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Review

Evolving Infection Risk and Management in Acute Leukemia in the Era of Modern Antileukemia Therapy

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Abstract

Background: Infectious complications remain the leading cause of morbidity and treatment-related mortality in patients with acute leukemia. Over the past two decades, the treatment of acute leukemia has shifted from conventional intensive chemotherapy toward targeted agents, antibody–drug conjugates, bispecific antibodies, and CAR T-cell therapies. These advances have substantially changed the epidemiology, spectrum, and mechanisms of infection. **Methods:** This review synthesizes evidence from pivotal clinical trials, real-world observational studies, and clinical practice guidelines. We evaluated infection-related adverse events reported in clinical trials of novel agents, including venetoclax, FLT3 and IDH inhibitors, bispecific T-cell engagers, CAR T-cell therapies, and menin inhibitors. We also reviewed real-world evidence on antimicrobial resistance, drug–drug interactions, and prophylactic strategies. **Results:** Infection risk in acute leukemia was historically dominated by prolonged neutropenia, mucosal barrier injury, and invasive fungal disease. Subsequent advances in supportive care were accompanied by increasing antimicrobial resistance and the introduction of targeted therapies, which began to alter infection patterns. More recently, novel therapies have further changed the nature of infectious risk. The focus has shifted from neutropenia alone to treatment-specific immune defects, including prolonged cytopenias, B-cell depletion, hypogammaglobulinemia, and viral reactivation. Differentiation syndrome and cytokine release syndrome may also resemble infection and complicate diagnosis. Real-world studies often report higher infection rates than pivotal trials, particularly among older patients and those with comorbidities. **Conclusions:** Infection risk in acute leukemia is no longer determined by neutropenia alone. It has become a therapy-specific challenge that requires mechanism-based risk stratification and individualized prophylaxis. Better adverse event reporting, careful management of drug–drug

interactions, and sustained immune support may help reduce infectious complications and improve treatment outcomes.

Key words: Acute leukemia; infectious complications; febrile neutropenia; targeted therapy; immunotherapy; antimicrobial prophylaxis; invasive fungal disease.

1. Introduction

Acute leukemia, encompassing acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), is characterized by uncontrolled proliferation of immature hematopoietic cells and severe immunosuppression (1). Infections complicate over 80% of acute leukemia treatments and account for 30-50% of treatment-related deaths, making them a critical determinant of clinical outcomes (2).The global burden of acute leukemia has remained substantial over the past decades. According to the Global Burden of Disease Study 2021, there were approximately 145,000 new cases of AML and 104,000 new cases of ALL worldwide in 2021 (3). In parallel, the case-fatality rate attributable to infectious complications has declined, partly driven by improved supportive care, the introduction of targeted therapies, and more effective empirical antifungal strategies that have substantially reduced mortality from invasive fungal complications in patients (Table 1) (4). However, this progress has been uneven across different patient populations. Elderly patients (aged ≥60 years) face a substantially higher risk of early death, with reported 60-day mortality rates of 41% during induction chemotherapy compared to lower rates in younger adults. This age-related disparity underscores the need for age-specific risk stratification and prophylactic approaches (5).

Before 2010, intensive chemotherapy regimens such as the "7+3" induction with cytarabine and anthracycline for AML and multi-agent chemotherapy for ALL defined the standard of care. Infection risk during this period was primarily driven by profound and prolonged neutropenia, mucosal damage, and central venous catheter-related infections, with bacterial bloodstream infections and invasive fungal diseases as the most common life-threatening complications. The decade 2010-2020 marked the emergence of targeted therapies and refined supportive care. While antimicrobial stewardship and risk-stratified prophylaxis improved outcomes, antimicrobial resistance, Clostridioides difficile infection, and drug-drug interactions with antifungals became major challenges (6,7). Since 2020, the acute leukemia treatment landscape has been revolutionized by venetoclax-based combinations, FLT3/IDH inhibitors, bispecific antibodies such as blinatumomab, antibody-drug conjugates like inotuzumab ozogamicin, CAR-T cells, and menin inhibitors. These agents have improved survival but have also reshaped infectious risk with neutropenia-independent immune defects, hypogammaglobulinemia, viral reactivation, and catheter-related infections becoming more prevalent (2,8,9).

The temporal boundaries of this review are not arbitrary but reflect pivotal regulatory approvals that redefined treatment paradigms. The year 2000 marked the widespread adoption of the "7+3" induction regimen as the global standard. The year 2010 witnessed the publication of the first major posaconazole prophylaxis trial and the initial clinical evaluation of FLT3 inhibitors in patients with AML. The year 2020 represents a watershed moment with the FDA approval of venetoclax for frontline AML, followed by the rapid expansion of CAR-T cell indications and bispecific antibodies for ALL. Each era thus carries distinct infection risk profiles that practicing clinicians must recognize to optimize

Table 1. Evolution of infectious complications in hematologic malignancies across treatment eras

Dimension	2000-2010 (Intensive Chemotherapy Era)	2010-2020 (Early Targeted Therapy Era)	2020-Present (Modern Immunotherapy/Cellular Therapy Era)
Core Immuno-deficiency Mechanisms	Severe neutropenia (10-14 days) + mucosal barrier damage + catheter-related immune impairment	Neutropenia + gut microbiota dysregulation + mild immunomodulation by early targeted agents	Specific immunodeficiency profiles: prolonged myelosuppression, B-cell depletion, T-cell dysfunction, prolonged immune reconstitution defects
Distribution of Major Infection Types	Bacteria 60-70%, Fungi 10-15%, Viruses 10-15%	Bacteria 55-65%, Fungi 8-12%, Viruses 15-20%, CDI 5-8%	Bacteria 40-50%, Viruses 20-30%, Fungi 10-20%, Treatment-related syndromes (DS/CRS) 10-15%
Leading Cause of Fatal Infection	Invasive aspergillosis (mortality 30-50%)	CRE sepsis (mortality 40-60%)	Delayed fungal infections post-CAR-T, CMV pneumonia, disseminated viral infections
Evolution of Key Pathogens	Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa), Aspergillus, Candida	ESBL-producing Enterobacterales, CRE, MRSA, Clostridioides difficile	Herpesviruses (HSV/VZV/CMV), Pneumocystis jirovecii, Candida auris, drug-resistant Aspergillus
Key Management Challenges	Early empiric antimicrobial therapy, difficulty in early fungal diagnosis	Antimicrobial resistance, drug-drug interactions (DDIs), insufficient implementation of TDM	Differentiation between infection and DS/CRS, prolonged hypogammaglobulinemia, tolerance in elderly patients
Standard Prophylaxis Strategies	Fluoroquinolone antibacterial prophylaxis + posaconazole antifungal prophylaxis (post-2007)	Risk-stratified prophylaxis + posaconazole TDM (trough concentration > 0.7μg/mL) + antimicrobial stewardship	Individualized prophylaxis + viral prophylaxis + IVIG replacement therapy + early recognition of treatment-related syndromes
Infection-related Mortality Rate	30-50% (overall); > 50% in elderly patients	25-35% (overall); 35-40% in elderly patients	20-30% (overall); > 40% in patients ≥75 years old

Abbreviation CDI: Clostridioides difficile Infection. DS: Differentiation Syndrome. CRS: Cytokine Release Syndrome. ESBL: Extended-spectrum β-lactamase. MRSA: Methicillin-resistant Staphylococcus aureus. TDM: Therapeutic Drug Monitoring. IVIG: Intravenous Immunoglobulin. HSV: Herpes Simplex Virus. VZV: Varicella-Zoster Virus. CMV: Cytomegalovirus.

patient management. Serious of important reviews have summarized contemporary practices for febrile neutropenia (FN), fungal prophylaxis, and targeted therapy-associated infections. However, recent phase III trials, real-world studies, and novel agents such as revumenib published through 2026 require an updated synthesis. This review provides a comprehensive analysis of 26 years of infection risk evolution in AL, integrating pivotal clinical trial data, mechanism-based risk stratification, and modern management strategies.

2. Before 2010: The Intensive Chemotherapy Era-Baseline Infection Risk and Foundational Management

2.1 Mechanisms of Infection Risk

Before 2010, infection risk in acute leukemia was governed by three interrelated factors: quantitative and qualitative neutrophil deficiency, as AML induction chemotherapy induced 10-14 days of severe neutropenia ($<0.5\times10^9$/L), impairing phagocytosis and bacterial/fungal killing, while ALL was characterized by combined neutropenia and lymphopenia, exacerbating immune dysfunction; additionally, mucosal barrier disruption, whereby chemotherapy-induced oral, gastrointestinal, and respiratory mucositis facilitated enteric bacterial translocation and fungal colonization, increasing bloodstream infection risk, and the integrity of the gut microbiome was severely compromised, allowing commensal organisms to invade systemic circulation, particularly during prolonged neutropenia (10); furthermore, iatrogenic immunosuppression, as indwelling venous catheter, broad-spectrum antibiotics, and corticosteroids further increased catheter-related bloodstream infections and opportunistic infections, with venous catheter becoming a persistent nidus for bacterial colonization while prolonged steroid use suppressed cellular immunity (11).

Beyond these three core mechanisms, emerging evidence highlights the role of genetic susceptibility in infection risk among acute leukemia patients. Polymorphisms in genes regulating innate immunity, such as Toll-like receptor pathways and nucleotide-binding oligomerization domain-containing protein 2, have been associated with increased susceptibility to bacterial sepsis during neutropenia. Similarly, variations in the dectin-1 and FCGR genes modulate the risk of invasive fungal infections. Although routine genetic screening for infection susceptibility is not yet clinically implemented, these findings suggest that host genetics may explain a portion of the interpatient variability in infection outcomes beyond traditional clinical risk factors. Although routine genetic screening is not currently recommended, these polymorphisms may help identify high-risk patients for targeted prophylactic strategies in future personalized medicine approaches. Concurrently, growing evidence has underscored the role of intestinal microecology in modulating infection susceptibility and treatment-related complications in patients with hematological malignancies, with emerging Chinese expert consensus providing standardized frameworks for microbiome assessment and intervention (12-14).

2.2 Infection Spectrum

2.2.1 Acute Myeloid Leukemia

Infectious complications mainly fall into three categories. Bacterial infections account for the highest proportion (60%-70%), with pathogens predominantly being Gram-negative organisms including E.coli, K.pneumoniae, and P.aeruginosa, which can cause bloodstream infections, pneumonia, and perianal sepsis; antibiotic resistance is a prominent issue, often leading to failure of first-line therapy. Invasive fungal diseases account for approximately 10%-15%, with Aspergillus and Candida species being the most common, and invasive aspergillosis is the leading cause of infection-related death during neutropenia, while its early diagnosis remains extremely difficult. As for viral infections, reactivation of herpes simplex virus and varicella-

zoster virus occurs in 10%-15% of cases, mostly seen in patients with prolonged neutropenia (2), and these complications frequently result in delays to chemotherapy scheduling.

An additional emerging concern during this era was the rising prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae. By the late 2000s, ESBL-producing E.coli and K.pneumoniae accounted for 15-20% of all Gram-negative bloodstream infections in acute leukemia patients in many tertiary care centers, severely limiting the efficacy of standard empiric regimens such as cefepime or piperacillin-tazobactam. This forced the increased use of carbapenems as empiric therapy, which in turn drove the selection of carbapenem-resistant organisms in subsequent years. The emergence of ESBL producers during this era set the stage for the multidrug-resistance crisis that would dominate the next decade.

2.2.2 Acute Lymphoblastic Leukemia

ALL exhibited a broader infectious spectrum due to combined B and T cell dysfunction, with bacterial infections such as Streptococcus pneumoniae and Staphylococcus aureus being predominant and associated with higher rates of pneumonia compared with AML, while encapsulated bacteria were more virulent in hypogammaglobulinemic patients. Invasive fungal diseases occurred in 8-12% of cases, which was less frequent than in AML, but the risk of Pneumocystis jirovecii pneumonia (PJP) was elevated by corticosteroids and asparaginase2, and PJP was associated with high mortality without prophylaxis. Viral infections were also common, with Epstein Barr virus and cytomegalovirus (CMV) reactivation driven by impaired cell-mediated immunity, and CMV reactivation often required prolonged antiviral therapy.

A distinctive feature of ALL-associated infections during 2000-2010 was the high rate of invasive fungal sinusitis, particularly in patients receiving prolonged courses of high-dose corticosteroids as part of anti-leukemic or anti-graft-versus-host disease therapy. Aspergillus and Rhizopus species were the predominant pathogens, with mortality rates exceeding 50% in cases of disseminated disease. The diagnostic challenge posed by fungal sinusitis-often presenting with nonspecific symptoms such as facial pain or nasal congestion-led to delays in antifungal therapy, highlighting the need for a high index of suspicion and low threshold for radiographic imaging in ALL patients with prolonged corticosteroid exposure.

2.3 Foundational Management Strategies

2.3.1 Febrile Neutropenia

Febrile neutropenia, defined as a single temperature of at least 38.3°C or a persistent temperature of at least 38°C for one hour with neutropenia, occurred in over 80 percent of acute leukemia patients during chemotherapy. Empiric broad-spectrum antibiotics such as cefepime and piperacillin-tazobactam were standard. By the late 2000s, early de-escalation (48-72 hours) in clinically stable patients without documented infection became accepted to reduce antimicrobial exposure and resistance risk.

The choice of initial empiric antibiotic regimen during this era was guided by local epidemiology and patient-specific risk factors. For patients with high-risk features, including prior fluoroquinolone prophylaxis, known colonization with resistant organisms, or hemodynamic instability, combination therapy with an antipseudomonal beta-lactam plus an aminoglycoside such as gentamicin or tobramycin or a second anti-Gram-negative agent like ciprofloxacin was often employed. However, the addition of vancomycin was reserved for patients with suspected catheter-related infections, severe mucositis, or known methicillin-resistant Staphylococcus aureus (MRSA) colonization, as routine vancomycin use was discouraged to prevent the emergence of vancomycin-resistant enterococci. This risk-stratified approach to empiric therapy represented a major advance over the uniform strategies of the 1990s.

2.3.2 Antifungal Prophylaxis: The Posaconazole Breakthrough

A landmark 2007 New England Journal of Medicine randomized controlled trial established posaconazole as the gold-standard antifungal prophylaxis for AML patients undergoing induction chemotherapy. Posaconazole reduced invasive fungal diseases incidence to 2% versus 8% with fluconazole/itraconazole and improved overall survival. Posaconazole's broad spectrum (activity against Aspergillus, Candida, Fusarium, Mucorales) made it the preferred agent, while fluconazole and itraconazole were phased out due to limited mold activity (2).

3. 2010-2020: Refined Supportive Care and the Rise of Antimicrobial Resistance

3.1 Evolving Infection Challenges

The 2010-2020 era was defined by supportive care optimization and emerging resistance threats, including the fluoroquinolone prophylaxis controversy, as fluoroquinolones reduced FN and bloodstream infections but drove 30-50% fluoroquinolone resistance and increased Clostridioides difficile infection risk, leading guidelines to restrict routine use to high-risk AML induction patients, while Clostridioides difficile infection became a major complication requiring prolonged oral therapy. Additionally, fungal prophylaxis individualization became a key focus, whereby posaconazole remained standard for AML but CYP3A4 inhibition complicated co-administration with chemotherapy and early targeted agents, and therapeutic drug monitoring with a trough target above 0.7 µg/mL became recommended for obese or malabsorbing patients , although poor adherence often reduced efficacy. Furthermore, the rise of multidrug-resistant pathogens, including carbapenem-resistant Enterobacterales (CRE) and MRSA infections, further limited empiric therapy options , with CRE infections having mortality rates exceeding 50%.

The rising tide of antimicrobial resistance during 2010-2020 was driven by multiple interconnected factors. The widespread use of fluoroquinolone prophylaxis in high-risk AML patients created selective pressure, leading to the dominance of fluoroquinolone-resistant E. coli strains within the gut microbiome. Additionally, the increasing use of carbapenems for empiric therapy of febrile neutropenia-driven by the high prevalence of ESBL producers-promoted the emergence of carbapenem-resistant organisms, including CRE and carbapenem-resistant P. aeruginosa. Furthermore, the limited development of new antibiotics targeting multidrug-resistant Gram-negative pathogens left clinicians with few therapeutic options once resistance emerged. By 2018, CRE bloodstream infections carried an attributable mortality of 40-60% in leukemia patients, underscoring the urgent need for antibiotic stewardship and novel antimicrobial development (15).

In response to the rising threat of multidrug-resistant pathogens, several management strategies have been adopted in high-risk leuekmia patients. For institutions with CRE prevalence exceeding 10% among Gram-negative bloodstream isolates, empiric therapy for FN may include two antipseudomonal agents from different classes such as a beta-lactam plus an aminoglycoside or a fluoroquinolone, or the addition of a polymyxin or tigecycline when CRE is suspected (16). For MRSA, while routine vancomycin use is discouraged, pre-emptive addition should be considered in patients with severe mucositis, hemodynamic instability, known MRSA colonization, or radiographic evidence of necrotizing pneumonia17. Antimicrobial stewardship programs play a critical role by providing center-specific antibiograms updated quarterly, which guide empiric therapy selection and facilitate early de-escalation once culture results are available (17). The development of rapid molecular diagnostic platforms such as multiplex PCR panels for blood cultures has reduced time to targeted therapy from 48-72 hours to 4-6

hours, representing a major advance in the management of multidrug-resistant infections in this vulnerable population (18).

3.2 Early Targeted Therapies and Infection Risk

By the late 2010s, the first wave of targeted agents entered clinical practice, altering infection patterns: FLT3 inhibitors (midostaurin): Added to induction chemotherapy for FLT3-mutated AML, midostaurin did not increase invasive fungal diseases risk but required posaconazole therapeutic drug monitoring due to CYP3A4-mediated interactions. Dose adjustments were critical; BCR-ABL tyrosine kinase inhibitors: Imatinib, dasatinib, and nilotinib for Philadelphia chromosome-positive (Ph+) ALL were associated with modest bacterial infection risk and CMV/hepatitis B virus (HBV) reactivation, particularly with dasatinib. HBV reactivation could be fatal.

4. 2020-present: The Modern Era-Targeted, Immune, and Cellular Therapy-Associated Infections

Since 2020, transformative therapies have redefined acute leukemia treatment and infection risk. Infection patterns have shifted from neutropenia-driven to immune-defect-specific, with distinct profiles for each agent class (2).

4.1 Venetoclax-Based Therapy: High Infection Risk from Sustained Cytopenia and Drug Interactions

Venetoclax, a BCL-2 inhibitor, combined with hypomethylating agents such as azacitidine or decitabine became first-line for older or unfit AML patients. The phase III VIALE-A trial involving 431 patients published in 2020 reported grade 3 or higher FN in 30% of those receiving venetoclax plus azacitidine compared to 10% with azacitidine alone, with pneumonia and sepsis as common severe adverse events. Key infection mechanisms include: prolonged myelosuppression, as venetoclax induces sustained cytopenias beyond traditional chemotherapy, with median ANC recovery delayed by 2-3 weeks (19); host vulnerability, because older AML patients have age-related immune senescence, impaired mucosal immunity, and frequent comorbidities (20); and CYP3A4 interactions, whereby strong CYP3A4 inhibitors such as posaconazole increase venetoclax exposure by 5-10 fold, requiring 50-75% dose reduction, and inadequate dose adjustment increases toxicity (21).

Real-world evidence from multicenter observational studies has substantially expanded our understanding of venetoclax-associated infection risk. A retrospective analysis of older AML patients treated with venetoclax-azacitidine across multiple centers reported a 5.6% incidence of proven or probable invasive fungal infections, a 33.6% incidence of documented bacterial infections, and a 54% rate of hospital admission for febrile neutropenia (22). Multivariable analyses have identified key predictors of infection risk, including the use of interacting concomitant medications, which was associated with a nearly tenfold increased risk (odds ratio 9.99, 95% confidence interval 3.18 to 31.45), and longer duration of neutropenia (23). These data suggest that the real-world infection burden of venetoclax-based therapy is substantial, particularly in patients with prolonged neutropenia or those receiving interacting concomitant medications. ECIL guidelines recommend antibacterial + systemic antifungal prophylaxis for venetoclax and hypomethylating agents combinations, with azole selection guided by CYP3A4 interaction risk (2).

4.2 FLT3 Inhibitors: Infection Risk Confounded by Chemotherapy Backbone

Gilteritinib (ADMIRAL trial, n=371,2019) and quizartinib (QuANTUM-First trial, n=539,2023) improved outcomes in FLT3-mutated AML but were associated with high infection rates in trial cohorts: Gilteritinib (relapsed/refractory AML): Grade ≥3 FN occurred in 45.9%, with pneumonia

and sepsis common (24). Relapsed disease increased baseline risk; Quizartinib + chemotherapy (frontline AML): Grade 3/4 FN occurred in 43%, pneumonia in 11%. Intensive chemotherapy amplified risk; FLT3 inhibitor-associated infections are platform-driven, attributable to intensive chemotherapy, prolonged cytopenia, and QT-prolonging effects that complicate azole co-administration (24,25). Whether these agents exert direct immunomodulatory effects beyond myelosuppression remains an area of active investigation (26).

4.3 IDH Inhibitors: Mild Infection Risk with Differentiation Syndrome Mimicry

Ivosidenib (IDH1) and enasidenib (IDH2) are oral agents for mutant IDH AML. Trials show no clear increase in infection risk, but a critical clinical challenge is differentiation syndrome (DS), which presents with fever, pulmonary infiltrates, and dyspnea-mimicking bacterial/fungal pneumonia2. Distinguishing differentiation syndrome from infection is essential to avoid unnecessary antibiotics/antifungals. Key distinguishing features include: rapid response to corticosteroids (typically within 24-48 hours), absence of microbiologic evidence of infection, and the frequent association with peripheral blood leukocytosis due to differentiation of blasts (27). DS occurs in 10-15% of patients, requiring prompt corticosteroids.

4.4 Menin Inhibitors: Emerging Infections in KMT2A-Rearranged Leukemia

Revumenib, the first menin inhibitor, received FDA breakthrough designation for KMT2A-rearranged acute leukemia in 2024. Phase I/II data (AUGMENT-101 trial, n=126,2025) reported infections (24%), FN (19%), bacterial infections (17%), and differentiation syndrome (12%) as common adverse events28. Menin inhibitor-related infections reflect targeted myelosuppression and overlapping DS/infection phenotypes, mirroring IDH inhibitor challenges (28).

4.5 ALL-Targeted Immunotherapies: B-Cell Depletion and Hypogammaglobulinemia

4.5.1 Blinatumomab (CD19/CD3 Bispecific Antibody)

Blinatumomab for relapsed/refractory B-ALL reduced chemotherapy-related mucositis and FN but induced B-cell aplasia and hypogammaglobulinemia, increasing risk of herpesvirus reactivation, PJP, and catheter-related infections (2). Guidelines recommend acyclovir prophylaxis for herpesvirus prevention, PJP prophylaxis, and intravenous immunoglobulin (IVIG) replacement therapy for patients with recurrent infections or significant hypogammaglobulinemia (29). Hypogammaglobulinemia may persist for 6 to 12 months following blinatumomab therapy.

4.5.2 Inotuzumab Ozogamicin (CD22 Antibody-Drug Conjugate)

The INO-VATE trial (n=326,2017) showed lower FN rates with inotuzumab versus standard chemotherapy (27% vs 52%) but higher hepatic veno-occlusive disease risk (13-14% vs <1%), which indirectly impairs post-transplant infection management. Routine antimicrobial prophylaxis is not recommended, but HBV screening is mandatory (30). Veno-Occlusive Disease /Sinusoidal Obstruction Syndrome increases infection risk post-transplant.

4.6 CAR-T Cell Therapy: Long-Term Immune Reconstitution Defects

CD19 CAR-T cells have revolutionized relapsed/refractory B-ALL but carry unique infectious risks spanning early (≤30 days) and late (>30 days) phases (Table 2). Early infections, including bacterial sepsis, are related to lymphodepleting chemotherapy and cytokine release syndrome (CRS)-induced immune dysregulation, with CRS-grade ≥3 increasing infection risk by 2- to 3-fold (31), while late infections, such as invasive fungal diseases, PJP, and persistent

Table 2. Infectious risks and prophylaxis for targeted and cellular therapies in hematologic malignancies.

Drug Class	Representative Agent	Grade ≥3 Infection Rate (Clinical Trial/Real-World)	Core Infection Type	Recommended Prophylaxis Strategy	Special Consideration
BCL-2 Inhibitors	Venetoclax + HMA	FN: 30%/58%; IFD: 2%/22%	Pneumonia, sepsis, invasive fungal disease, CMV reactivation	Antibacterial + systemic antifungal prophylaxis; Acyclovir antiviral prophylaxis	Reduce venetoclax to 100mg/day when co-administered with strong CYP3A4 inhibitors (posaconazole); simultaneous TDM of both agents is required
FLT3 Inhibitors	Gilteritinib	FN: 45.9%; Pneumonia: 15%	Sepsis, pneumonia, neutropenia-related infections	Standard chemotherapy prophylaxis; no additional enhanced antifungal prophylaxis recommended	Avoid co-administration with QT interval-prolonging drugs; dose adjustment and QTc monitoring are required when used with azoles
	Quizartinib + Chemotherapy	FN: 43%; Pneumonia: 11%			
IDH Inhibitors	Ivosidenib / Enasidenib	<10% (no significant increase)	Mild bacterial infections; DS	No routine enhanced prophylaxis required; basic Acyclovir prophylaxis	DS symptoms highly overlap with infection; empirical broad-spectrum antibiotics are contraindicated; Dexamethasone is first-line treatment for DS
Menin Inhibitors	Revumenib	Total infections: 24%; FN: 19%; DS: 12%	Bacterial infections, DS	Basic chemotherapy prophylaxis	Same as IDH inhibitors; critical to differentiate DS from infection
Bispecific Antibodies	Blinatumomab	Total infections: 34%/52%; CMV reactivation : 6%/18%	Herpesvirus reactivation, PJP, catheter-related infections	Acyclovir + Trimethoprim-Sulfamethoxazole (TMP-SMX) prophylaxis; IVIG for recurrent infections	B-cell depletion persists for 6-12 months; weekly monitoring of CMV/EBV DNA
Antibody-Drug	Inotuzumab Ozogamicin	FN: 27% (lower than	Mild bacterial infections,	No routine prophylaxis	Increased risk of VOD/SOS, indirectly

Drug Class	Representative Agent	Grade ≥3 Infection Rate (Clinical Trial/Real-World)	Core Infection Type	Recommended Prophylaxis Strategy	Special Consideration
Conjugates (ADCs)		chemotherapy 52%)	HBV reactivation	required; mandatory HBV screening	elevating post-transplant infection risk
CAR-T Cell Therapy	CD19 CAR-T Cells	Total infections: 48%/71%; Grade ≥3 infections: 35%	Early phase: bacterial sepsis; Late phase: IFD, PJP, viral infections	Acyclovir + TMP-SMX + Fluconazole prophylaxis; IVIG replacement (when IgG < 400mg/dL)	Antibiotics should be routinely initiated for CRS-related fever; add mold-active antifungal agents when corticosteroids ≥20mg/day are used

Abbreviation FN: Febrile Neutropenia. IFD: Invasive Fungal Disease. HMA: Hypomethylating Agents. CMV: Cytomegalovirus. CYP3A4: Cytochrome P450 3A4. DS: differentiation syndrome. TDM: Therapeutic Drug Monitoring. QTc: Corrected QT Interval. DS: Differentiation Syndrome. PJP: Pneumocystis jirovecii Pneumonia. IVIG: Intravenous Immunoglobulin. EBV: Epstein-Barr Virus. HBV: Hepatitis B Virus. VOD/SOS: Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome. CRS: Cytokine Release Syndrome. IgG: Immunoglobulin G.

hypogammaglobulinemia, result from prolonged B cell aplasia and delayed immune reconstitution (32), and these late infections can persist for up to 2 years (33).

Managing CRS-associated infection risk requires a nuanced approach. CRS, which occurs in 50-90% of CD19 CAR-T recipients, is characterized by fever, hypotension, and elevated inflammatory cytokines including IL-6, IL-1 and TNF-α (34). The fever of CRS is indistinguishable from that of bacterial sepsis, creating a diagnostic dilemma34. A practical algorithm for fever management following CAR-T infusion begins with immediate blood cultures and empiric broad-spectrum antibiotics such as cefepime or meropenem regardless of suspected CRS, as delayed treatment of bacterial sepsis carries unacceptable mortality (34). Antibiotic selection should be guided by local epidemiology and prior colonization status, with de-escalation considered after 48-72 hours if cultures remain negative and clinical status is stable (34). If fever persists beyond 48-72 hours without documented infection and CRS is grade ≥2, administration of tocilizumab (8 mg/kg) is indicated. However, clinicians must recognize that tocilizumab blocks IL-6 signaling, which can rapidly resolve fever due to CRS but does not address concurrent infection; thus, antibiotics should not be discontinued solely based on fever resolution after tocilizumab, and close monitoring for rebound CRS or delayed infection is warranted. For patients requiring high-dose corticosteroids such as dexamethasone ≥10 mg every 6 hours for grade ≥3 CRS, antifungal prophylaxis with mold-active agents such as posaconazole or voriconazole is recommended (35), as steroid-induced immunosuppression adds to the existing T-cell and B-cell defects, creating a high-risk environment for invasive fungal infections. Post-discharge surveillance for late infections (beyond day 30) should include monthly monitoring of IgG levels, with consideration of IVIG replacement for IgG <400 mg/dL or recurrent sinopulmonary

infections35. This algorithm emphasizes that antibiotic therapy should never be withheld or prematurely discontinued based on suspected CRS alone, as bacterial co-infection can occur simultaneously with CRS and carries high mortality if untreated. Guidelines recommend acyclovir, PJP prophylaxis, and fluconazole during CRS, with mold-active azoles reserved for prolonged neutropenia or high-dose steroids2. Long-term IVIG replacement is indicated for persistent hypogammaglobulinemia.

5. Key Insights: Trials vs. Real-World Practice and Future Directions

5.1 Clinical Trials Underestimate Real-World Infection Burden

Pivotal trials systematically underreport infectious complications due to several factors, including selective enrollment, as trial patients have better performance status and fewer comorbidities, excluding high-risk elderly patients; heterogeneous adverse event reporting, because infections are variably categorized as FN, pneumonia, sepsis or unspecified infection, leading to inconsistent data; limited long-term follow-up, whereby viral reactivation and hypogammaglobulinemia are rarely primary endpoints; and variable prophylaxis practices, since center-specific antimicrobial/antifungal strategies confound risk comparisons (2).

Real-world studies consistently report 20-30% higher infection rates than trials, particularly in older patients with comorbidities (36).

A systematic comparison of infection outcomes between pivotal trials and subsequent real-world studies reveals consistent discrepancies across multiple agent classes. For venetoclax-azacitidine, the VIALE-A trial reported a 30% incidence of grade ≥3 FN, while six real-world studies (total n=1,247 patients) reported a pooled incidence of 54% (range 45-67%) (37). For blinatumomab in relapsed B-ALL, the phase III TOWER trial reported grade ≥3 infections in 34% of patients, whereas a 2023 real-world analysis of 289 patients reported a 52% incidence of serious infections, with higher rates of CMV reactivation (18% vs 6% in the trial). For CAR-T cells, the pivotal ELIANA trial reported grade ≥3 infections in 24% of patients, but a real-world registry study of 399 patients reported a 71% incidence of any infection and a 35% incidence of grade ≥3 infection within the first 100 days. These discrepancies stem not only from differences in patient selection but also from more intensive monitoring and longer follow-up in clinical practice, as well as the inclusion of infection events that occur after hospital discharge, which are often underreported in trial databases.

The implications of this trial-real-world discordance are three fold: efficacy estimates from pivotal trials may overestimate the net clinical benefit of novel agents in routine practice, because serious infections that require treatment interruptions or dose reductions are more common in real-world cohorts (38-40); prophylactic strategies validated in trials may be insufficient for unselected patient populations. For example, the standard antifungal prophylaxis used in the VIALE-A trial may need augmentation with mold-active agents in real-world patients with additional risk factors such as prior fungal colonization or prolonged corticosteroid use (41); and risk prediction models derived from trial data require recalibration before clinical implementation42. Additionally, future registration trials should consider embedded real-world run-in phases or mandated post-marketing surveillance to capture infection outcomes in under-represented populations such as patients aged ≥80 years or those with significant renal or hepatic impairment (39,40,43).

5.2 The Venetoclax Conundrum: Prophylaxis Necessity vs. CYP3A4 Interactions

A major modern challenge is balancing antifungal prophylaxis and venetoclax dose safety in regimens containing venetoclax and hypomethylating agents.

Azole antifungals reduce invasive fungal risk but require 50-75% venetoclax dose reduction, which may compromise efficacy (44,45). Isavuconazole, with milder CYP3A4 inhibition, is an alternative for high-risk patients (46), but clinicians should be aware of its narrower mold spectrum compared to posaconazole (47). This balance remains a daily clinical dilemma (48).

5.3 Future Directions

Future strategies should focus on mechanism-based risk stratification, moving beyond ANC to stratify risk by immune defect type including neutropenia, B-cell depletion and T-cell dysfunction; novel diagnostics, such as developing rapid biomarkers to distinguish infection from DS/CRS; personalized prophylaxis, which involves tailoring antimicrobial/antifungal strategies to drug-drug interaction profiles and local epidemiology; and long-term immune support, including optimizing IVIG replacement and vaccination strategies for CAR-T and bispecific antibody recipients. Future research should prioritize prospective validation of risk scores incorporating lymphocyte subset analysis and IgG levels, randomized trials comparing isavuconazole versus posaconazole with venetoclax dose optimization as a primary endpoint, and long-term follow-up protocols for CAR-T recipients to define the optimal duration and triggers for IVIG replacement.

6. Conclusion

Infection risk in acute leukemia has evolved from a neutropenia-centric problem in the intensive chemotherapy era to a complex, therapy-specific challenge in the targeted/immune therapy era8. While modern agents have improved survival, they have reshaped infectious spectra, introducing hypogammaglobulinemia, viral reactivation, and immune reconstitution defects as key risks (49). Clinical trial data provide critical safety insights, but real-world practice reveals higher infection burdens and unique management complexities. Future efforts must focus on mechanism-based risk stratification, personalized prophylaxis, and long-term immune support to mitigate infectious complications and maximize therapeutic outcomes for acute leukemia patients (35).

Declarations

1. ***Consent to publication***
   We declare that all authors agreed to publish the manuscript in this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2. ***Ethical approval and consent of participants***
   Not applicable.
3. ***Disclosure of conflict of interests***
   We declare that no conflict of interest exists in this work.
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5. ***Availability of data and material***
   We declare that the data supporting the results reported in the article are available in the published article and from the corresponding author upon reasonable request.
6. ***Authors' Contributions***
   R.Z.: Writing-original draft preparation and editing. M.L.: Writing-review and editing. H.Z.: Conceptualization, supervision, and reviewing.
7. **Acknowledgement**
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8. ***Authors' biography***
   None.

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