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Review Article

Early Mortality and Infectious Complications During Induction Therapy in Adults with Acute Lymphoblastic Leukemia

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Summary

Acute lymphoblastic leukaemia is treated as a low-risk setting for invasive fungal infection, and antifungal prophylaxis is accordingly not recommended. Direct comparison shows patients receiving no prophylaxis having the same fungal infection rate as myeloid leukaemia patients who do receive it, despite less than half the duration of neutropenia.

Objectives: To review the published evidence on infectious complications during induction therapy for adult acute lymphoblastic leukaemia: how often they occur, which organisms are responsible, when in the course they cluster, which patients are at risk, and whether prophylaxis achieves what is assumed of it.

Material and Methods: Narrative review of prospective and retrospective cohorts, cooperative group trial analyses and comparative studies indexed in PubMed and the major haematology and infectious disease journals. Studies were eligible if they reported the incidence, microbiology, timing or outcome of infection during induction therapy in a defined adult acute lymphoblastic leukaemia population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Among 240 adults treated on a paediatric-inspired protocol across 18 centres, 145 (60 per cent) experienced at least one infectious episode. Bacterial infections accounted for 74.3 per cent, viral for 13.9, fungal for 10.1 and Pneumocystis for 1.7 per cent, with the bloodstream the commonest site and pneumonia in 14.6 per cent, half of it fungal. Infection clustered in the first course, affecting 40.5 per cent of patients, and invasive fungal infection occurred in 12.5 per cent. Mortality from infection was 3.3 per cent. Antibacterial, antiviral, antifungal and anti-Pneumocystis prophylaxis were variably given and none was associated with a significant reduction in infection rate. In a separate comparison of 552 chemotherapy episodes, invasive fungal infection occurred in 8.1 per cent of lymphoblastic episodes without antimould prophylaxis against 5.9 per cent of myeloid episodes with it ($p = 0.856$), despite median neutropenia of 8 against 18 days.

Conclusion: The assumption that shorter neutropenia makes lymphoblastic induction a low-risk setting for fungal infection is not supported by direct comparison. Age above 65 is the dominant risk factor, and observational data do not show benefit from the prophylaxis currently given.

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, AML – Acute Myeloid Leukaemia, Ph – Philadelphia Chromosome, IFI – Invasive Fungal Infection, BSI – Bloodstream Infection, PJ – Pneumocystis jirovecii, C1 – First Chemotherapy Course, CR – Complete Remission, CCI – Charlson Comorbidity Index, TRM – Treatment-Related Mortality, IRM – Induction-Related Mortality, HSCT – Haematopoietic Stem Cell Transplantation.

Keywords: Acute Lymphoblastic Leukaemia; Induction Therapy; Infectious Complications; Invasive Fungal Infection; Antimicrobial Prophylaxis

Introduction

Induction therapy for adult acute lymphoblastic leukaemia combines corticosteroids, vincristine, an anthracycline, cyclophosphamide and asparaginase over several weeks, and infection is the commonest serious complication of that combination [1,2]. Where patients die during induction, infection rather than resistant leukaemia is usually the immediate cause [3,4].

The infectious risk in this disease has conventionally been regarded as lower than in acute myeloid leukaemia, and the reasoning is straightforward: neutropenia after lymphoblastic induction is shorter, and the myeloid lineage dysfunction that characterises acute myeloid

leukaemia is absent [5,6]. On that basis, antifungal prophylaxis is routinely recommended for myeloid induction and not for lymphoblastic induction [5,7].

Two developments make that assumption worth re-examining. Adult protocols have converged on paediatric-inspired regimens of substantially greater intensity than their predecessors [1,8,9], and the age of patients treated with curative intent has risen. Both change the exposure without changing the guidance [2,10].

This review sets out how often infection occurs during modern adult induction, what organisms are responsible, when in the course it concentrates, and whether the prophylaxis currently given achieves what is assumed of it.

Material and Methods

Search strategy: PubMed and the archives of the major haematology and infectious disease journals were searched for studies of infection during induction for adult acute lymphoblastic leukaemia. Search terms combined acute lymphoblastic leukaemia and adult with infectious complications, bloodstream infection, invasive fungal infection, febrile neutropenia, induction mortality and antimicrobial prophylaxis. Reference lists of retrieved cohorts and trials were screened by hand.

Eligibility: Studies were included if they reported the incidence, microbiology, timing, risk factors or mortality of infection during induction therapy in a defined adult acute lymphoblastic leukaemia population, or compared infection rates between leukaemia subtypes. Studies in acute myeloid leukaemia are cited where they provide the comparator or establish the prophylaxis standard, and are identified as such.

Data extraction and handling: Design, cohort size, induction regimen, prophylaxis policy, definition of infectious episode and reported incidence or mortality were extracted as published. Prophylaxis policy is stated alongside every incidence figure, because the whole question at issue is what prophylaxis alters. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How much infection there is: The most detailed contemporary picture comes from 240 newly diagnosed adults with Philadelphia-negative disease treated according to a paediatric-inspired protocol across 18 centres in routine practice rather than trial conditions. At least one infectious episode occurred in 145 patients, 60 per cent of the cohort [11].

Bacterial infections accounted for 74.3 per cent of episodes, followed by viral at 13.9, fungal at 10.1 and *Pneumocystis jirovecii*

at 1.7 per cent (Figure 1). The bloodstream was the most frequently involved site, and pneumonia occurred in 14.6 per cent of episodes, half of which were fungal [11]. Mortality attributable to infection was 3.3 per cent [11].

Two features of that distribution differ from what myeloid induction produces. Viral infection accounts for a substantially larger share, reflecting the sustained lymphocyte depletion that corticosteroid-based regimens cause and that neutrophil counts do not measure. And half of the pneumonia was fungal, which in a population not receiving antifungal prophylaxis is the single most consequential observation in the cohort [11].

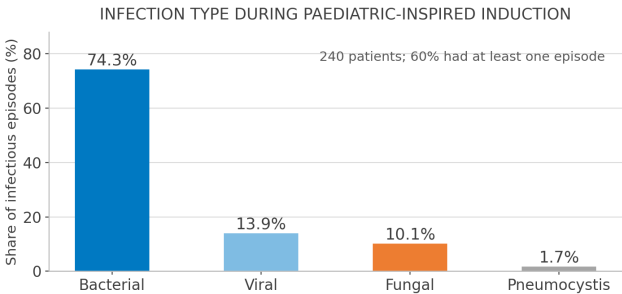


Figure 1: Distribution of infectious episodes by type in 240 adults on a paediatric-inspired protocol [11]

The burden concentrates in the first course: Infections were markedly more frequent during the first chemotherapy course, affecting 40.5 per cent of patients, and invasive fungal infection occurred in 12.5 per cent overall with most cases arising in that same first course (Figure 4) [11]. That clustering reflects the combination of untreated disease, high-dose corticosteroid exposure and the deepest neutropenia of the whole programme.

Timing within the course has been described precisely in a cooperative group analysis of 787 patients receiving five-drug induction. Bacterial infection occurred in 270 patients (34.3 per cent), who experienced 376 episodes, an average of 1.4 each. The median interval from the first day of induction to diagnosis of bacterial infection was 10 days, with a range of 7 to 14 [12]. Infection was classed as serious in 58 patients, and 57 presented with septic shock [12].

Regimen intensity influenced the rate. Patients receiving hyperfractionated cyclophosphamide with rituximab had bacterial infection in 40.7 per cent against 29.5 per cent among those receiving standard-dose cyclophosphamide without rituximab, a difference approaching but not reaching conventional significance ($p = 0.098$) (Figure 3) [12].

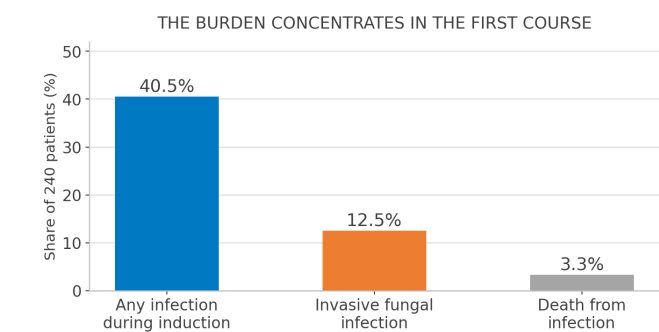


Figure 4: Infection, invasive fungal infection and infection-related death across the same cohort [11]

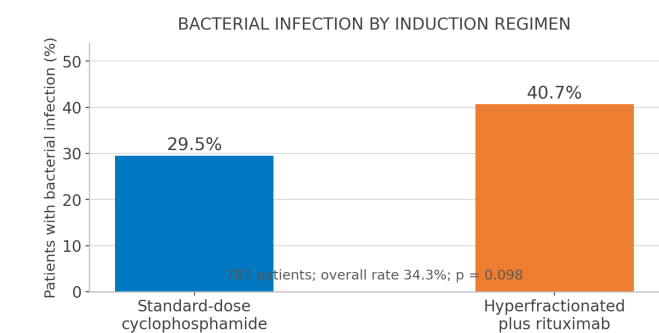


Figure 3: Bacterial infection rate by induction regimen in 787 patients [12]

Study	n	Setting	Principal reported finding
Ph-negative cohort [11]	240	18 centres	60% infected; IFI 12.5%; prophylaxis without effect
GRAALL-2005 analysis [12]	787	Cooperative group	34.3% bacterial infection; median day 10
Antimould era study [13]	552 episodes	Single centre	ALL without prophylaxis matches AML with it
Patel et al. 2017 [14]	90	UKALL14	16 induction deaths; sepsis with hepatotoxicity in eight
Pichler et al. 2013 [4]	—	Austrian registry	Toxicity rather than relapse drives adolescent excess

Table 1: Principal studies reviewed, with setting and the finding as reported by the original investigators

The comparison that undercuts the low-risk assumption: Antifungal prophylaxis is recommended for myeloid induction and not for lymphoblastic induction, on the reasoning that lymphoblastic disease carries lower fungal risk because neutropenia is shorter and myeloid lineage function is preserved [5,7]. A single-centre analysis

of 552 chemotherapy episodes, 393 myeloid and 159 lymphoblastic, tested that reasoning directly [13].

The premise held: median neutropenia was 8 days in lymphoblastic episodes against 18 in myeloid ones ($p < 0.001$), and antimould prophylaxis was given in 6.9 per cent of lymphoblastic against 56.0 per cent of myeloid episodes ($p < 0.001$). The conclusion did not. Invasive fungal infection occurred in 8.1 per cent of lymphoblastic episodes without prophylaxis against 5.9 per cent of myeloid episodes with it, a difference that was not significant ($p = 0.856$) (Figure 2) [13].

Within lymphoblastic episodes, invasive mould infection occurred in 4.7 per cent of those without prophylaxis and in none of the eleven that received it, though that denominator is too small to carry weight [13]. The comparison is between an unprophylaxed low-risk group and a prophylaxed high-risk one, and they come out level, which is not what the risk stratification predicts.

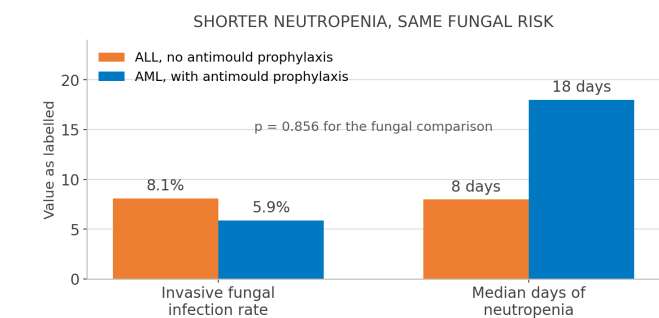


Figure 2: Fungal infection rate and neutropenia duration, lymphoblastic without prophylaxis against myeloid with it [13]

Who is at risk: Age dominates. In the multicentre cohort, older age was a risk factor for all types of infection, with the effect apparent above 55 and pronounced above 65, while comorbidity predicted only invasive fungal infection specifically [11]. That pattern matches the wider induction mortality literature, where age above 40 carried an odds ratio of 18.5 for treatment-related death in one trial and the patients who died had a median age of 56 [14].

Sepsis combined with hepatotoxicity accounted for eight of sixteen induction deaths in that trial, which illustrates how infection interacts with the organ toxicity of asparaginase-containing regimens rather than acting alone [14]. In adolescents, the excess mortality relative to children is driven by treatment-related complications rather than relapse [4].

What prophylaxis achieved: The most uncomfortable finding in the multicentre cohort concerns prophylaxis itself. Antibacterial, antiviral, antifungal and anti-Pneumocystis prophylaxis were all variably administered across the 18 participating centres, and none was associated with a significant reduction in infection rate [11].

That is an observational finding with the obvious confound: centres and clinicians give prophylaxis to patients they judge to be at

higher risk, so any protective effect is offset by selection. It is nonetheless striking that a cohort large enough to identify age as a risk factor could not detect benefit from four categories of prophylaxis [11]. Randomised evidence in paediatric leukaemia shows levofloxacin prophylaxis reduces bacteraemia [15,16], and the absence of a comparable adult signal here may reflect design rather than biology.

Comparison	Lymphoblastic	Myeloid
Median neutropenia	8 days	18 days [13]
Antimould prophylaxis given	6.9%	56.0% [13]
Invasive fungal infection	8.1%	5.9% [13]
Guideline recommendation	None	Posaconazole [5,7]

Table 2: The comparison between lymphoblastic and myeloid induction that the prophylaxis guidance rests on

Which organisms, and why it matters for empirical therapy: The bloodstream is the dominant site, and the organisms recovered in adult leukaemia broadly mirror those reported in haematological malignancy generally, with Gram-positive isolates predominating and coagulase-negative staphylococci common in line-associated infection [19]. Viridans group streptococci warrant separate attention because they produce a septic syndrome with shock and pulmonary involvement rather than an indolent course [20,21].

The organism mix shapes what empirical cover should target. Standard regimens are built around Gram-negative sepsis, which remains correct given its lethality, but a more targeted strategy against Gram-positive cocci in neutropenia has been argued for on epidemiological grounds [21]. Central venous access, in place from the first day of induction, is an independent risk factor for bloodstream infection across leukaemia populations [24].

Guideline groups have addressed antibacterial prophylaxis systematically in paediatric oncology [17], and the randomised evidence there is reasonably clear [15,16]. The adult lymphoblastic setting has no equivalent body of trial data, which is why the observational finding of no association with prophylaxis in the multicentre cohort is difficult to interpret rather than simply negative [11].

Infection as a component of induction mortality: Infection does not act alone. In the trial where sixteen of 90 patients died during induction, half of those deaths involved sepsis combined with hepatotoxicity rather than infection in isolation [14], and the same interaction between asparaginase-related organ toxicity and infectious risk shapes how regimens have been modified [22]. Age-adapted reduction of chemotherapy intensity has been shown to lower treatment-related mortality substantially [22].

Comparable patterns appear across the leukaemias. Paediatric myeloid cohorts show infection-related mortality falling across trial generations without the number of infectious episodes changing [18], which locates improvement in recognition and treatment rather than prevention. Whether the same holds in adult lymphoblastic disease has not been examined with comparable data [11,12].

Element	Adult ALL induction	Evidence base
Antibacterial prophylaxis	Variable practice	Randomised data paediatric only [15,16,17]
Antifungal prophylaxis	Not recommended	Risk model unsupported by direct comparison [5,13]
Anti-Pneumocystis prophylaxis	Standard	PJ accounted for 1.7% of episodes [11,12]
Empirical antibacterial cover	Gram-negative directed	Gram-positive organisms predominate [19,20,21]
Age-adapted dose reduction	Increasingly used	Reduces treatment-related mortality [22]

Table 3: Elements of infection management in adult induction and the evidence supporting each

Discussion

The central observation is a mismatch between a guideline's rationale and the data supporting it. Antifungal prophylaxis is withheld in lymphoblastic induction because neutropenia is shorter, and neutropenia genuinely is shorter, at 8 days against 18 [13]. But the fungal infection rate in unprophylaxed lymphoblastic episodes was 8.1 per cent against 5.9 per cent in prophylaxed myeloid ones, and the difference was not significant [13].

Two readings are possible and the data do not separate them. Either prophylaxis in myeloid disease is working well enough to bring a high-risk group down to the level of an unprotected lower-risk one, which would be a success rather than a problem. Or lymphoblastic induction is not the low-risk setting it is assumed to be, in which case the 12.5 per cent invasive fungal infection rate seen in the multicentre cohort is the cost of that assumption [11,13].

Why duration of neutropenia may be the wrong proxy

The risk model underlying antifungal guidance treats neutrophil count and its duration as the principal determinant of fungal susceptibility [5,7]. Modern lymphoblastic induction includes three weeks of high-dose corticosteroid, which impairs macrophage and T cell function in ways a neutrophil count does not capture, alongside asparaginase-related hepatic and metabolic disturbance [1,14].

If corticosteroid exposure contributes independently, then a regimen with short neutropenia and prolonged steroid exposure could carry fungal risk comparable to one with long neutropenia and no steroid, which is close to what the comparison shows [13].

Testing that would require stratifying fungal risk by cumulative steroid dose, which no study reviewed here reports.

Study limitations

The limitations belong to the underlying literature. The prophylaxis finding is observational and confounded by indication, since patients judged higher risk are more likely to receive it [11]. The comparison between lymphoblastic and myeloid fungal risk comes from a single centre over three years, with only eleven prophylaxed lymphoblastic episodes, so the within-disease comparison rests on very small numbers [13]. Definitions of infectious episode and of proven, probable and possible fungal infection differ between cohorts and materially affect reported incidence [11,13]. Induction regimens differ in corticosteroid dose, asparaginase scheduling and use of rituximab, all of which alter infectious risk [1,8,9,12,23,25]. And centres differ in isolation facilities, empirical antibiotic policy and diagnostic intensity, none of which is captured in multicentre incidence figures [11].

Two gaps deserve naming. No randomised trial has tested antifungal prophylaxis during induction for adult acute lymphoblastic leukaemia, so the recommendation against it rests on inferred rather than demonstrated low risk [5,13]. And no study reviewed here reports infection risk stratified by cumulative corticosteroid exposure, which the mechanistic argument identifies as the most plausible unmeasured contributor [1,11].

Conclusion

Infection affects 60 per cent of adults during modern paediatric-inspired induction for acute lymphoblastic leukaemia, is bacterial in three quarters of episodes, concentrates in the first course where it affects 40.5 per cent of patients, and kills 3.3 per cent. Invasive fungal infection occurs in 12.5 per cent, which is not the rate a low-risk setting should produce. Direct comparison found lymphoblastic episodes without antimould prophylaxis matching myeloid episodes with it, at 8.1 against 5.9 per cent, despite neutropenia lasting 8 days rather than 18. Age above 65 is the dominant risk factor, and in a cohort of 240 patients across 18 centres none of the four categories of prophylaxis in use was associated with a lower infection rate. The guidance withholding antifungal prophylaxis in this setting rests on a risk model that the comparative data do not support, and it has not been tested directly.

The trial that would settle it is straightforward to describe. Randomising adults undergoing paediatric-inspired induction to mould-active prophylaxis or none, with invasive fungal infection as the primary endpoint and age above 65 as a stratification factor, would answer a question currently settled by inference from neutrophil kinetics [5,13]. Given a 12.5 per cent event rate, it would not need to be large [11].

In the meantime the practical inference is narrower. Older patients, particularly above 65, carry the risk across every category of infection [11], and they are the group in whom the balance between prophylaxis and its harms is most likely to favour treating. Applying a uniform policy across an age range spanning five decades is the part of current practice that the data least support.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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