Pediatric ALL Treatment Modifications in Low- and Middle-Income Countries: A Systematic Review

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DOI https://doi.org/10.1200/GO-25-00286

ABSTRACT

PURPOSE For children with ALL in low- and middle-income countries (LMICs), treatment regimen adaptation based on local contexts is often necessary. However, the clinical impact of such modifications is poorly understood. The purpose of this study is to examine pediatric ALL treatment regimens used in LMICs, assess for patterns in adaptation to identify common barriers affecting global delivery of ALL care, and describe the breadth of outcomes.

METHODS Using the PRISMA guidelines, a systematic review was conducted, across seven databases, of ALL regimens use in LMICs in 2000-2021, documenting the geographic distribution of treatment backbone adoption, regimen modifications, and outcomes. Article characteristics were summarized using descriptive statistics.

RESULTS Of 13,900 articles, 125 met abstraction criteria. Data spanned 36 countries (6.4% low-income, 43.2% lower-middle–income, 50.4% upper-middle–income) and 163 regimens, of which 138 (84.6%) referenced a high-income ALL collaborative group regimen as a backbone. Sixty-four percent of regimens (n = 104) were adapted. Individual modifications (n = 390) were consolidated into 73 distinct regimen changes; reduction/omission of high-dose methotrexate, observed in 30 modified regimens (28.8%), was the most common. Implementation challenges, such as drug access and cost, were cited more frequently than toxicity as the rationale for modification; however, implementation outcomes (eg, feasibility, cost) were only measured in 6.4% of articles. Across all outcomes, 5-year overall survival was higher with modified versus unmodified regimens (P = .030).

CONCLUSION Although implementation barriers are primary drivers of ALL regimen adaptations globally, the paucity of reported implementation outcomes represents a methodological gap in the literature. Incorporating implementation science methods and frameworks is critical for the timely and effective delivery of innovative treatment regimens across resource settings.

ACCOMPANYING CONTENT

Data Supplement

Accepted October 10, 2025
Published December 15, 2025

JCO Global Oncol 11:e2500286

INTRODUCTION

Incremental advances through iterative cooperative group trials and refinement of risk-directed classification and therapy have transformed pediatric ALL from a uniformly fatal disease to the one with a contemporary 5-year overall survival (OS) exceeding 90% in high-income countries (HICs).[1,2] Historically, cooperative groups have incorporated effective treatment strategies from others into their treatment regimen backbone for subsequent clinical trials. Institutions where collaborative group trials were not historically active typically adopt the latest published regimens from collaborative groups as the standard of care.[3] Consequently, modern ALL treatment regimens share the same core medications, with modest variations in formulation, dosing, and schedule optimization, with remarkably similar outcomes in HICs.[3,4] However, a wide survival disparity persists in resource-limited settings, with the estimated 5-year net survival for pediatric ALL in 2015 being 22.4% in Africa, 52.6% in Asia, and 61.4% in Latin America, compared with >80% in Europe and North America.[5]

The WHO Global Initiative for Childhood Cancer (GICC) has highlighted the need to optimize treatment guidelines for ALL as one of its six index cancers.[6] This initiative emphasizes context-informed care and aims to generate appropriate, scalable ALL treatment guidance. Modifications to ALL regimens derived from HICs have improved local delivery; however, deriving scalable lessons from these approaches and comparing their clinical impact are made challenging by diverse risk-stratification strategies, ad hoc or mid-study modifications, incongruent nomenclature for risk groups and therapy phases, and lack of standardization in reporting outcomes. In addition, emerging modalities that support tailored risk stratification (minimal residual disease [MRD], genetic testing) and treatment intensification (blinatumomab, chimeric-antigen receptor T-cells), which are largely responsible for the increase in survival to >90% in high-income settings, pose significant implementation challenges in low- and middle-income countries (LMICs).

Implementation science focuses on understanding barriers to the systematic adoption of evidence-based interventions in the real-world setting to improve delivery and, ultimately, local effectiveness.[7] To guide future pediatric ALL treatment and identify generalizable, scalable lessons for the 90% of patients living in LMICs,[8] we examined the diversity of ALL regimens in resource-limited settings over the past 20 years, cataloged the range and rationales for adaptations, and characterized the clinical and implementation outcomes. By applying an implementation science–based approach, we aimed to enhance our understanding of challenges hindering ALL care delivery and identify context-informed guidance to improve treatment and scale successful approaches worldwide.

METHODS

Search Strategy and Selection Criteria

In collaboration with a medical librarian, a systematic review was conducted, using the PRISMA guidelines to design and apply an advanced Boolean search strategy across seven databases: PubMed, Web of Science, Scopus, Turning Research into Practice, Latin American and Caribbean Health Sciences Literature, the Cumulative Index to Nursing and Allied Health Literature, and the WHO Globus Index Medicus. The search was conducted from October 2020 to January 2021 and included articles published between January 2000 and January 2021. The Data Supplement includes the full search protocol, inclusion and exclusion criteria, and strategy for the databases used.

This study aimed to describe the heterogeneity and breadth of ALL regimen use and local modifications, maximizing inclusivity by extracting data from all available studies and assessing the representativeness of the sample; therefore, quality was assessed based on the regimen detail in the article. Treatment regimens in the original article and its supplement or referenced in another accessible article were reviewed. The frequency of reported survival and toxicity metrics and follow-up duration were summarized. To summarize survival outcomes, time points for event-free survival (EFS), OS, disease-free survival (DFS), and relapse-free survival (RFS) were grouped (≤2, 2 to <5, ≥5 years, or not specified). Survival data were not extracted from articles containing only survival curves without specifying outcome values. Modification rationales were extracted and organized based on intent. Articles were reviewed for implementation outcomes (eg, feasibility, appropriateness, cost as defined by the Proctor Conceptual Framework for Implementation Outcomes) and related terms.[9] Article aims were examined to determine whether implementation evaluation was a primary objective with associated metrics or only conceptualized in the narrative.

Data Analysis

Article characteristics were summarized using descriptive statistics. Continuous data were summarized using means and standard deviations (SDs) or medians and IQRs; categorical data were summarized as percentages. Complete remission (CR), EFS, OS, DFS, RFS, deaths in induction, deaths in remission, total deaths, and treatment abandonment were defined as reported in each article. The Kruskal-Wallis test was used to compare clinical outcomes between the top three most commonly used HIC collaborative group backbones.[10] Outcomes from modified and unmodified regimens were compared using the Wilcoxon rank-sum test. For all analyses, $P < .05$ was considered to represent statistical significance. Analyses were performed using R version 4.3.0.

RESULTS

The search identified 13,900 original articles. After screening (Data Supplement, Inclusion and Exclusion criteria) and removing duplicates, 125 articles were included (Data Supplement, Fig S1).

Global Patterns of Reporting and Study Design

Table 1 summarizes the characteristics of the included articles by study design, WHO region, and income classification at the time of publication.[11,12] A total of 35,967 children with ALL were represented, across 36 countries, with a median of 158 children per article (IQR, 216; range, 19-3,248). Most reports were from lower-middle–income countries (n = 54 of 125, 43.2%) or upper-middle–income countries (UMICs; n = 59 of 125, 47.2%), with the highest numbers of publications being from China (n = 23), India (n = 22), and Brazil (n = 11); four articles (3.2%) were published after the country transitioned to HIC status but described a study conducted while the country was a UMIC.

Twenty-eight articles (n = 28 of 125, 22.4%) reported outcomes of ≥2 regimens, resulting in 163 regimens for analysis (Table 1). Across regimens, 15.3% (n = 25 of 163)

TABLE 1. Article and Regimen Characteristics

Characteristic	Total Articles (N = 125, %), No. (%)	High-Income Countries (n = 4, 3.2%), No. (%)	Upper-Middle–Income Countries (n = 59, 47.2%), No. (%)	Lower-Middle–Income Countries (n = 54, 43.2%),[a] No. (%)	Low-Income Countries (n = 8, 6.4%), No. (%)
Region at the time of publication					
African	4 (3.2)	0	0	0	4 (50.0)
Americas	28 (22.4)	0	23 (39.0)	5 (9.3)	0
Eastern Mediterranean	21 (16.8)	0	7 (11.9)	14 (25.9)	0
European	18 (14.4)	4 (100)	10 (16.9)	4 (7.4)	0
South-East Asian	30 (24.4)	0	4 (6.8)	22 (40.7)	4 (50.0)
Western Pacific	24 (19.2)	0	15 (25.4)	9 (16.7)	0
Publication time period					
Early (2000-2010)	37 (29.6)	0	10 (16.9)	25 (46.3)	2 (25.0)
Late (2011-2021)	88 (70.4)	4 (100)	49 (83.1)	29 (53.7)	6 (75.0)
Study population					
B- and T-cell	105 (84.0)	4 (100)	44 (74.6)	49 (90.7)	8 (100)
B-cell only	13 (10.4)	0	11 (18.6)	2 (3.7)	0
T-cell only	7 (5.6)	0	4 (6.8)	3 (5.6)	0
Study population included AYA (≤35 years)	6 (4.8)	0	3 (5.1)	3 (5.6)	0
Study design					
Retrospective	67 (53.6)	3 (75.0)	29 (49.2)	31 (57.4)	4 (50.0)
Prospective	27 (21.6)[b]	1 (25.0)	16 (27.1)	8 (14.8)	2 (25.0)
Not listed	31 (24.8)	0	14 (23.7)	15 (27.8)	2 (25.0)
Study size					
Single-center	106 (84.8)	2 (50.0)	49 (83.1)	48 (88.9)	7 (87.5)
Multicenter (≥2)	19 (15.2)	2 (50.0)	10 (16.9)	6 (11.1)	1 (12.5)
Treatment regimens	(N = 163)	(n = 13)	(n = 74)	(n = 68)	(n = 8)
HIC backbone referenced in primary or related publication					
No	25 (15.3)	0	7 (9.5)	15 (22.1)	3 (37.5)
Yes	138 (84.7)[c]	13 (100)	67 (90.5)	53 (77.9)	5 (62.5)
BFM	62 (44.9)	10 (76.9)	28 (41.8)	24 (45.3)	0
St Jude Total	25 (18.1)	1 (7.7)	15 (22.4)	9 (17.0)	0
UKALL	17 (12.3)	0	2 (3.0)	12 (22.6)	3 (60.0)
COG	3 (2.2)	0	1 (1.5)	1 (1.9)	1 (20.0)
POG	2 (1.4)	0	1 (1.5)	1 (1.9)	0
FRALLE	2 (1.4)	0	0	2 (3.8)	0
MD Anderson	2 (1.4)	0	1 (1.5)	1 (1.9)	0
Mixed	17 (12.3)	0	15 (22.4)	1 (1.9)	1 (20.0)
Other	8 (5.8)	2 (15.4)	4 (6.0)	2 (3.8)	0
Described as modified or adapted or narrative about the regimen change included					
No	59 (36.2)	13 (100)	25 (33.8)	20 (29.4)	1 (12.5)
Yes	104 (63.8)	0	49 (66.2)	48 (70.6)	7 (87.5)
Details of modification included	88 (84.6)	NA	41 (83.7)	40 (83.3)	7 (100)
No details of modification	16 (15.4)	NA	8 (16.3)	8 (16.7)	0
Total distinct modifications across all regimens	309	0	170	123	16

(continued on following page)

TABLE 1. Article and Regimen Characteristics (continued)

Characteristic	Total Articles (N = 125, %), No. (%)	High-Income Countries (n = 4, 3.2%), No. (%)	Upper-Middle–Income Countries (n = 59, 47.2%), No. (%)	Lower-Middle–Income Countries (n = 54, 43.2%),[a] No. (%)	Low-Income Countries (n = 8, 6.4%), No. (%)
No. of changes per modified regimen, mean (SD)	3.47 (SD 2.6) Range, 1-12	NA	4.12 (3.05) Range, 1-12	3.07 (2.05) Range, 1-11	2.28 (0.95) Range, 1-4

NOTE. The table includes characteristics of 125 articles included in the review, stratified by World Bank income classification of the country of origin at the time of publication. Other backbones include ALGB, DFCI-00-01, the Dutch ALL-VI, the German Multicenter ALL protocol, NOPHO ALL-86, the Sallan protocol, and the UCLA protocol.

Abbreviations: AYA, adolescent and young adult; BFM, Berlin-Frankfurt-Münster; COG, Children's Oncology Group; FRALLE, FRench group for childhood ALL; HIC, high-income countries; NA, not applicable; POG, Pediatric Oncology Group; SD, standard deviation; UCLA, University of California Los Angeles; UKALL, UK ALL; UMICs, upper-middle–income countries.

[a]Reference 100 (Data Supplement) presented results from a multinational study that included three lower-middle–income countries (El Salvador [283 patients], Honduras [397 patients], and Nicaragua [303 patients]) and two UMICs (Panama [133 patients] and Costa Rica [197 patients]) as classified at the time of publication. As three of the countries were lower-middle–income countries and most of the patients included in the study lived in those countries, this article was categorized as originating from a lower-middle–income country.

[b]Twelve of 27 prospective studies were randomly assigned.

[c]Of these, 11 did not contain an attribution in the primary text, but this information was extracted from a related or referenced publication.

considered locally designed regimens without a named HIC backbone influence. Berlin-Frankfurt-Münster (BFM) regimen was the most-used HIC collaborative group backbone (n = 62 of 138, 44.9%), followed by St Jude Total (n = 25 of 138, 18.1%) and Medical Research Council United Kingdom ALL (UKALL; n = 17 of 138, 12.3%; Data Supplement, Fig S2). HIC backbone use varied within countries and by region (Data Supplement, Fig S2B-S2D). Only two countries (Czechia and Tanzania) adhered to a single HIC collaborative group backbone during the study period, likely reflecting sociopolitical ties or ongoing cooperative efforts. For all other countries, the publication record demonstrated the use of different HIC backbones between centers and over time. Compared with BFM- and St Jude–based regimens, UKALL-based regimens were more common in lower-middle–income countries and low-income countries (LIC; Table 1). After 2011, the relative use of BFM-based regimens increased from 29.8% (n = 14 of 47) to 41.4% (n = 48 of 116), whereas that of St Jude Total and UKALL-based regimens decreased from 17.0% (n = 8 of 47) to 14.7% (n = 17 of 116) and from 12.8% (n = 6 of 47) to 9.5% (n = 11 of 116), respectively.

Seventeen regimens (12.3%) were locally designed, combining elements from ≥2 HIC backbones (eg, protocol based on the BFM-90 and the LSA2L2 regimens) and categorized as mixed.[13]

The 28 articles containing ≥2 regimens were examined for transition patterns between different HIC collaborative group backbones and the presence/absence of modifications. Only one article compared the outcomes of an unmodified and modified version of the same HIC regimen.[14] Nine articles examined the local outcomes with iterative regimens from the same HIC collaborative group (eg, BFM 90 to BFM 95). In five articles, there were both changes between collaborative groups (eg, a transition from St Jude Total to a BFM-based regimen) and transitions between unmodified and modified regimens.

Regimen Modifications

Most regimens (63.8%, n = 104) were described as modified or adapted, or the article described regimen changes (Fig 1). Two articles reported using an original HIC regimen but described modifications, resulting in recategorization of the regimen as modified.[15,16]

The absolute number of published modified regimens increased after 2011; however, the proportion decreased from 72.3% (n = 34 of 47) to 60.3% (n = 70 of 116). The proportion of modified regimens was similar across the three most-used backbones, BFM (72.6% [n = 45 of 62]), St Jude (72.0% [n = 18 of 25]), and UKALL (64.7% [n = 11 of 17]), with the mean of 3.3 (range, 1-11), 4 (range, 1-8), and 2.6 (range, 1-4) changes per modified regimen, respectively.

Eighty-five percent (n = 91 of 104) of modified regimens contained descriptions of the change in the main text or the Data Supplement. From these modified regimens, 309 individual modifications were abstracted, averaging 3.47 (SD, 2.6; range, 1-12) changes per modified regimen (Table 1). While articles from LICs had the highest proportion of modified regimens (n = 7 of 8, 87.5% *v* 70.6% in lower-middle–income countries and 66.2% in UMICs), the mean number of changes per regimen increased with income level (2.28 in LIC, 3.07 in lower-middle–income countries, 4.12 in UMICs). Modifications were observed across all treatment phases and were consolidated into 73 distinct changes, including drug dosing modifications (adding/omitting drugs, increasing/decreasing dose/frequency, or substitution) and phase modifications (eg, adding steroid prephase, eliminating

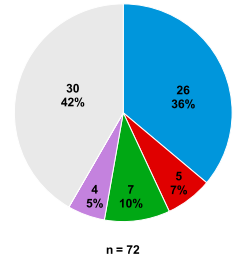
Phase	Categories	Subcategories	Supplemental Reference	Rationale	None	Improve Survival	Reduce Toxicity	Balance toxicity and s	Implementation Challenges	Consensus recommendation
Risk stratification	Started risk stratification		[118]	Improve survival		1				
	Assigned to single arm	NOS	[78], [80]	None	2					
		SR	[5], [24], [68], [90]	Diagnostic capabilities/no MRD (2), cost, logistics	1				4	
		IR/MR	[5], [36], [44]	Diagnostic capabilities, cost, balance toxicity/relapse	1			1	2	
		HR	[25]	Reduce relapse		1				
	Consolidated treatment groups	SR and IR (eliminated HR)	[69], [81], [108]	Balance toxicity/efficacy, reduce TRM, diagnostic capability/cytogenetics (2)	1		1	1	2	
	No MRD		[115]	None	1					
	Other		[64], [72], [86], [99]	None	4					
					10	2	1	2	8	0
Induction	Added prephase		[17], [22], [34], [41], [43], [50], [52], [66], [72], [94]	Reduce death (2), clinical condition (2), toxicity, reduce abandonment, balance toxicity/survival, improve survival	6	1	5	1	1	
	Drug substitution		[5], [7], [18], [21], [22], [27], [28], [31], [40], [41], [51], [52], [55], [67], [69], [71], [72], [81], [86], [94], [113], [116]	Drug availability (6), reduce CNS relapse (3), reduce death (2), toxicity (2), improve survival (2), balance efficacy and toxicity (2), cost, reduce abandonment, feasibility, infrastructure	10	5	4	2	10	
	Drug dose increased		[18], [41], [71], [77], [80], [101]	Target extramedullary leukemia	5	1				
	Drug dose decreased		[27], [28], [31], [34], [52], [67], [68], [83], [111], [124]	Toxicity (3), balance toxicity/efficacy (2), cost (2), supportive care (transfusions, hospitalization), laboratory capacity, lack of consensus about dose/route	5		3	2	4	1
	Drug omission		[8], [22], [23], [99], [111]	Cost, toxicity, long-term toxicity, balance toxicity/relapse	1		2	1	1	
	Drug addition		[99], [106]	Cost (covered by insurance), reduce relapse	1	1			1	
	Phase element modified	Ib (omitted, reduced intensity)	[27], [43], [100]	Balance toxicity/efficacy, reduce death, toxicity			1	2		
		Ib (added)	[99]	None	1					
		4 drug → 3 drug	[12], [69], [114]	Balance toxicity/efficacy (2), reduce TRM, complexity	1		1	1	1	
		Omit prephase	[19], [67], [77]	None	3					
		Reduced intensity (delayed intense drugs, added rest period)	[7], [17], [22], [29], [30], [86]	Toxicity (4), infection (2), reduce death in CR (2), cost, access to emergency care			8		2	
		Intensify induction	[7], [16]	Intensify new low-risk classification	1	1				
		No therapeutic window	[115]	None	1					
					35	9	24	9	20	1
Postinduction NOS	Drug dose decreased		[67]	None	1					
	Drug dose increased		[67], [87]	None	2					
	Drug addition		[67]	None	1					
					4	0	0	0	0	0
Consolidation	Drug dose decreased		[52], [60], [116]	Balance toxicity/efficacy, cost	2			1	1	
	Drug omission		[3], [77]	Toxicity, hospitalization, cost	1		1		2	
	Drug addition		[72], [111]	Cost (limited supply, randomized question to assess impact of addition in consolidation)	1				1	
	HD-MTX	Omitted	[25], [35], [77], [111], [113], [124]	Toxicity (3), cost (2), balance toxicity/survival, hospitalization, provider experience, clinical condition	1		4	1	4	
		Dose reduced	[2], [3], [8], [22], [24], [27], [28], [33], [34], [43], [46], [51], [55], [67], [70], [86], [92], [94], [98], [99], [100], [101], [102], [116]	No drug levels (9), toxicity (5), resource constraints/cost (4), balance toxicity/efficacy (3), supportive care (3), outpatient administration, drug availability (2), improve survival (2), balance toxicity (TRM)/relapse, CNS relapse, feasibility, clinical condition	8	3	6	4	20	
		Dose increased	[41], [72], [122]	Diagnostic capability (can newly measure levels), lack of consensus, reduce CNS and bone marrow relapse, increase systemic CNS treatment		2			1	1
		HD-MTX to Capizzi	[51]	Toxicity			1			
		HD-MTX added	[21], [106], [120]	Reduce CNS/testicular relapse (2), cost (covered by insurance), reduce cranial irradiation/late effects, balance toxicity/survival, complexity, newly trained staff/infrastructure		2	1	1	3	
	Leucovorin modification		[22], [55], [94], [98], [116]	No drug levels (2), toxicity, maintained MTX dose but increased leucovorin to maintain extramedullary efficacy	2	1	1		2	
	Drug substitutions	HD-MTX → HD ARA-C	[40]	Cost, outpatient administration, limited supportive care					3	
	Phase element modified	Consolidation omitted	[18], [114]	Feasibility, outpatient administration, toxicity	1		1		2	
		Reduced intensity	[71]	Cost					1	
		Increased duration	[117]	Improved survival		1				
					16	9	15	7	40	1
CNS-directed chemotherapy	Drug substitution		[24], [30], [31], [55], [67], [71], [111], [113], [116], [120]	Drug availability (2)	8				2	
	Reduced cranial irradiation (increased IT or systemic CNS-directed treatment)		[21], [22], [27], [34], [41], [46], [51], [63], [92], [122], [124]	Long-term toxicity (3), infrastructure (3), secondary malignancy (2), reduce relapse (2), reduce TRM, cognitive effects, measure MTX levels	2	2	7		4	
	Delayed IT therapy		[22], [43], [81], [98]	Clinical condition, diagnostic capacity, reduce CNS relapse, thrombocytopenia, provider comfort		1	2		2	
	Increased IT therapy		[23], [27], [51], [79], [81], [98]	CNS antileukemic effect	4	1				
					14	4	9	0	8	0

FIG 1. Pediatric ALL regimen modifications in LMICs by treatment phase and modification rationales. Rationale for modifications categorized based on the intent: to improve survival (eg, improve remission rate, decrease relapse, (continued on following page)

Continuation/maintenance	Drug substitution		[28], [41], [113]	Balance toxicity/efficacy	2			1		
	Drug dose increased		[27], [36], [62]	Balance toxicity/relapse	2			1		
	Drug dose decreased		[55], [111], [116]	Toxicity	1		2			
	Drug omission		[28], [55], [107], [116]	Toxicity, late effects/secondary malignancy	2		2			
	Phase element modified	Added VCR/Dex pulses	[18], [23], [67], [77], [80], [99]	None	6					
		Reduced VCR/Dex pulses	[41], [49], [119]	Interim results from the high-income collaborative group	2					1
		Prolonged duration	[12], [34], [98]	Balance toxicity/survival, toxicity	1		1	1		
		Shortened duration	[87], [94], [114]	Improve adherence, shorten immunosuppression, toxicity, complexity			2		2	
		All oral medication	[22]	Outpatient administration					1	
		Added rotational maintenance	[4], [63],	Improve survival	1	1				
		Other	[7], [22], [41], [63]	Reduce outpatient follow-up, cost, drug availability, reduce TRM, balance survival/toxicity			1	1	3	
					17	1	8	4	6	1
Intensification blocks	Drug dose decreased		[3], [41], [49], [23], [28], [55], [63], [66], [80], [92], [101], [116]	Toxicity (3), reduce TRM (2), balance toxicity/survival	9		5	1		
	Drug omission		[18], [22]	Feasibility, outpatient administration, toxicity, long-term toxicity			2		2	
	Drug dose increased		[41], [94], [101]	None	3					
	Drug addition		[41], [101], [122]	Reduce extramedullary and bone marrow relapse, increase systemic CNS leukemic treatment (2)	1	3				
	Drug substitution		[18], [51], [55], [66], [71], [72], [77], [80], [103], [107], [113], [116], [119]	Drug availability (7), improve survival, feasibility, outpatient administration, toxicity, reduce CNS relapse	5	2	1		9	
	Phase element modification (reduced intensity)	Reduction drug dosing and duration	[63], [77], [99]	Reduce TRM, cost, toxicity			2		1	
		Omit HR blocks	[86]	Reduce death in CR			1			
		2 → 1 DI	[69]	Balance toxicity/efficacy, reduce TRM			1	1		
		Treatment-free period after protocol II	[86]	Reduce death in CR, access to emergency care			1		1	
	Phase element modification (increase intensity)	Added HR blocks	[79]	None	1					
		Added early intensification	[21]	Reduce relapse		1				
		Added late consolidation/modified protocol II	[7]	None	1					
		1 → 2 delayed intensification	[117]	Improve survival		1				
		Early with or without late intensification	[12], [124]	None	2					
		1 → 2 reinduction	[55], [116]	None	2					
		Added reinduction phase (0 → 1)	[16]	Cost, drug availability					2	
		Added reinduction x1SR, x2IR, x3HR	[100]	Toxicity			1			
					24	7	14	2	15	0
Unspecified modification	Drug substitution		[30], [31], [51], [81], [102]	Drug availability (4), cost					5	
	Drug dose decreased		[14], [108]	Cost (reactive modifications based on ability to purchase)	1				1	
	Drug omission		[62], [63], [65], [94]	Drug availability (4)					4	
	Drug addition		[41], [80]	CNS penetration	1	1				
					2	1	0	0	10	0
				Total No. of times category cited as rationale for regimen modification	122	33	71	24	107	3
				Relative proportion each category cited as rationale for regimen change	33.9%	9.2%	19.7%	6.7%	29.7%	0.8%

FIG 1. (Continued). target extramedullary leukemia), to reduce toxicity (eg, reduce TRM, infection, immunosuppression, or late effects and improve the clinical condition), to balance survival/efficacy and toxicity, to address local implementation issues (eg, laboratory capacity, drug availability, feasibility/logistics/complexity, cost, infrastructure, regimen adherence, supportive care capacity, provider experience/comfort, abandonment), or because of a gap/change in knowledge (eg, publication of interim results or inadequate knowledge of optimal drug dosing), or none. The numbers under the Rationale column represent the number of times each explanation was cited by an article. If articles cited multiple rationales for a single change, all were included in the Rationale description, resulting in a total of 238 rationales. CR, complete remission; DI, delayed intensification; HD-MTX, high-dose methotrexate; HR, high risk; IR, intermediate risk; IT, intrathecal; LMICs, low- and middle-income countries; MR, medium risk; MRD, minimal residual disease; NOS, not otherwise specified; SR, standard risk; TRM, treatment-related mortality; VCR/Dex, vincristine/dexamethasone.

Drug Substitution	Phase of Modification	Implementation Challenges	Reduce Toxicity	Improve Survival	Balance Toxicity and Survival	Consensus Recommendation	None	Specific Rationale
L-Asparaginase → anthracycline	Induction	[51]						[51]: Drug availability
L-Asparaginase → cyclophosphamide	Induction	[18]	[18]					[18]: Improve feasibility (outpatient administration); reduce toxicity
L-Asparaginase → PEG-asparaginase	Induction						[41] [52]	--
PEG-asparaginase → L-asparaginase	Induction	[69]						[69]: Drug availability
PEG-asparaginase → L-asparaginase	Continuation/ maintenance						[113]	--
PEG-asparaginase → L-asparaginase or Erwinia	Not phase specific	[51] [81]						[51]: Drug availability, cost [81]: Drug availability
Cyclophosphamide → ARA-C	Continuation/ maintenance						[28]	--
Daunorubicin → doxorubicin	Induction	[51] [71] [81] [94]					[52], [55], [67], [69], [72], [86], [113], [116]	[51]: Drug availability, cost [71]: Drug availability [81] : Drug availability [94]: Drug availability
Daunorubicin → doxorubicin	Not phase-specific	[102]						[102]: Drug availability
Daunorubicin → epirubicin	Not phase-specific	[102]						[102]: Drug availability
Dexamethasone → prednisone	Induction	[86]	[7] [86]	[86]				[7]: Reduce toxicity death [86]: Reduce abandonment; reduce treatment related mortality; improve survival
Dexamethasone → prednisone	Intensification blocks	[18]						[18]: Feasibility
Doxorubicin → daunorubicin	Induction	[94]					[52]	[94]: Drug availability
Doxorubicin → daunorubicin	Continuation/ maintenance						[41]	--
Etoposide→ HD ARA-C	Intensification blocks						[55] [116]	--
Intrathecal substitution	CNS-directed therapy	[30] [31]					[24], [55] [67], [71] [111], [113] [116], [120]	[30], [31]: Drug availability (IT hydrocortisone → IT prednisolone) *Other specified IT changes: [24], [55], [71], [116]: Triple → single with methotrexate [67]: Methotrexate → methotrexate and cytarabine
HD-MTX → HD ARA-C	Consolidation	[40]						[40]: Cost, outpatient administration, and limited supportive care
HD-MTX → Capizzi	Consolidation		[51] [113]					[51], [113]: Toxicity
Prednisone → dexamethasone	Induction			[21] [22] [27] [40]	[27] [113]		[5] [28]	[21]: Reduce CNS relapse [22]: Reduce CNS relapse [27]: Reduce CNS relapse; balance toxicity/efficacy [40]: Improve outcomes in early T-cell precursor ALL [113]: Balance toxicity/efficacy
Prednisone → dexamethasone	Continuation/ maintenance				[28] [113]			[28], [113]: Balance toxicity/efficacy
Prednisone → high-dose methylprednisolone	Induction			[31]				[31]: Improve remission rate, improve survival
Prednisolone → methylprednisolone	Intensification blocks			[107]				[107]: Improve survival
Teniposide → etoposide + cyclophosphamide	Not phase-specific	[30] [31]						[30]: Drug availability [31]: Drug availability
Thioguanine → mercaptopurine	Intensification blocks	[51] [71] [77] [80]					[66] [72] [113]	[51]: Drug availability [71]: Drug availability [77]: Drug availability [80]: Drug availability
Vindesine → vincristine	Intensification blocks	[51] [80] [119]					[103]	[51]: Drug availability [80]: Drug availability [119]: Drug availability
Drug dose reductions								
Anthracycline	Induction	[27]			[27]			[27]: Cost, supportive care (transfusions, hospitalization); balance toxicity/efficacy
L-Asparaginase	Induction	[111]	[68] [111]			[111]	[26] [67]	[68]: Toxicity [111]: Laboratory capacity, cost; toxicity; lack of consensus about dose/route
L-Asparaginase	Consolidation	[60]			[60]			[60]: Cost; balance toxicity/efficacy
L-Asparaginase	Intensification blocks						[28] [55] [116]	--
L-Asparaginase	Not phase-specific	[108]						[108]: Cost (reactive modifications based on patient ability to purchase)
Cyclophosphamide	Postinduction NOS						[67]	--
Cytarabine	Induction						[52]	--
Daunorubicin	Induction				[34]		[83]	[34]: Balance toxicity/survival
Dexamethasone	Intensification blocks		[49] [63]		[49]		[66] [80] [101]	[49]: Toxicity; balance toxicity/survival [63]: Reduce treatment related mortality
Doxorubicin	Induction	[124]						[124]: Cost (only given in HR if the patient could afford it)
Doxorubicin	Continuation/ maintenance		[41] [92]					[55], [116]: Toxicity
Doxorubicin	Intensification blocks		[55] [63] [116]			[49]	[3]	[49]: Balance toxicity/survival [55]: Toxicity [63]: Reduce treatment related mortality [116]: Toxicity
Etoposide	Induction		[31]					[31]: Toxicity
Ifosphamide	Intensification blocks						[101]	--
Mercaptopurine	Induction						[52]	--
Mercaptopurine	Consolidation						[52], [116]	--
Mercaptopurine	Continuation/ maintenance		[55] [116]					[55]: Toxicity [116]: Toxicity
Mercaptopurine	Intensification blocks		[41] [92]					[41]: Toxicity [92]: Toxicity



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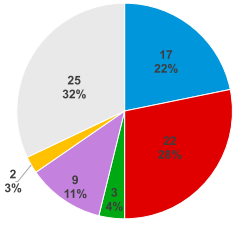
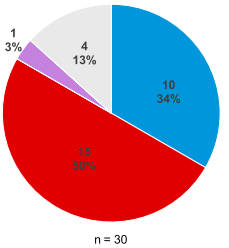


n = 78

FIG 2. Drug-specific modifications and rationales. Rationale for modifications categorized based on the intent: improve survival, reduce toxicity, balance toxicity and improve survival, implementation challenge, change or lack of consensus in the literature, or none. The numbers under the Rationale column represent the article citation found in the Data Supplement. If articles cited multiple rationales for a single change, all were included in the Rationale description. Pie charts demonstrate the proportion of rationale in each category of modification type to reduce regimen intensity (drug omission, reduction, substitution). HD ARA-C, high-dose cytarabine; HD-MTX, high-dose methotrexate; HR, high risk; PEG, pegylated asparaginase; TKI, tyrosine kinase inhibitor. (continued on following page)

(High-dose) Methotrexate	Consolidation	[8] [27] [33] [40] [43] [46] [51] [70] [86] [98] [99] [100]	[43] [51] [92] [100] [102]	[22] [28] [94]	[8] [24] [27] [34]		[2], [3] [55], [67], [101], [116]	[8]: Cost (resource constraints), supportive care capacity; balance toxicity/survival [22]: Reduce CNS relapse [24], [34]: Balance toxicity/survival [27]: Laboratory capacity (no drug levels, increased XRT in IR and HR because dose reduces MTX), feasibility; Balance toxicity/efficacy [28]: Improve results (improve survival in HR) [33]: Laboratory capacity (no drug levels) [40]: Cost, outpatient administration, supportive care capacity [46]: Laboratory capacity (no drug levels) [43]: Laboratory capacity (no drug levels); toxicity [51]: Drug access, laboratory capacity (no drug levels); toxicity; patients' condition [70]: Laboratory capacity (no drug levels), limited drug access, cost (resource constraints), supportive care capacity [86]: Laboratory capacity (no drug levels) [92]: Toxicity [94]: Improve results (improve survival in HR) [98]: Laboratory capacity (no drug levels) [99]: Cost [100]: Laboratory capacity (no drug levels); toxicity [102]: Toxicity
Methotrexate	Continuation/ maintenance		[102]					[55]: Toxicity [111]: Toxicity [116]: Toxicity
Prednisone	Induction						[67]	–
Thioguanine	Intensification blocks						[23]	–
Vincristine	Induction		[111]					[111]: Toxicity
Vincristine	Intensification blocks				[49]			[49]: Balance toxicity/survival
Vincristine	Continuation/ maintenance		[111]					[111]: Toxicity
Vincristine	Not phase-specific						[14]	–
Drug omission								
Anthracycline	Induction		[111]					[111]: Toxicity
L-Asparaginase	Induction	[99]						[99]: Cost
L-Asparaginase	Continuation/ maintenance		[28] [55] [116]					[28]: Toxicity [55]: Toxicity [116]: Toxicity
L-Asparaginase	Not phase-specific	[65]						[65]: Drug availability
Erwinia-asparainase	Not phase-specific	[94]						[94]: Drug availability
Cyclophosphamide	Induction		[22]					[22]: Long-term toxicity
Cyclophosphamide	Intensification blocks		[22]					[22]: Long-term toxicity
(High-dose) Cytarabine	Consolidation	[77]	[77]					[77]: Cost, hospitalization; toxicity
Doxorubicin	Intensification blocks		[22]					[22]: Long-term toxicity
Etoposide	Induction		[8]					[8]: Balance toxicity/relapse
Etoposide	Consolidation						[3]	–
Etoposide	Continuation/ maintenance		[107]					[107]: Late effects/secondary malignancy
Mercaptopurine	Induction						[23]	–
(High-dose) Methotrexate	Consolidation	[35] [77]	[25] [35] [77] [111]		[35]		[113] [124]	[25]: Toxicity [35]: Cost, provider experience; patients' clinical condition/toxicity; balance survival and toxicity [77]: Cost, need for hospitalization; toxicity [111]: Toxicity
Methotrexate	Not phase-specific	[65]						[65]: Drug availability
Thioguanine	Intensification blocks	[18]	[18]					[18]: Feasibility, outpatient administration; toxicity
TKI	Not phase-specific	[62] [63]						[62]: Drug availability [63]: Drug availability
Drug addition								
L-Asparaginase	Induction	[106]		[106]			[99]	[106]: Cost (covered by insurance); reduce relapse
L-Asparaginase	Consolidation	[111]						[111]: Cost (limited supply, randomized question to assess the impact of addition in consolidation)
L-Asparaginase	Intensification blocks			[41]				[41]: Target extramedullary leukemia
L-Asparaginase	Postinduction NOS						[67]	–
Cyclophosphamide	Intensification blocks			[122]				[122]: Reduce extramedullary and bone marrow relapse, increase systemic CNS leukemic treatment
Etoposide (HR only)	Intensification blocks			[122]				[122]: Reduce extramedullary and bone marrow relapse, increase systemic CNS leukemic treatment
Etoposide	Postinduction NOS						[67]	–
Ifosphamide (HR only)	Intensification blocks			[122]				[122]: Reduce extramedullary and bone marrow relapse, increase systemic CNS leukemic treatment
Mercaptopurine	Consolidation						[72]	–
Mercaptopurine (HR only)	Intensification blocks						[101]	–
(High-dose) Methotrexate	Consolidation	[120]	[120]	[21] [106]	[120]			[21]: Reduce CNS/testicular relapse [106]: Cost (covered by insurance); reduce relapse [120] Staff/Infrastructure, complexity; reduce late effects from cranial irradiation; balance toxicity/survival
TKI	Not phase-specific			[41] [80]				[41]: CNS penetration [80]: CNS penetration
Drug dose increase								
L-Asparaginase	Induction			[41] [71] [77] [80] [101]				[41]:Target extramedullary leukemia [71]:Target extramedullary leukemia [77]:Target extramedullary leukemia [80]: Target extramedullary leukemia [101]:Target extramedullary leukemia
L-Asparaginase	Continuation/ maintenance				[27] [62]			[27]: Balance toxicity/relapse [62]: Balance toxicity/relapse
Cytarabine	Intensification blocks						[41]	–
Cytarabine	Postinduction NOS						[67] [87]	–
Daunorubicin	Induction						[18]	–
Daunorubicin (HR only)	Intensification blocks						[101]	–
Etoposide (HR only)	Intensification blocks						[101]	–
(High-dose) Methotrexate	Consolidation	[72]		[122]		[72]	[41]	[72]: Diagnostic capability (can newly measure methotrexate levels); lack of dosing consensus [122]: Reduce CNS and bone marrow relapse, increase systemic CNS treatment
Methotrexate	Intensification blocks						[94]	–
Mercaptopurine	Continuation/ maintenance						[36]	–



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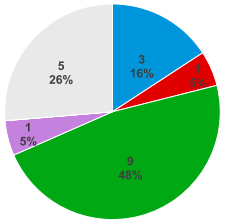

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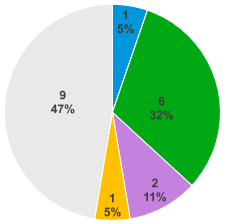


n = 19

FIG 2. (Continued).

intensification blocks, adding vincristine and steroid weeks in maintenance; Fig 1).

Chemotherapy-specific dosing modifications and rationale for modifications were further analyzed (Fig 2). High-dose methotrexate modifications to reduce intensity (omission, dose reduction, or substitution) were most common in 25.6% of articles (n = 32 of 125). Other common modifications to chemotherapy included asparaginase dose reduction, substitution, and omission (n = 12, n = 9, n = 6, respectively); substituting daunorubicin for doxorubicin (n = 12); intrathecal (IT) chemotherapy drug substitution (eg, replacing two doses of triple IT with four doses of methotrexate-only IT; n = 11); and adding a steroid prephase to induction (n = 10).

Modification Rationales

Across all individual modifications, 61% included one or more rationales for modification, which were categorized based on the declared intent: to improve survival (eg, improve remission rate, decrease relapse, target extramedullary leukemia), to reduce toxicity (eg, reduce treatment-related mortality [TRM], infection, immunosuppression, or late effects and improve the clinical condition), to balance survival/efficacy and toxicity, to address local implementation issues (eg, laboratory capacity, drug availability, feasibility/logistics/complexity, cost, infrastructure, regimen adherence, supportive care capacity, provider experience/comfort, abandonment), or because of a gap/change in knowledge (eg, publication of interim results or inadequate knowledge of optimal drug dosing).

The most cited reason for modification was to address an implementation challenge, followed by the intention to decrease toxicity (Fig 1). Thirty-six percent (n = 45 of 125) of articles cited implementation challenges, corresponding to 48 ALL regimen changes (Fig 3). The most-cited implementation challenges included drug unavailability (24%), treatment cost (23%), inadequate laboratory capacity (eg, inability to measure methotrexate levels; 19%), and infrastructure gaps (13%; eg, insufficient inpatient beds, insufficient outpatient support, inadequate emergency services). Drug substitutions were most frequently attributed to implementation challenges, namely, because of a lack of drug availability (22 of 26). Regimen changes including drug omissions and dose reductions were predominantly intended to reduce toxicity; however, implementation issues were also frequently cited. In drug dose reductions, the primary implementation barriers were cost and laboratory capacity, and in drug omissions, the primary implementation barriers were drug availability and cost (Fig 2).

When rationales were stratified by income level, more modifications were attributed to implementation barriers than to toxicity in LICs and lower-middle–income countries, with implementation issues being cited for 50% (n = 10 of 20) and 50.4% (n = 67 of 133) of regimens, respectively, compared with toxicity for 20% (n = 4 of 20) and 29.3% (n = 39 of 133), respectively. Interestingly, the proportions of modifications attributed to implementation barriers and toxicity were similar in articles from UMICs at 32.1% (n = 35 of 109) and 35.8% (n = 39 of 109), respectively.

Survival and Toxicity Outcomes

There was substantial variability in clinical outcomes reporting, including survival outcomes exclusively stratified by risk classification or study arm, outcomes across multiple regimens reported as a single summary value, and incomplete reporting of outcomes by regimen. This resulted in 177 distinct outcome records across the 125 articles and 163 regimens (Data Supplement, Table S2). Across articles, the CR rate was reported in 69.6% (n = 87), survival outcomes (EFS, OS, DFS, or RFS) in 95.2% (n = 119 of 125), relapse in 87.2% (n = 109), and measures of mortality (death in induction, death in remission, or total death) in 83.2% (n = 104). Abandonment, as a number of patients or a rate, was reported in 51.2% (n = 64). The median abandonment rate was 5.0% (IQR, 8%) and varied from zero to 48.3%.

Time frames for follow-up and reporting survival outcomes ranged from 2 to 15 years, with the most reported values at 2, 3, or 5 years. Across regimens reporting ≥5-year EFS and OS, median values were 67% (IQR, 26%) and 74% (IQR, 28%), respectively. Subanalyses evaluated the impact of regimen modification on clinical outcomes. The median ≥5-year OS was higher for modified regimens (n = 109) than for unmodified regimens (n = 68) at 79.2% versus 66.5%, respectively (P = .030).

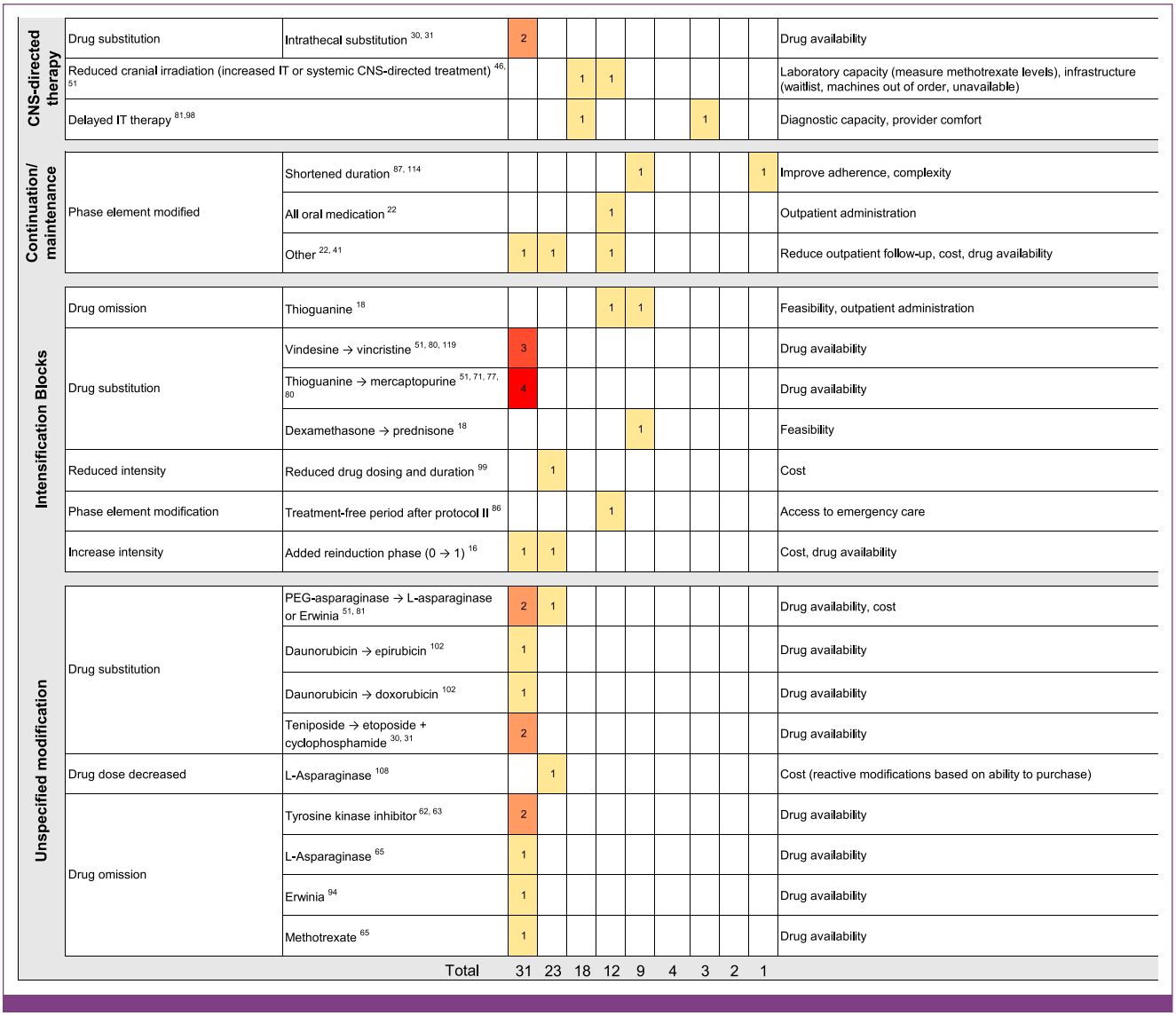
To describe general trends in survival across the regimens most used in LMIC settings, a subanalysis was conducted of the median rates for CR; ≥5-year EFS, DFS, RFS, and OS; toxicity; relapse; and abandonment for the three most-used HIC-derived regimens (BFM, St Jude, and UKALL) and for mixed regimens. This included 124 outcome records. There was no significant difference between survival outcomes (≥5-year EFS, DFS, RFS, and OS) for regimens based on the different HIC backbones. However, there were significant intergroup differences for relapse rate (P = .020), death in induction (P = .003), death in remission (P = .002), and abandonment rate (P = .002). Median relapse rates differed significantly among the four groups (P = .02), with the St Jude rate (10.6%) being significantly lower than those for BFM-based regimens (19.5%; adjusted P = .034) and mixed regimens (19.2%; P = .048). Median induction death rates differed significantly among regimens (P = .003), with rates being significantly higher for UKALL-based regimens than for BFM, mixed, or St Jude regimens (10.0%, 3.4%, and 0.9%, respectively; adjusted P = .008, P = .032, and P = .038, respectively). Median remission death rates differed significantly across regimens (P = .002), with rates being significantly higher for UKALL regimens than for BFM, mixed, or St Jude–based regimens (10.8%, 4.6%, 3.1%, and 2.6%, respectively; adjusted P = .026, P = .007, and P = .037, respectively). Abandonment

No. of distinct regimen changes driven by implementation issues: 48

No. of articles citing implementation challenges as rationales for modification: 45

Categories	Subcategories	Rationale: Drug Availability	Cost	Laboratory Capacity	Infrastructure	Feasibility/Logistics/Complexity	Supportive Care Capacity	Provider Experience/Comfort	Abandonment	Adherence	Description
Risk Stratification											
Assigned to the single arm	Standard risk only [5, 24, 68, 90]		1	2		1					Diagnostic capabilities (no MRD), cost, logistics
	Intermediate risk or medium risk only [5, 44]		1	1							Diagnostic capabilities, cost
Consolidated treatment groups	Eliminated high-risk arm [69, 81]			2							Diagnostic capability (cytogenetics)
Induction											
Added prephase [17]									1		Reduce abandonment
Drug substitution	Dexamethasone → prednisone [86]								1		Reduce abandonment
	Doxorubicin → daunorubicin [94]	1									Drug availability
	Daunorubicin → doxorubicin [51, 71, 81, 94]	4	1								Drug availability, cost
	PEG-asparaginase → L-asparaginase [69]	1									Drug availability
	L-Asparaginase → cyclophosphamide [18]				1	1					Feasibility, infrastructure
	L-Asparaginase → anthracycline [51]	1									Drug availability
Drug dose decreased	Anthracycline [27, 124]		1				1				Cost, supportive care (transfusions, hospitalization)
Drug omission	L-Asparaginase [99]		1								Cost
Drug addition	L-Asparaginase [106]		1								Cost (covered by insurance)
Phase element modification	4 → 3 drug [69]					1					Complexity
	Reduced intensity (delayed intense drugs, added rest period) [17, 86]		1		1						Cost, access to emergency care
Consolidation											
Drug dose decreased	L-Asparaginase [60]		1								Cost
Drug omission	HD-ARA-C [77]		1		1						Hospitalization, cost
Drug addition	L-Asparaginase [111]		1								Cost (limited supply, randomized question to assess the impact of addition in consolidation)
HD MTX	Omitted [35, 77]		2		1			1			Cost, provider experience, hospitalization
	Dose/intensity reduced [8, 27, 33, 43, 46, 51, 70, 86, 98, 99, 100]	2	3	9		1	2				No drug levels, resource constraints/cost, supportive care, drug availability, feasibility
	Dose increased [72]			1							Diagnostic capability (can newly measure levels)
	HD MTX added [106, 120]		1		1	1		1			Cost (covered by insurance), complexity, staff/provider experience, infrastructure
Leucovorin modification [98]				1							No drug levels
Drug substitution	HD MTX → high-dose cytarabine [40]		1		1		1				Cost, outpatient administration, limited supportive care
Phase element modified	Consolidation omitted [18]				1	1					Feasibility, outpatient administration
	Reduced intensity [71]		1								Cost

FIG 3. Implementation challenges cited as rationales for regimen modification. The numbers under the rationale column represent the number of times each explanation was cited by an article. The colors correspond to a heat map where single citations are represented by yellow, and the highest number of citations is represented by dark red. HD MTX, high-dose methotrexate; MRD, minimal residual disease; PEG, pegylated asparaginase. (continued on following page)



CNS-directed therapy	Drug substitution	Intrathecal substitution [30, 31]	2									Drug availability
	Reduced cranial irradiation (increased IT or systemic CNS-directed treatment) [46, 51]				1	1						Laboratory capacity (measure methotrexate levels), infrastructure (waitlist, machines out of order, unavailable)
	Delayed IT therapy [81,98]				1				1			Diagnostic capacity, provider comfort
Continuation/ maintenance	Phase element modified	Shortened duration [87, 114]					1				1	Improve adherence, complexity
		All oral medication [22]				1						Outpatient administration
		Other [22, 41]	1	1		1						Reduce outpatient follow-up, cost, drug availability
Intensification Blocks	Drug omission	Thioguanine [18]				1	1					Feasibility, outpatient administration
	Drug substitution	Vindesine → vincristine [51, 80, 119]	3									Drug availability
		Thioguanine → mercaptopurine [51, 71, 77, 80]	4									Drug availability
		Dexamethasone → prednisone [18]					1					Feasibility
	Reduced intensity	Reduced drug dosing and duration [99]		1								Cost
	Phase element modification	Treatment-free period after protocol II [86]				1						Access to emergency care
	Increase intensity	Added reinduction phase (0 → 1) [16]	1	1								Cost, drug availability
Unspecified modification	Drug substitution	PEG-asparaginase → L-asparaginase or Erwinia [51, 81]	2	1								Drug availability, cost
		Daunorubicin → epirubicin [102]	1									Drug availability
		Daunorubicin → doxorubicin [102]	1									Drug availability
		Teniposide → etoposide + cyclophosphamide [30, 31]	2									Drug availability
	Drug dose decreased	L-Asparaginase [108]		1								Cost (reactive modifications based on ability to purchase)
	Drug omission	Tyrosine kinase inhibitor [62, 63]	2									Drug availability
		L-Asparaginase [65]	1									Drug availability
		Erwinia [94]	1									Drug availability
		Methotrexate [65]	1									Drug availability
		Total	31	23	18	12	9	4	3	2	1	

FIG 3. (Continued).

rates differed significantly between regimens ($P = .002$), with higher median rates for BFM-based regimens compared with those for St Jude–based and mixed regimens (6.6%, 3.2%, and 0.9%, respectively; adjusted $P = 0.021$ and 0.022, respectively).

Heterogeneity of clinical outcomes, variable follow-up duration, and incomplete reporting of changes prevented meta-analysis of clinical results and evaluation of the impact of individual modifications.

Implementation Outcomes

Despite the high proportion of articles citing modifications attributed to implementation challenges (n = 44 of 91, 48%), implementation outcomes were reported in only eight articles (6.4%; Data Supplement, Table S1). Feasibility and cost were the only implementation outcomes measured, but 97 articles (77.6%) included a conceptual indication or discussion corresponding to an implementation outcome. The most referenced outcomes included appropriateness (local fit) in 39.2% of articles, cost (of regimen and regimen delivery) in 28.0%, and fidelity (adherence to the regimen as designed in the clinical trial) in 24.8%.

DISCUSSION

Modern pediatric ALL treatment regimens are complex health interventions that require intensive resources and expertise to deliver successfully. This study aimed to embrace this complexity, capture the heterogeneity of ALL treatment applications, and synthesize evidence from the past two decades. This implementation-informed approach identified generalizable lessons about ubiquitous barriers and the role of adaptation in global pediatric ALL treatment delivery.

In the 1980s and 1990s, twinning programs between institutions in HICs and LMICs were created to improve pediatric

cancer survival globally.[17] These often included implementing an HIC-derived ALL backbone; however, as this review shows, an unmodified HIC regimen did not guarantee the same survival outcome in LMICs.

Our data demonstrate that adaptation is a frequently used and critical *implementation strategy* to deliver ALL regimens outside a HIC context.[18] Adapting regimens to local contexts occurred for >60% of regimens in all phases of treatment, across all regions and resource levels, with similar modification rates across the most-used HIC collaborative backbones (BFM, St Jude, and UKALL). Although the proportion of adapted regimens was highest in articles from LICs, the degree of adaptation was highest in articles from UMICs, potentially demonstrating a greater capacity for planned, context-informed modifications and highlighting additional factors beyond financial burden driving regimen change. Interestingly, the proportion of modified HIC-derived regimens decreased as the trend to combine strategies from different HIC collaborative groups in "mixed" regimens emerged. These mixed regimens were associated with the lowest rate of treatment abandonment (0.9% [4.5]) and a comparable rate of relapse (19.2% [8.2]) with BMF-based and UK-ALL–based regimens (19.5% [17.9] and 18.8% [9.6], respectively), albeit higher than that of St Jude–based regimens (10.6% [12.0]). Still, given the small subset of regimens using this approach and the fact that the majority of mixed regimens occurred in the later treatment period, additional information about their implementation and clinical impact is needed.

Although rates of toxicity and relapse differed among HIC-derived regimens implemented in LMICs, there was no significant survival difference among regimens based on the three most common HIC collaborative groups. The differences observed in toxicity between different HIC backbones should be interpreted with caution as the use of the different regimens occurred across different contexts with varying income levels, supportive care, and infrastructure that may affect ease of implementation and feasibility of local administration.

Interestingly, the ≥5-year OS in modified regimens was higher than that in unmodified regimens, across geographic regions and income levels. This impact has been difficult to demonstrate in the past because, as demonstrated in this review, head-to-head comparisons of the same modified and unmodified regimens are rarely feasible. While the current data were insufficient to identify the specific cause of this difference, previous single-center studies have reported improved survival outcomes in modified versus unmodified regimens with significantly reduced toxicity.[14] This reinforces the positive impact of planned and rigorously evaluated modification and demonstrates, at a global level, what the scientific community has long acknowledged, that contextual adaptation is important in improving pediatric ALL survival in LMICs.

Historically, treatment toxicity was considered the primary driver of cancer treatment regimen modification,[19] with regimen changes occurring by design based on local clinical outcomes to reduce toxicity, relapse, and abandonment. However, this review has highlighted the equally substantial contribution of implementation challenges, resulting in modifications by necessity in response to local context and implementation barriers.

While this review noted some gaps in reporting standard clinical outcomes, global adherence to these accepted reportable outcomes (TRM, relapse, abandonment)[17,20] facilitates generalizable lessons learned about how intensity can be modulated to improve ALL survival. However, these clinical outcomes alone provide insufficient evidence about the underlying context and contextual challenges and provide no concerted mechanism for addressing these pervasive and persistent issues.

By synthesizing rationales from observed modifications, across geography and income levels, contextual data from this review can be used to design strategies to improve global pediatric ALL care delivery. First, this review identified ubiquitous implementation barriers affecting real-world ALL care delivery, including drug accessibility and cost. While efforts across the global community have emerged over the past 20 years to address some of these challenges, these findings emphasize that further prioritization and innovative solutions are needed.

For example, in 2007, the first WHO Essential Medicine List for Children (EMLc) was published to provide guidance to regional and national authorities to support drug access, including essential chemotherapies.[21] To determine its impact on access and treatment delivery, this review identified articles citing drug substitutions published ≥5 years after this first EMLc to examine the rationale for these modifications. Of the 15 such articles, 80% (n = 12) cited drug access as the reason for drug substitution, signifying that policy alone is an insufficient implementation strategy for change. This emphasizes the need for continuous commitment at a national and international level to improving drug access and affordability and the potential impact of concerted efforts and multifaceted strategies such as the Global Platform for Access to Childhood Cancer Medicines.[22]

Beyond drug access, the array of modification data from our review also highlights real-world pain points for ALL care delivery, which can be used proactively to inform efforts to harmonize feasible guidance for ALL treatment based on the evidence from contextual near peers. To support this, a globally representative working group used data from the review in developing the Adapted Resource Implementation Application (ARIA) Adapted Management Guideline for pediatric ALL.[23] Future studies will evaluate the impact of this approach on regimen delivery across varied resource settings, with the aim of optimizing patient survival when resources are limited.

In addition, the historic understanding of key barriers over the past two decades is important to inform the proactive

implementation and translation of emerging diagnostic modalities and treatments, such as MRD, genomics-based risk classification, and novel targeted therapies, which have resulted in paradigm shifting changes to ALL management in HIC settings but have currently failed to reach patients in many LMICs.

These data highlight the need to rethink the global oncology clinical research outcomes and reporting model to identify and share clinical and implementation strategies that improve ALL outcomes. While adaptation to local context is important to inform appropriate treatments, there is no formal process for reporting context and context-informed regimen changes, and these gaps ultimately limit the generalizability of rich practice-based evidence.

This proposed shift requires community reflection, method expansion, and integration of complementary methodologies such as implementation science, which provides consistent language for barriers and adaptation that facilitates comparative analysis and the formation of substantive conclusions to guide specific, feasible regimen recommendations in resource-limited contexts. Consensus-based reporting standards for implementation in pediatric oncology are critical to maximize future implementation success for ALL globally. At minimum, these standards should include explicit and consistent identification of barriers to implementing treatment regimens, guided by a determinant framework[24]; provide detailed descriptions of strategies[25,26] (eg, adaptation) to overcome challenges; and measure the impact of strategies by reporting implementation outcomes such as feasibility, cost, and appropriateness.[9] By incorporating common implementation language to describe challenges and the extent of the adaptation (*a local solution to overcome the challenge*) and by measuring the real-world impact on therapy delivery (*implementation outcomes*) in publications, we can better disseminate practical knowledge about care delivery that is needed to accelerate the translation of feasible regimens in similarly resourced settings and achieve the WHO GICC 2030 goals.[6]

Most publications reviewed were from lower-middle–income countries (42.2%) and UMICs (47.2%), reflecting the relative proportions of the respective populations. Publications from LICs were disproportionately underrepresented, probably reflecting the still-developing programs for pediatric cancer care and the relatively limited resources for publication in LICs. The variety of use and reporting limited conclusions about the role of radiation therapy in ALL and future studies are needed to further understand real-world implementation challenges affecting its delivery in LMICs. The comparison of median clinical outcomes is presented to provide a general trend in survival and toxicities across LMICs during this 20-year period and to assess how HIC-based regimens are used across regions and in a real-world setting outside of a clinical trial. No survival advantage was seen with a particular HIC-based backbone as is seen in comparisons of these regimens used in HIC settings,[2] and we note that the use of UKALL-based regimens occurred more in lower-resource settings than St Jude– and BFM-based regimens, which might have skewed observed clinical outcomes. Finally, by reflecting only published data and limiting the review to articles in English, our findings probably under-represent outcomes, modifications, and clinical practices at lower-resourced institutions that are yet to be reported or may be available to only a limited audience.

In conclusion, implementation challenges in LMICs have necessitated numerous adaptations of pediatric ALL regimens designed in HICs. Variable reporting of adaptations and rationales and the relative dearth of published implementation outcomes represent missed opportunities to disseminate innovative practice-based evidence and improve the translation of feasible ALL regimens globally. The proposed approach can identify patterns in adaptations with a solid evidence base, which will (1) enable local application by peers in similar resource settings, (2) address critical clinical questions regarding ALL, (3) create opportunities for bidirectional feedback to inform ALL regimen development, (4) minimize implementation gaps outside the clinical trial setting, and (5) inform national and international policies to prioritize and address continuous implementation challenges to improve survival of pediatric ALL globally.

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DISCLAIMER

The funders were not involved in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; in

the preparation, review, or approval of the article; or in the decision to submit the article for publication.

PRIOR PRESENTATION

Presented in part at the International Society of Paediatric Oncology 56th Annual Congress, Honolulu, HI, October 17-20, 2024.

SUPPORT

Supported by the American Lebanese Syrian Associated Charities.

DATA SHARING STATEMENT

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Research Funding: Amgen Foundation (Inst)
Uncompensated Relationships: Blincyto Humanitarian Access Program (Inst)

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Stock and Other Ownership Interests: Gladiator Biosciences (I), Coagulant Therapeutics (I)
Consulting or Advisory Role: Novartis, Sobi, KaliVir Immunotherapeutics (I)
Patents, Royalties, Other Intellectual Property: Spouse has patents pending for platform technology with application to oncology, diagnostics, anti-infections and for anti-bleeding technology (I)

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors would like to thank Julie Edrington, MSLS, from the St Jude Biomedical Library, for her work on the literature search strategy for this review, and Keith A. Laycock, PhD, ELS, from St Jude Scientific Editing, for editing of the manuscript.

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