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Review Article

Infectious Complications During Consolidation Therapy in Children with Acute Myeloid Leukemia (AML): A Review of Published Cohorts

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Summary

Children with acute myeloid leukaemia spend six to nine months neutropenic, and infection rather than leukaemia is what kills a substantial share of those who die in remission. Two consecutive multicentre trials from the same study group, a decade apart, provide an unusually clean comparison of what changed.

Objectives: To review the published evidence on infectious complications during consolidation and other post-induction phases in children treated for acute myeloid leukaemia: how often they occur, which organisms are responsible, how mortality has changed between trial generations, and what prophylaxis has been shown to achieve.

Material and Methods: Narrative review of multicentre trial cohorts, registry analyses, randomised prophylaxis trials and practice guidelines indexed in PubMed and the major haematology and infectious disease journals. Studies were eligible if they reported infectious complications or infection-related mortality in a defined paediatric leukaemia population, or the effect of a prophylactic intervention. No new patient data were generated and no patients were recruited; every rate quoted is one published by the original investigators.

Results: Across 304 children in one multicentre trial, 855 infectious episodes occurred, of which 61.2 per cent were fever without an identifiable source and 32.1 per cent were microbiologically documented; neutropenia was present in 74.1 per cent of episodes and 20 children died of infection-associated complications. In the successor trial enrolling 405 children a decade later, 1,326 infections occurred, averaging 3.3 per patient, but infection-related mortality fell from 5.4 to 1.5 per cent. Bloodstream isolates were predominantly Gram-positive (240 against 90 Gram-negative), with viridans group streptococci alone accounting for 112. Invasive fungal infection affected 3 per cent of patients. Children with Down syndrome died of infection at 17.9 per cent against 5.4 per cent in those without.

Conclusion: The number of infectious episodes did not fall between trial generations; the death rate did, by roughly two thirds. That pattern points to supportive care and earlier intervention rather than to infection prevention, and it means episode counts are a poor measure of whether a supportive care programme is working.

Abbreviations: AML – Acute Myeloid Leukaemia, ALL – Acute Lymphoblastic Leukaemia, BFM – Berlin-Frankfurt-Münster, BSI – Bloodstream Infection, CLABSI – Central Line-Associated Bloodstream Infection, CoNS – Coagulase-Negative Staphylococci, FUO – Fever of Unknown Origin, HAM – High-Dose Cytarabine and Mitoxantrone, IFI – Invasive Fungal Infection, VGS – Viridans Group Streptococci, HSCT – Haematopoietic Stem Cell Transplantation.

Keywords: Acute Myeloid Leukaemia; Consolidation Therapy; Infectious Complications; Viridans Streptococci; Antibacterial Prophylaxis

Introduction

Treatment for childhood acute myeloid leukaemia combines features that make infection close to inevitable. Intensive chemotherapy runs for six to nine months, each cycle produces prolonged severe neutropenia, central venous access is required throughout, and mucositis breaches the gastrointestinal barrier and permits bacterial translocation [1,2]. The chemotherapy also alters host defence directly, independently of the neutrophil count [3].

The consequence is that infection, rather than resistant leukaemia, accounts for a large share of deaths in children who reach remission [4,5,6]. Successive trial groups have documented this: treatment-related deaths during induction and first remission have been reported from British, Nordic, Dutch and North American cohorts, with infection the dominant cause in each [5,6,7,8].

What makes the paediatric acute myeloid leukaemia literature unusually informative is that one study group published detailed infection data from two consecutive multicentre trials a decade apart, using comparable methods [1,9]. That pairing allows the question to be asked directly: did supportive care change the number of infections, or only their consequences?

This review sets out what those cohorts show, which organisms dominate, how risk differs between patient groups, and what the randomised prophylaxis evidence has established.

Material and Methods

Search strategy: PubMed and the archives of the major haematology, paediatric oncology and infectious disease journals were searched for studies of infection in childhood acute myeloid leukaemia. Search terms combined acute myeloid leukaemia and paediatric with infectious complications, bloodstream infection, viridans streptococci, invasive fungal infection, consolidation therapy, antibacterial prophylaxis and treatment-related mortality. Reference lists of retrieved trials and guidelines were screened by hand.

Eligibility: Studies were included if they reported the frequency, microbiology or mortality of infectious complications in a defined paediatric leukaemia population, or the effect of a prophylactic intervention on those outcomes. Studies including relapsed acute lymphoblastic leukaemia or transplant recipients are cited where they provide the randomised evidence and are identified as such.

Data extraction and handling: Design, cohort size, trial protocol, definitions of infectious episode and reported rates were extracted as published. Whether a figure refers to episodes or to affected patients is stated throughout, because the two differ by a factor of roughly three in this population and are frequently conflated. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

How much infection there is: In the earlier of the two paired trials, the medical records of 304 children treated at 30 hospitals were reviewed. In total 855 infectious complications occurred: 523 episodes (61.2 per cent) were fever without an identifiable source, 57 (6.7 per cent) were clinically documented and 275 (32.1 per cent)

microbiologically documented. Neutropenia was present in 74.1 per cent of episodes, and pneumonia was radiologically diagnosed in 113 of the 855 episodes, 13.3 per cent [1].

The successor trial enrolled 405 children of median age 8.4 years and recorded 1,326 infections, an average of 3.3 infectious complications per patient. Fever without an identifiable source affected 56.1 per cent of patients, microbiologically documented infection 32.4 per cent and clinically documented infection 17.5 per cent (Figure 1) [9]. The distribution is nearly identical to the earlier trial, which is the first substantive finding: a decade of supportive care development did not reduce how often these children became infected.

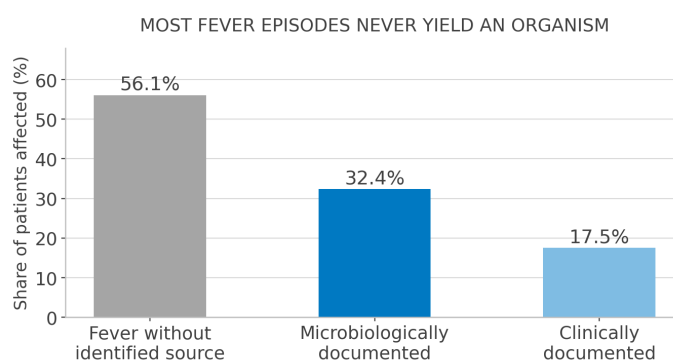


Figure 1: Classification of infectious episodes in 405 children treated on a multicentre protocol [9]

What did change was mortality: Infection-related mortality fell from 5.4 per cent to 1.5 per cent between the two trials (Figure 2) [1,9]. In the earlier cohort 20 children died of infection-associated complications, most of them during early induction [1]. In the later cohort three children died of Gram-negative bacteraemia and three of invasive aspergillosis [9].

A roughly two-thirds reduction in deaths with no reduction in episodes implicates recognition and treatment rather than prevention. The same direction of travel appears in the treatment-related mortality literature more broadly, where deaths in first remission fell across successive protocol generations in several national groups [4,6,7,8,10].

The distribution of deaths within therapy is equally informative. In the earlier cohort, 11 of the 20 infection-associated deaths occurred during early induction rather than in the post-remission cycles that account for most of the treatment duration [1]. A child in consolidation has a marrow in remission, recovered organ function and no coagulopathy, and tolerates the same depth of neutropenia far better than a child presenting with untreated disease. Reporting infection mortality for a protocol as a single figure therefore averages across two quite different clinical situations.

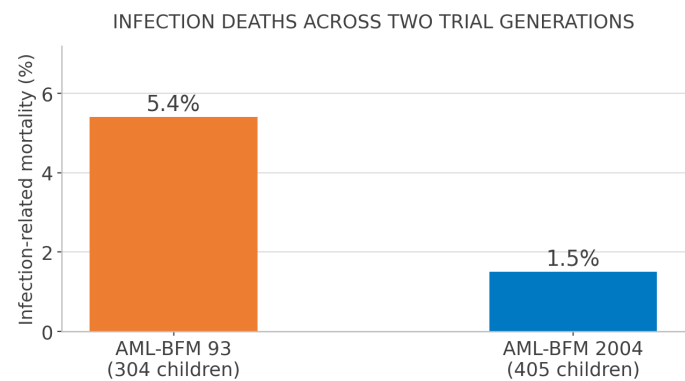


Figure 2: Infection-related mortality in two consecutive multicentre trials from the same study group [1,9]

Study	n	Setting	Principal reported finding
Riley et al. 1999 [7]	—	MRC AML 10	Treatment-related deaths in induction and first remission
Lehmbecher et al. 2004 [1]	304	AML-BFM 93	855 episodes; infection mortality 5.4%
Slats et al. 2005 [8]	—	Dutch group	Causes of death other than progressive leukaemia
Molgaard-Hansen 2010 [6]	—	Nordic	Early and treatment-related deaths, 1984-2003
Inaba et al. 2014 [17]	—	Single centre	Outpatient antibacterial prophylaxis feasible
Bochennek et al. 2016 [9]	405	AML-BFM 2004	1,326 infections; mortality down to 1.5%
Alexander et al. 2018 [15]	Rando mised	COG ACCL0934	Levofloxacin reduces bacteraemia in acute leukaemia

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

The organisms are predominantly Gram-positive: Across 405 children, 240 Gram-positive and 90 Gram-negative isolates were recovered from the bloodstream, and viridans group streptococci alone accounted for 112 of the Gram-positive isolates (Figure 3) [9]. Bacteraemia made up 71.6 per cent of microbiologically documented infections, with viridans streptococci responsible for over 30 per cent of them [9,11]. The earlier trial found the same pattern, with 202 Gram-positive against 42 Gram-negative isolates across 228 bloodstream episodes [1].

Viridans group streptococci are worth naming separately because they behave differently from other Gram-positive organisms in neutropenic children, causing a septic syndrome with a recognised risk of shock and pulmonary involvement rather than an indolent line

infection [12,13,14]. They originate from oral mucosa damaged by cytarabine, which is why they cluster in the high-dose cytarabine cycles that dominate consolidation [1,9].

Invasive fungal infection was diagnosed in 3 per cent of patients in the later trial, and was probable or proven in 15 patients in the earlier one [1,9]. That is a low incidence but a high case fatality: three of the six infection deaths in the later cohort were from invasive aspergillosis [9].

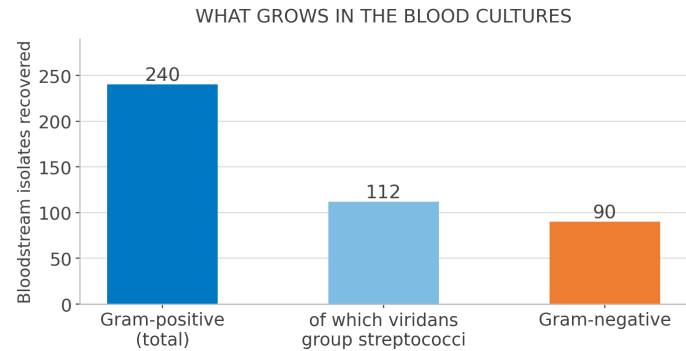


Figure 3: Bloodstream isolates recovered in a multicentre paediatric cohort [9]

Which children are most at risk: Down syndrome is the starkest single risk factor. In the earlier trial, 5 of 28 children with Down syndrome (17.9 per cent) died of infection-associated complications against 15 of 276 without (5.4 per cent) (Figure 4) [1]. The later trial excluded these patients from analysis for that reason [9].

Central venous access is the other consistently identified factor. Risk factors for bacteraemia and central line-associated bloodstream infection have been characterised specifically in children with acute myeloid leukaemia [16], and leukaemia and relapsed malignancy are independent risk factors for bloodstream infection across paediatric cancer centres more generally [18]. The organisms recovered mirror those reported in adult haematological malignancy [19].

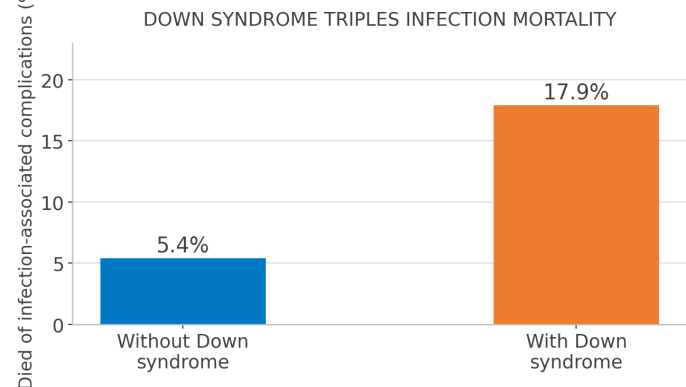


Figure 4: Infection-associated mortality by Down syndrome status in a multicentre cohort [1]

What prophylaxis achieves: The randomised evidence is now reasonably clear. In a multicentre trial randomising children with acute myeloid leukaemia or relapsed acute lymphoblastic leukaemia during two consecutive periods of severe neutropenia, levofloxacin prophylaxis significantly reduced bacteraemia, reduced febrile neutropenia and reduced exposure to broad-spectrum antibiotics, without a significant increase in invasive fungal disease, multidrug-resistant organisms or *Clostridioides difficile*-associated diarrhoea [15,20].

Antifungal prophylaxis has been addressed by a separate randomised trial in which caspofungin reduced invasive fungal disease compared with fluconazole in children and young adults with acute myeloid leukaemia [21]. Guideline groups have synthesised both strands into practice recommendations [22], and earlier meta-analysis had already established the general effect of antimicrobial prophylaxis in cancer patients [23]. Outpatient delivery of antibacterial prophylaxis has been shown feasible in this population [17], and single-centre follow-up has examined whether the resistance concerns materialise in practice [24,25].

Intervention or factor	Reported effect	Evidence
Levofloxacin prophylaxis	Reduces bacteraemia	Randomised multicentre trial [15,20]
Caspofungin over fluconazole	Reduces invasive fungal disease	Randomised trial in paediatric AML [21]
Down syndrome	Triples infection mortality	17.9% against 5.4% in one cohort [1]
Central venous access	Raises bacteraemia risk	Single-institution and multicentre analyses [16,18]
Mucositis from cytarabine	Source of viridans streptococcal sepsis	Organism distribution across both trials [1,9,12]

Table 2: Interventions and risk factors with the effect reported for each

Why most episodes never yield an organism: The single largest category in both trials is fever without an identifiable source, at 61.2 and 56.1 per cent respectively [1,9]. That is not a failure of microbiology so much as a property of the population: blood cultures are drawn from children already receiving broad-spectrum antibiotics, volumes obtainable from a small child are limited, and a proportion of febrile episodes in profound neutropenia reflect mucosal inflammation or cytokine release rather than a culturable pathogen [3,12].

The practical consequence is that empirical therapy has to be started and continued on clinical grounds in the majority of episodes, and de-escalation cannot be guided by a result that never arrives. Guideline groups have addressed this by defining risk-stratified empirical regimens rather than pathogen-directed ones [22]. It also means that any audit counting microbiologically confirmed infection

captures under a third of the clinical burden [1,9].

Invasive fungal infection: uncommon but disproportionately lethal: Fungal disease was diagnosed in 3 per cent of patients in the later trial and was probable or proven in 15 patients in the earlier one [1,9]. Against that low incidence, invasive aspergillosis accounted for three of the six infection deaths in the later cohort, meaning a complication affecting roughly one child in thirty caused half the infectious mortality [9]. Comparable incidence figures have been reported from multicentre Italian surveillance of non-lymphoblastic leukaemia [11].

This asymmetry is what justifies antifungal prophylaxis despite the low event rate, and the randomised comparison of caspofungin against fluconazole in this exact population addressed it directly [21]. It also explains why prolonged neutropenia, rather than any single cycle, is the relevant exposure: the risk accumulates across the six to nine months of therapy rather than concentrating in one phase [2,3].

Organism group	Frequency	Clinical significance
Viridans group streptococci	112 isolates	Septic syndrome with shock and pulmonary involvement; arises from cytarabine mucositis [9,12,13]
Other Gram-positive	128 isolates	Largely coagulase-negative staphylococci; usually line-associated and rarely fatal [9,16]
Gram-negative	90 isolates	Fewer episodes but three of six infection deaths in the later cohort [9]
Fungi	3% of patients	Low incidence, high case fatality; three deaths from invasive aspergillosis [9,21]

Table 3: Organism groups recovered from the bloodstream, with the clinical significance reported for each [9]

Discussion

The paired trials support a conclusion that is easy to state and easy to miss. Between the two cohorts, the number of infectious episodes per patient did not fall and the distribution between fever of unknown origin, clinically documented and microbiologically documented infection barely moved [1,9]. Infection-related mortality nonetheless fell from 5.4 to 1.5 per cent. Whatever improved, it was not prevention.

The plausible explanation is faster recognition and more aggressive early treatment of febrile neutropenia, together with better antifungal therapy. That has a practical implication for how supportive care programmes are audited: counting infectious episodes measures the wrong thing. A unit that halved its death rate while its episode count stayed flat would look unchanged on the metric most commonly collected.

Why consolidation differs from induction

Deaths in the earlier trial clustered in early induction, with 11 of 20 occurring there [1], which reflects the tumour burden, coagulopathy and organ dysfunction present at diagnosis. Consolidation cycles produce comparable or deeper neutropenia but in a patient whose marrow is in remission and whose organ function has recovered, so the same infection is more survivable.

The organism mix also shifts. High-dose cytarabine, which dominates consolidation, damages oral mucosa and drives viridans streptococcal bacteraemia specifically [1,9,12,13]. That is an argument for phase-specific rather than uniform empirical antibiotic policy, since a regimen optimised against Gram-negative sepsis at induction may be poorly matched to the dominant organism during consolidation.

What the episode count is good for

Nothing above argues that counting infectious episodes is worthless. Three episodes per patient across therapy is a measure of how much hospital time, intravenous antibiotic exposure and interrupted chemotherapy a family should expect, and it is the right figure to quote when consenting parents [9]. It also tracks resource use, which is what determines whether outpatient management of low-risk febrile neutropenia is worth establishing [17].

The error is treating it as a quality indicator. Because episode frequency was essentially unchanged between the two trials while deaths fell by two thirds, a unit measuring only episodes would have concluded that nothing improved [1,9]. Mortality, time to first antibiotic dose and intensive care admission are the outcomes that moved, and they are the ones worth auditing.

Implications for empirical antibiotic policy

If viridans streptococci account for over 30 per cent of bacteraemias and arise specifically from cytarabine-damaged mucosa, then the organism a child is most likely to grow depends on which cycle they are in [9,12]. Standard empirical regimens are built around Gram-negative cover, which remains correct at induction where Gram-negative sepsis causes most deaths [1,9], but is a poorer match to the dominant organism during high-dose cytarabine consolidation.

Fluoroquinolone prophylaxis complicates this further, because viridans streptococci with reduced levofloxacin susceptibility have been described in neutropenic patients receiving exactly that prophylaxis [15,25]. The randomised data show a net benefit [15], but the organism most likely to cause severe sepsis during consolidation is also the one under most selective pressure, which is a reason to keep monitoring rather than to withhold prophylaxis.

Study limitations

The limitations belong to the underlying literature. Both principal cohorts collected infection data retrospectively from medical records across many hospitals, so ascertainment depends on local

documentation [1,9]. Definitions of an infectious episode, and the threshold for calling an infection clinically documented, differ between studies and limit comparison beyond the paired trials [1,9,18]. Supportive care policy, including empirical antibiotic choice and antifungal use, was not standardised across participating centres and changed over the decade separating the two trials, which is precisely the variable of interest [9,22]. The randomised prophylaxis evidence combines children with acute myeloid leukaemia and relapsed acute lymphoblastic leukaemia, so the effect specific to acute myeloid leukaemia consolidation is inferred [15,20]. And children with Down syndrome were excluded from the later cohort, removing the highest-risk group from the comparison [1,9].

Two gaps deserve naming. No study reviewed here reports infectious complications separately by consolidation cycle, so the assumption that risk is uniform across cycles is untested [1,9]. And the long-term consequences of routine fluoroquinolone prophylaxis for resistance patterns in this population remain under investigation rather than settled [24,25].

Conclusion

Children treated for acute myeloid leukaemia experience roughly three infectious episodes each during therapy, and that figure did not change between two multicentre trials a decade apart. Infection-related mortality over the same interval fell from 5.4 to 1.5 per cent, which locates the improvement in recognition and treatment rather than prevention. Gram-positive organisms dominate the bloodstream isolates, with viridans group streptococci alone accounting for 112 of 240, and they arise from cytarabine-damaged oral mucosa during the cycles that make up consolidation. Invasive fungal infection is uncommon at around 3 per cent but accounts for half the infection deaths. Levofloxacin prophylaxis reduces bacteraemia and caspofungin reduces invasive fungal disease in randomised trials. Auditing episode counts rather than outcomes would have missed the entire improvement of the past two decades.

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Conflict of Interest

No author holds an interest that competes with this work.

Ethics Statement

Published studies alone are surveyed in this article. Since no patient was recruited and no clinical record newly opened, ethical approval was not sought.

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