Invasive Pilzinfektionen bei Kindern mit akuten Leukämien und nach HSCT

Andreas H. Groll, M.D.

Infectious Disease Research Program
Center for Bone Marrow Transplantation and
Department of Pediatric Hematology/Oncology
University Children's Hospital Münster, Germany

andreas.groll@ukmuenster.de

Disclosures

- **Grants**
  - **Gilead, Merck, Sharp & Dohme, Pfizer**
- **Consultant**
  - **Amplyx, Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Mundipharma, Pfizer, Scynexis**
- **Speakers' bureau**
  - **Astellas, Basilea, F2G, Gilead, Merck, Sharp & Dohme, Pfizer**

Invasive Fungal Diseases (IFDs)

- **Important cause of infectious morbidity in pediatric patients with cancer or HCT**
- **Display constant epidemiological shifts**
- **Remain difficult to diagnose and to manage**
- **Jeopardize control of underlying condition**
- **Associated with high case fatality rates**

Risk Factors and Epidemiology

Pediatric Cancer/HSCT Patients at Risk for Invasive Fungal Diseases

- **Major risk factors are similar as in adults**
- **Underlying conditions, however, their treatment, prognosis and comorbidities are different**
- **Evaluation of the natural incidence of IFDs in pediatric patients relies on historical data of limited quality**
  - **prophylactic/empiric use of antifungals in the majority of contemporary case series**
  - **differences in use of diagnostic procedures, IFD definitions, population denominators, and fungal pathogens included**

Stratification of Risk of IFDs in Pediatric Cancer / HCT Patients

Risk stratum	Patient population
High risk (≥ 10 % p/p)	-acute myeloblastic leukemia -recurrent acute leukemia's -allogeneic HCT -high risk acute lymphoblastic leukemia *
Low risk (≤5 % p/p) **	-standard risk acute lymphoblastic leukemia * -non-*Hodgkin* lymphoma's -autologous HCT
Sporadic occurrence **	-pediatric solid tumors -brain tumors -*Hodgkin's* lymphoma

* depending on the protocol and risk factors including age, steroid exposure, and granulocytopenia

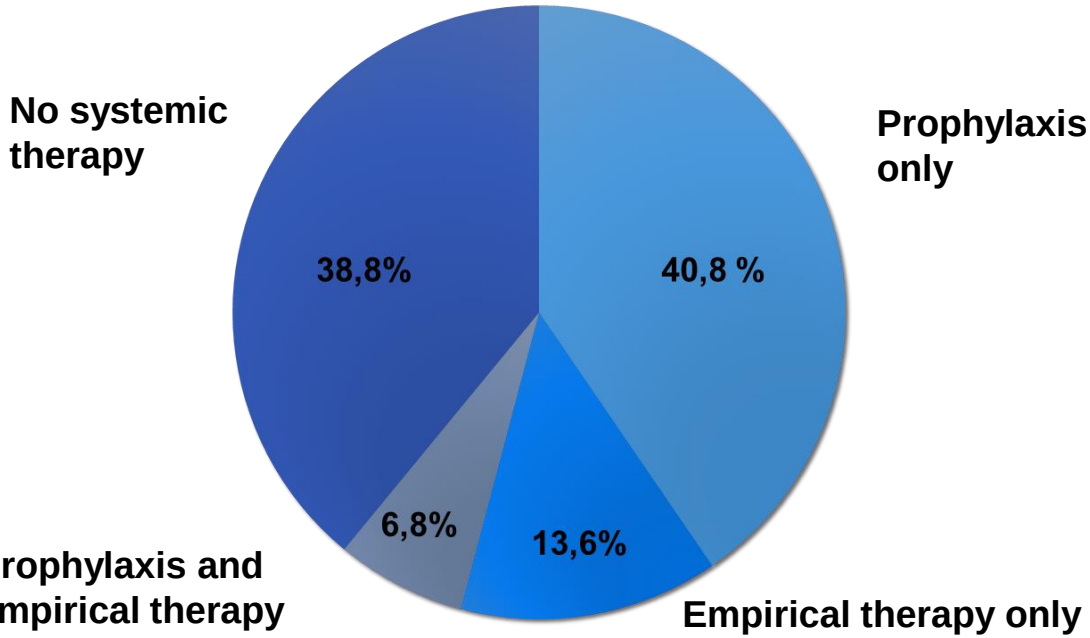
** consider that low and sporadic risk is not equal to no risk

! Case fatality rates between 20 and 70 % dep. on type of IFD and host status

for references, see Groll et al, Lancet Oncology 2021 (ECIL Guideline)

IFDs in Autologous HCT - the Münster Experience (103 Procedures, 2005-2015)

- **no case of invasive yeast or proven/probable mold infection**
- **nine cases (8.7%) with criteria of a possible pulmonary mold infection and received mold active therapy for a median of 14 days (r, 7-35)**
- **one patient died from unrelated toxic endothelial damage at day + 83**



- *low morbidity from IFDs*
- *considerable use of systemic antifungal agents for prevention and/or management of suspected IFDs*

Linke et al. Mycoses 2019

IFDs in Leukemia/Lymphoma - Prospective Multicenter Study (211 Treatments, 2014-2016)

Prospective data collection of all consecutive children with acute leukemia, leukemia relapse, Non-Hodgkin lymphoma treated in 3 European Centers throughout intensive chemotherapy with last follow-up at 12 months

- **11 proven/probable IFDs in 211 chemotherapeutic treatments (5.2%), all during induction/ re-induction chemotherapies; no case fatalities**
  - **candidemia (3), unspec. mold (2), *A.fumigatus/Rhizopus* (1); prob. aspergillosis (5)**
  - ***6 IFDs in 133 ALL patients (4.5%) (4 SR/MR, 2 HR)***
  - ***2 IFDs in 23 AML (8.7%)***
  - ***3 IFDs in 23 leukemia relapses (13.6%)***
  - ***no IFD 32 NHL***
- **Significant differences among centers regarding imaging, and the choice, initiation and duration of prophylaxis**

Lehrnbecher et al. Front Microbiol 2019

IFDs in allo-HCT
– the Muenster Experience

Study Methods

- **Single center, retrospective observational cohort study at *JACIE*-certified transplant center**
- **Inclusion criteria**
  - **Allogeneic HSCT for malignant / nonmalignant disorders between 2005 and 2015**
  - **Admission to Dept. of Pediatric Hematology/Oncology**
- **Cases identified through EBMT registration file**
- **Last follow-up: January 2017**

Linke et al. Mycoses 2019 b

Patient Demographics

- **200 patients / 221 HSCT procedures 2005-2015**
  - **leukemia in 67%, bone marrow failure in 22%**
  - **mean age 9.0 (r, 0,5 – 22) yrs**
  - **standard conditioning regimens**
    - **myeloablative 67.4%, non-myeloablative 32.6%**

- **Median time to engraftment: 22 days (r, 9-50)**
- **Median time to discharge: 34 days (r, 17-194)**

Linke et al. Mycoses 2019 b

Occurrence of IFDs through Day +365

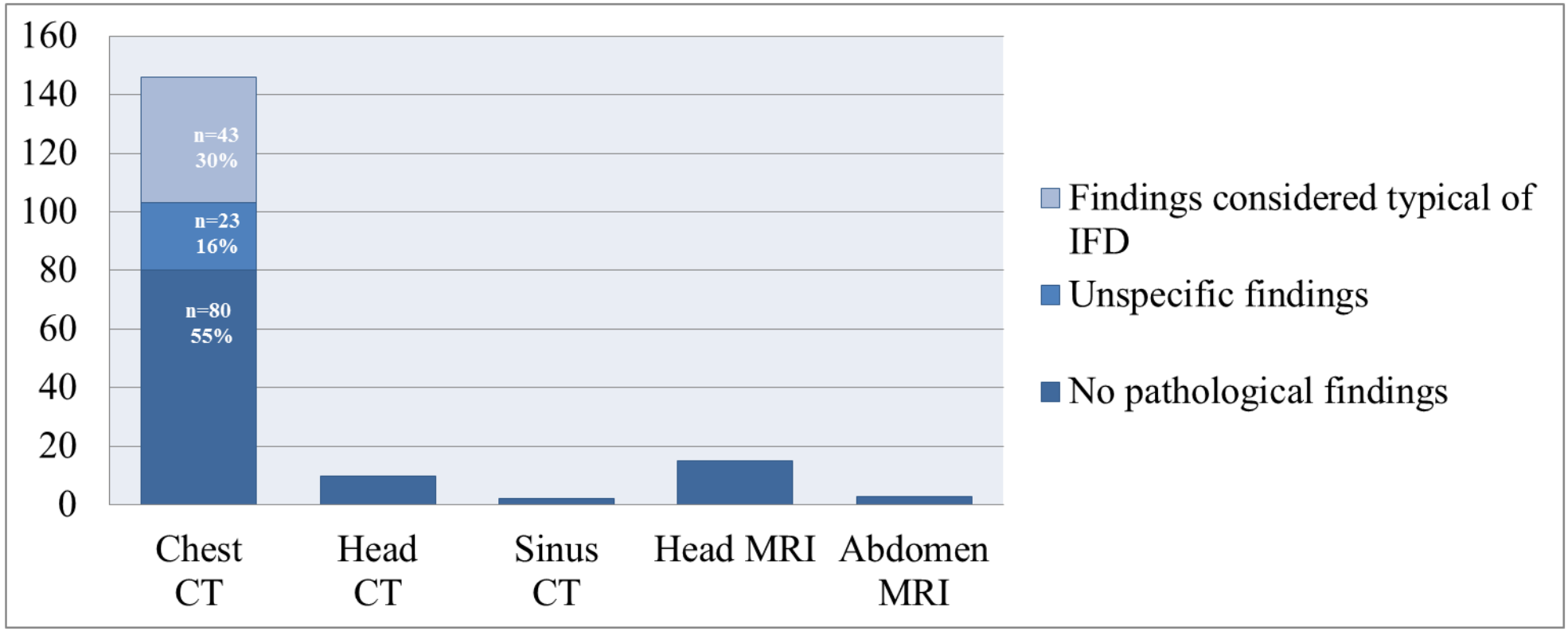
	IFD before HSCT		Tx until engraftment		Engraftment until d +180		After day +180		Total IFDs after HSCT	
	n	%	n	%	n	%	n	%	n	%
possible	18	8.1	23	10.4	6	2.7	0	0	29	13.1
probable	6	2.7	2	0.9	0	0	5	2.3	7	3.2
proven	2	0.9	3	1.4	2	0.9	3	1.4	8	3.6
total	26	11.8	28	12.6	8	3.6	8	3.6	44	19.9
probable + proven	8	3.6	5	2.3	2	0.9	8	3.6	**15**	**6.8 ***

** 7 probable (4 GAL only)*
4 proven IA, 4 candidemia

** 221 allogeneic HSCT procedures in 200 patients*

Linke et al. Mycoses 2019 b

Imaging studies and Principal Findings



** 221 allogeneic HSCT procedures in 200 patients*

Linke et al. Mycoses 2019 b

Bronchoscopy and Microbiology

- ***Bronchoscopy*** documented in 20 cases (9.0%) during the observation period

  In 5 cases (2.3%) one or more criteria for IFD were fulfilled (macroscopic and microscopic aspects, cultures, GM-Antigen from BAL)

- ***Blood culture:*** 4 cases of candidaemia (1.8%), no growth of mold organisms

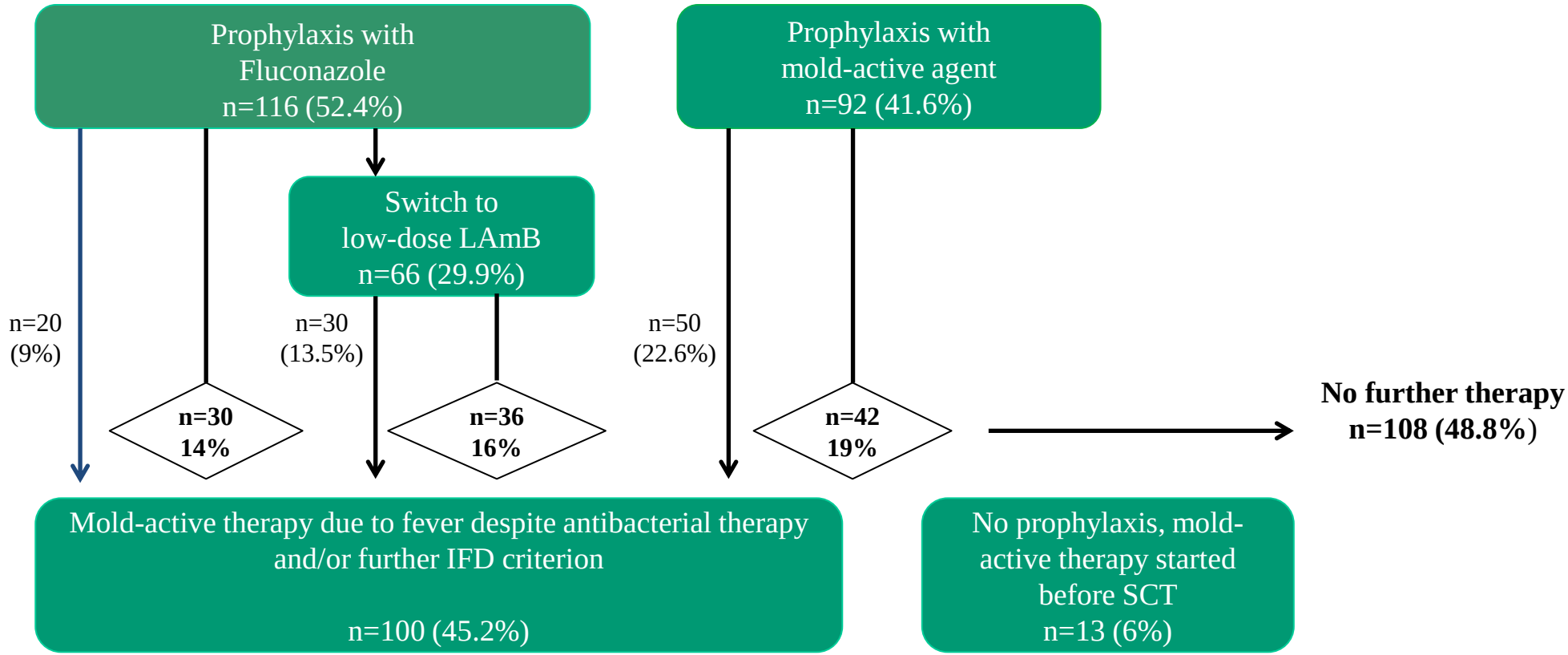
- ***Antigen testing***

Galactomannan	tested cases	positive
blood	60	11
bronchoalveolar/tracheal	9	4
pleural secretion	1	1
Cerebrospinal fluid	1	0
ß-D-Glucan		
blood	unknown	1

- ***PCR*** showed presence of *Aspergillus flavus* in broncho-alveolar fluid in 1 case (0.5%).

Linke et al. Mycoses 2019 b

Antifungal Prophylaxis and Treatment



** 221 allogeneic HSCT procedures in 200 patients*

Linke et al. Mycoses 2019 b

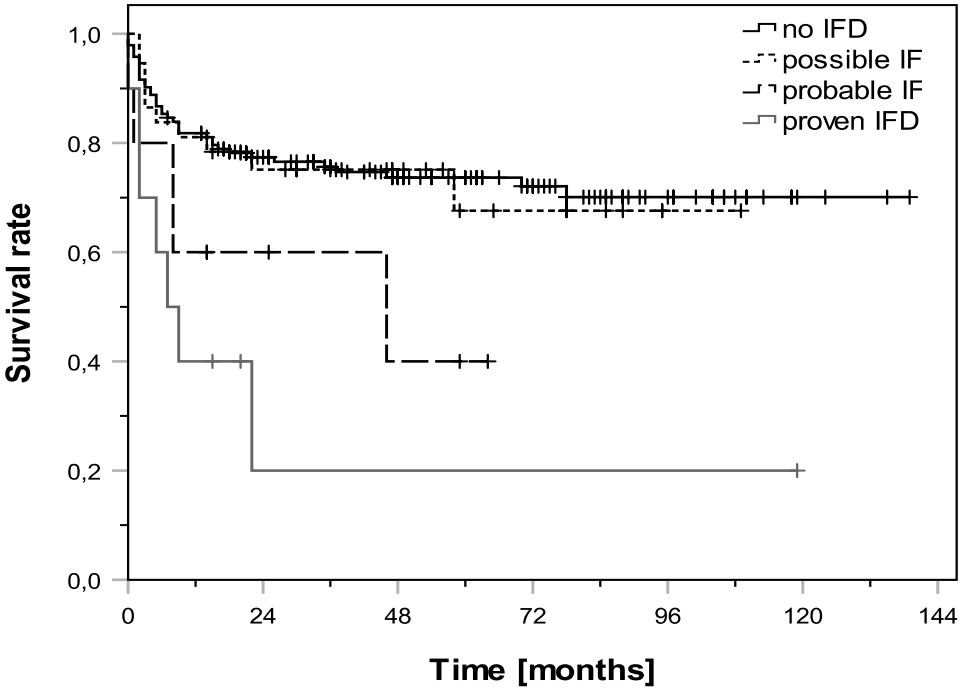
Outcome

- **Overall mortality at the last follow-up, one year after the inclusion of the last patient, was 30% in the entire cohort**
- **In 7 instances, death was attributable to IFD (IFD-related overall mortality: 3.5%; IFD-related case fatality rate: 46.7%)**
- **The diagnosis of proven/probable IFD post-transplant was associated with a significantly reduced survival probability in comparison to patients without IFD and in comparison to patients fulfilling criteria of possible IFDs**

Linke et al. Mycoses 2019 b

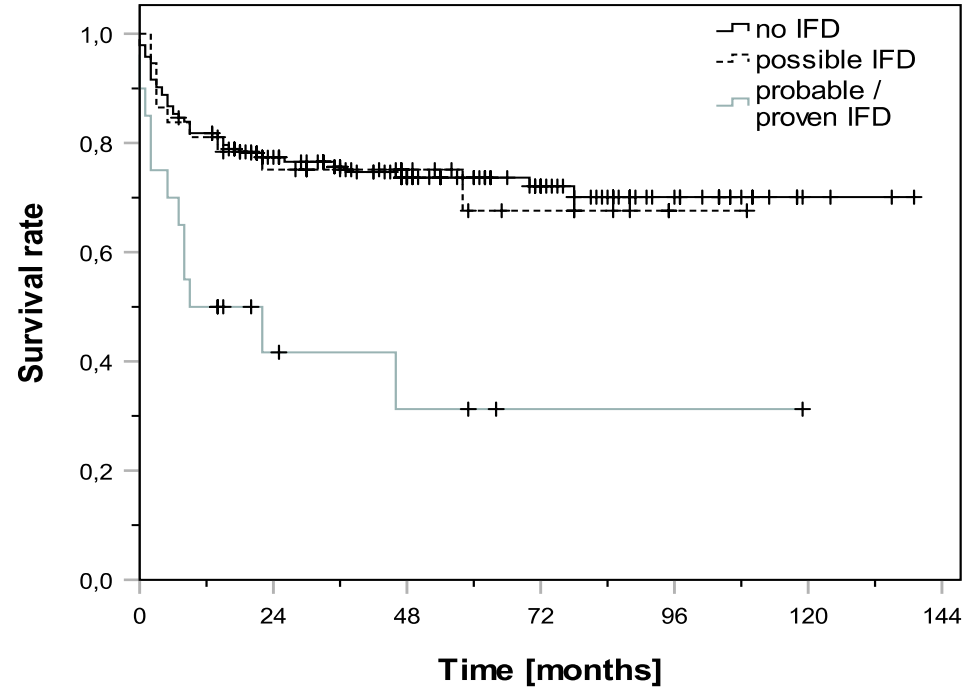
Long-Term Survival Probability

A



no IF vs. proven IFD p=0.001
possible vs. proven IFD p=0.003

B



no IFD vs. proven/probable IFD p=0.001
possible vs. proven/probable IFD p=0.007

** 200 patients with 221 allogeneic HSCT procedures*

Linke et al. Mycoses 2019 b

Predictors for proven/probable IFDs

Univariate Analysis

Predictor for probable or proven IFD after SCT		P-value
Age	(<=9y/>=10y)	0.274
Gender	(male/female)	0.784
Relapse	(none/1.-3.)	0.409
No. of transplant	(first/second,third)	1.000
Donor	(MUD/MMUD/MSD/MMFD)	0.549
Stem cell source	(BM/PBSC/CB)	0.625
Time to engraftment	(<=28d/>28d)	1.000
G-CSF	(yes/no)	0.236
GvHD acute	(grade 0-1/grade 2-4)	0.268
GvHD chronic	(yes/no)	**0.004**
Steroids	(yes/no)	0.269
EBV	(yes/no)	0.582
CMV	(yes/no)	0.312
Adenovirus	(yes/no)	**0.058**
Virusstatic therapy	(yes/no)	0.527
Rituximab	(yes/no)	1.000

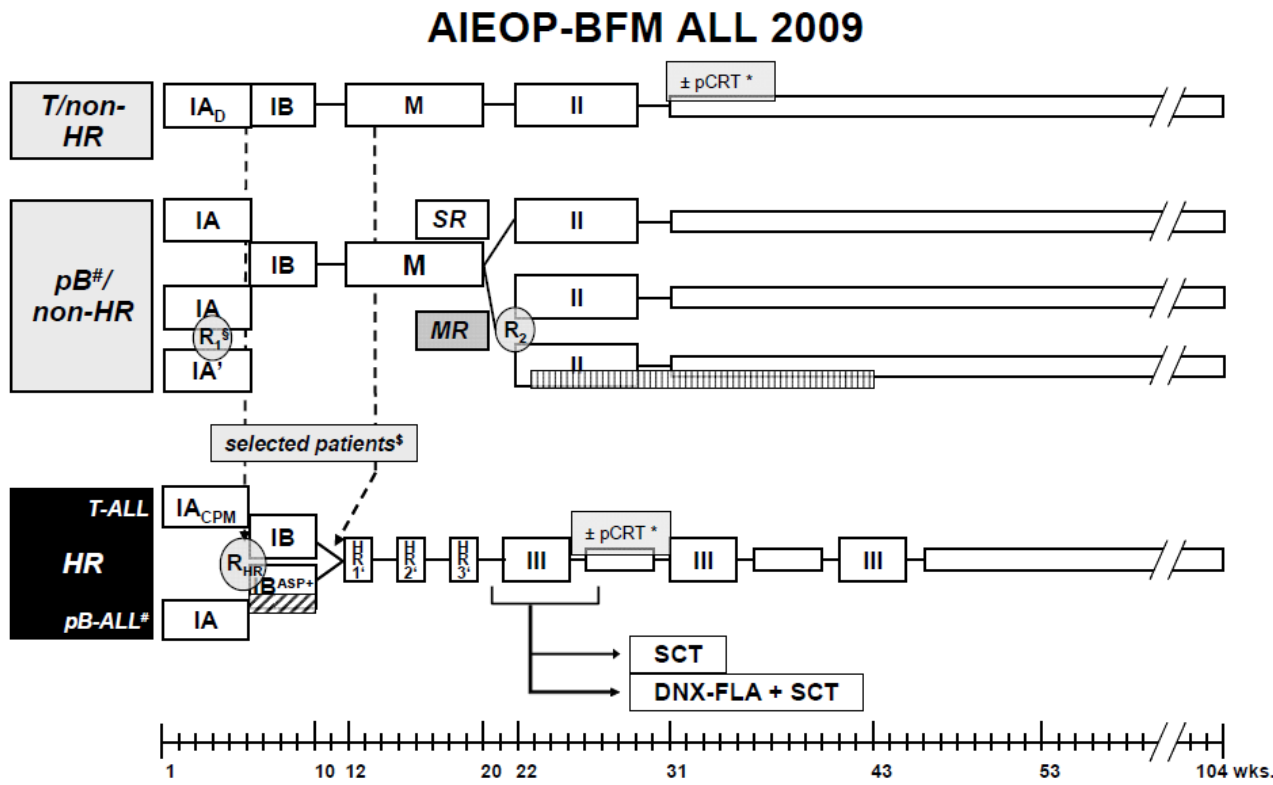
- *Type of prophylaxis (fluconazole vs. mold-active) had no impact on possible/probable/proven IFDs until engraftment (12.1 vs. 13%, p=0.836)*

Linke et al. Mycoses 2019 b

IFDs in AIEOP-BFM ALL 2009, an International Multicenter Trial

Invasive Fungal Diseases in AIEOP-BFM 2009

Analysis of a total of 6136 children (median age, 5.2 years) enrolled in the prospective randomized multi-center study AIEOP-BFM 2009



Lehrnbecher et al, Leukemia 2022

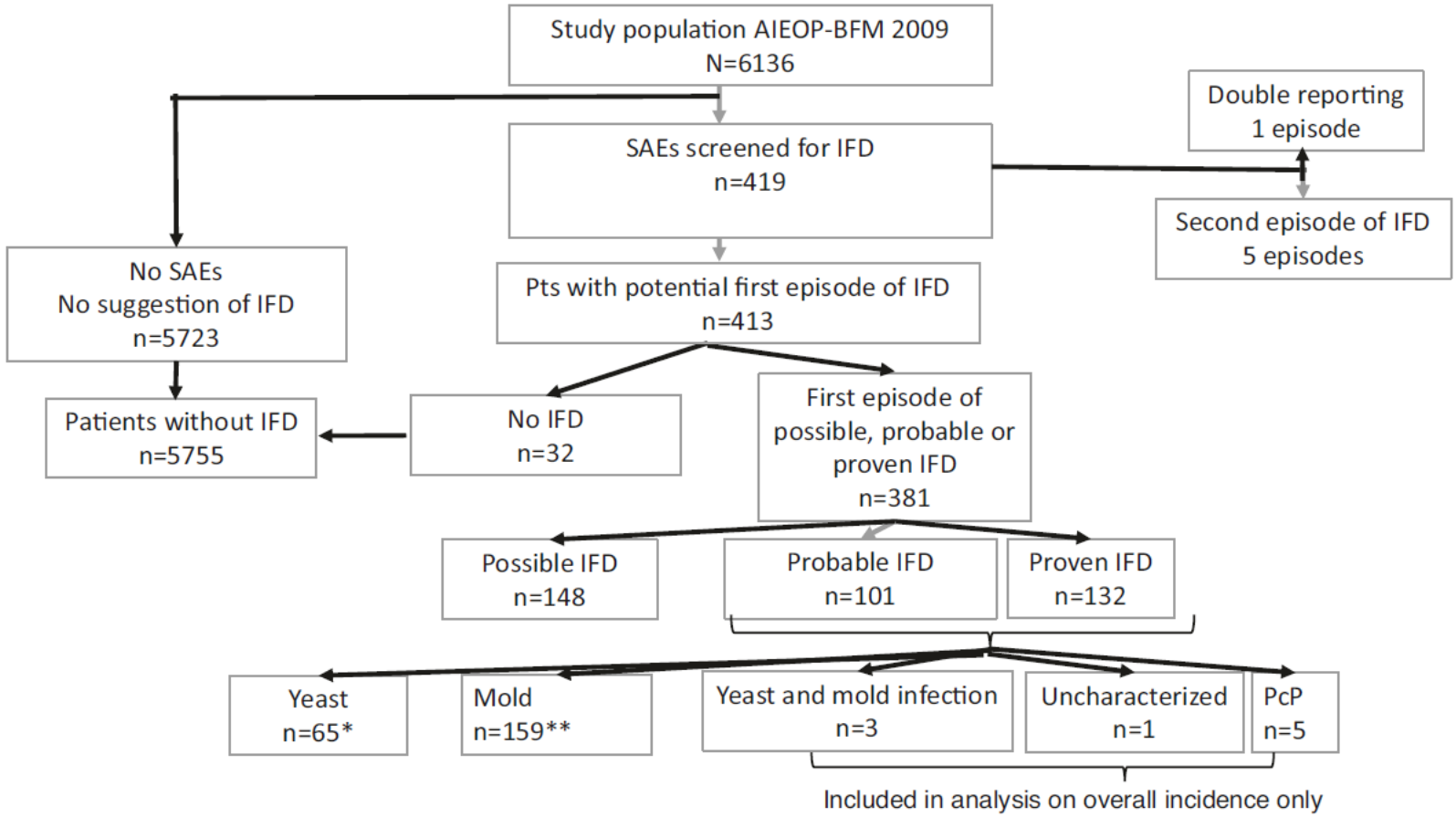
Invasive Fungal Diseases in AIEOP-BFM 2009

Country	n
Italy	2045
Austria	367
Switzerland	239
Germany	2338
Czech Republic	399
Australia	317
Israel	274
Sex	
male	3453
female	2526
Age	
0-<2 years	420
2-<6 years	2985
6-<12 years	1537
12-<15 years	567
15-<18 years	474
Down Syndrome	
no	5832
yes	147
Immunophenotype*	
Precursor B All	5125
T-ALL	832
Blast count in bone marrow on day 15 by flow-cytometry	
<0.1%	2040
<10%	2969
≥10%	720
Risk group (final)	
Standard risk (SR)	2004
Intermedium risk (MR)	2632
High risk (HR)	1343

Lehrnbecher et al, Leukemia 2022

Invasive Fungal Diseases in AIEOP-BFM 2009

- **Reporting of IFD as SAE was mandatory**
- **2 experts independently categorized IFD as prov/prob/possible IFD *(Donnelly 2019)***



Lehrnbecher et al, Leukemia 2022

Invasive Fungal Diseases in AIEOP-BFM 2009

	No IFD [n (%)]	Proven/probable IFD [n (%)]
Country		
Italy	1985 (97.1)	60 (2.9)
Austria	360 (98.1)	7 (1.9)
Switzerland	231 (96.7)	8 (3.3)
Germany	2257 (96.5)	81 (3.5)
Czech Republic	375 (94.0)	24 (6.0)
Australia	292 (92.1)	25 (7.9)
Israel	255 (93.1)	19 (6.9)
Sex		
male	3332 (96.5)	121 (3.5)
female	2423 (95.9)	103 (4.1)
Age		
0-<2 years	405 (96.4)	15 (3.6)
2-<6 years	2904 (97.3)	81 (2.7)
6-<12 years	1495 (97.2)	43 (2.8)
12-<15 years	525 (93.4)	37 (6.6)
15-<18 years	426 (89.9)	48 (10.1)
Down Syndrome		
no	5614 (96.3)	218 (3.7)
yes	141 (95.9)	6 (4.1)
Immunophenotype*		
Precursor B All	4956 (96.7)	169 (3.3)
T-ALL	778 (93.5)	54 (6.5)
Blast count in bone marrow on day 15 by flow-cytometry		
<0.1%	1979 (97.1)	61 (2.9)
<10%	2880 (97.0)	89 (3.0)
≥10%	659 (91.5)	61 (8.5)
Risk group (final)		
Standard risk (SR)	1952 (97.4)	52 (2.6)
Intermedium risk (MR)	2553 (97.0)	79 (3.0)
High risk (HR)	1250 (93.1)	93 (6.9)

*only evaluable data included

Lehrnbecher et al, Leukemia 2022

Mortality due to IFD in AIEOP-BFM 2009

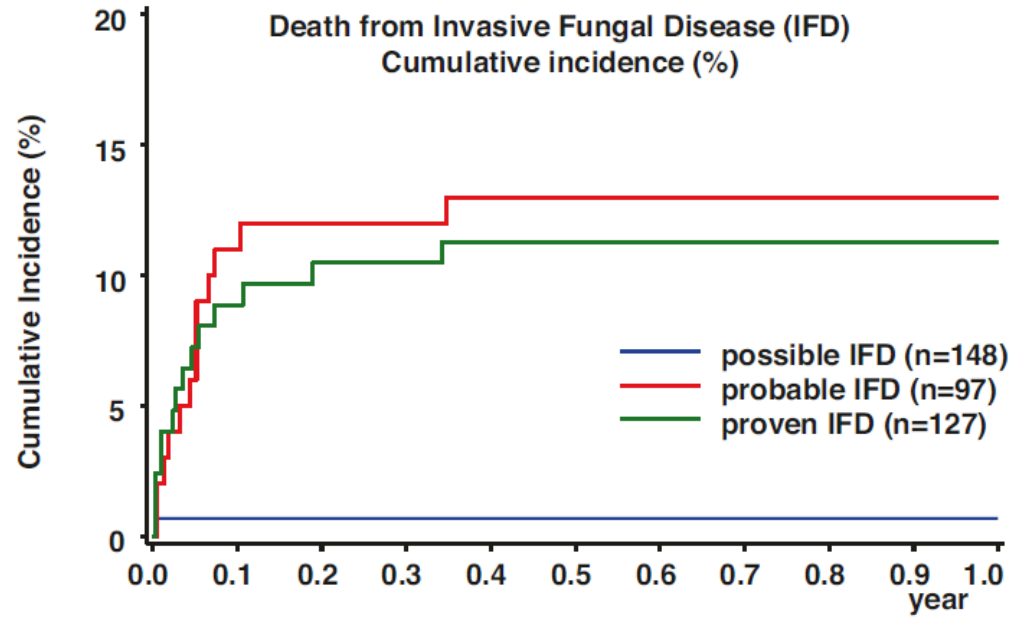
Mortality of IFD at 6 and 12 weeks after diagnosis:

- **10.7% and 11.2%, respectively**

Mortality of IFD at 1 year after diagnosis:

- **overall 12.1%**
  - **6.1% yeast infection**
  - **14.5% mold infection**

Overall mortality from IFD in the study population: 0.44%



Lehrnbecher et al, Leukemia 2022

Impact of IFDs on Outcome of Pediatric ALL

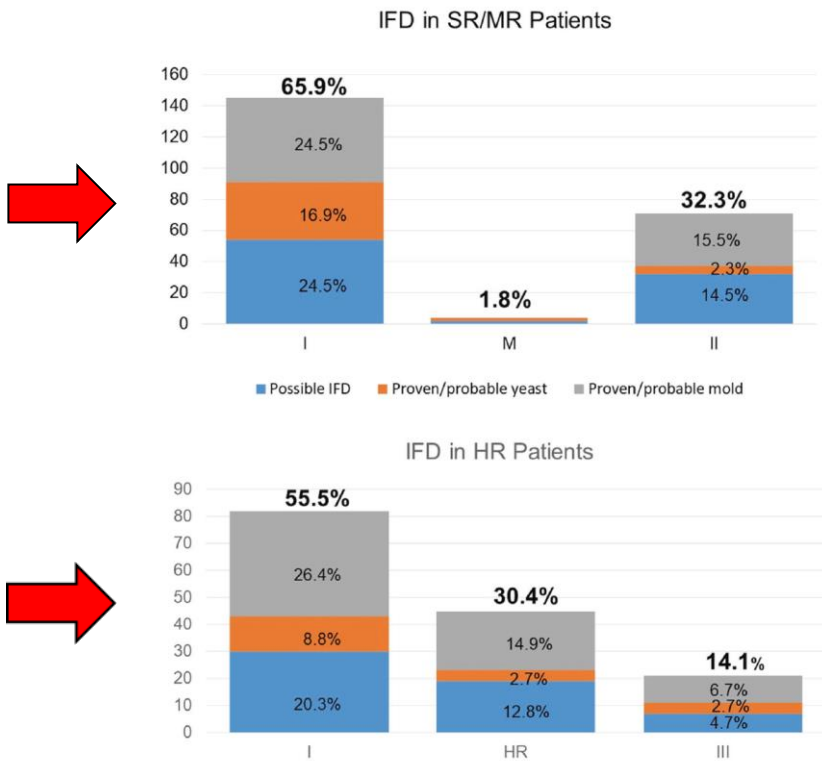
	Event-free survival			Overall survival		
#	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI
Age						
0-<12 years	<0.001	1.34	1.14-1.57	<0.001	1.73	1.38-2.16
12-<18 years						
Proven/probable IFD						
no	<0.001	1.88	1.43-2.47	<0.001	2.58	1.85-3.61
yes						
Immunophenotype*						
Precursor B All	0.026	0.80	0.66-0.97	0.07	1.25	0.98-1.60
T-ALL						
Genetic aberration						
others	<0.001	0.62	0.50-0.77	<0.001	0.50	0.34-0.75
ETV6/RUNX1						
Blast count in bone marrow on day 15						
<10.%	<0.001	1.52	1.26-1.83	<0.001	1.76	1.36-2.27
≥10%						
PCR MRD (final)*						
SR/MR	<0.001	2.09	1.77-2.47	<0.001	2.668	2.08-3.4
High						

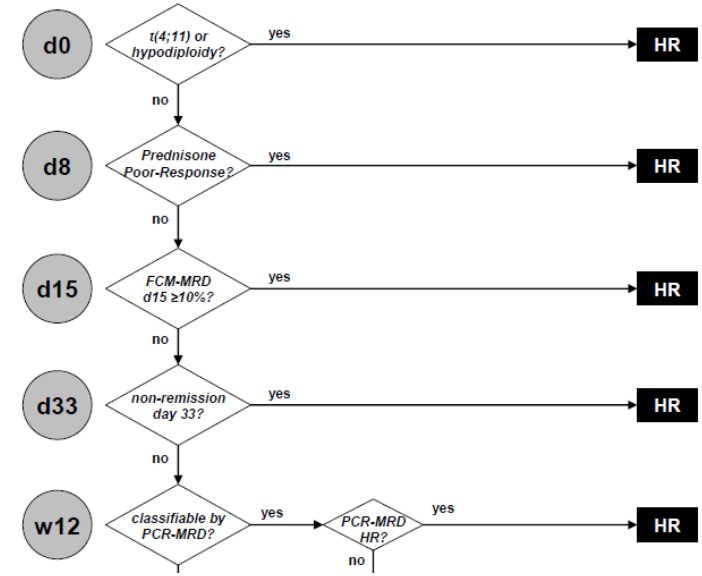
Multivariate analysis EFS and OS

Lehrnbecher et al, Leukemia 2022

Invasive Fungal Diseases in AIEOP-BFM 2009

	All	Invasive fungal disease					
		No		Possible		Proven/probable	
	N	*N*	%	*N*	%	*N*	%
Risk group (final)							
Standard risk (SR)	2043	1952	95.5	39	1.9	52	2.5
Intermedium risk (MR)	2681	2553	95.2	49	1.8	79	2.9
High risk (HR)	1403	1250	89.1	60	4.3	93	6.6





Lehrnbecher et al, Leukemia 2022

Multivariate Analysis to Assess Risk for IFD

			Multivariate analysis		
#	No IFD (n (%)	Proven/probable IFD (n (%))	P value	OR	95% CI
Sex					
male	3332 (96.5)	121 (3.5)	0.09	1.3	0.96-1.7
female	2423 (95.9)	103 (4.1)			
Age					
0-<12 years	4804 (97.2)	139 (2.9)	<0.0001	2.8	2.1-3.8
12-<18 years	951 (91.8)	85 (8.2)			
Down Syndrome					
no	5614 (96.3)	218 (3.7)	0.88	0.93	0.37-2.3
yes	141 (95.9)	6 (4.1)			
Immunophenotype*					
Precursor B ALL	4956 (96.7)	169 (3.3)	0.12	1.3	0.9-1.9
T-ALL	778 (93.5)	54 (6.5)			
Blast count in bone marrow on day 15 by FCM					
<10.%	4849 (97.0)	150 (3.0)	<0.0001	2.3	1.7-3.2
≥10%	659 (91.5)	61 (8.5)			

OR Odds ratio; CI confidence interval; IFD invasive fungal disease

*only evaluable data included

first row standard

Lehrnbecher et al, Leukemia 2022

Summary

Summary

- Incidence rates are within the rates reported in the literature
- Invasive fungal diseases have significant impact upon event-free and overall survival in pediatric ALL and post allo HCT
- Delayed blast clearance, adolescent age (ALL) and presence of GVHD are conditions with significant associations to IFDs
- Data confirm intuitive risks (pancytopenia, augmented immunosuppression) and identify patients with indication for antifungal prophylaxis
- Survival plots seem to validate current disease definitions into proven/probable versus possible infections

www.nature.com/leu

Leukemia

ARTICLE OPEN

Check for updates

ACUTE LYMPHOBLASTIC LEUKEMIA

Invasive fungal diseases impact on outcome of childhood ALL – an analysis of the international trial AIEOP-BFM ALL 2009

Thomas Lehrnbecher[1,13], Andreas H. Groll[2,13], Simone Cesaro[3], Julia Alten[4], Andishe Attarbaschi[5], Draga Barbaric[6], Nicole Bodmer[7], Valentino Conter[8], Shai Izraeli[9], Georg Mann[5], Anja Möricke[4], Felix Niggli[7], Martin Schrappe[4], Jan Stary[10], Ester Zapotocka[11], Martin Zimmermann[12,14] and Sarah Elitzur[9,14]

ORIGINAL ARTICLE

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Epidemiology and management burden of invasive fungal infections after autologous hematopoietic stem cell transplantation: 10-year experience at a European Pediatric Cancer Center

Christina Linke[1,2,3] | Athanasios Tragiannidis[1,2,3] | Martina Ahlmann[2,3] | Birgit Fröhlich[2,3] | Maria Wältermann[2,3] | Birgit Burkhardt[2,3] | Claudia Rossig[2,3] | Andreas H. Groll[1,2,3]

DOI: 10.1111/myc.13029

ORIGINAL ARTICLE

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Epidemiology, utilisation of healthcare resources and outcome of invasive fungal diseases following paediatric allogeneic haematopoietic stem cell transplantation

Christina Linke[1] | Karoline Ehlert[2] | Martina Ahlmann[1] | Birgit Fröhlich[1] | Daniela Mohring[1] | Birgit Burkhardt[1] | Claudia Rössig[1] | Andreas H. Groll[1]

Incidence and Outcome of Invasive Fungal Diseases in Children With Hematological Malignancies and/or Allogeneic Hematopoietic Stem Cell Transplantation: Results of a Prospective Multicenter Study

frontiers in Microbiology

Thomas Lehrnbecher[1], Stefan Schöning[1], Fiona Poyer[2], Jamina Georg[1], Andreas Becker[1], Kathrin Gordon[3], Andishe Attarbaschi[2†] and Andreas H. Groll[3†]*