

Supplementary Material

Patients

In total, 215 immunocompromised patients from a pediatric (n=124) and an adult cohort (n=91) at high risk for IFD were recruited, and 1016 serial PB specimens (n=689 and n=327 from pediatric and adult patients, respectively) were prospectively collected during 376 febrile neutropenic (FN) episodes (n=265 in children and n=111 in adults). The FN episodes with at least two sequential PB specimens amenable to evaluation were considered for further analysis, resulting in a total of 935 PB specimens (n=610 in the pediatric and n=325 in the adult setting) derived from 315 FN episodes (n=205 and n=110, in children and adults, respectively) in 195 patients (n=106 children and n=89 adults) available for comprehensive investigation. The median age of pediatric patients, who were hospitalized at the St. Anna Children's Hospital (Vienna, Austria) or the Princess Máxima Center (Utrecht, the Netherlands), was 6 years (range 0-18; 55% male, 45% female). The underlying diseases in the pediatric patient cohort included acute lymphoblastic leukemia (ALL, 74%), acute myeloid leukemia (AML, 8%), neuroblastoma (4%), lymphoma (3%) and, in rare instances, other malignant disorders (11% in total). The median age of adult patients, who were hospitalized at the Vienna General Hospital (Vienna, Austria), the I. P. Pavlov First Saint Petersburg State Medical University (Saint Petersburg, Russian Federation), or the Hanusch Hospital (Vienna, Austria) was 56 years (range 19-81; 66% male, 34% female). The underlying diseases in the adult cohort included AML (60%), ALL (16%), lymphoma (13%), multiple myeloma (9%) and, in rare instances, other malignant disorders (2%). Diagnoses were established according to the criteria and classification of the World Health Organization (WHO).

Antifungal prophylaxis

In line with the low incidence of IFD at any level, most patients had received antifungal prophylaxis, which was administered before and during the majority of FN episodes analyzed, covering 67.3% (n=74) of episodes in the adult cohort and 82.9 % (n=170) in the pediatric cohort. Information on antifungal prophylaxis in the patients studied is provided in Table S1.

IFD classification

Patients were classified according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) guidelines¹. The IFD probability was determined as follows: i) possible IFD (host criterion plus clinical criterion or positive mycological finding), ii) probable (host criterion plus clinical criterion and positive mycological finding), and iii) proven (host criterion plus successful fungus recovery by culture). In the absence of any host or clinical criterion, or the lack of any mycological evidence for an infection, patients were classified as IFD negative, in line with the EORTC/MSG guidelines¹. Results of the molecular screening methods used in the present study, panfungal PCR and internal transcribed spacer 2 (ITS2) PCR^{2,3}, were not considered in the classification of IFD.

Sample processing

Serum and PB samples were collected during neutropenic episodes at the onset of fever, and subsequently after 24 and 48 hours. The samples were stored at -80°C until analysis. Serum samples were tested for cell wall antigens (galactomannan and 1,3-β-D-glucan) as described⁴. For molecular testing, 2-3 mL of peripheral blood were treated with DNase to remove free DNA, and blood cells were lysed to isolate intact microorganisms. Samples were spiked with PhHV (phocine herpes virus) DNA as internal control to exclude the presence of inhibitors affecting the efficiency of PCR amplification⁵. Enzymatic and mechanical lysis were combined to achieve efficient release of fungal genomic DNA, which was purified on spin-columns included in the MoYsis™ kit and eluted in 100 µl DNase-free water. DNA samples were immediately subjected to analysis by panfungal PCR and ITS2 PCR or stored at -80°C until analysis.

Panfungal PCR

Panfungal PCR was performed as described³. Briefly, the purified microbial DNA was analyzed by a two-reaction real-time PCR protocol covering a large spectrum of fungi (>80 species) including essentially any fungus with potential relevance in the clinical setting, but also many other fungal species not

associated with pathogenicity in humans. An additional PCR reaction detecting previously spiked PhHV (phocine herpes virus) sequences was used as an internal control for the inhibition of amplification⁵. Primers and probes were designed to detect the 28S gene of moulds (reaction I), or yeasts and Zygomycetes (reaction II), respectively³. Each real-time PCR reaction of 25 µl included TaqMan Gene Expression Master mix, primers (4 fmol), TaqMan probe (100 fmol) and DNA template (5 µl). Positive controls (100 fg DNA of *A. fumigatus* and *C. albicans*, respectively), and negative controls (non-template control and water control) were present in each run. Real-time PCR was performed using a TaqMan 7500 Instrument with the standard 9600 Emulation protocol and results were analyzed using the thresholds described in our previous studies^{3,5}.

ITS2 PCR and sequencing

ITS2 PCR was performed as described previously². Briefly, the purified microbial DNA was amplified in a two-round nested PCR reaction using primers designed to bind within conserved regions flanking the ITS2 region. Amplicons of this highly variable region in the fungal genome were used for identification of the fungal genus or species, if possible. The first PCR reaction contained AmpliTaq DNA Polymerase buffer, MgCl₂ (2.5 µM), dNTPs (800 pmol), ITS1 and ITS4 primers (4 fmol), UNG (uracil DNA-glycosylase, 0.5 U), AmpliTaq DNA Polymerase (2.5 U) and DNA template (5 µl) in a volume of 25 µl. The second, nested 50 µl PCR reaction, contained AmpliTaq DNA Polymerase buffer, MgCl₂ (2.5 µM), dNTPs (800 pmol), ITS86, ITS86_krusei and ITS4 primers (4 fmol), AmpliTaq DNA Polymerase (2.5 U) and 6 µl of the first-round amplification product as template. Positive controls (100 fg DNA of *A. fumigatus* and *C. albicans*, respectively) and negative controls (non-template control and water control) were present in each run.

Sequencing

Nested PCR products yielding visible bands upon electrophoresis in agarose gels were purified using a Gel extraction kit (Qiagen, Hilden, Germany) and analyzed by Sanger sequencing using primers flanking the highly variable ITS2 region (ITS1 and ITS4)². Sequences were analyzed by NCBI BLAST⁶ to facilitate

76 fungal identification at the genus level. The ITS2 region is highly variable between fungal genera but
77 does not commonly permit identification of fungal species due to insufficient variability at this level.

78 Prevention of external contamination

79 The measures employed to prevent exogenous contamination as an occasional source of positive PCR
80 assays included blood collection via central venous catheters under sterile conditions, sample
81 processing in laminar flow cabinets, and the use of multiple negative controls in each step of molecular
82 analysis⁷. Moreover, about 85% of the specimens investigated tested negative for any fungal DNA
83 traces, suggesting that contamination was not a relevant issue.

84 Classification of fungal genus pathogenicity in immunocompromised patients

85 While the pathogenicity of certain fungal genera in the immunocompromised setting is well established
86 by experimental and clinical evidence, the clinical relevance of several fungal genera in
87 immunocompromised patients is less clear. It is of note that anecdotal reports have also implicated
88 fungi generally regarded as non-pathogenic in clinically relevant invasive infections in the
89 immunocompromised setting. To assess the reported occurrence of individual fungi in
90 immunocompromised patients, a search in PubMed using the search term "*fungal genus* AND
91 immunocomp* AND patient*" was performed. Additionally, to determine the putative pathogenicity
92 of the spectrum of fungi detected in the patient cohorts investigated in the present study, a query
93 interrogating all fungal genera identified was run using "FungiQuest"⁸, a search tool from FungiScope™,
94 which compiles data on the occurrence of fungal infections of less commonly observed fungi in the
95 clinical setting. For the purpose of classification in the present study, the hits of both searching engines
96 were summed and subjected to an internally established classification: all genera above 400 hits were
97 regarded as proven, between 50 and 399 hits as probably pathogenic, between 1 and 49 hits as possibly
98 pathogenic, and those without any hits were considered as fungi with unknown but presumably absent
99 pathogenicity.

Statistical methods

Categorical variables were presented in numbers and percentages. Data were analyzed by Chi square test (χ^2) or Fisher's exact test using relative risk (RR) for the calculation of the effect size and 95% confidence interval (CI). A *P* value of < 0.05 was considered significant. All calculations were done with the Graph Prism 9.3 software.

Occurrence of fungal DNAemia

Analysis of the data derived from patients who had a higher clinical index for IFD, and were classified as proven, probable or possible IFD, revealed no statistically relevant differences in the occurrence of fungal DNAemia to the entire cohort of patients studied: fungal DNAemia was observed in 15.5% in the entire cohort (n=145) versus 17.2% in patients with proven, probable or possible IFD. We have compared the occurrence of fungi displaying different levels of pathogenicity in humans (based on the definition provided) in samples from patients with probable or proven IFD (n=4; 17.4%) versus patients with possible IFD or without any evidence for IFD (n=91; 10.0%), and the data revealed no statistically significant difference between patients displaying different levels of IFD (Fisher's exact test: *p*=0.3, RR=1.7, 95% CI 0.7-3.8). However, due to the rare occurrence of proven and probable IFD in the patient cohorts studied, the analysis of individual IFD levels is of marginal statistical relevance. The underlying diseases in the patients studied were quite diverse and the number of patients per disease entity was not large enough to perform statistically relevant comparisons. By contrast, when comparing the occurrence of fungal DNAemia between samples from female (n=50; 11.7%) and male (n=95; 18.7%) patients, the higher incidence in males was statistically significant ($\chi^2(1)=8.8$, *p*=0.003, RR=0.6, 95% CI 0.5 to 0.9). The significantly higher occurrence of fungal DNAemia observed in male in comparison to female patients was an unexpected finding, although there are hints in the literature indicating a higher susceptibility of males to specific fungal infections involving particularly *Cryptococcus*⁹ and *Aspergillus*¹⁰. However, relevant assessment of the observation made would require multivariate analysis within larger studies.

Potential clinical relevance of rarely pathogenic fungi in the immunocompromised setting

To assess the clinical relevance of the detected fungi in the immunocompromised setting we employed two independent sources, namely PubMed and FungiQuest⁸, using the search criteria outlined in the Methods section. While PubMed permits the identification of essentially all publications on fungal infections, FungiQuest focuses particularly on individual, less commonly observed fungi. Although the use of the indicated two sources for the incidence of fungi in the human setting may not provide completely exhaustive data, the probability of overlooking the relevance of a fungal genus is rather low. Nevertheless, a broader search strategy might identify some additional cases of rare fungi occurring as human pathogens. The occurrence of *Malassezia*, a yeast commonly found on human skin and capable of causing invasive infections under certain conditions¹²⁻¹⁴, was surprisingly common, particularly in the pediatric patient cohort, and exogenous contamination of the blood samples might offer a possible explanation for this observation. Similarly, *Cladosporium*, the most frequently detected fungal genus in the present study, has been considered a contaminant in some studies^{15,16}. However, it may also represent an emerging and potentially pathogenic fungus, as 43 hits were found in PubMed when using the searching algorithm outlined above. Cases of IFD associated with *Cladosporium* in immunocompromised patients were reported in several publications¹⁷⁻¹⁹, and the FungiQuest query tool, representing a registry for emerging fungal infections⁸, revealed 15 cases of IFD caused by *Cladosporium* spp. Other examples of fungi with questionable association with pathogenicity in immunocompromised individuals include *Penicillium* spp., known as plant pathogens and allergens in humans, which were mostly considered to be contaminants, but have also been reported to cause IFD in immunocompromised patients²⁰. The lack of adequate immune surveillance in severely immunocompromised patients extends the spectrum of fungi capable of causing invasive infections in this setting, and it is difficult therefore to completely exclude individual fungi as potential causes of IFD.

Limitations of the study

Contaminated food or drugs produced by exploiting fungi are well-known sources of circulating fungal DNA in PB²¹⁻²³, and this might potentially explain some of the findings in the current study. Semi-synthetic β -lactam antibiotics may contain traces of *Penicillium*, which is involved in the production²⁴⁻²⁶. In the present study, *Penicillium* DNA was identified by ITS2-PCR and sequencing in seven cases, and all these patients were treated with semi-synthetic β -lactam antibiotics at the time of sample collection, but the correlation was not statistically significant.

Similar studies often employed other samples, such as formalin-fixed, paraffin-embedded tissues²⁷, sterile and nonsterile fluids other than blood²⁸, different panfungal PCR protocols such as the amplification of the 18S rRNA gene²⁹ or the ITS1 region²⁸, thus making a comparison with our results difficult. The reported higher incidences of IFD in some studies correlated with higher detection rates of fungal DNAemia, in the range between 30 and 63%²⁷⁻²⁹, while the present study identified fungal DNAemia in only 15% of the samples collected, in line with the low incidence of IFD observed and the common use of antifungal prophylaxis.

While *Candida* and *Aspergillus spp.* have been the most commonly detected fungal pathogens in immunocompromised patients with invasive fungal infection, wide use of broad-spectrum antifungal prophylaxis has resulted in an increasing occurrence of hitherto rarely observed fungal genera. These observations underline the importance of panfungal screening approaches permitting the detection of essentially any fungus of potential clinical relevance²⁷⁻²⁹. However, screening assays involving the use of panfungal PCR approaches are still regarded as experimental, although the diagnostic potential of molecular diagnostics in the immunocompromised setting is well recognized.

As stated above, a major limitation of the present study was the rare occurrence of probable or proven IFD in the patient cohorts investigated, which precluded assessing the full diagnostic potential of broad-spectrum PCR assays, such as the pan-fungal and ITS2 PCR approaches used. Nevertheless, the broad-spectrum screening methods used revealed an unexpectedly high proportion of putatively non-

176 pathogenic fungi in patients displaying fungal DNAemia, which may not be of clinical relevance even in
177 the severely immunocompromised setting. It is of paramount importance therefore to combine broad-
178 spectrum screening methods with ensuing identification of the detected fungi at the genus or species
179 level and to confirm the results by repeated testing. This is an apparent prerequisite for appropriate
180 interpretation of diagnostic data, which may help preventing unnecessary treatment or providing a
181 basis for appropriate antifungal therapy in clinical practice.

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
1	STA	P	4	F	ALL	negative	no	<i>Malassezia</i>	yes	Paromomycin	yes	Piperacillin& Tazobactam	yes	Amphotericin B	no	-
2	STA	P	16	M	Burkitt lymphoma	IFD possible	no	<i>Cladosporium</i>	yes	Paromomycin	yes	Piperacillin& Tazobactam; Amikacin; Meropenem; Vancomycin	yes	Amphotericin B; Voriconazole	yes	Amphotericin B
2	STA	P	16	M	Burkitt lymphoma	IFD possible	no	<i>Coniosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem	yes	Amphotericin B	no	-
6	STA	P	5	M	ALL	IFD possible	yes	<i>Hyphodontia</i>	no	-	yes	Vancomycin	yes	Voriconazole	-	-
7	STA	P	1	F	ALL	negative	no	<i>Trichoderma</i>	yes	Paromomycin	yes	Amikacin	yes	Amphotericin B	no	-
7	STA	P	1	F	ALL	negative	no	<i>Pyrenophora</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin& Tazobactam	yes	Amphotericin B	no	-
9	STA	P	13	F	ALL	negative	no	<i>Capronia</i>	no	-	yes	Piperacillin& Tazobactam	yes	Sulfamethoxazole& Trimethoprim	no	-
10	STA	P	5	F	ALL	IFD possible	no	<i>Malassezia</i>	yes	Paromomycin	yes	Amikacin; Piperacillin& Tazobactam	yes	Amphotericin B	no	-
10	STA	P	5	F	ALL	IFD possible	no	<i>Cryptococcus</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin& Tazobactam	yes	Amphotericin B	no	-
10	STA	P	6	F	ALL	negative	yes	<i>Epicoccum</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin& Tazobactam	yes	Amphotericin B	yes	Amphotericin B
11	STA	P	3	M	ALL	IFD possible	no	<i>Malassezia</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Amikacin	yes	Amphotericin B	no	-
11	STA	P	3	M	ALL	IFD possible	no	<i>Malassezia</i>	yes	Paromomycin	yes	Piperacillin& Tazobactam; Amikacin	yes	Voriconazole	no	-
12	STA	P	8	M	ALL	negative	no	<i>Exophiala</i>	no	Paromomycin	yes	Piperacillin& Tazobactam	yes	Amphotericin B	no	-
12	STA	P	8	M	ALL	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Amikacin	yes	Amphotericin B; Voriconazole	no	-
12	STA	P	9	M	ALL	negative	no	<i>Diaporthe</i>	yes	Paromomycin	yes	Piperacillin& Tazobactam	yes	Amphotericin B	no	-
13	STA	P	2	F	ALL	negative	no	<i>Penicillium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Piperacillin& Tazobactam; Amikacin	yes	Amphotericin B	no	-
13	STA	P	3	F	ALL	negative	no	<i>Malassezia</i>	yes	Paromomycin	yes	Piperacillin& Tazobactam	yes	Amphotericin B	no	-

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
15	STA	P	13	M	ALL	negative	no	<i>Wallemia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam	yes	Amphotericin B	yes	Amphotericin B
16	STA	P	5	M	Renal cell carcinoma	negative	yes	<i>Malassezia</i>	no	-	yes	Vancomycin	yes	Sulfamethoxazole & Trimethoprim	no	-
19	STA	P	13	F	Renal cell carcinoma	negative	yes	<i>Cladosporium</i>	no	-	yes	Ceftazidime	yes	Voriconazole	no	-
20	STA	P	4	F	ALL	negative	yes	<i>Malassezia</i>	no	-	yes	Piperacillin & Tazobactam ; Amikacin	no	-	yes	Amphotericin B
20	STA	P	4	F	ALL	negative	yes	<i>Malassezia</i>	no	-	yes	Meropenem; Vancomycin	no	-	yes	Amphotericin B
21	STA	P	11	M	ALL	negative	no	<i>Botrytis</i>	no	-	yes	Piperacillin & Tazobactam	no	-	no	-
22	STA	P	12	M	ALL	IFD possible	yes	<i>Laetiporus</i>	no	-	yes	Vancomycin	no	-	no	-
22	STA	P	12	M	ALL	IFD possible	yes	<i>Ciboria</i>	no	-	yes	Vancomycin	no	-	yes	Amphotericin B
23	STA	P	3	F	ALL	negative	no	<i>Malassezia</i>	yes	Sulfamethoxazole & Trimethoprim	no	-	yes	Amphotericin B	no	-
23	STA	P	3	F	ALL	negative	no	<i>Knufia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	no	-	yes	Amphotericin B	no	-
24	STA	P	4	M	ALL	negative	no	<i>Malassezia</i>	yes	Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
24	STA	P	4	M	ALL	negative	no	<i>Trichosporon</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Amikacin	yes	Amphotericin B	no	-
24	STA	P	4	M	ALL	negative	no	<i>Daedaleopsis</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam Amikacin	yes	Voriconazole	no	-
25	STA	P	17	F	ALL	negative	no	<i>Microcycluspora</i>	yes	Paromomycin	yes	Vancomycin	yes	Amphotericin B	no	-
34	STA	P	8	M	AML	negative	yes	<i>Talaromyces</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Vancomycin; Amikacin	yes	Amphotericin B; Voriconazole	no	-
36	STA	P	4	F	ALL	negative	yes	<i>Malassezia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
36	STA	P	4	F	ALL	negative	yes	<i>Plectosphaerella</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Vancomycin; Meropenem	yes	Amphotericin B	yes	Caspofungin

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
40	STA	P	1	M	ALL	negative	no	<i>Cryptococcus</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam; Vancomycin	yes	Amphotericin B	yes	Voriconazole
40	STA	P	1	M	ALL	negative	no	<i>Peniophora</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam; Vancomycin	yes	Amphotericin B	yes	Voriconazole
45	STA	P	9	M	ALL	negative	no	<i>Cladosporium</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam	yes	Amphotericin B; Voriconazole	no	-
45	STA	P	9	M	ALL	negative	no	<i>Rhodocollybia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam; Teicoplanin	yes	Amphotericin B; Voriconazole	no	-
47	STA	P	4	F	ALL	negative	no	<i>Peniophorella</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam	yes	Amphotericin B	yes	Voriconazole
50	STA	P	5	F	ALL	negative	no	<i>Coniothyrium</i>	no	-	yes	Piperacillin & Tazobactam; Amikacin	no	-	yes	Voriconazole
53	STA	P	7	M	ALL	negative	yes	<i>Inocybe</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Meropenem	yes	Amphotericin B	yes	Amphotericin B
56	STA	P	4	M	ALL	negative	no	<i>Hyphodontia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
56	STA	P	4	M	ALL	negative	no	<i>Penicillium</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
60	STA	P	2	M	T-cell lymphoblastic lymphoma	negative	no	<i>Debaryomyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
60	STA	P	2	M	T-cell lymphoblastic lymphoma	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
60	STA	P	2	M	T-cell lymphoblastic lymphoma	negative	no	<i>Debaryomyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
61	STA	P	3	F	ALL	negative	no	<i>Alternaria</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
63	STA	P	4	M	ALL	negative	no	<i>Leptosphaeria</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
63	STA	P	4	M	ALL	negative	no	<i>Malassezia</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
64	STA	P	2	F	ALL	negative	no	<i>Debaryomyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
65	STA	P	7	M	ALL	negative	no	<i>Malassezia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam	yes	Amphotericin B	no	-
65	STA	P	7	M	ALL	negative	no	<i>Alternaria</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam	yes	Amphotericin B	no	-
66	STA	P	2	M	ALL	negative	no	<i>Yarrowia</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
67	STA	P	14	F	ALL	negative	yes	<i>Pithomyces</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Teicoplanin	yes	Amphotericin B	yes	Voriconazole
69	STA	P	15	F	ALL	negative	no	<i>Ganoderma</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
70	STA	P	4	M	ALL	negative	no	<i>Filobasidium</i>	yes	Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
70	STA	P	4	F	ALL	negative	no	<i>Malassezia</i>	yes	Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
72	STA	P	9	F	ALL	negative	no	<i>Aureobasidium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Amikacin	no	-	yes	Voriconazole
73	STA	P	7	M	ALL	negative	no	<i>Penicillium</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
74	STA	P	3	F	ALL	negative	no	<i>Cryptococcus</i>	yes	Paromomycin; Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
75	STA	P	1	M	AML	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Amikacin; Piperacillin & Tazobactam; Teicoplanin	yes	Amphotericin B	yes	Amphotericin B

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
75	STA	P	1	M	AML	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Teicoplanin; Amikacin	yes	Amphotericin B	yes	Amphotericin B
75	STA	P	1	M	AML	negative	no	<i>Blumeria</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem; Amikacin; Teicoplanin	yes	Amphotericin B	yes	Amphotericin B
75	STA	P	1	M	AML	negative	no	<i>Alternaria</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam	yes	Amphotericin B	yes	Amphotericin B
75	STA	P	1	M	AML	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Piperacillin & Tazobactam; Teicoplanin; Amikacin	yes	Amphotericin B	yes	Amphotericin B
76	STA	P	3	M	ALL	negative	yes	<i>Torula</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Ceftriaxone	yes	Voriconazole	no	-
77	STA	P	11	M	ALL	negative	no	<i>Armillaria</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	no	-	yes	Amphotericin B	no	-
78	STA	P	4	M	ALL	negative	no	<i>Bulleromyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Teicoplanin; Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
78	STA	P	4	M	ALL	negative	no	<i>Filobasidium</i>	n.a.	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
78	STA	P	4	M	ALL	negative	no	<i>Aureobasidium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Teicoplanin	yes	Amphotericin B	yes	Amphotericin B
79	STA	P	14	M	Burkitt lymphoma	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	no	-	yes	Amphotericin B	no	-
80	STA	P	3	M	ALL	negative	no	<i>Cladosporium</i>	no	-	yes	Piperacillin & Tazobactam; Amikacin	no	-	no	-
81	STA	P	18	M	AML	negative	no	<i>Myxotrichum</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin; Teicoplanin	yes	Meropenem; Amikacin	yes	Amphotericin B	yes	Fluconazole; Voriconazole
82	STA	P	6	M	ALL	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Meropenem; Vancomycin	yes	Amphotericin B	yes	Voriconazole; Amphotericin B
82	STA	P	6	M	ALL	negative	no	<i>Sporobolomyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Meropenem; Vancomycin	yes	Amphotericin B	yes	Voriconazole; Amphotericin B

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
82	STA	P	6	M	ALL	negative	no	<i>Alternaria</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
82	STA	P	6	M	ALL	negative	no	<i>Cryptococcus</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Amikacin	yes	Amphotericin B	no	-
83	STA	P	6	M	ALL	negative	no	<i>Cryptococcus</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Amikacin	yes	Amphotericin B	no	-
83	STA	P	6	M	ALL	negative	no	<i>Epicoccum</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Voriconazole
83	STA	P	7	M	ALL	negative	no	<i>Myxotrichum</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Clarithromycin; Meropenem; Teicoplanin	yes	Amphotericin B	yes	Voriconazole
83	STA	P	6	M	ALL	negative	no	<i>Leptosphaeria</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Teicoplanin; Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Voriconazole
84	STA	P	9	F	ALL	negative	no	<i>Itersonilia</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
84	STA	P	9	F	ALL	negative	no	<i>Coprinopsis</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
84	STA	P	9	F	ALL	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
84	STA	P	9	F	ALL	negative	no	<i>Debaryomyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
84	STA	P	9	F	ALL	negative	no	<i>Aureobasidium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
86	STA	P	12	M	ALL	negative	yes	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Amikacin; Teicoplanin	yes	Amphotericin B	no	-
87	STA	P	4	M	ALL	negative	yes	<i>Alternaria</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	no	-	yes	Amphotericin B	yes	Voriconazole
88	STA	P	3	M	ALL	negative	no	<i>Epicoccum</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	no	-	yes	Amphotericin B	no	-

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
89	STA	P	12	M	AML	negative	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Teicoplanin; Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Voriconazole
90	STA	P	4	F	ALL	negative	no	<i>Flammulina</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
91	STA	P	2	M	ALL	negative	no	<i>Peniophora</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
91	STA	P	2	M	ALL	negative	no	<i>Exophiala</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam	yes	Amphotericin B	no	-
92	STA	P	2	F	ALL	negative	no	<i>Debaryomyces</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
93	STA	P	17	M	ALL	negative	no	<i>Exophiala</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
93	STA	P	17	M	ALL	negative	no	<i>Tetracladium</i>	yes	Sulfamethoxazole & Trimethoprim; Paromomycin	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	no	-
95	STA	P	3	M	ALL	negative	no	<i>Knufia</i>	yes	Paromomycin; Pentacarinat	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
95	STA	P	3	M	ALL	negative	no	<i>Coprinellus</i>	yes	Paromomycin; Pentacarinat	yes	Piperacillin & Tazobactam; Amikacin	yes	Amphotericin B	yes	Amphotericin B
1	UTR	P	4	M	Neuroblastoma	negative	YES	<i>Trichoderma</i>	yes	Ciprofloxacin	yes	Ceftazidime	yes	Itraconazole	yes	Miconazole
1	UTR	P	4	M	Neuroblastoma	negative	YES	<i>Malassezia</i>	yes	Ciprofloxacin	yes	Colistin	yes	Itraconazole	yes	Miconazole
2	UTR	P	10	M	Rhabdoid stomach tumor	negative	no	<i>Cladosporium</i>	-	-	yes	Amoxicillin; Gentamicin	yes	Voriconazole	no	-
3	UTR	P	9	M	Burkitt lymphoma	negative	no	<i>Penicillium</i>	yes	Ciprofloxacin	yes	Amoxicillin; Gentamicin	yes	Itraconazole	no	-
3	UTR	P	9	M	Burkitt lymphoma	negative	no	<i>Candida</i>	yes	Ciprofloxacin	yes	Amoxicillin; Gentamicin	yes	Itraconazole	no	-
5	UTR	P	16	F	ALL	IFD probable	no	<i>Malassezia</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Ceftazidime	yes	Itraconazole	no	-
5	UTR	P	16	F	ALL	IFD probable	no	<i>Diutina</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Azithromycin	yes	Itraconazole	no	-
7	UTR	P	11	M	ALL	negative	no	<i>Cladosporium</i>	yes	Ciprofloxacin; Sulfamethoxazole & Trimethoprim	yes	Ceftazidime	yes	Itraconazole	no	-

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
8	UTR	P	2	F	Neuroblastoma	negative	no	<i>Mycena</i>	yes	Ciprofloxacin	yes	Meropenem	yes	Itraconazole	no	-
11	AKH	A	48	M	Multiple myeloma	IFD possible	yes	<i>Alternaria</i>	no	-	yes	Cefepime	yes	Fluconazole	no	-
12	AKH	A	54	M	ALL	IFD possible	no	<i>Malassezia</i>	yes	Trimethoprim	yes	Piperacillin& Tazobactam	no	-	no	-
12	AKH	A	54	M	ALL	IFD possible	no	<i>Fusarium</i>	yes	Trimethoprim	yes	Piperacillin& Tazobactam	no	-	no	-
24	AKH	A	46	M	ALL	IFD possible	no	<i>Polyporaceae</i>	no	-	yes	Piperacillin& Tazobactam	yes	Fluconazole	no	-
25	AKH	A	79	F	ALL	IFD possible	no	<i>Malassezia</i>	yes	Ciprofloxacin	yes	Piperacillin& Tazobactam	yes	Fluconazole	no	-
25	AKH	A	79	F	ALL	IFD possible	no	<i>Mycosphaerella</i>	no	-	yes	Piperacillin& Tazobactam	yes	Fluconazole	no	-
26	AKH	A	74	F	AML	negative	no	<i>Alternaria</i>	no	-	yes	Piperacillin& Tazobactam Moxifloxacin	yes	Fluconazole	no	-
27	AKH	A	44	F	T-cell lymphoma	negative	no	<i>Penicillium</i>	yes	Ciprofloxacin	yes	Piperacillin& Tazobactam	yes	Fluconazole	yes	Amphotericin B; Fluconazole
28	AKH	A	66	M	AML	negative	no	<i>Penicillium</i>	yes	-	yes	Piperacillin& Tazobactam	yes	Posaconazole	no	-
29	AKH	A	54	M	ALL	negative	no	<i>Capnoidales</i>	no	-	yes	Piperacillin& Tazobactam	no	-	no	-
30	AKH	A	58	F	ALL	IFD possible	no	<i>Penicillium</i>	yes	Ciprofloxacin	yes	Cefepime	yes	Fluconazole	no	-
34	AKH	A	63	F	AML	IFD possible	no	<i>Cladosporium</i>	yes	-	no	-	yes	Fluconazole	no	-
40	AKH	A	38	M	AML	negative	no	<i>Lecytophthora</i>	no	-	yes	Piperacillin& Tazobactam	yes	Posaconazole	no	-
40	AKH	A	38	M	AML	negative	no	<i>Alternaria</i>	no	-	yes	Piperacillin& Tazobactam	no	-	no	-
41	AKH	A	25	F	AML	negative	no	<i>Trichosporon</i>	yes	Trimethoprim	no	-	no	-	no	-
41	AKH	A	25	F	AML	negative	no	<i>Epicoccum</i>	no	-	yes	Piperacillin& Tazobactam	no	-	no	-
41	AKH	A	25	F	AML	negative	no	<i>Aureobasidium</i>	yes	Ciprofloxacin	yes	Piperacillin& Tazobactam	yes	Itraconazole	no	-
47	AKH	A	26	M	AML	negative	no	<i>Cladosporium</i>	yes	Levofloxacin	yes	Piperacillin& Tazobactam	yes	Posaconazole	no	-
47	AKH	A	26	M	AML	negative	no	<i>Stemphylium</i>	yes	Levofloxacin	yes	Piperacillin& Tazobactam	yes	Posaconazole	no	-
48	AKH	A	30	M	ALL	IFD possible	no	<i>Saccharomyces</i>	no	-	yes	Piperacillin& Tazobactam	no	-	no	-
54	AKH	A	24	F	Burkitt lymphoma	negative	no	<i>Debaromyces</i>	no	-	yes	Piperacillin& Tazobactam	no	-	no	-

nr.	Center	P/A	Age (years)	Gender	Underlying disease	IFD scoring	HSCT	Fungal genus (NCBI BLAST)	AB prophylaxis	AB prophylaxis	AB treatment	AB treatment	AM prophylaxis	AM prophylaxis	AM treatment	AM treatment
55	AKH	A	61	M	Multiple myeloma	negative	yes	<i>Fusarium</i>	no	-	yes	Piperacillin& Tazobactam	no	-	no	-
1	HAN	A	73	M	Multiple myeloma	IFD possible	yes	<i>Cladosporium</i>	no	-	yes	Linezolid; Meropenem	yes	Amphotericin B	yes	Voriconazole; Amphotericin B
1	HAN	A	73	M	Multiple myeloma	IFD possible	yes	<i>Hypodonthia</i>	no	-	yes	Linezolid; Meropenem	yes	Amphotericin B	yes	Voriconazole; Amphotericin B
2	HAN	A	71	M	AML	IFD possible	no	<i>Cladosporium</i>	no	-	yes	Piperacillin& Tazobactam	yes	Amphotericin B; Posaconazole	no	-
3	HAN	A	68	F	AML	negative	no	<i>Cladosporium</i>	yes	Trimethoprim	yes	Teicoplanin	yes	Posaconazole	no	-
7	HAN	A	58	M	AML	negative	no	<i>Aspergillus</i>	no	-	yes	Amikacin; Piperacillin& Tazobactam	yes	Amphotericin B inhalation; Amphotericin B	no	-
9	HAN	A	58	M	CML	negative	no	<i>Candida</i>	no	-	yes	Vancomycin; Meropenem	yes	Posaconazole	no	-
13	HAN	A	36	M	AML	negative	no	<i>Peniophora</i>	yes	Trimethoprim	yes	Meropenem	yes	Amphotericin B inhalation	no	-
17	HAN	A	64	M	AML	negative	no	<i>Saccharomyces</i>	yes	Trimethoprim	yes	Piperacillin& Tazobactam	yes	Amphotericin B inhalation	no	-
20	HAN	A	66	M	Multiple myeloma	IFD probable	yes	<i>Cladosporium</i>	yes	Trimethoprim	yes	Teicoplanin; Cefepime	yes	Amphotericin B inhalation	yes	Amphotericin B
1	STP	A	59	M	AML	IFD proven	no	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem	no	-	no	-
2	STP	A	32	M	AML	IFD possible	yes	<i>Vuilleminia</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Cefoperazone& Sulbactam	no	-	no	-
2	STP	A	32	M	AML	IFD possible	yes	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Cefoperazone& Sulbactam	no	-	no	-
3	STP	A	27	F	AML	negative	yes	<i>Naevalea</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem; Tigecycline	no	-	no	-
5	STP	A	22	M	T-cell lymphoma	negative	yes	<i>Malassezia</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem	no	-	no	-
5	STP	A	22	M	T-cell lymphoma	negative	yes	<i>Cladosporium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem	no	-	no	-
6	STP	A	43	F	ALL	negative	yes	<i>Cylindrobasidium</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem	no	-	no	-
13	STP	A	26	M	AML	negative	yes	<i>Pyrenochaeta</i>	yes	Sulfamethoxazole & Trimethoprim	yes	Meropenem; Vancomycin	no	-	no	-

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184 **Table S1. Patient characteristics**

185 Abbreviations: nr., patient number; P/A, pediatric/adult; F, female; M, male; STA, St. Anna Children’s Hospital, Vienna, Austria; UTR, Princess Máxima Center,
186 Utrecht, The Netherlands; AKH, Vienna General Hospital, Vienna, Austria); HAN, Hanusch Hospital, Vienna, Austria; STP, I. P. Pavlov First Saint Petersburg State
187 Medical University, Saint Petersburg, Russian Federation; AB, antibiotic; AM, antimycotic.

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