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Clinical presentation and outcome of invasive mould disease in paediatric patients with acute lymphoblastic leukaemia

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ABSTRACT

Background: Childhood acute lymphoblastic leukaemia (ALL) cure rates have improved, but invasive mould disease (IMD) remains a life-threatening complication. Here, we evaluate the epidemiology, clinical presentation, treatment and outcome of IMD in paediatric patients with ALL.

Methods: Patients (1–18 years) treated according to the Dutch Childhood Oncology Group (DCOG) ALL-11 protocol from 2012–2021 were analysed for probable and proven IMD. Data was extracted from the Dutch national registry and the electronic health care system.

Results: Among 643 patients with ALL, 47 (7.3%) were diagnosed with a probable (n = 29) or proven (n = 18) IMD. Aspergillosis was diagnosed in 42 (89%) patients. Forty-one episodes (87%) occurred during the induction (n = 20) and first consolidation (n = 21) course. The median age at ALL diagnosis was 5 years [IQR 3–10] in the overall group versus 14 years [IQR 7–16] in the IMD group. Two-third of the patients did not receive mould-active prophylaxis. The most prevalent clinical symptoms at presentation were persistent fever and respiratory symptoms. The lungs were the most common site of infection with involvement in 44 (94%) patients, followed by the CNS in 16 (34%) patients. The 6-week and 12-week mortality rate after IMD diagnosis was 10.6% and 14.9%, respectively.

Discussion and conclusion: In our paediatric cohort a notable incidence of probable and proven IMD was observed during the early stages of treatment. Remarkable is the high frequency of CNS involvement. These findings highlight the importance of effective prophylactic strategies and warrant early brain imaging.

1. Introduction

Acute lymphoblastic leukaemia (ALL) has shown significant progress with respect to the 5-year survival rate, exceeding 90% for paediatric patients. Despite this progress in survival rate, a portion of patients still face challenges in attaining complete cure, due to incurable relapses and toxic deaths [1]. Among the various causes of death, infectious diseases, including invasive mould disease (IMD), have emerged as a leading factor [2,3].

IMD primarily arises due to a weakened immune response. Since the administration of chemotherapy to children with ALL severely compromises their immune system during parts of their treatment, they are

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at-risk for developing IMD. The reported incidence rates of IMD in children with ALL vary from 0.5–7.1% worldwide [4–9]. In the AIEOP-BFM ALL2009 clinical trial, the documented incidence rate was 2.6% [6]. The difference between these rates is influenced by various factors such as the treatment protocol, the use of mould-active prophylaxis and the geographical area [4–9].

Despite its significance, research focusing on the epidemiology, clinical features, treatment, and outcome of IMD in children with ALL is limited. However, comprehending the epidemiology of IMD throughout the entire treatment protocol is crucial for identifying high-risk treatment courses and determining the potential benefits of mould-active treatment strategies, including prophylaxis and diagnostic-driven strategies. Moreover, recognising the clinical signs and symptoms during the initial presentation of IMD is essential for early diagnosis and timely initiation of mould-active treatment. Consequently, there is a need for a better understanding of the clinical aspects of IMD to enhance its management and outcomes.

In this study, we evaluate the incidence and describe the clinical signs and symptoms at initial presentation, treatment and outcome of IMD in paediatric patients treated according to the Dutch Childhood Oncology Group (DCOG) ALL-11 protocol from 2012 to 2021.

2. Methods

This study was a national multi-centre, retrospective cohort study on incidence, clinical presentation, treatment and outcome of IMD in children with ALL. The study population consisted of all newly diagnosed patients with ALL in the Netherlands, who started treatment according to the DCOG ALL-11 protocol between April 2012 and August 2018 [10]. The follow-up period extended until the end of ALL treatment up to June 2021. Patients were treated in the following centres in The Netherlands: Princess Máxima Center for Pediatric Oncology (Utrecht), Wilhelmina Children's Hospital (Utrecht), Radboud university medical center (Nijmegen), Erasmus Medical Center (Rotterdam), VU University Medical Center (Amsterdam), Amsterdam Medical Center (Amsterdam), Academic Hospital Maastricht (Maastricht), Leiden University Medical Center (Leiden) and University Medical Center Groningen (Groningen).

All patients underwent a diagnostic-driven approach with once weekly, and if feasible twice weekly, serum galactomannan screening during the induction course (week 0–5) and first consolidation course (week 6–10). Triazole prophylaxis was withheld during the induction course due to weekly vincristine use and the relevant drug interactions. Subsequently, children received mould-active prophylaxis with itraconazole during their first consolidation course. Therapeutic drug monitoring (TDM) was only routinely performed for itraconazole in a limited number of centres. After risk stratification for their ALL treatment, the protocol for mould-active prophylaxis is different for the three risk groups for ALL treatment (SRG, MRG and HRG). The standard risk group (SRG) received no mould-active prophylaxis beyond first consolidation. The medium risk group (MRG) received mould-active prophylaxis during the first 12 weeks of maintenance treatment for those who got doxorubicin. The high risk group (HRG) received mould-active prophylaxis during their HRG blocks and re-induction therapy. During HRG blocks and re-induction therapy, serum galactomannan was screened once weekly, and if feasible twice weekly.

In case of repeated positive serum galactomannan or persistent fever (>96 h) in neutropenia while receiving broad-spectrum antibiotics, the following diagnostics were performed according to the protocol: High-Resolution Computed Tomography (HRCT) thorax, and if not recently performed, serum galactomannan. In case of an abnormal HRCT thorax suggestive of pulmonary fungal infection, further diagnostics (bronchoalveolar lavage, biopsy on indication) were performed. Magnetic Resonance Imaging (MRI) of the cerebrum/sinuses was performed based on the discretion of the centre-specific physicians. In case of a positive MRI, if feasible, cerebrospinal fluid analysis and/or biopsy of the lesion were performed. The standard antifungal treatment for a suspected pulmonary and/or cerebral IMD in children with ALL was voriconazole in combination with liposomal amphotericin B. Protocol deviations were possible at the discretion of the treating physician. In the absence of documented azole resistance and when stable voriconazole trough levels were reached, treatment was switched to voriconazole monotherapy. TDM was routinely performed in patients receiving voriconazole.

All Serious Adverse Events and toxicity adverse events were prospectively registered as part of the national registry of the DCOG, including systemic or invasive fungal infections. The following variables were obtained from the DCOG ALL-11 database and the electronic health care system (EHRS): demographics (age, sex, immunophenotype and genotype of ALL), disease characteristics (duration of ALL treatment until (suspected) IMD, treatment phase, use of mould-active agents, classification and characteristics of the IMD episode (clinical manifestations at presentation, galactomannan values, species, resistance analyses, involved sites, treatment and outcome).

2.1. Definitions

Proven and probable mould infections were defined according to the European Organization for Research and Treatment in Cancer/Mycoses Study Group 2008 (EORTC/MSG) criteria [11]. Categorisation of IMD was conducted independently by two researchers (DB en TW) using the EORTC/MSG criteria.

2.2. Statistical analysis

Descriptive statistics were presented as the median and interquartile ranges (IQR) for continuous data and frequencies and percentages for categorical data. For baseline characteristics, the Mann-Whitney U test was used to compare continuous data and the Pearson's chi-square test or Fisher's exact test were used to compare categorical data between patients with and without mould infection.

2.3. Ethics

All patients provided written informed consent for the DCOG ALL-11 protocol, including studies on its side effects. The study protocol was approved by and the Medical Ethics Assessment Committee Utrecht (19–163/C).

3. Results

643 children with newly diagnosed with ALL were included in this study. Forty-seven (7.3%) patients developed a probable or proven IMD. A total of 29 probable (62%) and 18 proven (38%) IMD episodes were categorised according to the EORTC criteria. The median age at ALL diagnosis was 5 years [IQR 3–9], and 39% was female in the non-IMD group versus 14 years [IQR 7–16; p = .000], and 57% (p = .014) in the IMD group. The baseline characteristics are presented in Table 1. In 42 out of 47 episodes (89%) aspergillosis was diagnosed, with an identified pathogen in 23 patients. *Aspergillus fumigatus* being the most commonly identified pathogen in 19 of the23 patients. In one patient a mixed infection with *Aspergillus*, *Fusarium* and *Alternaria* was documented. Resistance analysis was performed in 19 isolates from 23 patients, and voriconazole resistance (MIC $\geq$ 1.0 mg/L) of *Aspergillus* isolates was found in four out of 19 isolates (21%), *Mucorales* spp. were isolated in three patients (6%), and *Alternaria* spp. in two patients (4%). A detailed overview is given in Table 2.

3.1. Disease characteristics

Forty-one out of 47 episodes (87%) occurred during the induction (n = 20, 42.6%) and first consolidation (n = 21, 44.7%) course. The median duration of ALL treatment until the diagnosis of an IMD episode

Table 1
Demographic characteristics.

	Overall group	Non-IMD group	IMD group	p-value
Number of patients, N (%)	643 (100)	596 (92.7)	47 (7.3)	
Median age at ALL diagnosis, years (IQR)	5(3–10)	5(3–9)	14 (7–16)	.000[a]
Sex, N (%)				
Male	383 (59.6)	363 (60.1)	20 (42.6)	.014[b]
Female	260 (40.4)	233 (39.1)	27 (57.4)	
Type of ALL, N (%)				
Pro-B ALL	13 (2.0)	10 (1.7)	3 (6.4)	.075[c]
c-ALL	364 (56.6)	334 (56.0)	30 (63.8)	
Pre-B ALL	174 (27.1)	166 (27.9)	8 (17.0)	
T-ALL	92 (14.3)	86 (14.4)	6 (12.8)	
Genetic variation, N (%)				
Down syndrome	17 (2.6)	17 (2.9)	0 (0)	.627[c]

Abbreviations: IMD = invasive mould disease; ALL = acute lymphoblastic leukaemia; pro-B ALL = precursor B acute lymphoblastic leukaemia with no expression of CD10; c-ALL = common acute lymphoblastic leukaemia; Pre-B ALL = precursor B-lineage acute lymphoblastic leukaemia; T-ALL = T-lineage acute lymphoblastic leukaemia.
[a] Mann-Whitney U Test.
[b] Pearson's Chi-Square Test.
[c] Fisher's exact test.

Table 2
EORTC/MSG classification.

	EORTC/MSG classification	
	Proven *N (sample type)*	Probable *N*
Number of invasive mould disease	17	30
Species		
Aspergillus		
A. fumigatus	10 (liquor n = 1, biopsy n = 7, pleural fluid n = 1, abscess n = 1)	9[$]
A. flavus	1 (biopsy)	1
A. nidulans	1 (biopsy)	
A. terreus	1 (biopsy)	
Not further specified^	1 (puncture)	18[#]
Mucorales		
Lichtheimia corymbifera	1 (biopsy)	
Cunninghamella bertholletiae	1 (biopsy)	
Not further specified~	1 (biopsy)	
Alternaria		2*

^ based on positive GM and/or positive *Aspergillus* PCR and/or histology typical for *Aspergillus*.
[$] 1x positive PCR for *Aspergillus* fumigatus and *Aspergillus* versicolor. 1x mixed infection with *Fusarium* and *Alternaria.*
2x positive culture for *Penicillium* nalgiovense.
~ based on histology typical for *Mucorales* in BAL fluid and lung biopsy.
* 1x mixed infection with *Trichophyton* rubrum.

was 42 days (IQR 33–70). Prior to the presentation of an IMD, no mould-active prophylaxis was administered in the protocol course preceding IMD diagnosis in 32 out of 47 episodes (68%).

In 45 out of the 47 patients with IMD (96%) serum galactomannan was routinely screened. In only two of these patients, a positive galactomannan result was the only indication for further diagnostic work-up. In another three patients, a positive galactomannan result was observed among other clinical symptoms that were associated with a different condition. In these three patients the positive galactomannan result triggered further diagnostic work-up regarding IMD. In another 10 of the 45 patients, positive galactomannan results were observed at any time during the course of the IMD. Serum galactomannan remained negative in 30 patients, including the three patients with a *Mucorales* infection and one with an *Alternaria* infection.

The clinical symptoms at presentation are described in Table 3. In 29 out of 47 episodes (62%), patients presented with persistent fever, in the majority of these episodes during neutropenia (n = 27). In seven of these 29 episodes fever was the single clinical symptom at presentation. Respiratory symptoms were present in 20 out of 47 episodes (43%). In five of these 20 episodes, respiratory symptoms were the single clinical symptom at presentation. CNS symptoms were present in eight out of 47 episodes (17%). Skin lesions were present in five out of 47 episodes (11%).

Table 3
Clinical symptoms at presentation.

Symptoms at presentation	
Fever *N* (%)	29 (61.7)
Neutropenia *N*	27
Respiratory *N* (%)	20 (42.6)
Coughing *N*	11
Dyspnoea *N*	6
Oxygen demand *N*	8
Other[$] *N*	7
CNS *N* (%)	8 (17.0)
Convulsions *N*	5
Reduced consciousness *N*	1
Other[#] *N*	5
Dermatological N (%)	5 (10.6)
Skin leasion(s) *N*	5
Other* *N* (%)	5 (10.6)

[$]Painful respiration; thoracic pain (stuck to breathing); thoracic pain (sharp stab), tachypnea.
[#] headache; bradyphrenia; speech impediments, hand tremors, hand weakness.
*periorbital oedema, jaw pain, stomach ache, numbness in fingertips, circulatory insufficiency; acute thoracic pain.

The involved sites of infection are outlined in Table 4. The lungs were the most frequently affected site of infection, with pulmonary involvement observed in 44 of the 47 patients (94%). In 21 of these 44 patients, the lungs were the only site of infection. Cranial MRI was performed in 37 out of 47 patients, with CNS involvement in 16 out of 37 patients (43%). Eight out of 16 patients did not present with clinical symptoms associated with CNS infection. One of these infections was a rhino-cerebral infections, with involvement of the sinuses and without involvement of the lungs. In total, in four out of 47 patients (8.5%), the sinuses were involved. The skin was involved in five out of 47 patients (11%).

3.2. Treatment

An overview of the IMD treatment is outlined in Table 5. For *Aspergillus* infections (including 1 mixed infection), in 11 of 42 patients (26%) were treated with liposomal amphotericin B or triazole monotherapy. In 31 of 42 patients (74%) were treated with a combination therapy of liposomal amphotericin B and/or a triazole and/or an echinocandin. For *Mucorales* infections (n = 3), two patients were treated with liposomal amphotericin B monotherapy and one patient with a combination therapy of liposomal amphotericin B and a triazole. For *Alternaria* infections (n = 2), one patient was treated with triazole monotherapy and the other patient with amphotericin B and triazole

Table 4
Localisation invasive mould disease.

Pulmonal *N* (%)	44 (93.6)
Cerebral *N*	13
Cerebral/sinuses *N*	2
Cerebral/skin *N*	1
sinuses/nasopharynx *N*	1
skin *N*	1
disseminated* *N*	4
Rhino-cerebral/skin nose/sinuses *N* (%)	1 (2.1)
Skin (disseminated) *N* (%)	2 (4.3)

* 1x CNS involved.

Table 5
Treatment IMD.

Aspergillus infection* *N* (%)	42 (89.4)
Monotherapy with polyene or triazole *N*	11
Combination therapy with polyene and/or triazole and/or echinocandin *N*	31
Mucorales infection *N* (%)	3 (6.4)
Monotherapy with polyene *N*	2
Combination therapy with polyene and triazole *N*	1
Alternaria infection *N* (%)	2 (4.2)
Monotherapy with triazole *N*	1
Combination therapy with polyene and triazole *N*	1
Local therapy	
Rickham/Omaya reservoir *N*	5
Sinuses *N*	2
Interferon gamma *N*	1
Granulocyte transfusion *N*	1
Chirurgic procedure(s)	
Episodes *N*	17
Type of procedure(s)	
Aspergillus spp.	
Removal/drainage abscess (brain) *N*	2
Debridement (brain) *N*	2
FESS *N*	1
Lobectomy *N*	2
FESS/lobectomy *N*	1
FESS/debridement (brain) *N*	1
Debridement abscess (neck) *N*	1
FESS/adenotomy *N*	1
Mucorales spp.	
FESS/Debridement (brain) *N*	1
Lobectomy *N*	2
Alternaria spp.	
Debridement (skin) *N*	2
Aspergillus spp., Fusarium spp., Alternaria spp.	
FESS/debridement (brain/skin) *N*	1
Outcome	
Recovered without sequelae *N*	29
Recovered with sequelae *N*	9
Lobectomy *N*	4
Epilepsy, hemiparesis *N*	2
Incomplete spinal cord injury *N*	1
Convulsions *N*	1
Epilepsy, non-traumatic brain injury, visual complaints *N*	1
Died during IMD episode *N*	8
Lost to follow-up *N*	1

Abbreviations: FESS = Functional Endoscopic Sinus Surgery
* 1x mixed infection

combination therapy.

In seven out of 47 episodes (15%), local therapy was given in conjunction with systemic therapy. Local therapy of the CNS included the administration of mould-active agents using a Rickham/ Omaya reservoir (n = 5) or by local treatment of the sinuses (n = 2).

In 17 out of 47 patients (36%) additional surgery was performed in the context of load reduction for an *Aspergillus* infection (n = 11), a *Mucorales* infections (n = 3), an *Alternaria* infection (n = 2) and for a mixed infection (n = 1). Beyond mould-active therapy, host directed strategies, such as interferon gamma and a granulocyte transfusion, were each administered in one out of 47 episodes (2%).

3.3. Outcome

Eight of 47 patients (17%) died during the IMD episode. Seven of these deaths were likely related to IMD. One patient died because of recurrent leukaemia. In four of these seven episodes, the patient was in complete remission for ALL. Table 5 describes the outcome of the patients who developed an IMD. The 6-week mortality rate after IMD diagnosis was 10.6% (5/47), and the 12-week mortality rate was 14.9% (7/47). One patient died after 12-weeks.

Among 39 surviving patients, 29 resulted in recovery of the patients without sequelae. Nine patients recovered with sequelae, and one patient was lost to follow up.

4. Discussion

By evaluating a large cohort of patients treated according to the standardised treatment protocol for childhood ALL in The Netherlands, we aimed to provide insights into the epidemiology, clinical features, treatment and outcome of IMD in this vulnerable population.

The incidence rate of 7.3% for probable or proven IMD in our cohort is at the upper limit of the incidence rates ranging from 0.5% to 7.1% previously reported in paediatric (sub)populations with ALL [4–9]. In the clinical AIEOP-BFM ALL2009 trial the reported incidence of IMD was 2.6% [6]. The majority of IMD occurred during the induction and first consolidation course (week 0–10) in our cohort, which is in line with the occurrence of invasive fungal disease (IFD) described in other studies with paediatric haemato-oncology populations [4–6,8]. The fact that these infections mainly occur during this phase of treatment can be explained by different factors, such as the use of high dose glucocorticoids, intensive chemotherapy with subsequent severe neutropenia [2,3] and the lack of suitable prophylaxis. In 68% of our population, IMD occurred in the absence of mould-active prophylaxis. The majority of the patients with mould-active prophylaxis received itraconazole and without TDM, potentially leading to sub-therapeutic drug levels. During the early courses of ALL treatment in our study, mould-active prophylaxis was not part of the treatment protocol during the induction course (week 0–5). This is due to the elevated risk of developing neurotoxicity when the chemotherapeutic agent vincristine is combined with azoles [12]. The high occurrence of IMD during the induction and first consolidation course emphasises the need to optimise mould-active strategies during these early ALL treatment courses. More research is needed regarding alternative regimens for mould-active strategies, such as intermittent regimens with either amphotericin B or echinocandins.

While the strength of this study is the uniformity of ALL treatment among our patients, its retrospective nature potentially introduces bias and difficulties compared to controlled studies. The identification of mould infections in our study was based on reported adverse events and serious adverse events, as part of the prospective ALL-11 registry. With this approach, the 'possible' mould infections that were not reported might have been missed. Nonetheless, we believe that we were able to identify all clinically relevant, proven and probable, mould infections in our cohort. Furthermore, two researchers of our group independently categorised the reported mould-infections to reduce potential bias. The (EORTC/MSG) criteria from 2008 were used for categorisation, given the time frame of our study.

Our data shows that paediatric patients with IMD are significantly older than those who do not develop IMD. These results align with a comparable AIEOP-BFM ALL 2009 cohort, where patients aged $\geq$ 12 years had a significantly higher risk of developing IMD [6]. Existing literature indicates that treatment toxicity is typically less severe in younger children compared to older children [13], but the biological basis for this phenomenon remains unclear. Further studies should examine this phenomenon in more detail to understand whether mould-active strategies need to be stratified based on age.

The majority of our patients were routinely screened by assessing serum galactomannan during neutropenia. A positive galactomannan result was the trigger for further diagnostic work-up in only 11% of the episodes. These results indicate that the value of serum galactomannan as early marker for IMD is limited in children with ALL. These results are in contrast with the ECIL-8 guidelines, which suggests comparable performance of serum galactomannan testing between children and adults [14]. Nonetheless, the performance of the serum galactomannan test diminishes with the administration of mould-active agents. Consequently, serum galactomannan screening should be restricted in patients receiving mould-active agents [14].

The clinical symptoms observed at initial presentation in our paediatric cohort were unspecific, with persistent fever and respiratory symptoms being the most prevalent symptoms. Among the affected sites, the significant involvement of the CNS is noteworthy. Particularly as

half of these patients were initially asymptomatic. Our findings are consistent with a cohort of paediatric patients receiving chemotherapy or undergoing HSCT with proven or probable IFD with CNS involvement. Almost one-third of these patients did not initially present with neurological symptoms [15]. This finding underscores the consideration of early imaging for detecting CNS involvement, regardless of CNS symptoms. In an earlier case report comparable results were found regarding CNS involvement and the authors advise screening of extra-pulmonary sites [16]. Furthermore, these findings are in line with the ECIL-8 guidelines, where cranial imaging is recommended in patients with proven or probable pulmonary fungal infection, irrespective of CNS symptoms [14].

Suitable prophylactic strategies need to be explored, specifically during high risk treatment courses as the induction and first consolidation course. We have started a new prophylactic strategy with twice-a-week micafungin during the induction course from August 2018. The use of prophylactic itraconazole is currently optimised by introducing TDM. Regarding IMD treatment, the voriconazole resistance frequency for *Aspergillus* isolates was 21% in our population. As this percentage exceeds the 10% resistance threshold, initial combination therapy in this population seems therefore justified [17].

The impact of IMD in children with ALL has not extensively been described. In the recently published study with a AIEOP-BFM ALL 2009 cohort, of which the treatment protocol closely relates to the ALL-11 protocol, the 6 week mortality rate was 10.7%, and the 12-week mortality rate was and 11.2% [6]. These findings closely align with the rates observed within in our paediatric cohort.

In conclusion, the findings from our study contribute to the existing knowledge of IMD in children with ALL. This knowledge could play a role in refining diagnostic and treatment strategies aiming to improve IMD management and reduce IMD mortality. Based on our findings, the necessity of galactomannan screening could be discussed, specifically during courses with mould-active prophylaxis. Additionally, the notable frequency of CNS involvement highlights the importance of implementing standard brain imaging when IMD is suspected. Future research should focus on effective prophylaxis during at-risk treatment courses, particularly during the induction and first consolidation course.

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CRediT authorship contribution statement

Didi Bury: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Corline E.J. Parmentier:** Investigation, Writing – review & editing, Formal analysis. **Wim J.E. Tissing:** Conceptualization, Investigation, Supervision, Writing – review & editinga. **Rob Pieters:** Writing – review & editing. **Louis J. Bont:** Writing – review & editing. **Roger J. Brüggemann:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Tom F.W. Wolfs:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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