ANNEX

Table S1. Characteristics of the included studies on treatment-related toxicity in children with AML and ALL.

Author (year)	Country / consortium	Study design	Cancer type	Number of patients	Age	Treatment protocol	Drug / exposure	Treatment phase	Type of toxicity	Severity definition Grade	Key findings
ALL											
Santos de Faria et al. (2014) (17)	Brazil	Prospective observational single-center study	ALL	92	Median 6 years	Standard ALL chemotherapy protocols	Methotrexate-based chemotherapy	Early phase (Day 0–7 after initiation)	Oral mucositis	NCI CTC (2006); Grade 1–2 definitions reported	Mucositis at Day 7 in 70.7%; among mucositis cases: Grade I 60%, Grade II 40%. HSV-1 associated with higher severity (OR≈4.10, p=0.03). CMV showed protective association in multivariable model.
Eipel et al. (2016) (18)	Hungary (6 centers)	Retrospective pharmacogenetic cohort study	ALL	346	Median 4.95 years	ALL-BFM 90/95	High-dose glucocorticoids during early protocol phases (prednisone	Protocol phases 1–2 (high-dose GC phase)	Hepatotoxicity; glucose metabolism abnormalities; hypertension;	Lab thresholds (no CTCAE)	N363S carriers (9.24%) had higher hepatotoxicity (31% vs 11%) and glucose abnormalities

							60 mg/m²/day and/or dexamethasone 10 mg/m²/day)		CNS/behavioral toxicity		(19% vs 3%). ≥1 toxicity 65.7% vs 34.1%; ≥2 toxicities 21.7% vs 6.7%. 5-year EFS 93.1% vs 71.9%; OS 91.2% vs 76.7%. ER22/23EK not associated with toxicity; Bcl-1 no significant association.
Vora et al. (2006) (19)	UK & Ireland (multicenter)	Randomized controlled trial (ALL97/99)	ALL	1498	Median 4 years	ALL97 / ALL97-99	6-thioguanine (40 mg/m²) vs 6-mercaptopurine (75 mg/m²)	Interim maintenance + continuing therapy	Infectious mortality; hepatotoxicity (VOD, portal hypertension)	WHO grade 3–I for severe toxicity; VOD defined by clinical criteria (McDonald criteria).	TG 750; MP 748. TG reduced isolated CNS relapse (2.5% vs 4.6%) but increased death in remission (3.9% vs 1.7%, p=0.01) and infection-related deaths (22 vs 9). VOD occurred in 11% of TG; chronic portal hypertension ~5%; no overall survival benefit.
Nazir HF et al., 2017 (20)	Oman (Sultan Qaboos University Hospital)	Retrospective observational study (2006–2016)	ALL	103	Median 7 years	UK ALL 2003 / 2011	Vincristine 1.5 mg/m²	Vincristine-containing phases (early treatment)	Vincristine-induced peripheral neuropathy	CTCAE v4.0	Neuropathy incidence 19%; autonomic involvement 42%; severe cranial neuropathy in 2 cases. Dose

											omission required in >50%; pyridoxine/pyridostigmine did not prevent progression. 16/19 had motor Grade ≥3
Liu et al., 2017 (21)	China (Beijing Children's Hospital)	Retrospective pharmacogenetic cohort study	ALL	322	Median 4 years	BCH-2003; CCLG-2008	High-dose methotrexate	Consolidation	Severe oral mucositis	CTCAE v4.0	Grade 3–4 mucositis 12%; SLCO1B1 rs10841753 associated with MTX levels (p=0.017); ABCB1 rs1128503 associated with longer hospitalization (p=0.006); SLCO1B1 rs4149056 and SLC19A1 rs2838958 associated with worse EFS. High MTX level >0.25 μmol/L at 48h
Tong et al., 2014 (22)	Netherlands & European pediatric centers	Prospective observational cohort	ALL	89	Median 4.9 years	DCOG ALL-10 (medium risk)	PEG-asparaginase 2,500 IU/m² × 15 doses	Intensification phase (~30 weeks)	Dyslipidemia; pancreatitis; thrombosis; central neurotoxicity	CTCAE v3.0	Hypertriglyceridemia 47%; hypercholesterolemia 25%; central neurotoxicity ~10%; pancreatitis and thrombosis rare.

											Dyslipidemia correlated with asparaginase activity; toxicities did not require treatment discontinuation.
Sari et al. (2021) (23)	Indonesia (single centre)	Prospective pilot cohort	ALL	32	Median 5 years	Indonesian ALL Protocol 2013	HD-MTX 1 g/m² (24h infusion, no loading dose)	Consolidation (68 cycles total)	Hepatotoxicity 32.2% (G3–4: 4.4%); neutropenia 30.7% (G3–4: 26.4%); nephrotoxicity 8.8% (G3: 1.4%); febrile neutropenia 5.8%; thrombocytopenia 5.6%; mucositis 4.3%; delayed MTX clearance 4.4%	CTCAE v3.0; Nephrotoxicity defined by Lab thresholds;	Toxicity generally mild; no lethal events. No significant association between MTX levels and toxicity except hepatotoxicity; absence of loading dose may explain lower MTX levels. MTX levels at 24h/48h
Mateos et al. (2021) (24)	Australia (national multicenter cohort)	Retrospective cohort + GWAS	ALL	1251	Median 4.9 years	BFM- and COG-based frontline protocols	Intrathecal and IV methotrexate	Induction, consolidation, CNS-directed phases	Central neurotoxicity (95 cases; 7.6%): stroke-like syndrome, seizures, speech deficits, encephalopathy	CTCAE v4.03	G1 4.2%, G2 62.1%, G3 31.6%, G4 2.1%/ Age ≥10 years and AST >G3 independent risk factors; recurrence after re-exposure 12.9%; discontinuation of IT MTX associated with

											higher CNS relapse (5-year CNS RFS 89.2% vs 95.4%).
van Schie et al., 2011 (25)	Netherlands (DCOG ALL-10)	Retrospective within-patient comparative study	ALL	20	Mean/median NR.	DCOG ALL-10	Vincristine ± azole antifungals	Induction / MR / HR phases	Peripheral neuropathy; constipation; CNS toxicity	CTCAE v3.0; Grade ≥3 reported	Grade ≥3 peripheral neuropathy 60%; Grade ≥3 constipation 30%; toxicity observed only with azole co-administration; significantly increased neurotoxicity ($p<0.001$); reversible after azole discontinuation.
Kapoor et al., 2012 (26)	India (single centre)	Retrospective cohort	ALL	41	Median 6 years	Institutional ALL protocol	HD-MTX 5 g/m² (24h infusion)	Consolidation	Mucositis 39% (G3–4: 5.4%); fever 28%; neutropenia ≥G3 24.8%; thrombocytopenia ≥G3 2.2%; ALT elevation 34.9% (G3–4: 3.1%); rash 5.6%	CTCAE v3.0	149 HD-MTX cycles. Severe organ toxicity rare; no nephrotoxicity or neurotoxicity; no toxic deaths; HD-MTX feasible with monitoring.
Kałużna et al., 2015 (27)	Poland	Prospective pharmacog	ALL	47	Median 5 years	ALL IC BFM 2009	HD-MTX 5 g/m² ×4	Consolidation (Protocol M)	Hepatotoxicity 18.9–61.1%; myelotoxicit	Lab thresholds Severe toxicity	677T allele and combined genotypes associated with

		enetic cohort							y 60.8–82.6%; nephrotoxicity 8.9–16.7%; infections 8.9–41.7%	graded WHO grade 3–4	delayed MTX clearance and increased toxicity; 677CC/1298AA genotype protective.
De Pietri et al. (2020) (28)	Denmark (NOPHO)	Prospective observational cohort	ALL	51	Median 3.7 years	NOPHO ALL 2008	Standard induction polychemotherapy	Induction (Day 1–29)	Inflammatory mucositis (IM) 54%; bacteremia 27%; systemic inflammation peak at Day 15	CTCAE v4.0 (Grade 0–II)	IM ≥G1 in 54% (G1 42%, G2 12%); bacteremia 27%; systemic inflammatory response peaked mid-induction.
den Hoed et al., 2015 (29)	Netherlands (DCOG ALL-10)	Prospective multicenter cohort	ALL	134	Median 5.3 years	DCOG ALL-10	HD-MTX 5 g/m² ×4 + 6-MP	Consolidation (Protocol M)	Mucositis ≥G3 20%; skin 7%; diarrhea 3%; neurotoxicity 3%; acute liver toxicity 5%; kidney toxicity 1%	CTCAE v3.0 (≥Grade 3)	Severe mucositis most frequent; associated with higher erythrocyte folate and ABCC4 rs7317112 wild-type; not associated with plasma MTX levels.
Lopez-Lopez et al., 2011 (30)	Spain (SHOP group)	Retrospective multicenter cohort	ALL	115	Mean 5.5 years	LAL-SHOP 99 / 2005	HD-MTX 3–5 g/m²	Consolidation	Hepatotoxicity 29.4%; mucositis 10.8%; nephrotoxicity 8.8%; vomiting 21.6%;	WHO toxicity scale (Grade 2–4 reported)	Grade 2–4 (39.7%). SLCO1B1 rs4149056 associated with higher MTX levels and toxicity; MTX >0.2 μM correlated with

									overall toxicity 51%		complications; genetic variants predicted HD-MTX toxicity risk.
Teusink et al., 2012 (31)	USA (single center)	Retrospective cohort	ALL	31	Median 6 years	Standard induction protocol	Vincristine ± fluconazole prophylaxis (4 mg/kg/day)	Induction (+ 3-month follow-up)	Peripheral neuropathy; constipation; infections	Neuropathy assessed using modified Balis scale (no CTCAE grading)	Neuropathy 48% overall (69% with fluconazole vs 27% without; p=0.03); constipation 42%; dose modification 6%; fungal infection 9.7%; bacterial infection 39%. Concomitant fluconazole associated with increased VCR-induced neuropathy; age independent predictor.
Schilstra et al., 2022 (32)	Australia & New Zealand (9 centers)	Prospective registry cohort	ALL	260	Median 5 years	COG- or iBFM-based protocols	Multi-agent chemotherapy	First 12 months of therapy	Treatment-related toxicities (TRT): VTE 7.7%; neurotoxicity ≥G3 11.9%; bone toxicity 5.4%; pancreatitis 5.0%	NCI CTCAE v4.03	Symptomatic TRT in 28.5%; most events occurred early; incidence comparable to ERASE cohort; HRQoL significantly reduced during first year.

Rokkanen et al., 2024 (33)	Finland (Oulu University Hospital)	Retrospective single-center cohort	ALL	73	Mean 6.6 years	NOPHO ALL-2008	Multi-agent chemotherapy (incl. vincristine, PEG-asparaginase)	Entire therapy (~2.5-year follow-up)	VIPN 96%; osteonecrosis 26%; allergy/anaphylaxis 21%; pancreatitis 7%; CNS toxicity 7%; thrombosis 6%; hepatic impairment 3%; severe bleeding 3%	PdL definitions graded 1–5 (VIPN, thrombosis, osteonecrosis) and CTCAE v5.0 (CNS, pancreatitis, allergy, bleeding);	no Grade 5 events. ≥1 toxicity in nearly all patients; multiple toxicities in ~48%; treatment modified due to toxicity in 51%.
Wu et al., 2020 (34)	China (single center)	Prospective cohort	ALL	91	Mean 5.7 years	CCCG-ALL-2015	PEG-asparaginase 2000 U/m² IM	Induction (Days 6 and 26)	Any AE: 14.3% (13/91); Anaphylaxis: 7.7% (rash 4.4%, shock 1.1%, dyspnea 1.1%, complex reaction 1.1%); Acute pancreatitis: 4.4%; GI toxicity: 2.2% (abdominal pain/diarrhea 1.1%, nausea/vomiting 1.1%)	Clinically diagnosed; no CTCAE grading reported	Reduced L-asp activity and increased anti-L-asp antibody, Asn and Gln levels strongly associated with anaphylaxis risk (AUC for Asn 0.964; L-asp 0.927); biomarkers not associated with non-anaphylactic AEs; switching to Erwinia L-asp performed after anaphylaxis
	Saudi Arabia (King Faisal Specialist Hospital)	Retrospective cohort	ALL	156	Mean/median NR.	Standard/high-risk protocols	Prednisone vs dexamethasone ±	Induction (4 weeks + 2-week follow-up)	Gastritis; hyperglycemia; hypertension;	Hypertension graded per NCI CTC; myopathy graded 1–4; other	Pred 106; Dex 50. Dexamethasone associated with higher gastritis

Belgaumi et al., 2003 (35)						± daunorubicin	daunorubicin		myopathy; serious infections	toxicities clinically recorded	(46% vs 23.6%) and weight gain; daunorubicin increased overall toxicity (p<0.01); no mortality difference between groups.
Mogensen et al., 2020 (36)	Denmark (NOPHO ALL2008)	Retrospective cohort	ALL	127	Median 4.5 years	NOPHO ALL 2008	Multi-agent chemotherapy	First 2.5 years of therapy	Thromboembolism 5.5%; osteonecrosis 7.2%; pancreatitis 18.2%	PdL definitions (no CTCAE)	Dyslipidemia at diagnosis associated with increased thrombosis risk (HR 9.3; p=0.011); no association with pancreatitis or osteonecrosis.
Fermer et al., 2025 online ahead of print (37)	Sweden (national cohort)	Retrospective population cohort	ALL	351 (ALLTogether 117; ALL-2008 234)	Median 4 years	ALLTogether vs NOPHO ALL2008	Early PEG-asparaginase; dexamethasone vs prednisone; anthracycline differences	Induction + Consolidation 1	Hyperglycemia; osteonecrosis; hepatic toxicity; pancreatitis; infections	Clinically diagnosed; no CTCAE grading reported	Total toxic load was similar between the groups (2.5 vs 2.3 events per patient). The ALLTogether protocol was associated with a higher incidence of hyperglycemia and osteonecrosis, and a lower incidence of hepatic toxicity. Weight gain >10% occurred in 55.6% vs 18.5%

											of patients ($p < 0.001$).
Kloos et al., 2019 (38)	Netherlands	Prospective cohort	ALL	126	Median 4.0 years	DCOG ALL-10	HD-MTX ± PEG-asparaginase	Consolidation (HD-MTX courses)	Leukopenia G3–4 59% vs 30%; neutropenia G3–4 86% vs 62%; ALT/AST G3–4 28% vs 12%; neurotoxicity G3–4 5% vs 0%	CTCAE v4.03 (G1–G4)	Hematologic toxicity most frequent; higher severe neutropenia and leukopenia when MTX administered after asparaginase.
Mostafa-Hedeab et al., 2020 (39)	Egypt (NCI Cairo University)	Prospective cohort	ALL	94	Mean 7.6 years	Maintenance therapy	Oral methotrexate 50 mg/m² weekly	Maintenance	Anemia 27.7%; thrombocytopenia 14.9%; ALT elevation 31.9%; AST elevation 29.8%; bilirubin 6.4%	CTCAE v4.03; laboratory thresholds used; no stratification by grade severity	MTHFR C677T and A1298C polymorphisms not significantly associated with MTX toxicity ($p>0.05$).
Zawitkowska et al., 2019 (40)	Poland (14 centers; multicenter)	Retrospective cohort	ALL	1872	Median 5.3 years	ALL IC-BFM 2002	Standard multi-agent chemotherapy	Induction, consolidation, HR blocks, reinduction	Severe (G3–4): infections 32.3%; hepatotoxicity 28.2%; GI 20.4%; cardiac 2.7%; neurologic 2.9%; renal <1.5%; skeletal <1.5%; non-	NCI CTC v2.0 (modified by GPOH)	Only G3–4 included; 902 patients had ≥1 toxicity ≥G3. Infections/liver/GI most frequent; mainly induction/reinduction; ≥3 severe toxic episodes → worse OS/EFS;

									relapse toxic mortality 3.7%		HR group worse outcomes
Qureshi et al., 2010 (41)	UK (UKALL 2003; 21 centers)	Prospective cohort within trial	ALL	1824	Mean/median NR.	UKALL 2003	PEG-E. coli asparaginase 1,000 U/m²	Mainly induction (also consolidation/DI)	Symptomatic VT 3.2% (59/1824); 90% during ASNase exposure; 70% during induction; CVL-related VT = 50% of events (1.6% overall); cerebral sinus thrombosis = 36% of events (1.1% overall); recurrence after re-exposure 0%; major bleeding 0%	UKALL2003 (no CTCAE grading reported)	VT clustered with ASNase + steroid; re-exposure under LMWH appeared safe; asparagine depletion maintained
Anastasopoulou et al., 2022(42)	Nordic countries (NOPHO)	Population-based cohort	ALL	1464	Median 5 years	NOPHO ALL2008	Multi-agent therapy (incl. HD-MTX, ASNase, VCR, DEXA)	Entire treatment (mostly first 6 months)	Any acute CNS toxicity 9.2%; PRES 3.6% (52/1464); sinus venous thrombosis 1.9% (28/1464); isolated seizures 1.1% (16/1464); hypertensive	Clinically diagnosed (no CTCAE grading reported)	Events occurred mainly within the first 6 months of therapy. Age ≥10 years was associated with a higher risk (16.3% vs 7.4%). Overall survival was not significantly different between groups. Seizures

									encephalopathy 0.5%; MTX-related stroke-like syndrome 0.4%; intracranial hemorrhage 0.2%		were the most common event.
Kranjcec et al., 2024 (43)	Croatia (single center)	Retrospective cohort (10 y)	ALL LL	56	Median 4.3 years	ALL-IC BFM 2009 (± Interfant-06)	MTX (IV+IT), Ara-C, ASNase	Mainly induction/reinduction (≤8 months)	Acute neurotoxicity 19.6% (11/56); seizures 83.3% of events; status epilepticus 40%; leukoencephalopathy n=5; PRES n=2; ischemia n=1; life-threatening CTCAE G4 = 25% (of events)	CTCAE v5.0; MRI + EEG during events	HR group associated (p=0.0176); most within 21 days of IT MTX; majority recovered; prolonged AED therapy 54.5%
Xu et al., (2025) (44)	China (Hebei; single center)	Retrospective cohort (2020–2024)	ALL	292	Median 4.9 years	CCLG-ALL-2018 (VDLP/VDLD)	Multi-agent induction	Induction	Sepsis 49.32%; pneumonia 32.19%; neutropenia G3–4 56.51%; anemia G3–4 26.37%; thrombocytopenia G3–4	CTCAE v5.0	Infections most frequent; severe myelosuppression; PEG-associated coagulopathy; severe complications increase hospital costs

									8.90%; ALT/AST ≥G2 13.36% (G3–4 5.14%); bilirubin ≥G2 27.05%; pancreatitis 3.77%; thrombosis 0.68%; neurotoxicity 7.88%; myocardial injury 8.22%; TLS 2.05%		
Lynggaard et al., 2022 (45)	NOPHO ALL2008 (Nordic/Baltic)	Prospective multicenter cohort	ALL	1155	Median 4 years	NOPHO ALL2008	PEG-asparaginase + AEA monitoring	Post-induction (consolidation and later)	AspTox 26.7% (308/1155); allergy 13.9%; pancreatitis 6.0%; TE 3.7%; osteonecrosis 4.4%	PdL definitions (no CTCAE)	AspTox not assoc. with AEA overall; higher AEA assoc. with pancreatitis and osteonecrosis; not TE/relapse
Mesegué et al., 2021 (46)	Spain (ALL-SEHOP-PETHEMA 2013; single center)	Retrospective comparative cohort	ALL	126	Median 6.3 years	ALL-SEHOP-PETHEMA 2013	Native E. coli ASNase vs PEG-ASNase 1,000 IU/m² IM	Induction, reinduction, consolidation, maintenance	Allergy 11.9% overall; 24.7% (native→PEG) vs 4.1% (PEG upfront); pancreatitis 7.9%; silent inactivation	Allergy graded by CTCAE v4.0 (severe = G3–4); pancreatitis per PdL definitions	PEG-asparaginase upfront significantly reduced allergy incidence (p=0.0085); pancreatitis did not differ between groups (NS); therapeutic asparaginase

									5.9%		activity (SAA ≥100 IU/L) achieved in >90% of samples.
Arzanian et al., 2009 (47)	Iran (Mofid Children's Hospital)	Descriptive cross-sectional	ALL	ALL 70, other 5	Mean 6.5 years	ALL induction (Pred + VCR weekly×4 + L-ASP ± anthracycline)	Vincristine 1.5 mg/m² weekly×4	Induction	Decreased Achilles reflex (78%) and patellar reflex (53%) were common. Weakness (70%) and paresthesia (>4 years, 71%) predominated; less frequent were ptosis (15%), hoarseness (12%), constipation (12%), abdominal pain (12%), and jaw pain (6%).	Clinically diagnosed; no CTCAE grading reported	Neurotoxicity common but mostly mild; often after ~day 14; age >4 y assoc. with greater severity
Abaji et al., 2017 (48)	Canada (QcALL) + USA (DFCI replication)	Genetic assoc. (WES/EWAS) + chart review	ALL	302 (discovery) + 282 (replication)	Age not reported (only <10 / ≥10 categories)	DFCI ALL 87-01/91-01/95-01/00-01	ASNase (E. coli; some Erwinia)	Induction (1 dose in some eras) + 20–30 w consolidation	Allergy 15.9% (48/302); pancreatitis 5.0% (15/302); thrombosis 3.3% (10/302) in discovery	Clinically diagnosed; no CTCAE grading reported	rs3809849 (MYBBP1A) assoc. with all 3 toxicities; pancreatitis signals replicated (MYBBP1A, SPEF2, IL16)

									(thrombosis NR in replication)		
Parasole et al., 2010 (49)	Italy (AIEOP-BFM ALL-2000; single institution)	Retrospective cohort	ALL	253	Median 5.7 years	AIEOP-BFM ALL-2000	Multi-agent chemo incl. IT MTX + HD-MTX	Across phases	CNS complications 11% (27/253); within CNS events: PRES 37%; stroke 18.5% (hem 11%, ischemic 7.5%); temporal epilepsy 7.5%; HD-MTX toxicity 7.5%; SIADH 3.7%; idiopathic 26%	Clinically diagnosed; no CTCAE grading reported	Mostly reversible; PRES most common; 89% had recent IT MTX; long-term sequelae rare. ICU admission 29.6%; sequelae 7.5%
Figliolia et al., 2008 (50)	Brazil (São Paulo; single center)	Retrospective cohort	ALL	169	Mean/median NR	ALL-BFM-95 / ALL-BFM-2002	Protocol-based chemo	All phases	Oral mucositis 46% (77/169); >1 manifestation 31.1% of mucositis cases	Clinically diagnosed; no CTCAE grading reported	Mucositis associated with ALL-BFM-95 (OR 2.59; p=0.009)
Finkelstein et al., 2017 (51)	USA/Canada (DFCI 05-001)	Prospective cohort + pharmacogenetics	ALL	615	Median 4.9 years	DFCI 05-001	MTX + steroids + ASNase	Post-induction	Osteonecrosis 9.7% (60/615); fractures 22.1%	Clinically diagnosed; no CTCAE grading reported	The TS 2R/2R genotype was associated with an increased risk of osteonecrosis in children

									(136/615)		younger than 10 years and fractures in those aged 10 years or older.
Millan et al., 2018 (52)	Argentina (Hospital Garrahan)	Retrospective cohort	ALL	1379	Mean 9 years	Multiple protocols	MTX (IV+IT), ASNase, VCR, steroids	Mostly induction	Neurotoxicity 3.6% (49/1379); within cases: MLE 35.4%; CVT 26.5%; VCR vocal cord paralysis 14.2%; stroke/vasospasm 14%; severe polyneuropathy 6.1%; MTX myelopathy 2%; pseudotumor cerebri 2%	CTCAE v3.0 (G2–4);	MLE most common; CVT linked to ASNase; most during induction; 57% full recovery
Alpman et al., 2023 (53)	Sweden (Karolinska; single center)	Retrospective cohort	ALL	70	Median 4 years	NOPHO ALL-2008 / EsPhALL / infant	Anthracycline-containing chemo	During tx + early follow-up	Pericardial effusion 13.6%; intracardiac thrombosis 8.5%; hypertension 20%; reduced LVEF/LVSF during tx 0%; at follow-up 1.7%	Echo/ECG-based cardiac dysfunction (Simpson/Teichholz LVEF; GLS); no CTCAE	Cardiac dysfunction: >10% drop to LVEF <53% or LVSF <0.28; HTN >95th percentile; Early CV toxicities common; standard LVEF/LVSF monitoring may miss risk

Youssef et al., 2021 (54)	Egypt (single center)	Prospective observational pharmacogenetic	ALL	88	Mean 5.1 years	CCG / Total XV	E. coli ASNase	During ASNase therapy	Hypersensitivity 11.36%; pancreatitis 9.09%; thrombosis 6.82%	CTCAE v3.0 (G1–5);	The ATF5 C362T (TT/CT) genotype was associated with a reduced risk of pancreatitis. No assoc. with hypersensitivity/thrombosis; variant assoc. with better OS/EFS
Guo et al., 2024 (55)	China (single center)	Retrospective pharmacogenetic cohort	ALL	106	Mean/median NR	CCCG-ALL-2015	HD-MTX 3–5 g/m²	Consolidation (1st course)	≥G1: leukopenia 72%; neutropenia 50%; anemia 91.5%; thrombocytopenia 8.5%; ALT 64.2%; AST 61.3%; vomiting 6.6%; mucositis 7.5%	CTCAE v5.0; analysis ≥G1	The ABCB1 C3435T TT genotype was associated with an increased risk of leukopenia, neutropenia, and mucositis, while MTHFR variants showed no significant association.
Boonyawat et al., 2021 (56)	Thailand	Prospective cross-sectional pharmacogenetic	ALL	99	Mean 4.5 years	ThaiPOG	6-MP 50 mg/m²/day	Maintenance	Myelotoxicity by thresholds (per CBC episodes): ANC<1500 45.4%; ANC<500 5.4%; Hb<10 10.5% (Hb<8 1.5%); Plt<150k	Lab-threshold definitions (no CTCAE)	The NUDT15 c.415C>T variant was associated with lower absolute neutrophil counts (ANC). ITPA variants showed no significant association. Co-occurrence of variants was

									10.2% (<50k 1.0%)		associated with a further decrease in AN
Schmidt et al., 2021(57)	Romania	Retrospective cohort	ALL	165	Median 5 years	ALL IC-BFM 2002	Native E. coli ASNase	Induction + consolidation + DI	Any toxicity 49.7%; hypersensitivity 24.1% (among hypersensitivity: ≥G3 12.5%); hepatotoxicity 19.4% (among hepatotoxicity: ≥G3 62.5%; G5 12.5%); hypoproteinemia 9.1%; hyperTG ≥G3 6.7%; hyperglycemia ≥G3 4.2%; pancreatitis 3% (severe 40% of AAP); thrombosis 2.4%; cerebral thrombosis 1.2%; osteonecrosis 3.7%	CTCAE v5.0	No single toxicity independently affected OS/EFS; TRM 3%; age>10 hyperglycemia; age>14 osteonecrosis/hyperTG
Levinsen et al.,	Denmark / NOPHO	Retrospective analysis of	ALL	411	Median 4.5	NOPHO ALL-	HD-MTX 5 g/m² + 6-	Consolidation (HD-MTX	WBC<2×10⁹/L 34%; ANC<1×10⁹/	Lab thresholds (no CTCAE)	A total of 1,749 courses were analyzed.

2015 (58)		prospectiv e data			years	1992/2000	MP	courses).	L 52%; Plt<100×10⁹/ L 17%; ALT>3×UL N 28%		Myelotoxicity was associated with the 6-mercaptopurine (6-MP) dose, while intermediate TPMT activity was not associated with an increased risk.
Zobeck et al., 2023 (59)	USA (Texas Children's Hospital)	Retrospect ive cohort	ALL	375	Mean/m edian NR	Institutional protocols	HD-MTX 4,000–5,000 mg/m²	During HD-MTX	High-grade nephrotoxicit y rare (0.5%); delayed clearance common (36%); Delayed clearance >72 h 36.1%, >96 h 10.9%	Creatinine CTCAE v5.0;	Hispanic ethnicity and Native American ancestry ↑ risk; rs2838958 (SLC19A1) and rs7317112 (ABCC4) associated with delayed clearance
Kearney et al., 2009 (60)	USA (DFCI ALL Consortium; Boston)	Retrospect ive cohort analysis	ALL	403	Median 4.6 years (overall cohort); pancreat itis group median 7.1 years	DFCI ALL 87-01/91-01/95-01/00-01	L-asparaginas e (E. coli, PEG, Erwinia)	Induction + consolidation (20–30 weeks ASNase)	Asparaginase -associated pancreatitis. Incidence was 7% (28/403).	Lab thresholds (no CTCAE)	Age 10–18 years increased risk (OR 2.4; p<0.05). Most were hospitalized (93%), 57% required TPN, pseudocysts occurred in 18%, and recurrence after re-challenge was 63%. No pancreatitis-related mortality and no significant difference in

											long-term EFS.
van Bunningen et al., 2025 online ahead of print (61)	Sweden (national; ALLTogether vs NOPHO)	Retrospective matched cohort	ALL	345	Mean/median NR	ALLTogether vs NOPHO ALL-2008	Multi-agent; anthracyclines restricted in ALLTogether; DEXA vs pred; PEG-ASNase	Induction + consolidation 1	Infectious episode 79.5%; BSI 33.1%; sepsis 20.5%; IFD 3.3%; ICU 3.8%	Definitions for infection/FN/BSI; no CTCAE grading	Induction toxicity was higher in ALL-2008, whereas consolidation toxicity was higher in ALLTogether. Anthracycline use and age 1–9 years were associated with increased infectious toxicity. DEXA was associated with lower toxicity severity.
AML+ALL											
Linares Ballesteros et al., 2021 (62)	Colombia (HOMI; Universidad Nacional de Colombia)	Prospective descriptive cohort	ALL AML	ALL (94), AML (18)	Median age 6.3 y (ALL), 9.0 y (AML	Risk-adapted ALL (BFM-based ALL-IC); standard AML induction/consolidation	Anthracyclines (doxorubicin equivalents; cumulative dose up to 270 mg/m² in ALL and 298 mg/m² in AML)	ALL: Induction + consolidation + reinduction (≤1 year). AML: Induction + end of treatment	Early-onset cardiotoxicity occurred in 17.9% of patients and included decreased LVEF, abnormal GLS, ECG abnormalities, and pulmonary or systemic hypertension.	Echo/ECG-based cardiac dysfunction (Simpson/Teichholz LVEF; GLS); no CTCAE	ALL: Early cardiotoxicity ~14%; higher in high-risk ALL; significant LVEF decline after ≥150 mg/m²; GLS >15% predictive (OR 19.5); BNP not predictive. AML: Early cardiotoxicity 39% (7/18); LVEF decline >10% strongly predictive (OR

											42.4); significant dysfunction after 180–298 mg/m²; troponins not predictive.
Knoderer et al., 2007 (63)	USA (Indiana Univ.; Riley Hospital)	Retrospective cohort (5-year review)	ALL AML	ALL (218), AML (36)	Mean 6.8 years overall; pancreatitis group 8.8 years	Standard pediatric leukemia protocols	Asparaginase (E. coli, PEG, Erwinia)	All therapy phases	Asparaginase-associated pancreatitis 13% (33/254)	CTCAE v3.0: G1	Most cases were mild (82%, grade 1–2). Older age was associated with higher risk (p=0.001), while no association was found with cumulative dose. Time to AAP was longer with PEG-asparaginase compared to E. coli (p=0.02). Increased risk was observed with prednisone and daunomycin use. No reliable predictor was identified.
Sultana et al., 2023 (64)	Bangladesh	Case–control	ALL AML	ALL (72) AML (30) (control)	Mean 8,3 Mean 8,4	Modified UKALL 2003 MRC-12	Vincristine 1.5 mg/m²	Induction (Day 1–35) Induction	ALL: VIPN occurred in 29.2% (21/72) of patients. AML: Peripheral neuropathy was observed in 10% (3/30)	Ped-mTNS + CTCAE v4.0	ALL: Age ≥10 years significantly increased the risk (OR 6.9; 95% CI 1.9–24.4).

Hsiao et al., 2023 (65)	USA (LEARN network; Children's Hospital of Philadelphia, Children's Healthcare of Atlanta, Texas Children's Hospital)	Retrospective multicenter cohort using electronic health records	ALL and AML	ALL 963 AML 171	Mean/median NR	Standard multi-agent chemotherapy for ALL and AML	Multi-drug chemotherapy; nephrotoxic exposure during leukemia therapy	Entire frontline therapy (diagnosis through completion of chemotherapy)	Acute kidney injury (AKI), acute kidney disease (AKD), chronic kidney disease (CKD)	AKI graded using CTCAE v5.0 (creatinine increase Grades 1–4) and KDIGO stages 1–3; moderate–severe AKI defined as CTCAE Grade 2–4 or KDIGO Stage 2–3	AKI occurred in 25% of ALL and 32% of AML patients by CTCAE, but in 84% and 74% respectively by KDIGO criteria. Moderate–severe AKI was observed in 8% (ALL) and 16% (AML), while severe AKI (KDIGO stage 2–3) occurred in 50% and 43%. CRRT was required in 1% of ALL and 4% of AML. AKD without AKI occurred in 18% and 23%, and CKD was rare (~2%). The highest incidence was during induction and early chemotherapy phases.
Youssef et al., 2015 (66)	Egypt (National Cancer Institute, Cairo University)	Case series / descriptive observational study	ALL AML	ALL 8 AML 5	Mean/median NR	Standard chemotherapy protocols including intrathecal or high-dose	Methotrexate (intrathecal / high-dose)	During chemotherapy after MTX administration	Neurotoxicity (acute MTX-related leukoencephalopathy)	Not graded (clinical neurological manifestations reported)	ALL: Neurotoxicity mainly presented as seizures (75%), followed by headache

						methotrexate					(12.5%) and focal neurological deficits (12.5%). MRI showed bilateral centrum semiovale lesions with restricted diffusion. AML: Neurotoxicity manifested as headache (40%) and focal neurological deficits (40%), followed by seizures (20%) and altered mental status (20%). MRI abnormalities involved the centrum semiovale, bilateral in 60% and unilateral in 40%.
Shafey et al. (2013) (67)	Canada (The Hospital for Sick Children, Toronto)	Retrospective chart review	ALL AML	ALL 449 AML 89	Median ALL 7.0; AML 10.0	Contemporary ALL/AML chemotherapy (1999–2008)	Systemic chemo ≤30 d and/or corticosteroids ≤14 d pre-event	Mostly early therapy; ALL: induction–maintenance; AML: induction + consolidation/intensification	GI toxicity: enteritis, typhlitis, colitis, enterocolitis (radiology-defined)	Not CTCAE/WHO; diagnosis based on imaging (bowel wall thickening by US/CT/X-ray)	Incidence: ALL 33/449 (7.3%) vs AML 13/89 (14.6%). Total 51 episodes: enteritis 15.7%, typhlitis 29.4%, colitis 37.2%, enterocolitis 17.6%.

											Neutropenia at onset 74.5%; fever+neutropenia during episode 68.6%. Complications: sepsis 13.7%, obstruction 5.9%; ICU 13.7%; surgery 1 case; 2 deaths not attributed to colitis.
Erbaş et al., 2023 (68)	Türkiye (Dokuz Eylül University Children's Hospital, single center)	Retrospective cohort study	ALL AML	ALL 127 AML 26	Median 6.5 years	ALL-BFM / AML-BFM protocols	Chemotherapy-associated febrile neutropenia episodes	Induction 52.4%; consolidation 38.2%; maintenance 4.4%; reinduction 4.9%	Febrile neutropenia; bloodstream infection; viral, bacterial and fungal infections; severe complications; mortality	FN defined by standard temperature + ANC criteria; severe complications defined as oxygen requirement, hypotension/shock, inotrope need, ICU admission, or mechanical ventilation; no CTCAE grading	Fever focus was identified in 48% of FN episodes; the most common focus was bloodstream infection (16.5%), including catheter-unrelated BSI in 11.8% and catheter-related BSI in 4.7%. Other common foci were URTI (9.6%), LRTI (7.6%), UTI (5.6%), acute gastroenteritis (4.7%), and invasive fungal infection (5.8%), while more than one fever focus was present in

											5.3% of episodes. Severe complications occurred in 7.8%
AML											
Lohmann et al., 2016 (15)	NOPHO (Denmark, Sweden, Norway, Finland, Iceland) + Hong Kong	Population-based cohort (analysis of NOPHO-AML 2004 protocol)	AML	318	Median 6.4 years	NOPHO-AML 2004 (2 induction + 4 consolidation; high-dose cytarabine-based)	Multi-agent AML chemotherapy (cytarabine, anthracyclines, etoposide, mitoxantrone, fludarabine, gemtuzumab ozogamicin)	Induction + consolidation (6 courses analyzed)	Grade 3–4 toxicities occurred in **90%** of patients. The most common events were **infections (79%)** and **poor general condition (65%).** Other toxicities included **abdominal pain/constipation (28%), hypoxia (23%), bilirubin elevation (4.2%), cardiac toxicity (3.8%), hemorrhage (2.9%), renal toxicity (2.6%), thrombosis (2.2%),**	WHO criteria G3–4	Grade 3–4 toxicity occurred in 90%, mainly infections (79%); TRM was 4.6%. Age 10–17 years increased risk of sepsis with hypotension (HR 2.3) and showed a trend toward lower OS (64% vs 76%). Overweight status (>+1 SD BMI) was associated with higher oxygen requirement (HR 1.9) and severe toxicity.

									peripheral neurotoxicity (2.0%), allergic reactions (1.6%), hyperglycemia (1.3%), and central neurotoxicity (4.9%).		
Bochennek et al., 2016 (12)	Germany (AML-BFM; 37 centers)	Prospective multicenter cohort	AML	405	Mean 8.4 years	AML-BFM 2004	Intensive multi-agent chemo (cytarabine, anthracyclines, etoposide, 2-CDA)	Induction + consolidation + intensification	Fever of unknown origin 56.1%; clinically documented infections 17.5%; microbiologically documented infections 32.4%; bacteremia 71.6% of microbiologically documented infections (Gram+ 72.7%, Gram− 27.3%), invasive fungal infection 3%, ICU admission 13.6%,	EORTC/MSG criteria. Clinically/microbiologically documented infections (CTCAE not used)	There were 3.3 infectious episodes per patient. Infection-related mortality was lower than in AML-BFM 93 (1.5% vs 5.4%). Gram-positive bacteremia predominated, and invasive fungal disease was rare (3%).

									infection-related mortality 1.5%		
Getz et al., 2019 (AAML0531) (14)	USA / COG multicenter	Secondary analysis of prospective multicenter clinical trial	AML	1022	Mean 10 years	COG AAML0531 (anthracycline-based intensive chemo ± gemtuzumab ozogamicin)	Anthracyclines (daunorubicin cumulative ~300 mg/m²) ± GO	During induction + consolidation	Cardiotoxicity: ~12% overall; symptomatic LV dysfunction ~1–2%; decline in SF below protocol threshold during therapy; some therapy modifications	Echo/ECG-based cardiac dysfunction (Simpson/Teichholz LVEF; GLS); no CTCAE	Most events occurred during therapy. Cardiotoxicity associated with inferior OS. GO did not significantly increase cardiotoxicity. Higher cumulative anthracycline exposure correlated with dysfunction.
Zengin et al., 2017 (69)	Turkey (single center)	Retrospective cohort	AML	49	Mean 8.5 years	Intensive AML chemo (standard induction + consolidation)	Cytarabine + anthracyclines ± etoposide	Induction + consolidation	Infection-related mortality 14% (7/49); overall mortality during therapy 22% (11/49); Gram− infections 67.2%, Gram+ 32.7%; IFD reported (incl. fatal cases)	Clinically diagnosed; no CTCAE grading reported	High infection-related mortality without routine antibacterial/antifungal prophylaxis, Most fatal infections during induction/consolidation.

Miller et al., 2019 (70)	USA (Children's Healthcare of Atlanta/Emory)	Retrospective cohort	AML	105	Median 7 years	Conventional AML induction	Multi-agent AML induction chemo (anthracycline + cytarabine-based)	Induction (to day 42 or next cycle)	Respiratory AEs: hypoxia, pulmonary edema, pleural effusion, dyspnea, apnea, ARDS, pulmonary hemorrhage, bronchospasm	CTCAE v4.0	Respiratory adverse events occurred in 49.5%, with 90.5% being grade 3–5. Fluid overload was strongly associated (<10 days aHR 5.46; ≥10 days aHR 13.0), as was infection lasting ≥10 days (aHR 14.9). Induction mortality was 4.8%, mainly due to ARDS or hypoxia with infection.
Creutzig et al., 2006 (11)	Germany/Austria/Switzerland/Czech Republic (75 centers)	Multicenter randomized phase III trial	AML	473	Mean/median NR	AML-BFM 98 (AIE → HAM → consolidation ± G-CSF → maintenance)	Cytarabine + idarubicin + etoposide; HAM (HD Ara-C + mitoxantrone); ± G-CSF	Induction, intensification, consolidation	Severe infections = G3–4; early death ≤42 days Early death 3.2%, severe infections (G3–4) 40% vs 28% in consolidation comparison (P=0.02), bleeding (G3–4) 31% vs 17% (P=0.007), severe infections	Modified NCI CTCAE v3.0	Short-cycle consolidation reduced treatment duration and trended to fewer toxic deaths. G-CSF shortened neutropenia but not severe infections. HAM did not improve survival but acceptable toxicity.

									with/without G-CSF 41.1% vs 37.7% (NS)		
Yeoh et al., 2021 (71)	Australia (TERIFIC multicenter)	Retrospective multicenter cohort	AML	63	Median 11.7 years	COG AAML0531 / AAML1031	Intensive AML polychemo (anthracycline-based)	Mainly during primary AML therapy (75.8%); 38% during first cycle	Invasive fungal disease (IFD): 23 proven, 13 probable, 30 possible (66 IFD episodes); moulds incl. non-Aspergillus, Candida spp.	EORTC/MSG criteria. Clinically/microbiologically documented infections (CTCAE not used)	High IFD prevalence despite prophylaxis (overall 20.7%; proven/probable during primary AML 10.3%). Early onset common; highest mortality with Lomentospora prolificans. All-cause 6-month mortality 16.7%, IFD-related 7.6%.
O'Brien et al., 2002 (72)	Australia & New Zealand (ANZCCSG)	Two consecutive single-arm trials (non-randomized comparison across consecutive protocols, 1986–1999)	Pediatric AML (incl. APL/M3)	262 evaluable	Median age: 6.3 y (Group 1) vs 7.0 y (Group 2)	ANZCCSG AML I (daunorubicin in induction/early consolidation) vs AML 2 (idarubicin in induction/early consolidation);	Anthracycline choice during induction/early consolidation: daunorubicin vs idarubicin (10 or 12 mg/m²) with Ara-C–based backbone (Group 1	Remission induction (courses 1–2; toxicity assessed after induction)	Non-hematologic grade 3–4: GI, renal, pulmonary, cardiac toxicity, infections	Toxicity graded by Children's Cancer Group toxicity and complications criteria, reported as Grades 3–4	Induction remission rates were high in all groups (≈95% with daunorubicin vs ≈91% with idarubicin). Idarubicin was associated with higher grade 3–4 toxicity (GI 25% vs 4.9%; renal 4.4% vs 0%; lung 9.4% vs 3%), while infections were less

							daunorubicin n=102; Group 2 idarubicin n=160; subgroup: 10 mg/m² n=106; 12 mg/m² n=53)				frequent (16.3% vs 28%). The higher idarubicin dose (12 mg/m²) resulted in more grade 3–4 GI toxicity (43% vs 16% at 10 mg/m²). No significant OS or EFS benefit was observed with idarubicin.
Ávila Montiel et al., 2023 (73)	Mexico (tertiary hospital)	Retrospective cohort	AML	36	Mean 9 years	Modified NOPHO AML-93	Anthracycline + cytarabine-based chemo	All phases	IFD: 15/129 infectious events (11.6%), patients with IFD 13/36, IFD mortality 15.3% (2/13), Aspergillosis 7, candidemia 4, mean neutropenia 21 days	EORTC/MSG criteria (CTCAE not used)	IFD incidence was higher than in international reports. Prolonged neutropenia was the main risk factor, and antifungal prophylaxis was inconsistent. IFD directly caused death in two patients.
Temming (2011) (74)	United Kingdom (single center)	Retrospective cohort	AML	124	Mean 2.9 years	MRC AML10 / AML12	Anthracyclines (550–610 mg/m² DNR-equivalent) ± amsacrine	During therapy + follow-up	Early cardiotoxicity 13.7%, late cardiotoxicity 17.4%, clinical cardiomyopathy ~6.5% (8/124), cardiac mortality	Echo/ECG-based cardiac dysfunction (Simpson/Teichholz LVEF, GLS), no CTCAE	Early cardiotoxicity strongly predicted late cardiotoxicity (OR 9.18). Higher treatment intensity increased risk. Subclinical dysfunction often

									1.6% (2 cases)		resolved, but some patients required long-term therapy. Two deaths were attributed to cardiomyopathy.
Dix D. et al., 2012 (13)	Canada (15 centers)	Retrospective population-based cohort	AML	341	Median 7.1 years	POG/CCG/MRC-based	Cytarabine-based chemo ± corticosteroids	All chemotherapy courses	Sterile-site microbiologically documented infection: 24.5% of courses, sepsis 7.6% of courses, infectious death 1.3% of courses, patient-level cumulative incidence: any sterile-site infection 63.9%, bacteremia 54.3%; clinically documented infection 77.1%, proven IFI 38 cases	EORTC/MSG criteria (CTCAE not used)	Across 1,277 courses, longer systemic corticosteroid exposure independently increased the risk of sterile-site infection, bacteremia, Gram-positive and Gram-negative infection, fungal infection, sepsis, and infectious death. Steroid duration was the only significant predictor of infectious mortality (OR 1.05 per day; p=0.001).
Sung et al., 2007 (16)	USA/Canada (COG)	Prospective cohort within phase III	AML	492	Mean 9.6 years	CCG 2961 (IdaDCTER ± fludarabine)	Cytarabine + anthracyclines ±	Induction + consolidation + intensification	Microbiologically documented infection >60% per	Clinically diagnosed; no CTCAE grading reported	Infections were extremely common, and fungal infections were a major

		trial					fludarabine		phase, Gram+ 39–50%, Gram− 18–28%, fungal 14–21% per phase, IRM 11% ±2%, infectious deaths 58, Aspergillus deaths 31%, Candida 25.9%		contributor to mortality. Predictors of infection-related mortality included age >16 years, nonwhite ethnicity, and underweight BMI. Polymicrobial infections were frequent among fatal cases.
Sun (2018) (75)	USA (St. Jude, single center)	Retrospective cohort	AML	111	Mean 8.6 years	AML02	IV vancomycin prophylaxis vs none	Post-induction neutropenic courses	Nephrotoxicity (pRIFLE): Risk 48.5%, Injury 11.2%, Failure 0.5%, hepatotoxicity (CTCAE): ≥G1 53.4%, ≥G2 14.7%, ≥G3 5.4%; CDI 0.9% vs 6.5% (p=0.007)	AKI per pRIFLE; hepatotoxicity per CTCAE v4.03;	Vancomycin prophylaxis did not increase nephrotoxicity or hepatotoxicity and significantly reduced CDI. There was no increase in severe renal failure, and most toxicities were mild to moderate.
Wen (2024) (76)	China (multicenter)	Prospective clinical cohort	AML	45	Mean 9.3 years	CCLG-AML 2019	Venetoclax (≤200 mg/m²/day) + cytarabine ± homoharringtonine or HMA	Induction (Day 1–28)	Hematologic: G4 neutropenia 100%, leukopenia 64.4%, thrombocytopenia 64.4%, G3 anemia 93.3%. Febrile	NCI-CTCAE v4.03; AE	Hematologic toxicity was universal. Infections and febrile neutropenia were extremely common but mostly grade 3. Tumor lysis syndrome

									neutropenia 97.8% (G3). Infections 97.8% (G3 93.3%, G4 4.4%). TLS 24.4% (all G3). Pancreatitis 6.7% (G3), renal toxicity 6.7% (G3), DIC G3–4 11.1%, Grade 5: 0%		occurred in 24.4% with no grade 4–5 events. There were no treatment-related deaths, and toxicity was manageable in the context of a high response rate.
Du Plessis et al., 2017 (77)	Canada (British Columbia Children's Hospital)	Retrospective cohort	Pediatric AML	53	Median 9.1 years	COG AML protocols AAML03P1, AAML0531, AAML1031	Multi-agent chemotherapy including cytarabine-based regimens; exposure to nephrotoxic drugs (vancomycin, aminoglycosides, amphotericin B)	Induction cycles 1–2 and intensification cycle 3	AKI occurred in 64.2% (34/53) of patients.	AKI defined using KDIGO criteria based on serum creatinine increase; severe AKI = KDIGO stage 2–3; urine output not included	Severe AKI in 43% (23 patients) with 24 severe episodes. Total 46 AKI episodes across chemotherapy cycles. Mean duration of severe AKI 26.1 days. Older age ≥10 years strongly associated with AKI (OR 12.39) and severe AKI (OR 20.75). Severe sepsis was an independent risk factor during induction (OR 13.38).

Fisher et al., 2010 (78)	USA (PHIS database; 37 children's hospitals)	Retrospective national database cohort (PHIS)	Pediatric AML	831	Median 9.14 years	AML induction chemotherapy regimens identified from inpatient chemo patterns	Nephrotoxic anti-infectives exposure (vancomycin, aminoglycosides, amphotericin B products, antivirals) + carbapenems severity-of-illness proxies	Any hospitalization within 1 year from AML diagnosis	ARF incidence: 16.2% (135/831) within 1 year.	ARF defined by presence of ICD-9-CM ARF code during hospitalizatio. CTCAE grading not available	ARF occurred early in 56.3% of cases and was associated with higher in-hospital mortality (30% vs 10.1%). Older age, Black race, and prolonged vancomycin or carbapenem use increased ARF risk.
Lin et al., 2018 (79)	Taiwan (National Taiwan University Hospital, single center)	Retrospective chart review / single-center cohort	AML	78	Median 9.9 years	Taiwan Pediatric Oncology Group protocols	Intensive AML chemotherapy; anti-infective exposure in context of neutropenia (not a single drug-specific toxicity study)	Across chemotherapy courses before HSCT; induction, post-remission, salvage, and palliative phases	22 IFI episodes occurred in 16/78 patients; overall IFI incidence 20.5%, proven/probable IFI 11.5%. Candida spp. caused 59.1% of IFIs;	EORTC/MSG 2008 criteria: proven, probable, possible IFI	prolonged neutropenia, elevated ALT/creatinine, endotracheal intubation, and inotrope use were associated with IFIs. Overall IFI mortality was 53%, with highest mortality in pulmonary aspergillosis (80%).
Lehrnbecher et al., 2004 (80)	Germany (AML-BFM 93; 30 centers)	Retrospective analysis of a prospectiv	AML	304	Median 5 years 10 months	AML-BFM 93	Intensive multi-agent AML chemothera	Intensive treatment phases: induction, consolidation,	304 patients experienced 855 infectious episodes (2.8	No CTCAE grading; infections classified as FUO / clinically	Bloodstream infections were most common, predominantly Gram-positive,

		e multi-institutional clinical trial					py	HAM, HAE	per patient): 61.2% FUO, 6.7% clinically documented, and 32.1% microbiologically documented. Neutropenia was present in 74.1% of episodes.	documented / microbiologically documented; proven, probable, possible IFI	while pneumonia occurred in 13.3% of episodes. Proven/probable invasive fungal infection was identified in 15 patients. Infection-related mortality was 6.6% (20/304), higher in children with Down syndrome (17.9% vs 5.4%), with most deaths occurring during early induction.