REVIEW

Acute toxic complications of chemotherapy in children with acute lymphoblastic leukemia and acute myeloid leukemia: A systematic review

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ABSTRACT

Background: Intensive chemotherapy for childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is associated with substantial toxicity that affects treatment tolerability and outcomes.
Aim: To summarize the evidence on acute chemotherapy-related toxic complications in children with ALL and AML.
Methods: This systematic review was conducted in accordance with PRISMA guidelines; the protocol was registered in PROSPERO (CRD420251248980). A literature search was performed in PubMed, Web of Science, Scopus, and Google Scholar for studies published between 2000 and 2025. Studies involving patients with newly diagnosed ALL or AML receiving polychemotherapy and reporting acute toxic effects were included. Owing to substantial heterogeneity across studies, no meta-analysis was performed. After screening 614 records, 70 studies were included in the review.
Results: The most frequently reported complications were infectious, hematologic, gastrointestinal, hepatic, neurologic, renal, cardiac, thrombotic, and metabolic toxicities. The highest rates of severe toxicity were observed during induction and early consolidation. Infectious complications remained the leading cause of severe morbidity and treatment-related mortality, particularly in AML. In ALL, marked interstudy variability was noted in the reported rates of mucositis, neurotoxicity, hepatotoxicity, and toxicities associated with methotrexate, vincristine, and asparaginase, whereas in AML, severe infectious, respiratory, and cardiotoxic events predominated in the setting of highly intensive treatment regimens. The risk of complications depended on leukemia subtype,

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treatment phase, protocol composition, patient age, cumulative drug exposure, and supportive care practices. **Conclusion:** Systematizing these data is important for the early identification of high-risk patients, optimization of monitoring strategies, and improvement of supportive care. (www.actabiomedica.it)

Key words: ALL, AML, children, chemotherapy-related toxicity, acute toxicity; infectious complications, systematic review

Introduction

Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are the major pediatric acute leukemias and differ substantially in their biology, treatment intensity, and toxicity profiles. ALL accounts for approximately 75–80% of childhood leukemia cases (1), whereas AML is less common but generally associated with a more aggressive course and poorer prognosis (2). Despite major therapeutic advances, chemotherapy-related toxicity remains a key determinant of treatment tolerability, protocol adherence, and non-relapse morbidity and mortality (3,4). Current treatment protocols rely on intensive multi-agent chemotherapy and are associated with a broad range of infectious, hematologic, gastrointestinal, hepatic, renal, neurologic, cardiac, thrombotic, and metabolic complications (5,6). The incidence and severity of these toxicities vary according to leukemia subtype, treatment phase, drug exposure, patient age, and supportive care strategies (4,7,8), with the greatest burden typically observed during induction and early consolidation (8,9). Although numerous studies have addressed treatment-related toxicity in pediatric ALL and AML, the evidence remains fragmented, with most reports focusing on individual complications, specific agents, or particular treatment phases. Therefore, a systematic synthesis of the available data is needed. The aim of this review was to summarize the spectrum, incidence, and severity of acute toxic complications of polychemotherapy in children with ALL and AML, and to evaluate their associations with treatment phases, chemotherapeutic agents, and clinical risk factors.

Materials and Methods

This work is a systematic review carried out in accordance with the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (10). Study protocol registered in PROSPERO (CRD420251248980).

Search strategy

To identify studies evaluating the frequency of toxic complications associated with chemotherapy protocols in children with ALL and AML, a search of the PROSPERO database was first conducted; however, no analogous studies were identified. Therefore, a systematic search was performed in the PubMed, Web of Science, and Scopus databases covering the period from January 2000 to December 2025. Google Scholar was used as a supplementary source to identify additional potentially relevant studies. The search was initiated on December 8, 2025, and completed on February 12, 2026. Search terms combined controlled vocabulary and free-text keywords related to the population, exposure, and outcomes of interest, including: “acute lymphoblastic leukemia”, “acute myeloid leukemia”, “children”, “pediatric”, “chemotherapy”, “toxicity”, “adverse effects”, “complications”, “treatment-related toxicity”, “organ toxicity”, “infectious complications”, “neurotoxicity”, “hepatotoxicity”, “nephrotoxicity”, and “cardiotoxicity.” The search strategy was adapted for each database according to its indexing system and search interface. In addition, the reference lists of all included studies and relevant review articles were manually screened to identify

further eligible publications not captured by the database search. After merging records from all databases, duplicate citations were removed prior to screening to ensure that each study was assessed only once.

Eligibility criteria

Study inclusion criteria:

1. children and adolescents aged 0 to 18 years;
2. patients with a diagnosis with a primary diagnosis of ALL and AML;
3. patients receiving polychemotherapy as the main method of treatment;
4. studies that evaluated the acute toxic effects of polychemotherapy (Acute toxicity was defined as adverse events occurring during active chemotherapy or within protocol-defined treatment phases, excluding long-term survivorship outcomes);
5. observational studies (cohort, case-control studies (≥5 patients) and cross-sectional studies, randomized and non-randomized clinical trials;
6. publications in English from January 2000 to December 2025.

Exclusion criteria:

1. non-paediatric population;
2. mixed population without separate data on children;
3. other types of leukemia (CML, CLL, JMML, MDS, MPN, MPAL);
4. only relapsed/refractory cases;
5. HSCT/BMT, post-transplant stage;
6. radiation therapy;
7. monotherapy or only symptomatic treatment;
8. immune-effector therapy (e.g., CAR T-cells);
9. only diagnostic tests;
10. only survival/remission;
11. only late toxic effects of polychemotherapy;
12. reviews, letters, editorials;
13. clinical cases;
14. preclinical studies (in vitro / on animals);
15. articles not in English;
16. year of publication before 2000

Study selection, data extraction, and synthesis

The literature review and study selection were conducted in accordance with PRISMA recommendations. Following database searching, duplicate records were removed, and two reviewers (A.B. and I.J.) independently screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were then retrieved and assessed against predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus. Data extraction was performed independently by the same two reviewers using a standardized form approved by all authors. For each included study, the following information was collected: author and year of publication, country, study design, leukemia type, sample size, patient age, treatment protocol, main drug or drug class of interest, treatment phase, type of toxicity, and key findings relevant to toxicity and treatment. Because of substantial clinical and methodological heterogeneity across the included studies, including differences in leukemia subtype, treatment protocols, toxicity definitions, grading systems, and outcome reporting, meta-analysis was not performed. Instead, the findings were synthesized narratively. Studies were grouped by leukemia subtype (ALL, AML, or mixed cohorts) and then categorized according to toxicity domain, including infectious, hematologic, neurologic, gastrointestinal, hepatic, renal, cardiac, metabolic, and thrombotic complications. Within each category, findings were summarized with respect to toxicity frequency, severity, treatment phase, implicated agents, reported risk factors, and clinical outcomes such as treatment modification, intensive care admission, or mortality.

Risk of bias and quality assessment

Methodological quality was assessed using the Mixed Methods Appraisal Tool (MMAT). After two initial screening questions, each study was evaluated using five design-specific criteria according to its methodological category. The appraisal considered the appropriateness of the study design, sampling strategy, outcome measurement, completeness of data, risk of

confounding or bias, and the suitability of the analytical approach. For mixed-methods studies, integration of qualitative and quantitative components was also assessed. Studies were not excluded solely on the basis of quality; rather, the appraisal informed interpretation of the findings.

Results

Figure 1 presents the flow diagram illustrating the study selection process. A total of 614 publications were identified through the initial systematic search. After removal of duplicate records and sources

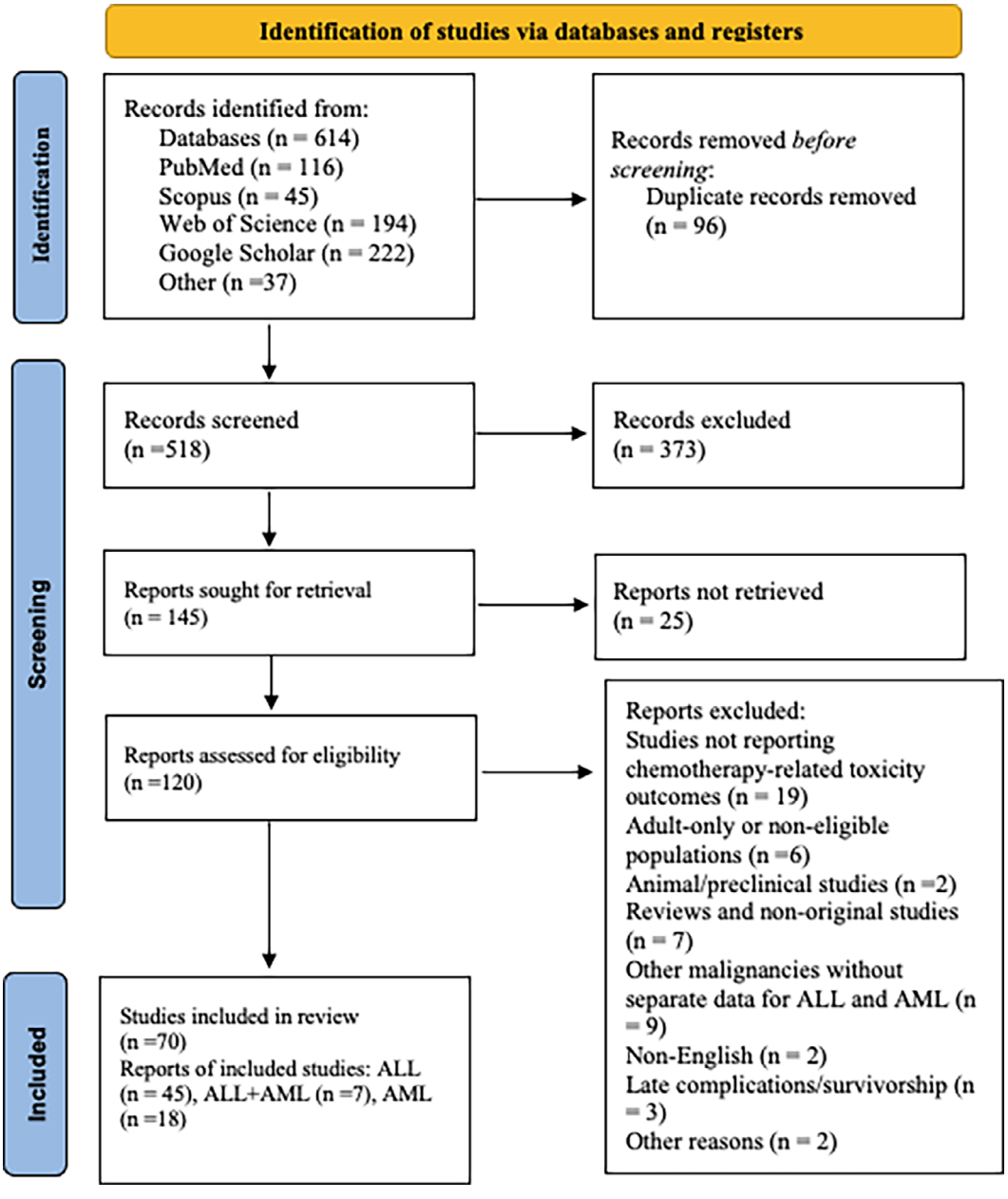

Figure 1. The flowchart of study selection.

deemed clearly irrelevant based on titles and abstracts, 518 records remained for further screening. At the eligibility assessment stage, 373 studies were excluded. Following title and abstract screening, 145 publications were selected for full-text retrieval; however, 25 full-text articles could not be obtained. Therefore, 120 full-text articles were assessed for eligibility, and 70 studies were ultimately included in the final review.

General characteristics of the included studies

The systematic review included studies involving pediatric patients with ALL and AML who received intensive polychemotherapy within national and international treatment protocols (including COG, NOPHO, AML-BFM, DCOG, and others). Most of the included studies were retrospective cohort studies or secondary analyses of prospective clinical trial protocols (11, 12–16). Geographically, the studies were conducted in North America, the Nordic countries, Germany, Turkey, China, and other regions, reflecting substantial variability in clinical practice patterns and supportive care approaches. The majority of studies primarily focused on the induction phase, which is characterized by the highest intensity of cytotoxic exposure and, consequently, the greatest risk of severe complications. A general overview of the included studies is presented in Table S1.

Acute toxicity profile in ALL and AML

The included studies showed that the acute toxicity profile of ALL and AML has both common features and significant differences. The results are presented below for the main toxicity domains.

Hematologic toxicity

Hematologic toxicity was one of the most frequent complications of therapy for acute leukemias in children, however, its profile varied according to leukemia subtype, treatment phase, and the agents used. In ALL, myelosuppression was most commonly associated with HD-MTX, particularly during the consolidation phase and in combination with 6-MP or asparaginase, whereas in AML, cytopenias were almost universal during intensive induction therapy. Overall, in ALL, reported rates ranged from 8.9% to 82.6% for myelotoxicity, with severe neutropenia reported in 56.51%, anemia in 26.37%, and thrombocytopenia in 8.90% during induction, while in AML, Grade 4 neutropenia reached 100%, leukopenia and thrombocytopenia 64.4%, Grade 3 anemia 93.3%, and febrile neutropenia/infections 97.8%. In ALL, the most pronounced hematologic toxicity was observed during consolidation courses containing HD-MTX. Levinsen et al. (58) and Kloos et al. (38) described clinically significant leukopenia, neutropenia, and thrombocytopenia, including severe forms (Grade 3–4), with toxicity increasing when methotrexate was administered after asparaginase. Kałużna et al. (27) and Guo et al. (55) confirmed the role of pharmacogenetic factors, demonstrating associations of myelotoxicity with genotype, MTX clearance, and the ABCB1 variant. Even with less intensive methotrexate regimens, Sari et al. (23) and Kapoor et al. (26) reported neutropenia, thrombocytopenia, and episodes of febrile neutropenia. During other treatment phases, Boonyawat et al. (56) documented neutropenia during maintenance therapy with 6-MP, whereas Xu et al. (44) reported severe neutropenia in 56.51% of patients, anemia in 26.37%, and thrombocytopenia in 8.90% during induction. In AML, hematologic toxicity was deeper and nearly universal. Wen et al. (76) reported Grade 4 neutropenia in 100% of patients, leukopenia and thrombocytopenia in 64.4%, Grade 3 anemia in 93.3%, and febrile neutropenia and infections in 97.8% of children. Similarly, Løhmann et al. (15), Lehrnbecher et al. (80), and Bochennek et al. (12) showed that profound and prolonged neutropenia in AML was closely associated with a high frequency of infectious complications.

Thus, hematologic toxicity occupied a central place in both leukemia subtypes; however, in ALL it was more strongly related to HD-MTX, thiopurines, and patient pharmacogenetic characteristics, whereas in AML it mainly reflected the high intensity of therapy and was a key determinant of severe infectious toxicity.

Infectious toxicity

Infectious complications were among the most clinically significant consequences of therapy for acute leukemias in children and were closely related to the depth and duration of neutropenia. In ALL, reported infection rates ranged from 3.3% to 79.5% depending on the type of infectious event and treatment phase, including Grade 3–4 infections in 32.3%, bacteremia in 27–33.1%, sepsis in 20.5–49.3%, pneumonia in 32.2%, and invasive fungal infections in 3.3–9.7%. These complications were observed mainly during the early intensive phases of therapy. Zawitkowska et al. (40), van Bunningen et al. (61), Xu et al. (44), De Pietri et al. (28), and Teusink et al. (31) consistently showed that infections were common in ALL, although they generally had a more favorable course than in AML. In AML, infectious toxicity was more severe, with Grade 3–4 infections reported in 28–79%, microbiologically documented infections in more than 60% of patients, invasive fungal infections in 20.5%, and overall infectious episodes reaching 97.8% during venetoclax-containing induction. Treatment-related mortality ranged from 1.5% to 4.6%, while IFI-related mortality reached 53%. Løhmann et al. (15), Bochennek et al. (12), Creutzig et al. (11), Lehrnbecher et al. (80), Sung et al. (75), Lin et al. (79), Yeoh et al. (71), Ávila Montiel et al. (73), and Wen et al. (76) demonstrated that profound and prolonged neutropenia in AML was associated with a markedly higher burden of severe infectious complications. Thus, infectious toxicity in both leukemia subtypes was closely linked to myelosuppression; however, its clinical significance was substantially greater in AML, where it represented one of the major non-relapse complications of therapy.

Gastrointestinal toxicity

Gastrointestinal toxicity was a frequent complication of therapy for acute leukemias in children and included mucositis, gastritis, pancreatitis, and hepatobiliary disorders. In ALL, reported rates ranged from 7.5% to 70.7% depending on the specific endpoint, including mucositis (7.5–70.7%), hepatobiliary toxicity (18.9–61.1%), elevated transaminases (28–64%), pancreatitis (9.09–13%), and gastritis (23.6–46%). These complications were mainly associated with methotrexate, 6-mercaptopurine, asparaginase, and glucocorticosteroids. Santos de Faria et al. (17), Kapoor et al. (26), and Guo et al. (55) reported variable rates of mucositis, whereas Kałużna et al. (27), Levinsen et al. (58), and Guo et al. (55) documented hepatobiliary toxicity and transaminase elevation. Knoderer et al. (63) and Youssef et al. (66) described asparaginase-associated pancreatitis, and Belgaumi et al. (35) reported steroid-associated gastritis. In AML, gastrointestinal toxicity was less frequent than hematologic and infectious complications but remained clinically relevant. Severe mucosal-abdominal manifestations were reported in 28–40%, enteritis/typhlitis/colitis /enterocolitis in 14.6%, elevated transaminases in 53.4% for ≥Grade 1 and 5.4% for ≥Grade 3, and Grade 3 pancreatitis in 6.7%. Creutzig et al. (11), Shafey et al. (67), Sun et al. (75), and Wen et al. (76) showed that gastrointestinal toxicity in AML was mainly associated with intensive cytarabine- and anthracycline-containing therapy. Thus, in ALL, gastrointestinal toxicity was more often drug-specific and usually reversible, whereas in AML it more often reflected treatment intensity and could require treatment modification.

Cardiotoxicity

Cardiotoxicity during the treatment of acute leukemias in children was predominantly associated with anthracyclines and manifested as impaired myocardial contractility, echocardiographic abnormalities, and, less commonly, clinical cardiomyopathy. Overall, in ALL, reported rates ranged from 2.7% to 20% depending on the specific cardiovascular endpoint, including early cardiotoxicity in 14%, severe Grade 3–4 cardiotoxicity in 2.7%, pericardial effusion in 13.6%, intracardiac thrombosis in 8.5%, and arterial hypertension in 20%. In ALL, cardiotoxicity was less frequent and more often presented as early subclinical changes. Linares Ballesteros et al. (62) reported early cardiotoxicity in approximately 14% of patients, particularly at cumulative anthracycline doses of ≥150 mg/m². In the multicenter cohort by Zawitkowska et al. (40), severe Grade 3–4 cardiotoxicity occurred in 2.7% of patients. Alpman et al. (53) additionally described pericardial effusion in 13.6%, intracardiac thrombosis in 8.5%, and arterial hypertension in 20% of patients. In AML,

cardiotoxicity was generally more pronounced, with reported rates ranging from 1.6% to 39%, including early cardiotoxicity in 13.7–39%, late cardiotoxicity in 17.4%, overall cardiotoxicity in approximately 12%, symptomatic left ventricular dysfunction in 1–2%, clinical cardiomyopathy in 6.5%, and cardiac mortality in 1.6%. Linares Ballesteros et al. (62) reported early cardiotoxicity in 39% of patients at cumulative doses of 180–298 mg/m², with a decline in LVEF of more than 10% being the strongest predictor. Getz et al. (14) reported an overall cardiotoxicity rate of approximately 12%, although symptomatic left ventricular dysfunction was observed in only 1–2% of patients. In the study by Temming et al. (74), early cardiotoxicity occurred in 13.7%, late cardiotoxicity in 17.4%, clinical cardiomyopathy in approximately 6.5%, and cardiac mortality in 1.6%. Thus, in both leukemia subtypes, cardiotoxicity was predominantly anthracycline associated; however, in ALL it was more often limited to early or moderate abnormalities, whereas in AML it occurred more frequently and was associated with higher cumulative anthracycline exposure and greater treatment intensity.

Neurotoxicity

Neurotoxicity was a clinically significant complication of therapy for acute leukemias in children and included both peripheral and central neurologic disorders. It was most commonly associated with vincristine, methotrexate, and, indirectly, asparaginase. Overall, the reported frequency of neurotoxicity in ALL varied widely depending on the toxicity type, assessment method, and treatment phase, whereas the available data for AML were more limited. In ALL, the most frequent form of neurotoxicity was VIPN, with reported rates ranging from 19% to 96%. Nazir et al. (20) reported a frequency of 19%; van Schie et al.(25) showed neuropathy ≥Grade 3 in 60% of patients receiving vincristine in combination with azole antifungals; Teusink et al. (31) reported neuropathy in 48% of children; Arzanian et al. (47) described a broad spectrum of clinical manifestations; Rokkanen et al. (33) identified signs of VIPN in 96% of patients during therapy; and Sultana et al. (64) reported VIPN during induction in 29.2% of children with ALL. Central neurotoxicity in ALL was more commonly associated with methotrexate and generally ranged from 3% to 20% across studies. Mateos et al. (24) reported a frequency of 7.6%, Anastasopoulou et al. (42) reported 9.2% acute CNS events, Parasole et al. (49) and Millan et al. (52) described a broad spectrum of methotrexate-associated manifestations, Kranjčec et al. (43) reported an incidence of approximately 20%, Tong et al. (22) reported central neurotoxicity in about 10% of patients receiving PEG-asparaginase, and Xu et al. (44) documented neurotoxicity in 7.88% of patients. In AML, the available data were limited, and reported rates of neurotoxicity were generally lower, ranging from 2.0% to 10%. Løhmann et al. (15) reported Grade 3–4 central neurotoxicity in 4.9% of patients and peripheral neurotoxicity in 2.0%. Youssef et al. (66) described methotrexate-associated leukoencephalopathy, and Sultana et al.(64) reported peripheral neuropathy in 10% of children with AML. Thus, neurotoxicity in ALL was more frequent and clinically more heterogeneous, with a predominant role of VIPN and methotrexate-associated CNS events, whereas in AML severe neurologic complications were reported less often and within a narrower frequency range.

Nephrotoxicity

Nephrotoxicity in children with acute leukemias varied depending on leukemia subtype, assessment criteria, chemotherapy intensity, and the concomitant use of nephrotoxic anti-infective agents. Overall, in ALL it was less frequent and usually milder, whereas in AML renal injury was observed more often and was clinically more significant. In ALL, nephrotoxicity was most commonly evaluated in the context of high-dose methotrexate therapy, with reported rates ranging from 0% to 16.7% across studies, while severe renal toxicity generally did not exceed 0.5–1.5%. Sari et al. (23) reported nephrotoxicity in 8.8% of HD-MTX cycles, with Grade 3 toxicity in only 1.4% of cases. Den Hoed et al. (29) documented severe renal toxicity ≥Grade 3 in only 1% of patients, Kałużna et al. (27) reported rates of 8.9–16.7%, and Lopez-Lopez et al. (30) reported 8.8%, whereas Kapoor et al. (26) observed no cases of nephrotoxicity. According to Zobeck et al. (59), Grade 2 creatinine elevation occurred in 8.9% of

patients, while Grade 3–4 elevation was seen in only 0.5%; in the multicenter cohort by Zawitkowska et al. (40), Grade 3–4 renal toxicity was observed in fewer than 1.5% of patients. In AML, nephrotoxicity occurred substantially more often, with reported rates ranging from approximately 2.6% to 64.2% depending on the assessment criteria and clinical context, severe AKI reached 43%. Løhmann et al. (15) reported Grade 3–4 renal toxicity in 2.6% of patients, and Wen et al. (76) reported Grade 3 renal toxicity in 6.7%. The highest rates were described by Du Plessis et al. (77), in whom AKI according to KDIGO criteria occurred in 64.2% of patients and severe AKI in 43%. Hsiao et al. (65) likewise showed that, according to CTCAE criteria, AKI occurred in 32% of children with AML versus 25% in ALL, while moderate-to-severe AKI occurred in 16% versus 8%; when KDIGO criteria were applied, the frequency was even higher. Fisher et al.(78) reported ARF in 16.2% of children during the first year after diagnosis, and Sun et al. (75) showed that AKI during vancomycin prophylaxis was frequent, although most episodes were mild to moderate. Thus, in ALL, nephrotoxicity was generally uncommon, was more often associated with HD-MTX, and usually had a mild-to-moderate course, whereas in AML, renal injury developed substantially more often, particularly during induction, and more strongly reflected the combined effects of intensive therapy, sepsis, and nephrotoxic concomitant medications. The reported frequency depended considerably on the assessment criteria used: rates based on CTCAE were lower, whereas KDIGO identified a greater number of AKI episodes.

Thromboembolic complications

Thromboembolic complications were a clinically significant, although less frequent, component of toxicity during antileukemic therapy in children. They have been most extensively studied in ALL, where they were more commonly associated with asparaginase, glucocorticosteroids, central venous catheters, and early treatment phases. In most studies, the incidence of thrombosis in ALL ranged from 2% to 8%, although in some reports it varied more widely (32,33,44,66). The largest dataset in ALL was reported by Qureshi et al. (41), in which symptomatic venous thrombosis occurred in 3.2% of children; 90% of episodes developed during asparaginase therapy, 70% during induction, approximately half were associated with a central venous catheter, and 36% were cerebral venous sinus thromboses. Similar results were reported by Lynggaard et al. (45) and Abaji et al. (48), with thrombotic complications observed in 3.7% and 3.3% of patients, respectively. Anastasopoulou et al. (42) and Millan et al. (52) further showed that some neurotoxic episodes were represented by cerebral venous sinus thrombosis, while Mogensen et al. (36) found that dyslipidemia at diagnosis was associated with an increased risk of thrombosis. For AML, the available data were much more limited. Løhmann et al. (15) reported severe Grade 3–4 thrombosis in 2.2% of patients, indicating the relative rarity of severe thrombotic events during intensive AML therapy. Wen et al. (76) reported Grade 3–4 disseminated intravascular coagulation in 11.1% of patients, however, this complication should be considered separately from classical venous thromboembolism. Thus, in ALL, thromboembolic complications occurred more often during induction and were closely associated with asparaginase, central venous catheters, and the risk of cerebral venous sinus thrombosis, whereas in AML, severe thrombotic events were reported less frequently, although their clinical significance remained high.

Bone complications

Skeletal complications in children with acute leukemias have been studied predominantly in ALL and are represented mainly by osteonecrosis. In most studies, its incidence ranged from 3.7% to 9.7%: Mogensen et al. (36) reported 7.2%, Lynggaard et al. (45) 4.4%, Schmidt et al. (57) 3.7%, and Finkelstein et al. (51) 9.7%, whereas Rokkanen et al. (33) reported a higher frequency of 26%. In addition, Finkelstein et al. (51) reported fractures in 22.1% of patients and suggested a possible role of genetic factors, while Fermer et al. (37) noted a higher incidence of osteonecrosis with the ALLTogether protocol compared with NOPHO ALL2008. For AML, data on skeletal complications were extremely limited, and in most studies these complications were not assessed as independent outcomes.

Overall, the included studies indicate that the acute toxicity profile differs substantially between ALL and AML. In ALL, drug- and phase-specific complications are more characteristic, particularly those associated with HD-MTX, asparaginase, and vincristine, whereas in AML, the toxicity burden is more strongly driven by treatment intensity and is manifested by more severe myelosuppression, infectious complications, and organ toxicity. In both leukemia subtypes, hematologic and infectious toxicities had the greatest clinical significance, whereas other complications were more dependent on specific treatment regimens and population characteristics.

Discussion

The present systematic review showed that the profile of acute treatment-related toxicity in children with ALL and AML has both shared and distinct features. In both entities, hematologic and infectious complications were of greatest clinical significance; however, the overall toxicity burden was more severe in AML. In contrast, in ALL, complications were more often drug- and phase-specific and were closely associated with high-dose methotrexate, asparaginase, vincristine, and thiopurines. A 2025 review of acute treatment-related toxicities in pediatric ALL identified six major toxicity domains, including VTE, osteonecrosis, neurotoxicity, MTX-associated nephrotoxicity/delayed elimination, and asparaginase-associated pancreatitis, and emphasized that these toxicities may be reduced through targeted treatment adaptations (5). Overall, our review supports this pattern and further shows, through comparison with AML, that a substantial proportion of the clinical burden in ALL is driven by drug-specific toxicities occurring in the setting of relatively less pervasive cytopenia-dependent toxicity. One of the key findings of this review is that the differences between ALL and AML are likely largely determined by contemporary treatment protocols. In AML, complications were driven predominantly by profound and prolonged myelosuppression, as shown by Løhmann et al. (15), Lehrnbecher et al. (80), Bochennek et al. (12), and Wen et al. (76). Severe cytopenia appears to underlie the high incidence of infectious and organ-related complications. In ALL, by contrast, many toxic events were closely linked to specific drugs and treatment phases. Hematologic and renal toxicity were more often observed during HD-MTX therapy (23,27,58,59), neurotoxicity during treatment with vincristine and methotrexate (20,24,42), and thromboembolic complications and pancreatitis during asparaginase exposure (41,45,63). Hematologic toxicity occupied a central place in the complication profile of both entities; however, in AML it was almost universal and largely determined the subsequent infectious burden. This is consistent with the fact that infectious complications were among the main contributors to morbidity and treatment-related mortality, particularly in AML. The high frequency of severe infections, bacteremia, and invasive fungal infections reported by Løhmann et al. (15), Sung et al. (16), Lehrnbecher et al. (80), and Lin et al. (79) underscores the need for aggressive infection monitoring and prevention in this group. In ALL, infections were also common, especially during the early intensive phases of therapy (40,44,61), although their course was more favorable in most cohorts. Contemporary systematic reviews and meta-analyses suggest a dual effect of antibacterial prophylaxis in pediatric acute leukemias: reduced rates of bacteremia and febrile neutropenia are accompanied by increased fluoroquinolone resistance and overall antibiotic exposure (81). During induction, such prophylaxis may also reduce the risk of bacteremia and, in some settings, infection-related mortality, although the recommendations and supporting evidence remain heterogeneous (82). Our review also identified several important organ-specific differences. In ALL, neurotoxic complications were more prominent, particularly VIPN and methotrexate-associated CNS events (20,24,31,42). Drug interactions also played an additional role, especially the combination of vincristine with azole antifungals (25), which increases exposure and may result in severe neurotoxicity; based on clinical case analyses, this combination should be avoided whenever possible (83). Systematic reviews further indicate that VIPN remains a dose-limiting toxicity of vincristine, with risk influenced by age, dose, pharmacokinetics, and genetic factors, although cross-study comparability is limited by heterogeneity in neuropathy assessment (84,85). In AML, neurotoxicity was

reported much less frequently. At the same time, renal and cardiac toxicity in AML likely had greater clinical relevance, reflecting the combined effects of intensive chemotherapy, sepsis, and concomitant nephrotoxic and cardiotoxic exposures (14,65,65,74,77,78). Available studies suggest that kidney injury during therapy for pediatric acute leukemias is multifactorial, that AKI is common in pediatric oncology and increases the risk of CKD, and that drug-related nephrotoxins play an important role (65,86). Despite their lower frequency, thromboembolic complications, pancreatitis, and skeletal toxicity remained clinically important. In ALL, the incidence of thrombosis was 2–8% and was closely associated with asparaginase, glucocorticosteroids, and central venous catheters, particularly during induction (41,45,48). A meta-analysis of 17 prospective studies including 1,752 children estimated the overall risk of thrombosis at 5.2% and demonstrated clustering of events during induction, as well as associations with asparaginase exposure and several concomitant factors (87). Pancreatitis also frequently led to treatment modification (63,66). At the same time, a systematic review of pancreatitis risk factors highlights the limited and fragmented evidence base, including the small number of eligible studies, poor reproducibility of risk factors across studies, and the substantial impact of differences in pancreatitis definitions and treatment intensity/regimens (88). Cardiotoxicity in AML should be interpreted in light of a systematic review demonstrating marked heterogeneity in its definitions and reported frequency, while confirming cumulative anthracycline dose as a robust risk factor and underscoring the need for standardized cardiac monitoring (89). This is consistent with the view that cardiotoxicity in AML requires protocol-based monitoring and cardioprotection (90). Skeletal complications, particularly osteonecrosis, were observed predominantly in ALL (33,36,51), and their risk likely depended on age, genetic factors, and protocol characteristics (37). These findings have practical implications for monitoring and individualized supportive care. In ALL, particular attention should be paid to treatment phases involving HD-MTX, asparaginase, vincristine, and 6-mercaptopurine, whereas in AML, priority should be given to early detection of profound neutropenia, infectious complications, renal dysfunction, and cardiotoxicity. In addition, findings from several studies suggest that pharmacogenetic markers may serve as promising tools for toxicity risk stratification (27,51,55).

Strengths and weaknesses of the study

The results of this review should be interpreted in light of the substantial clinical and methodological heterogeneity of the included studies. The studies differed considerably with respect to population characteristics, treatment protocols, definitions of toxic events, severity grading systems, and completeness of outcome reporting. Variability was particularly pronounced for nephrotoxicity, neurotoxicity, and gastrointestinal complications. This heterogeneity precluded meta-analysis and justified the use of a narrative synthesis. The strengths of this review include its broad coverage of acute toxic complications in ALL and AML, the direct comparison of the two principal forms of acute leukemia within a single analytical framework, and the inclusion of data not only on complication frequency but also on severity, risk factors, and clinical consequences. At the same time, the review has several limitations: a substantial proportion of the included studies were retrospective and single-center in design, data on several complications in AML were limited, and the search was restricted to English-language publications.

Conclusions

Overall, the findings of the present review indicate that acute treatment-related toxicity in children with ALL and AML has a heterogeneous but clinically consistent profile. In AML, the toxicity burden is driven more strongly by treatment intensity, profound myelosuppression, and severe infectious and organ-related complications, whereas in ALL, drug- and phase-specific toxic events are more prominent. These findings underscore the need for differentiated monitoring strategies, early preventive interventions, and personalized supportive care, and they also highlight the need for more standardized prospective studies of toxicity in pediatric hemato-oncology.

List of Abbreviations (alphabetical):

AEA — asparaginase enzyme activity
AE — adverse event
AKD — acute kidney disease
AKI — acute kidney injury
ALLTogether — ALLTogether protocol
Ara-C — cytarabine
AspTox — asparaginase-associated toxicity
BSI — bloodstream infection
CBC — complete blood count
CCCG — Chinese Children's Cancer Group
CCLG — Chinese Children's Leukemia Group
CDI — Clostridioides difficile infection
CKD — chronic kidney disease
CRRT — continuous renal replacement therapy
CVL — central venous line
CVT — cerebral venous thrombosis
EORTC/MSG — European Organization for Research and Treatment of Cancer / Mycoses Study Group
FN — febrile neutropenia
FUO — fever of unknown origin
GI — gastrointestinal
GO — gemtuzumab ozogamicin
GPOH — German Society of Pediatric Oncology and Hematology
Hb — hemoglobin
HMA — hypomethylating agent
HRQoL — health-related quality of life
HSCT — hematopoietic stem cell transplantation
IFI — invasive fungal infection
KDIGO — Kidney Disease: Improving Global Outcomes
LMWH — low-molecular-weight heparin
L-ASP — L-asparaginase
LRTI — lower respiratory tract infection
MLE — methotrexate-related leukoencephalopathy
MRI — magnetic resonance imaging
MSG — Mycoses Study Group
NS — not significant
Plt — platelet count
pRIFLE — pediatric Risk, Injury, Failure, Loss, End-stage renal disease
SAA — serum asparaginase activity
SIADH — syndrome of inappropriate antidiuretic hormone secretion
TE — thromboembolism
TG — thioguanine
TPMT — thiopurine S-methyltransferase
TRM — treatment-related mortality
TRT — treatment-related toxicity
URTI — upper respiratory tract infection
UTI — urinary tract infection
VCR — vincristine
VT — venous thrombosis
VTE — venous thromboembolism
WBC — white blood cell count
WHO — World Health Organization toxicity scale

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