Incidence, Risk Factors and Prophylaxis use Concerning Invasive Fungal Infections in Children with Newly Diagnosed Acute Lymphoblastic Leukemia

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ABSTRACT

Background. With achievable acute lymphoblastic leukemia (ALL) survival rates of 80-90%, non-leukemic events lead to a high proportion of treatment failure. An important cause of morbidity and mortality related to intensified chemotherapy is infection.

Procedure. In this study, the incidence, severity and related pathogen of severe invasive fungal infections (IFI) in the induction and intensification phase reported during the Dutch Childhood Oncology Group (DCOG) ALL-10 protocol were evaluated. IFI grade 3 /4 and grade 5 (death) were reported. Also risk factors for IFI were studied. Additionally, the antifungal policy of all Dutch pediatric oncology centers according to two Dutch national protocols were compared.

Results. Out of 776 patients, 38 cases (5%) of severe IFI were revealed. 35/38 cases (92%) occurred during the induction phase. 33/38 cases (87%) were graded as severe IFI (grade 3 /4), and the others as grade 5. The pathogen was significantly related to the severity of IFI (p = 0.024). In 19 cases (50%) IFI was caused by candida; none of these were fatal. 17/38 (45%) patients had an IFI caused by aspergillus of which 4 were fatal. Regarding all IFI, younger median age (OR, 1.5; CI 0.037;0.834) and Down syndrome (OR, 4.7; CI 1.880;11.545) were risk factors for development of IFI.

Conclusions. Administration of an antifungal agent should be (re)considered during the induction phase. This agent should especially be effective against aspergillus. Younger median age and Down syndrome as risk factor for IFI should be confirmed by other studies.

Key words: Childhood Acute Lymphoblastic Leukemia; fungal infection; incidence; prophylaxis

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer. It represents approximately 25% of cancer diagnoses among children younger than 18 years of age, with a peak incidence at 2 till 6 years.[1] Due to the contemporary modern combination chemotherapy protocols to treat childhood ALL and the introduction of supportive care, very high cure rates have been reached. Almost 80-90% of the children achieve continuous remission (5-years event-free survival).[1] However, morbidity and mortality due to intensified chemotherapy is a significant burden for children receiving therapy [2-4]; with infection as the most common cause.[3,5,6] In particular, children with prolonged neutropenia and/or severe immunosuppression are at increased risk for infection and other morbidities.[4,5]

Invasive fungal infection (IFI) are major contributors of infections.[5,7] A recent IBFM study revealed 144 cases (3%) of IFI, from a total of 4867 ALL patients.[8] They also found that higher age and female gender appeared to impose a significant risk for the development of IFI. Long-term morbidities could be associated with severe IFI despite of successful antifungal therapies. In addition, chemotherapy is often delayed, which can lead to an increased risk of ALL recurrence.[3]

Itraconazole is often used as an antifungal agent in the current treatment protocols.[2,4] However, studies have shown that in the induction phase of the ALL treatment the use of this agent could lead to severe adverse events (AE) of vincristine (VCR).[2,9,10] This can be explained by the inhibition of CYP3A4 by itraconazole and P-glycoprotiene.[9,10] For this reason, Dutch pediatric oncology centers do not administer itraconazole in induction anymore, and up till now in some pediatric oncology centers no other antifungal agent is given. However, using corticosteroids and higher intensity chemotherapy, fungal prophylaxis during induction therapy seems to be useful to decrease the risk to develop IFI.[11,12] To study this hypothesis, more insight in the need and effectiveness of fungal prophylaxis is warranted.

The aim of this study was to reveal and compare the incidence and severity of IFI between the induction phase and the intensification[1], and between the Dutch pediatric oncology centers during the Dutch Childhood Oncology Group (DCOG) ALL-10 protocol. Additionally, differences in the antifungal policy between these centers were studied. Also, risk factors of IFI were evaluated.

[1] During the induction and intensification treatment, a comparable combination of chemotherapy is being administered. These are: vincristine, anthracycline, asparaginase and a glucocorticoid (prednisone or dexamethasone). Prednisone is used in the induction and dexamethasone in the intensification.

METHODS

Patients

Children were uniformly treated according to the DCOG ALL-10 protocol. This was a nation-wide prospective, multicenter cohort study wherein all children and adolescents between the age of 1 year till 19 years were treated. Patients were included between 1 November 2004 and 1 April 2012. The treatment protocol was used in seven pediatric oncology centers. Since 2012, ALL is treated according to the DCOG ALL-11 protocol for children and adolescents (1-19 year).

Children were stratified into three risk groups based on levels of minimal residual disease (MRD) during initial treatment: standard risk (SR), medium risk (MR) and high risk (HR). 25% of patients received SR therapy, 65% MR and 10% HR therapy.[13] Assignment to the medium risk group was based on a prednisone good response at day 8 and cytomorphological complete remission at day 33 and minimal residual disease (MRD) positivity at day 33 and/or day 79, but MRD level at day 79<10^{-3} and no presence of the t(4;11) (q11;q23) translocation or the corresponding fusion gene MLL/AF4 in the leukemia cells at diagnosis.

The ALL-10 treatment protocol was approved by the Institutional Review Board and was monitored by members of the DCOG, which reviewed safety and efficacy data annually. Informed consent was obtained from all parents/guardians and from patients (if 12 years or older).

Incidence and Severity of IFI

Data collected during the ALL-10 protocol include all AE's and serious adverse events (SAE's) of the participating patients.

The incidence, severity and pathogen of IFI were studied using the ALL-10 database. All induction (phase 1a and phase 1b) patients were studied, and those who were stratified as MR were evaluated for the occurrence of IFI. Of the MR patients, the first 19 weeks (intensification phase) were included in this study. The severity of IFI was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (appendix II).[14] In case of grade 3/4 the patient received intravenous (IV) antifungal therapy. The pathogen was divided into three groups: aspergillus, candida and others.

Additionally, antifungal policies were studied to compare the strategies used in the different treatment centers. Designated pediatric oncologists from all centers were invited to

complete a questionnaire concerning their antifungal policy during the ALL-10 and ALL-11 protocols (appendix I).

Statistical Analysis

To compare patient characteristics between patients with or without IFI, the Mann-Whitney U-test for continuous variables and the Fisher's exact test for categorical variables were used. Patients with IFI were analysed for incidence in a two-by-two contingency table for severity (severe = grade 3 /4; death = grade 5) and of whom the pathogens were known by using the Fisher's exact test. This test was also used to evaluate the influence of antifungal agents on the incidence of IFI in the total population during the induction phase 1a.

Since July 2007 the antifungal agent itraconazole was not administered anymore during induction 1a. To evaluate whether this adjustment affected the incidence of IFI, two periods were evaluated (November 2004 – July 2007 and July 2007 – April 2012) on incidence of IFI during the induction phase 1a by using the Wilcoxon signed ranks test.

To determine which variables contributed to the risk for developing IFI, multivariate logistic regression analysis was conducted. The following putative risk factors were investigated: age at diagnosis, gender and Down syndrome.

Statistical analyses were performed using the software packages SPSS for Windows version 21 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 5.01 (GraphPad Prism Inc., San Diego, CA, USA). A two-sided p-value < 0.05 was considered statistically significant. Data are presented as medians (ranges) unless otherwise specified.

RESULTS

Patients

A total of 776 patients were included in this analysis (54% boys). The median age was 5.0 years (range 1-18 years). The majority of the patients (56%) was between the 2 and 6 years of age. A number of 662 patients (85%) had B-ALL and 489 out of 776 patients (63%) were stratified as MR.

Table 1 shows that there were no significant differences between groups; except for Down syndrome. The detailed IFI patients are shown in appendix III.

Table 1. Characteristics of patients with and without IFI

Characteristics	**No IFI** N (%)	**IFI *** N (%)	***P*-value****
Patients	738 (95%)	38 (5%)	
Gender			0.09
Boys	403 (55%)	15 (39%)	
Girls	335 (45%)	23 (61%)	
Median age (range) at diagnosis	5.0 (1-18)	4.0 (1-18)	ns
Age category 1-9 yr	557 (75%)	32 (84%)	
Age category 10- 18 yr	181 (25%)	6 (16%)	
Down syndrome	33 (5%)	7 (18%)	**0.002**
Immunophenotype			ns
B-ALL	626 (85%)	34 (90%)	
T-ALL	112 (15%)	4 (10%)	
Risk Group			ns
SR	187 (25%)	6 (16%)	
MR	467 (63%)	22 (58%)	
HR	76 (10%)	5 (13%)	
Unknown (missing)	8 (1%)	5 (13%)	

*Grade 3 /4 and grade 5

** All Fisher's Exact Tests, except for "Risk Group" which was evaluated with the Chi Square Test.
ns, not significant.

Incidence and Severity of IFI

A total of 38 patients (5%) had an IFI during the induction 1a, induction 1b or intensification (Table 2). 35/38 IFI (92%) occurred during induction and 3/38 (8%) in the intensification. The incidence of IFI showed a range from 0%-10% between the centers of the total of patients treated according to the ALL-10 protocol.

The pathogen was significantly related to the severity of IFI (p = 0.024). In 19 cases (50%) IFI was caused by candida; none was fatal. 17/38 (45%) patients had an IFI caused by aspergillus of which four cases were fatal. 2/38 (5%) patients had an IFI caused by another pathogen than aspergillus or candida, one of these had a fatal outcome. 33/38 cases (87%) were graded as severe IFI and the remaining 5 cases (13%) were fatal.

Table 2. Pathogen and severity of IFI

		Severity			*P*-value
Pathogen		**Grade 3 /4**	**Grade 5**	**Total**	**0.024***
	Aspergillus	13 (34%)	4 (11%)	17 (45%)	
	Candida	19 (50%)	0 (0%)	19 (50%)	
	Others	1 (2.5%)	1 (2.5%)	2 (5%)	
Total		33 (87%)	5 (13%)	38 (100%)	

* Fisher's Exact Test
Grade 3 / 4 = Severe IFI; Grade 5 = Death
Others = zygomycete (severe), candida and aspergillus simultaneous (death)

Antifungal Policy

All centers followed a different antifungal policy during the ALL-10 protocol (appendix IV). Four centers administered an antifungal agent during induction phase 1a. In two of these centers itraconazole was administered. From June 2007 and onwards itraconazole is not prescribed anymore during induction phase 1a. A similar incidence of IFI during induction 1a before (3,4%) and after (3,5%) this adjustment was found (*ns*). No significant difference was found in the incidence of IFI between centers which prescribed an antifungal agent during induction phase 1a and centers which did not (p = 0.162).

Concerning the antifungal policy during the ALL-11 protocol, six centers follow the national consensus supportive care. This implies itraconazole during the phases induction 1b and MR

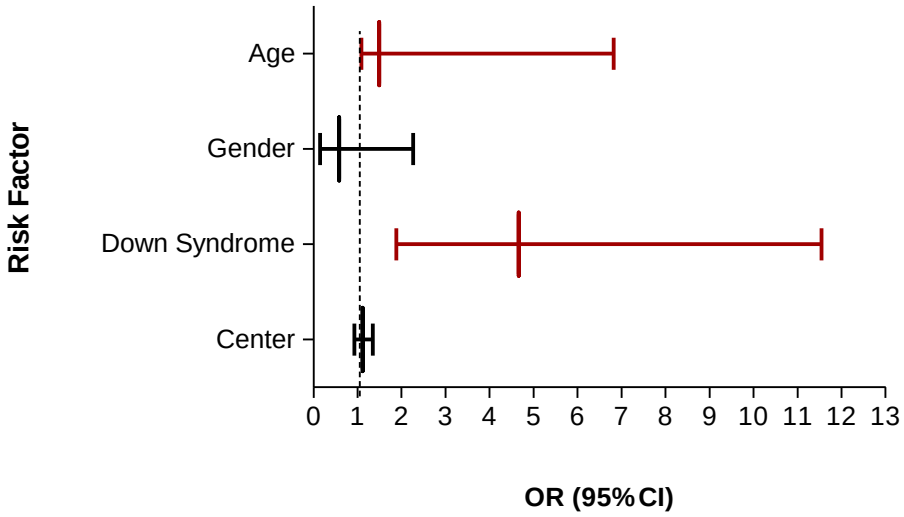
intensification. During other treatment phases no prophylaxis is given. In the remaining center no antifungal agent in none of the treatment phases is administered.

Risk Factors

Multivariate logistic regression analysis after adjustment for treatment center revealed median younger age (OR, 1.5; CI 0.037;0.834) and Down syndrome (OR, 4.7; CI 1.880;11.545) to be independent risk factors for development of IFI (Figure 1). Model fit was assessed using the Hosmer and Lemeshow test. This test of goodness of fit showed that the model was not significant, suggesting it does fit the data (p = 0,086).

The parameter age was logarithmically transformed with the Shapiro-Wilk test. It was found that the log values of age were normally distributed. All these values were back-transformed into median age values.

To account for collinearity the interaction term age*gender was entered into the model, showing no influence (p = 0,091).



OR, Odds Ratio; CI, Confidence Interval.

Fig 1. Risk factors for the development of IFI.

DISCUSSION

This study resulted in a few important findings. First, an incidence of 5% of severe IFI during induction 1a, induction 1b and the intensification phases was revealed. In 92% IFI occurred during the induction phase (1a). The majority of fatal cases of IFI was caused by aspergillus. Second, no significant difference was found in the incidence of IFI between centers which prescribed an antifungal agent during this treatment phase and centers which did not. Third, younger median age and Down syndrome were found to be independent risk factors for the development of IFI.

In the literature different incidences of IFI were reported. Ansari *et al*. found 87 out of 617 (14%) hematological patients with IFI.[15] This was a retrospective study in which IFI cases were extracted from patients' files. Also patients with acute myeloid leukemia were included. Patients with AML have an increased risk of IFI since they are treated according to a more intensive protocol. Therefore, this resulted in a higher IFI incidence. Also, cases with oral candida infection (the majority) were included, which is not defined as IFI in the current study and possibly may explain the major difference in incidence. Sahbudak *et al*. found an incidence of 24%.[16] Between 2005 and 2013, a total of 125 children who were treated for ALL were also retrospectively reviewed. Patients did not receive primary fungal prophylaxis, except oral nystatin, and this may have affected the incidence rate. A recent prospective IBFM study revealed 144 IFI cases during the induction from a total of 4867 patients (3%) treated according to the ALL-BFM 2000 protocol.[8] This percentage is in line with the current findings. However, the comparison of incidence IFI rates across different studies is difficult; because of the heterogeneity in the definitions, along with differences in patient cohorts, in terms of the age range included and the proportion of high-risk patients.

The majority of IFI occurred during the induction phase (1a). This is also found in other studies.[6,8,11,15-17] Also, 4/5 deaths due to IFI were in this protocol phase. The presence of steroids and antracyclines in induction chemotherapy may explain the more frequent occurrence of IFI, since both items could cause severe myelosuppression.[15,16]

The difference in overall incidence of IFI between the centers included in this study analysis, showed a range from 0% - 10%. This wide range could be due a lack of reporting cases of IFI to the DCOG, heterogeneity in the population and/or differences in antifungal policy. For instance, one (middle large) center in the current study would not had a patient with severe IFI. This is in contrast with the other oncology centers.

In this study, no significant difference was found in the incidence of IFI between centers which prescribed an antifungal agent during induction phase 1a and centers which did not (*p* = 0.162). However, it was not possible to check on patient level whether they indeed received an antifungal agent or not. The distribution was based on the antifungal policy per center as answered by the oncologist in the questionnaire. Also, please not that this result is based on a small number of IFI cases. A review that included thirty-two trials involving 4287 patients found that antifungal prophylaxis reduced IFI incidence and the number of deaths.[18] Which encourages the administration of antifungal prophylaxis.

It is known that aspergillus and candida are the most common pathogens causing IFI, and 'others' is less than 10%. (3,5) In this study, the major fatal cases were caused by aspergillus, followed by candida; which is in line with other studies.[8,15] The pathogen was found to be significantly related to the severity of IFI. Aspergillus is widely associated with high morbidity and mortality.[15,17] Therefore, special attention should be paid to this pathogen in the prevention of IFI.

During the ALL-10 protocol, all centers had their individual antifungal policy. The following agents were prescribed to prevent IFI: nystatin, fluconazole, amphotericin B, itraconazole and voriconazole. A recent review described the efficacy of nystatin from relevant clinical trials in patients with severe immunodeficiency.[19] From the 14 included trials, it was concluded that the effect of nystatin (given orally) to immunosuppressed patients was not better than that of placebo. It was shown to be widely recognized that it is a relatively ineffective drug. It was also found that fluconazole was more effective in preventing IFI than nystatin. Moreover, nystatin is only used in the prevention of candida infections and not against aspergillus and other fungi. A recent analysis of 93 pediatric ALL patients who received fluconazole, itraconazole, or posaconazole as oral antifungal monoprophylaxis showed comparably effectiveness.[20] Rates of potentially drug-related adverse events were higher in the fluconazole and itraconazole groups compared to patients receiving posaconazole. Moreover, fluconazole is not effective in the prevention of aspergillus. Voriconazole showed to be effective as an antifungal agent in pediatric ALL patients.[3] Prophylaxis treatment was administered during intensive chemotherapy in a two year period. However, just like itraconazole, this antifungal agent leads to severe AE's of VCR and therefore is not appropriate during induction therapy.[21] A recent review studied thirty-two randomised clinical trials in which amphotericin B, fluconazole, ketoconazole, miconazole, itraconazole or voriconazole compared were compared with placebo or no treatment in

cancer patients with neutropenia.[18] They found that Intravenous amphotericin B was the only antifungal agent that reduced total mortality.

Different potential risk factors exist for the development of IFI. Younger age was found as a risk factor for IFI. This is confirmed by another study, in which incidence of IFI showed a decline in older patients.[15] However, this was not multivariable tested. Striking is the finding in the study of G. Mann, *et al.* They found a significant risk of IFI in children with higher age. Therefore, this need to be further investigated. Also, Down syndrome was found to be an independent risk factor. This predominance has been seen in previous studies.[6,22] It is known that Down syndrome is associated with increased susceptibility to infections, caused by a reduction in B-cell and moderate immunodeficiency.[22,23] Also these patients show an increased response to chemotherapy induced mucositis and prolonged myelosuppression.[22,24] In some studies, female gender appeared to impose a significant higher risk.[6,8] Another study found male sex to be a risk factor of IFI.[11] However, they included all patients with any diagnosed hematological malignancy. The striking findings may therefore be due to population differences. In the present study, there were more girls than boys with IFI, but no significant difference was found. However, it reached statistical significance. Gender as a risk factor for IFI may be due to the result of sex differences in immunological response to infections or differences in toxicity after cytotoxic chemotherapy.[6] However, since this need to be confirmed and the findings regarding whether boys or girls are at risk are contradictory, further study on this possible risk factor is warranted.

For a proper interpretation of the findings, some more study limitations should be mentioned. IFI was revealed from the DCOG ALL-10 database. Despite the accuracy of the database and of this study, cases of severe IFI could have been missed and/or incorrectly graded. Some cases were monitored in the electronical medical patient files, but in the majority this could not be done. Also, please note that the results are based on small numbers of IFI cases.

In conclusion, this study showed an incidence of 5% of severe IFI (grade 3 / 4 and grade 5) in ALL patients; 13% were fatal. The majority of IFI occurred during induction phase 1a, including fatal cases. Therefore, the administration of an antifungal agent should be (re)considered during this treatment phase. This agent should especially be effective against aspergillus. Intravenous amphotericin B may be suggested during induction in the prevention of IFI, but this need to be further investigated. Younger median age and Down syndrome appeared to be potential risk factors; this should be confirmed by other studies.

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APPENDICES

I Questionnaire

II CTCAE version 3.0

III Patients details IFI population

IV Antifungal policy per center during the DCOG ALL-10 treatment protocol

Appendix I - Questionnaire

SCHIMMELPROFYLAXE ALL-10 en ALL-11

In onderstaande acht vragen wordt u gevraagd naar het soort en de dosis schimmelprofylaxe die tijdens (de verschillende behandelfases van) het ALL-10 en ALL-11 protocol in uw kinderoncologisch centrum werd/wordt gegeven.

ALL-10 behandelprotocol

1. **Werd er schimmelprofylaxe voorgeschreven?**

Ja / Nee

2. **Welke soort schimmelprofylaxe werd voorgeschreven tijdens de verschillende behandelfases?**

- **Inductie:**

1A……

1B……

- **Consolidatie/ M:**

……..…..

- **MRG:**

Intensificatie……

Onderhoud:……...

- **HRG:**

……

3. Wat was de dosis en frequentie van de schimmelprofylaxe gedurende de behandelfases?

- **Inductie:**

1A……

1B……

- **Consolidatie/ M:**

……..…..

- **MRG:**

Intensificatie……

Onderhoud:……...

- **HRG:**

……

4. **Is er gedurende ALL-10 iets veranderd in het beleid aangaande schimmelprofylaxe?**
   (Indien *'ja'*, graag zo nauwkeurig mogelijk de datum van deze verandering aangeven)
   (Indien 'nee', ga verder naar vraag 6)

Ja / Nee

5. **Wat was de motivatie voor deze verandering?**

……

ALL-11 behandelprotocol

6. **Is er ten opzichte van het ALL-10 protocol iets veranderd aan het beleid ten aanzien van schimmelprofylaxe in het ALL-11 protocol?**
   (Indien 'nee', einde vragenlijst)

Ja / Nee

7. **Welke soort schimmelprofylaxe wordt momenteel voorgeschreven tijdens de verschillende behandelfases?**
   Graag daarbij de standaard, alsmede de (eventuele) alternatieve profylaxe vermelden.

- **Inductie:**

1A……

1B……

- **Consolidatie/ M:**

……..…..

- **MRG:**

Intensificatie……

Onderhoud:……...

- **HRG:**

……

8. Wat is de dosis en frequentie van de schimmelprofylaxe gedurende de behandelfases?

- **Inductie:**

1A……

1B……

- **Consolidatie/ M:**

……..…..

- **MRG:**

Intensificatie……

Onderhoud:……...

- **HRG:**

……

Ruimte voor eventuele overige opmerkingen/aantekeningen

……

Hartelijk dank voor uw medewerking!

APPENDIX II - CTCAE Version 3.0

The CTCAE contains of a set of criteria for the standardized classification of AE's of drugs used in cancer therapy. AEs are listed accompanied by their descriptions of severity (Grade). It grades 1 through 5 with clinical descriptions of severity for each AE based on the following general guideline:

Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE
Grade 5 Death related to AE

INFECTION						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

APPENDIX III - Patient details IFI-population

Patient	Center	Gender	Down	Age	Diagnosis	Risk Group	IFI grade	Pathogen	Protocol phase	Profylaxes
1	3	Boy	No	1	B-ALL	SR	Severe	Candida	Induction 1a	No
2	6	Girl	No	3	B-ALL	MR	Severe	Others	Induction 1a	Itraconazole
3	1	Girl	No	16	B-ALL	MR	Severe	Aspergillus	Induction 1a	No
4	5	Girl	Yes	8	B-ALL	MR	Severe	Aspergillus	Induction 1a	Fluconazole
5	7	Boy	Yes	5	B-ALL	MR	Severe	Candida	Induction 1a	Amfotericine B
6	1	Girl	Yes	2	B-ALL	-	Death	Aspergillus	Induction 1a	No
7	2	Boy	No	2	B-ALL	SR	Severe	Aspergillus	Induction 1a	Itraconazole
8	2	Girl	Yes	18	B-ALL	-	Death	Aspergillus	Induction 1a	Itraconazole
9	1	Girl	No	3	B-ALL	MR	Severe	Candida	Intensification	No
10	2	Girl	No	3	B-ALL	-	Death	Others	Induction 1b	Itraconazole
11	6	Girl	No	3	B-ALL	MR	Severe	Candida	Induction 1a	No
12	2	Girl	No	5	B-ALL	MR	Severe	Aspergillus	Induction 1a	No
13	3	Girl	No	3	B-ALL	MR	Severe	Candida	Induction 1b	Itraconazole
14	3	Girl	No	10	B-ALL	MR	Severe	Aspergillus	Induction 1a	No
15	3	Boy	No	8	T-ALL	HR	Severe	Candida	Induction 1a	No
16	2	Boy	No	6	B-ALL	SR	Severe	Aspergillus	Induction 1a	No
17	2	Girl	Yes	4	B-ALL	MR	Severe	Candida	Induction 1b	Itraconazole
18	6	Boy	No	1	T-ALL	HR	Severe	Candida	Induction 1b	Itraconazole
19	3	Boy	No	8	T-ALL	HR	Severe	Candida	Induction 1b	Itraconazole
20	6	Girl	No	7	B-ALL	SR	Severe	Aspergillus	Induction 1a	No
21	6	Girl	No	5	B-ALL	MR	Severe	Aspergillus	Induction 1a	No
22	1	Boy	No	4	T-ALL	HR	Severe	Aspergillus	Induction 1b	No
23	2	Boy	No	2	B-ALL	HR	Severe	Aspergillus	Induction 1b	Itraconazole
24	2	Boy	No	2	B-ALL	MR	Severe	Candida	Induction 1a	No
25	1	Girl	No	2	B-ALL	MR	Severe	Aspergillus	Induction 1b	No

26	3	Girl	No	2	B-ALL	MR	Severe	Candida	Intensification	Itraconazole
27	6	Boy	No	2	B-ALL	MR	Death	Aspergillus	Intensification	Itraconazole
28	3	Girl	No	2	B-ALL	MR	Severe	Candida	Induction 1a	No
29	1	Girl	No	2	B-ALL	MR	Severe	Aspergillus	Induction 1a	No
30	1	Girl	No	2	B-ALL	SR	Severe	Candida	Induction 1a	No
31	3	Boy	No	2	B-ALL	MR	Severe	Candida	Induction 1a	No
32	2	Girl	Yes	9	B-ALL	-	Severe	Aspergillus	Induction 1a	No
33	3	Girl	Yes	7	B-ALL	MR	Severe	Candida	Induction 1a	No
34	3	Boy	No	12	B-ALL	-	Death	Aspergillus	Induction 1a	No
35	1	Girl	No	13	B-ALL	MR	Severe	Candida	Induction 1a	No
36	3	Boy	No	2	B-ALL	SR	Severe	Candida	Induction 1a	No
37	3	Boy	No	10	B-ALL	MR	Severe	Candida	Induction 1a	No
38	2	Girl	No	5	B-ALL	MR	Severe	Candida	Induction 1a	No

Appendix IV – Fungal policy per center during the DCOG ALL-10 treatment protocol

Center nr	Protocol Phase	Prophylaxes	Dose / Frequency	Comments
1	No fungal profylaxes was given.			
2	Induction 1a	Itraconazole suspension	6 mg/kg, 1dd	Until June 2007. Afterwards no prophylaxis.
	Induction 1b	Itraconazole suspension	6 mg/kg, 1dd	
	Consolidation	None		
	MR Intensification	Itraconazole suspension	6 mg/kg, 1dd	
	MR Maintainance	None		
	HR	Itraconazole suspension	6 mg/kg, 1dd	
3	Induction 1a	None		
	Induction 1b	Itraconazole suspension	6 mg/kg, 1dd	
	Consolidation	None		
	MR Intensification	Itraconazole suspension	6 mg/kg, 1dd	
	MR Maintainance	None		
	HR	Itraconazole suspension	6 mg/kg, 1dd	
4	Induction 1a	Nystatine	100.000E/kg, 4dd	
	Induction 1b	Nystatine	100.000E/kg, 4dd	
	Consolidation	None		
	MR Intensification	Nystatine	100.000E/kg, 4dd	
	MR Maintainance	Nystatine	100.000E/kg, 4dd	
	HR	Itraconazole suspension	6 mg/kg, 1dd	
5	All phases	Fluconazole	3-6 mg/kg, 1dd	In case of neutropenia.
	HR	Itraconazole p.o/iv	3-5 mg/kg, 1dd	

6	Induction	1a	Itraconazole suspension	6 mg/kg, 1dd	Until June 2007. Afterwards no prophylaxis.
	Induction	1b	Itraconazole suspension	6 mg/kg, 1dd	
	Consolidation		None		
	MR Intensification		Itraconazole suspension	6 mg/kg, 1dd	Not given when vincristine was administered.
	MR Maintainance		None		
	HR		Itraconazole	6 mg/kg, 1dd	
7	Induction	1a	Amfotericine B	150-600 mg, 3dd	
	Induction	1b	Itraconazole suspension	5 mg/kg, 1dd	Replaced by voriconazole suspension when not tolerated.
	Consolidation		Fluconazole suspension	3 mg/kg, 1dd	If microbiological proven candida and/or persistent neutropenia.
	MR Intensification		Itraconazole suspension	5 mg/kg, 1dd	
	MR Maintainance		None		
	HR		Itraconazole suspension	5 mg/kg, 1dd	If hospitalized with severe neutropenia.