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Invasive fungal diseases in patients with new diagnosed acute lymphoblastic leukaemia

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Summary

Background: Patients with acute leukaemia have a high incidence of fungal infections. This has primarily been shown in acute myeloid leukaemia and is different for acute lymphoblastic leukaemia. Until now no benefit of mould active prophylaxis has been demonstrated in the latter population.

Methods: In this retrospective single-centre study, we analysed the incidence, clinical relevance, and outcome of invasive fungal diseases (IFD) as well as the impact of antifungal prophylaxis for the first 100 days following the primary diagnosis of acute lymphoblastic leukaemia.

Results: In 58 patients a high rate of proven, probable, and possible fungal infections could be demonstrated with a 3.4%, 8.6%, and 17.2% likelihood, respectively. The incidence might be even higher, as nearly 40% of all patients had no prolonged neutropenia for more than 10 days, excluding those from the European Organization of Research and Treatment of cancer and the Mycoses Study Group criteria for probable invasive fungal disease. The diagnosed fungal diseases had an impact on the duration of hospitalisation, which was 13 days longer for patients with proven/probable IFD compared to patients with no signs of fungal infection. Use of antifungal prophylaxis did not significantly affect the risk of fungal infection.

Conclusion: Patients with acute lymphoblastic leukaemia are at high risk of acquiring an invasive fungal disease. Appropriate criteria to define fungal infections, especially in this population, and strategies to reduce the risk of infection, including antifungal prophylaxis, need to be further evaluated.

KEYWORDS
acute lymphoblastic leukaemia, fungal infection, galactomannan, incidence, mortality

1 | INTRODUCTION

Invasive fungal diseases (IFD) can become a life-threatening complication for patients with haematological malignancies. Patients with prolonged neutropenia—especially those with acute leukaemia and recipients of allogeneic stem cell transplantation—are associated with the highest risk of acquiring invasive aspergillosis.[1-3] In an Italian multicentre cohort study, the incidence of fungal infections was 4.6% for all haematological patients, and 12% was the highest rate for patients with acute myeloid leukaemia (AML). The associated mortality due to IFD was approximately 39%.[4] In this study, the rate of IFD in patients with acute lymphoblastic leukaemia (ALL) was

about 6.5%. The incidence of IFD in adult patients with ALL seems to be lower than that in AML, but data in this specific malignancy are limited.[5,6] Mariette et al retrospectively analysed the incidence and outcome in a French multicentre study investigating the treatment of ALL. Here, 65 IFD (6.7%) cases were detected in 969 patients with ALL. In contrast to most data for AML, invasive candidiasis 33 (3.4%) was more often diagnosed than invasive aspergillosis 26 (3.3%). The attributable mortality rates were 21.2% and 15.4%, respectively.

In contrast to the remission-inducing therapy for AML, which is most often based on cytarabine and an anthracycline, protocols for treatment of ALL have a broader and regional variability. This can result in different durations of neutropenia and associated infections. Antifungal prophylaxis with an azole, especially posaconazole, has been shown to be effective in preventing IFD and is generally recommended in AML patients.[7,8] Triazoles for prophylaxis in patients with ALL are not recommended, as interaction with vinca alkaloids may result in increased neurotoxicity.[9-11] In addition, for a combination of itraconazole and cyclophosphamide, an increased hepatotoxicity resulting from a changed metabolism of the latter has been published.[12] A similar effect for other triazoles cannot be excluded. The need for antifungal prophylaxis in lymphoblastic leukaemia is not well defined. Nevertheless, fluconazole and topical antifungals such as amphotericin oral solution, are often administered, but both compounds are not effective against mould infections.

In this retrospective single-centre study, we analysed the incidence, risk factors, and outcome of IFD as well as the clinical evidence for IFD and the impact of antifungal prophylaxis in ALL patients.

2 | PATIENTS AND METHODS

All patients at the University of Würzburg Medical Center with newly diagnosed ALL between May 2005 and June 2015 were included in the study. Additional criteria for inclusion were being aged 16 years or older and receiving remission induction chemotherapy for treatment of ALL at the medical centre. Patients only receiving palliative care or no chemotherapy at our centre, with a history of stem cell transplantation, or insufficient clinical data, were excluded.

Patients were receiving chemotherapy for treatment of ALL according to the GMALL (German Multicentre ALL) protocol. Here, prednisone was given as prophase therapy for 1 week, followed by phase I induction over 4 weeks, consisting of vincristine, daunorubicin, L-asparaginase, and prednisolone. Phase II induction consisted of cyclophosphamide and four courses of cytosine and a CNS-therapy with intrathecal methotrexate. For consolidation, two 5-day courses of Ara C and etoposide were combined with a single dose of intrathecal methotrexate. Thereafter, a re-induction with vincristine, daunorubicin, dexamethasone, cyclophosphamide, and Ara C over a period of 6 weeks was administered. This was followed by a final maintenance therapy with daily mercaptopurine and weekly MTX for 24 months, with monthly pulses of vincristin, and dexamethasone (10 mg/m^2) for 5 days. The GMALL protocol for the elderly

mainly included dose reductions. Although applied several times, the duration of each steroid application was shorter than 10 days.[13]

Patients were identified by retrospective systemic review of the diagnosis related groups coding data system and by reviewing the local centre registry of cancers. All patients fulfilling the inclusion criteria were observed for the following 100 days after the primary diagnosis of ALL. Electronic and paper case report forms, laboratory data and microbiological data were reviewed and documented for data collection. Fever was defined as a temperature of >38.3°C or twice a day of at least 38.0°C. All data were pseudonymised using an 11-digit coding before analysis.

Invasive fungal disease were classified using the criteria defined by the European Organization of Research and Treatment of cancer and the Mycoses Study Group (EORTC/MSG), revised in 2008.[14] In order to better examine patients without proven/probable IFD in more detail, in addition, patients with at least one microbiological and/or clinical criterion (eg positive galactomannan and nodular infiltrate in chest CT) or a microbiological criterion and a host factor but not fulfilling EORTC/MSG criteria for possible, probable, or proven invasive fungal diseases were described as 'patients with sign for IFI' and calculated separately.

For this study, all radiological images were interpreted by local radiologists and in case of signs of mould infection or any unspecific reporting, they were additionally reviewed by a specialist of infectious diseases experienced in diagnosing pulmonary mould infections. As indications for the administration of antifungals were classified retrospectively as prophylaxis, empirical, or targeted therapy, all information at the onset of administration was taken into account. Antifungal prophylaxis was defined as the administration of systemic antifungal agents for at least three days without any sign of fungal disease.

Statistical analyses were performed using the SPSS 23.00 program (IBM). In case of normal distribution of results, the mean and standard deviation (mean ± SD) are reported. Statistical significance was calculated by analysis of variance (AONOVA) and t test. In the case of non-normal distribution of data, the median and interquartile range (Median [IQR_RSB]) are reported. Here, significance was calculated using the Mann-Whitney-*U* test. For cross-classified tables, the Chi-Quadrat test and exact test according to Fisher and Yates were used for calculation. A *P*-value <.05 was considered significant.

Informed consent was obtained from the local ethics committee and the Administrative Department for data protection.

3 | RESULTS

3.1 | Patients

Sixty-three adolescent or adult patients with newly diagnosed ALL were identified in the 10-year study period at our centre. Five patients had to be excluded because insufficient data were available. Of the remaining 58 patients with ALL, 23 were female (39.7%) and 35 were male (60.3%). The median age was 49.2 years (±14.4 years,

range 17-87 years), and was not significantly higher for women (53.1 ± 15.4 years) compared to men (46.6 ± 16.8 years). The median BMI at hospitalisation was 27.2 kg/m² (24.1-31.3 kg/m²) with no underweight cases and three patients above 30 and 35 kg/m², respectively. In 42 patients, B-ALL (72.4%) was diagnosed, while in 13 patients, T-ALL was found (22.4%), and in three patients, an undifferentiated ALL (5.2%) subtype was diagnosed. Treatment in 43 patients consisted of the standard GMALL and 11 patients followed the GMALL elderly protocol, while two only had a prophase treatment and were passed by before further chemotherapy was started. In their medical history, two patients had a rheumatic disorder, 11 had evidence of diabetes mellitus, five a solid tumour (seminoma, prostate-, thyroid-, and two had breast cancers), two had a previous Hodgkin lymphoma and one had already an ALL. The latter occurred more than 10 years prior to the current diagnosis and was therefore not classified as relapse but as a new leukaemia.

3.2 | IFD

According to the EORTC/MSG criteria, two patients (3.4%) had a proven IFD, one systemic aspergillosis, proven by liver biopsy, and one case of candidemia caused by *C parapsilosis*. In five patients (8.6%), probable IFD was diagnosed and in ten patients a possible IFD (17.2%) was diagnosed. Additionally, six patients had at least signs of fungal disease. Of these, three had a positive GM test - one GM and a ß-D-Glucan test- and two showed no microbiological evidence, but a chest CT scan demonstrated infiltrates typical for a fungal infection (Table 1). In total, 39.7% of all patients had at least some criteria for a fungal disease and 35 patients (60.3%) had no signal for a fungal infection.

3.3 | Criteria for IFD in ALL

Host factor: Prolonged neutropenia is the major host factor for patients with acute leukaemia. In this survey, in 35 (60.3%) of all patients, severe neutropenia lasting for more than ten days has been documented, including all 15 patients with probable or possible IFD

and both patients with proven disease. Sixteen of these patients never developed signs of IFD. In four of six patients with a radiological or microbiological sign of infection, this or another host factor was absent. The mean duration of neutropenia for the 35 patients with this positive host factor was 22.2 ± 10.0 days. One patient was receiving an allogeneic stem cell transplant, but a probable IFD was already diagnosed before this procedure.

Radiology: In total, 180 CT scans of the chest were performed (median 3/patient [1-5]); in 49 patients, this was done at least once including all 23 patients with at least one criterion of IFD. Infiltrates of the lung compatible or typical for pulmonary fungal infection were detected in five patients with probable aspergillosis infection, but also in 13 patients with no further evidence of a mould infection.

Microbiology: In total, 635 tests for Galactomannan in serum were carried out (mean 10.95 ± 7.8 per patient). Seven patients had at least one positive result (Figure 1). Of these, three could be classified as probable aspergillosis, but four others either had no host factor or no typical lung infiltrate. Ten bronchoscopies in nine patients (15.5%) were performed, providing evidence of moulds in five patients. One patient had a positive galactomannan serum-test, and *Pneumocystis jiroveci* was detected in BAL. In another patient, bacterial pneumonia caused by *Serratia marcescens* was confirmed by bronchoscopy. Hyphe was demonstrated by microscopy of tracheal secretion in one patient, and three patients had a positive ß-D-glucan test, but no blood culture was positive for yeasts.

3.4 | Antifungals

Antifungal prophylaxis was administered to 26 patients (44.8%) for a median of 20.5 days (10.5-40.5). In most cases, fluconazole was used as prophylaxis (n 23, 71.9%). This compound was changed six times to at least one other antifungal drug (posaconazole [1], caspofungin [4], and liposomal amphotericin B [4]). Eight of the patients developed signs of infection, in contrast to 15 out of 32 patients without antifungal prophylaxis (not significant) (Table 2). No significant effect of antifungal prophylaxis on duration of hospitalisation, days of fever, or incidence of non-fungal infections could be detected.

TABLE 1 Specific findings for six patients with 'signs of IFI' but not fulfilling definitions of ERTC/MSG for IFD; * patients 2 and 3: time between neutropenia and positive GM test was more than 6 wk

Patient	Duration of neutropenia	Radiological criteria	Days of fever (d)	Positive GM
1	—	No	5	1 of 13
2	22 d	No	19	1 of 9
3	27 d	No	11	1 of 3
4	—	3 of 6 chest CTs positive	11	—
5	—	1 of 3 chest CT positive	4	—
6	2 × d total 18 d	5 of 5 chest CTs positive	1	5 of 18 + 1 in BAL

Abbreviations: CT, computer tomography; GM, galactomannan serum test.

Half of all patients received at least one antifungal therapy (n = 29, 50%), which can be classified as empirical in 8 (13.8%), pre-emptive in 11 (19%) and targeted in 10 (17.2%). All patients with possible, probable or proven IFD had an antifungal treatment, but eight out of 35 patients (22.2%), for whom no IFD criterion was documented, received at least one antifungal therapy. The majority of all treated patients received sequentially or in combination more than one antifungal agent, resulting in a mean of 48.5 ± 33.6 daily derived doses per patient. The most frequently administered antifungals have been voriconazole (19), fluconazole (14), liposomal amphotericin B (14), caspofungin (10), posaconazole (5) and anidulafungin (3).

3.5 | Clinical course and outcome

Fever appeared in 51 of the 58 patients at least once, with a median of 5.0 (1.8-11.0) days of fever. Patients without signs of IFD had significantly less fever (median 3.0 days [1.0-5.0]) compared to patients with proven or probable IFD (13.0 days [9.0-21], $P < .01$) and to all patients with at least one criterion for a fungal infection (11.0 days [9.0-18.0] $P < .01$).

The median duration of hospitalisation within the first 100 days after primary diagnosis of ALL was significantly longer for patients with proven or probable IFD (87.0 days, [79.0-101.0 days] P: .004) and for those with at least one sign of infection (84.0 days, [79.0-92.8 days] $P < .001$) compared to all patients without signs of IFD (74.0 days [49.0-80.0 days]. In addition, the duration of stay on an intensive care unit (ICU) was significantly different for patients with proven/probable IFD versus no sign of IFI (9.0 days vs 2.0, P: .04). In 41 patients (70.7%), at least one bacterial infection was diagnosed.
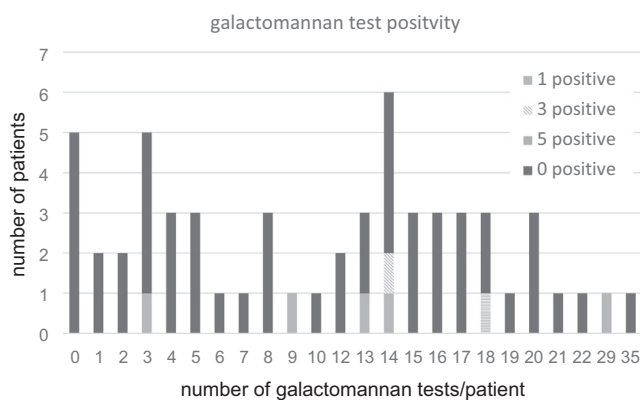

FIGURE 1 Distribution of galactomannan serum tests in 58 acute lymphoblastic leukaemia patients, GM-galactomannan

Here, the rate was also significantly higher for patients with signs (21/23) compared to those without signs of IFI (20/35; P: .007). The mean duration of antibiotic therapy for all patients was 84.2 days (±47.5). The defined daily doses of antibiotic therapy were significantly different for patients without any sign of fungal infection (59.4 ± 36.8 days) compared to patients with at least one criterion of fungal infection (121.8 ± 40.6 days) or patients with probable or proven IFD (122.7 ± 22.1 days).

Six of the 58 patients with ALL died during the observation period, and one was lost in the follow-up. As five of these patients had no sign of fungal infection, IFD was not associated with increased mortality.

4 | DISCUSSION

In this single-centre retrospective study, we investigated the incidence of IFD in 58 patients with a newly diagnosed ALL and analysed the attributable criteria for IFD, risk factors, impact of antifungal prophylaxis and outcome.

With a median age of 49 years and 72% having B-cell ALL, our patients present a typical population for adults with ALL. The age is similar to the mean age listed in the National Registry (Robert Koch Institute) and a previous publication.[15] The applied protocol (GMALL-German Multicentre Study Group on Adult Acute Lymphoblastic Leukemia) is broadly used, at least in Germany, but there are similar protocols in other regions of the world.

In this study, we identified 12.1% of patients with proven or probable IFD. Additionally, 17.2% of patients had a possible infection. In a recent multicentre study, similar rates of proven and probable IFD for ALL patients without (11.7%) and with antifungal prophylaxis (8.7%) were reported.[16] A small Australian study including 32 patients had comparable results with 12.5% of probable/proven and 19.4% of possible fungal infections.[5] These rates are higher than those previously published in Italy and France. In the SEIFEM survey, a rate of 6.5% in 1173 ALL patients was documented, and Mariette et al reported an incidence of 6.7% in their retrospective analysis of a study for the treatment of ALL.[4,15] Similar to these data, Doan et al[6] detected in 98 ALL patients 5% proven and probable and 6% possible IFD. The higher incidence in our population might be caused by a different chemotherapy regimen and degree of immunosuppression or, more likely, be the result of a consistent diagnostic approach.

In contrast to other studies, we report the intensity of the diagnostic investigations performed. This seems to be essential for

TABLE 2 Antifungal prophylaxis

		Invasive fungal diseases (according to EORTC-MSG 2008)			
		No IFD (n = 41)	Possible IFD (n = 10)	Probable IFD (n = 5)	Proven IFD (n = 2)
Antifungal prophylaxis	Yes (n = 26)	21	3	2	0
	No (n = 32)	20	7	3	2

analysing the epidemiological data of IFD. Only if microbiological tests and CT scans are performed regularly, whenever needed or repeatedly (eg, galactomannan twice weekly) and if invasive procedures including bronchoscopy and biopsy are performed whenever indicated, IFD can be diagnosed properly and in a timely manner. Several studies have shown an incidence of IFD, which was much higher in autopsy than previously diagnosed during the lifetime of a patient.[2,17]

With more than ten galactomannan serum tests and three chest CT scans per patient, the recommended standard procedures for diagnosis of an invasive aspergillosis have been conducted in an appropriate way.[18] In particular, CT scans of the lung are important for early diagnosis of IFD.[19,20] In this study, six of seven patients with probable or proven IFD (85.7%) had a pulmonary manifestation.

Nearly 40% of all patients in this study had no host criteria for diagnosis of probable IFD. A duration of neutropenia of more than 10 days, as requested by the EORTC/MSG criteria 2008,[14] is present in nearly all patients with acute myeloid leukaemia receiving remission induction chemotherapy. This situation might be different for patients with ALL and may result from a different chemotherapy protocol with several timely interrupted parts of application for a longer duration. For example, one of our patients had two incidences of severe neutropenia with a neutrophil count below 500/μL for exactly nine days each. Despite a positive galactomannan test and nodular infiltrates in his chest CT, this patient did not fulfil the EORTC/MSG criteria of probable IFD. Altogether, four patients in this study had a positive galactomannan, but no host factor was identified in an adequate time frame. The EORTC/MSG criteria have been recommended to define a homogenous population infected by IFD to enable suitable and comparable clinical trials of antifungal therapy. It seems reasonable that if these criteria are used for clinical practise or epidemiology, the rate of IFD in ALL patients or in other haematological malignancies is underestimated, for example with repeated courses of slightly shorter durations of neutropenia,.

The EORTC/MSG criteria for the definition of a possible fungal disease, especially aspergillosis, strictly include cases with host factors and clinical evidence, but for which mycological evidence is lacking. In our study, a high rate of galactomannan testing is documented, but the formal host factor is not applicable for all patients. We therefore analysed and listed patients separately, which did not fulfil all criteria for a probable or proven IFD but had some evidence for a fungal infection, at least either a positive microbiological test or a radiological sign. This group included 6 further patients (10.3%), all of whom received an antifungal prophylaxis or therapy. Therefore, adding this group more likely presents the clinical indication and the need for antifungal treatment in ALL.

Eleven fungal pathogens have been isolated, including *Aspergillus* spp. and *Candida* spp., four times each. In two additional patients, hyphal pathogens have been demonstrated by microscopy, and here, aspergillosis is also probable. This distribution of fungal germs, although small in number, is similar to previously published data.

Pagano reported that 57.6% of IFD cases in haematological patients were caused by *Aspergillus* spp. and 32.5% *Candida* spp.[4] Other surveys had a similar distribution of candidiasis and aspergillosis.[15,21]

In our study, the overall survival in patients with ALL was high, and fungal infections had no impact on mortality. This is in contrast to most data and may be supported by intensified diagnostic tests and early initiation of therapy. Nevertheless, acquiring a fungal infection had a significant effect on the clinical course of the patients. Patients with proven or probable IFD—but also the group of patients with possible IFD or just signs of fungal infection—had a significantly prolonged hospitalisation compared to the group of patients without criteria for IFD. Patients with proven or probable fungal disease were hospitalised for an additional 13 days and in a median 1 week longer in the ICU. Thus difference is not only clinically relevant, but adds substantial costs to the clinics or healthcare budget for the treatment of fungal infections.

Antifungal prophylaxis might be a tool to avoid this infectious complication. In the study reported here, prophylaxis had no impact on the incidence of fungal disease. Most of our patients were receiving fluconazole, which is not effective in preventing mould infections. A multicentre international phase III study, comparing liposomal amphotericin B 5 mg/kg intravenously or placebo twice weekly, was not able to demonstrate a reduction of fungal infections in ALL patients either.[16] Taking into account the relevant incidence of IFD in our study and in similar populations, new approaches to define and prevent fungal infections in ALL patients are warranted.

Our study has several limitations. Mainly, it is a small single-centre cohort that is analysed retrospectively. On the other hand, the documented intense diagnostic tools support reliable results and add information to already published information.

5 | CONCLUSION

We demonstrated a relevant incidence of IFD in patients with newly diagnosed acute lymphoblastic leukaemia. This infection had an impact on the clinical course of the patients. Definitions for IFD in this specific cohort of patients must be discussed, and strategies to avoid this infection are needed.

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