature of ALL treatment. Presumably, maintenance therapy eradicates MRD, perhaps by inducing leukemia progenitor differentiation.[40] The cornerstone of ALL maintenance is oral weekly methotrexate and daily mercaptopurine. Methotrexate potentiates mercaptopurine by reducing de novo purine synthesis, which leads to greater incorporation of thiopurines into DNA and RNA. Interestingly, evening dosing of mercaptopurine appears to be more efficacious.[41] Maintaining dose intensity of methotrexate and mercaptopurine during maintenance is significantly positively associated with EFS; however, excessive dose escalation is to be avoided, since periodic suspension because of neutropenia has a negative impact on EFS.[42] Host genotype for thiopurine methyltransferase (TPMT), the enzyme responsible for mercaptopurine metabolism, significantly affects drug activity.[43] Homozygosity for a mutant allele occurs in approximately 1 in 300 persons and results in very high thioguanine levels, profound myelosuppression, and an increased risk of second malignancies at standard mercaptopurine doses; heterozygosity occurs in 10% of the population and results in moderately elevated levels and toxicities. Some groups therefore employ prospective TPMT genotyping to guide mercaptopurine dosing. Several studies have compared thioguanine and mercaptopurine during maintenance.[44-46] Both are prodrugs that require conversion to active metabolites, thioguanine nucleotides, with thioguanine requiring fewer steps and also demonstrating greater CNS penetration. However, despite the superior bioavailability of thioguanine, all three studies demonstrated serious adverse effects—primarily hepatotoxicity (vaso-occlusive disease and chronic portal hypertension)—that have led to rejection of its prolonged use during maintenance therapy. Also, intravenous mercaptopurine has not been shown to be more advantageous than oral mercaptopurine during maintenance therapy.[47]

The optimal duration of maintenance is likely regimen-dependent but appears to fall somewhere between 2 and 3 years of total treatment. The Tokyo Children’s Cancer Study Group reported a 5-year EFS of 60% for patients who received a total of 12 months of treatment, demonstrating that a
sizeable number of patients do achieve cure with this short duration, but that an unacceptable proportion, distributed across all risk groups, relapse.[48] The BFM Study Group further demonstrated that 24 months of treatment resulted in fewer relapses than did 18 months.[27] Thus, somewhere between 2 and 3 years of treatment appears to be optimal, with shorter durations increasing relapses and longer durations increasing remission deaths.[49] Some groups use a longer duration of therapy in boys while others do not; whether increased treatment duration ameliorates their survival disadvantage remains unclear.

The benefit of vincristine and dexamethasone pulses during maintenance therapy is uncertain and regimen-dependent. Some studies have shown benefit,[49,50] while others have not.[51,52] In general, the benefit of maintenance pulses appears to be most significant in older treatment regimens that did not utilize dexamethasone and an intensive reinduction phase.

**Hematopoietic Stem-Cell Transplant and Relapse**

Hematopoietic stem-cell transplantation (HSCT) is considered in first remission for a subset of very high-risk childhood ALL cases, such as those that involve induction failure, severe hypodiploidy, and the Philadelphia chromosome (Ph). Management of Ph-positive ALL has become more controversial as treatment with chemotherapy combined with imatinib and later-generation tyrosine kinase inhibitors has demonstrated excellent early outcomes, comparable or superior to HSCT.[53] Indications for HSCT in adult ALL are also controversial. Traditionally, HSCT in a first complete remission was considered the best curative option in general for adult ALL, but recent studies have yielded conflicting data regarding the relative benefit of chemotherapy versus HSCT in both standard- and high-risk disease.[54,55]

![FIGURE 2](image-url)

**Survival After Relapse for Patients Who Experience Isolated Marrow Relapse (A), Concurrent Marrow Relapse (B), and Isolated Central Nervous System (CNS) Relapse (C)**

Although significant survival gains have been made in ALL, relapsed ALL is still the fourth most common childhood malignancy,[56] and survival following relapse remains poor in both children and adults. Moreover, progress in treating relapsed ALL has been halting; in a recent retrospective review of nearly 10,000 children treated in COG trials between 1988 and 2002, there was no improvement in survival from early- to late-era trials within this period.[57] The single most important positive prognostic factor is duration of first remission (see Figure 2). Prognosis is best in those patients with late relapse (over 36 months from diagnosis), followed by those with intermediate relapse (18 to 36 months from diagnosis), and finally those with early relapse (less than 18 months from diagnosis).[58] Other significant positive prognostic factors include isolated extramedullary relapse, B-cell rather than T-cell immunophenotype, female gender, younger age at diagnosis, and MRD negativity following reinduction and prior to HSCT.[56]

![TABLE 3](image-url)

**Selected Novel Therapeutic Agents in ALL**
Second remission can generally be achieved in 70% of early relapses and in 95% of late relapses using intensive conventional chemotherapy, but duration is often brief, leading to poor EFS rates of approximately 30% to 40% overall.[56] Both remission and EFS rates following second or greater relapse are dismal. HSCT does not necessarily improve outcomes compared to chemotherapy, and it is often not an option—eg, for patients who lack a suitable donor, those whose remission is not sustained, or those who have active infection or compromised organ function. Generally, HSCT is recommended for early bone marrow relapse, whereas chemotherapy is preferred in late bone marrow relapse and any isolated extramedullary relapse. The generally poor EFS rates in relapsed ALL, whether treated with chemotherapy or HSCT, indicate the need for novel therapeutic approaches. Several promising novel agents currently advancing in clinical trials are listed in Table 3.

**Conclusions**

Survival in ALL has improved dramatically as a result of sophisticated classification schemas that tailor therapy according to multiple risk factors, optimal combinations of chemotherapeutic agents, and delivery of effective CNS prophylaxis that obviates the need for radiation for the majority of patients. Nevertheless, significant challenges remain. Outcomes remain poor in several subgroups, including infants, MRD-positive patients, and patients who carry adverse genetic features. Severe toxicities have complicated the delivery of effective therapy in particular subgroups—eg, infections in patients with Down syndrome, and avascular necrosis in adolescents. Achieving further advances through clinical trials has become more challenging as the number of prognostic factors multiplies and patients are carved into ever-smaller categories. Despite these challenges, novel approaches continue to yield new insights into disease pathogenesis and treatment, and progress continues toward the goal of cure for ALL.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**

**REFERENCES**


Source URL: http://www.diagnosticimaging.com/oncology-journal/management-strategies-acute-lymphoblastic-leukemia

Links:
[1] http://www.diagnosticimaging.com/review-article