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## **Antifungal Combination Therapy for Invasive Fungal Infections in a Paediatric Oncology and Haematology Department: A Retrospective Analysis of Practice**

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1 **Abstract**

2 **Background:** Invasive fungal infections (IFI) are an important cause of morbidity and mortality in  
3 children with leukaemia. International guidelines recommend a monotherapy for most IFI. The use of  
4 antifungal combination therapy (ACT) has been reported, but clinical data supporting these  
5 combinations are scarce, particularly in paediatrics.

6 **Objective:** To describe, among patients treated in our department, the situations in which an ACT  
7 was used.

8 **Results:** Between January 2017 and December 2020, 239 patients (406 hospital stays) benefited from  
9 systemic antifungals. Among them, ACT was prescribed for 14 (5.9%) patients (13 leukaemia, 1  
10 aplastic anaemia) corresponding to 16 (3.9%) hospital stays. IFI cases treated with ACT were mainly  
11 proven (n=9) or probable (n=4). Seven cases required admission to the intensive care unit. The most  
12 commonly used antifungal agents were liposomal amphotericin B (n=13), caspofungin (n=12) and  
13 voriconazole (n=9). In 13 cases, monotherapy was prescribed as first-line therapy and changed to an  
14 ACT for an uncontrolled infection. But in 3 cases, the ACT was started immediately. The response at  
15 12 weeks after diagnosis of proven/probable IFI was successful in 12 cases (92.3%). The only IFI-  
16 related death was attributed to disseminated mucormycosis. ACT were generally well tolerated. In 4  
17 cases, adverse events led to the discontinuation of the offending antifungal agent.

18 **Conclusion:** This retrospective analysis of practices shows that the use of ACT in our paediatric  
19 haemato-oncology department is rare, and concerns the most severe cases and/or those not  
20 responding to the first line treatment. In most cases, ACT was efficient and well tolerated.

21

22

23 **Keywords:** invasive fungal infection; antifungal agents; combination therapy; leukaemia; children.

24 **Introduction**

25 Invasive fungal infections (IFI) are a major cause of mortality and morbidity in children with  
26 haematological malignancies. IFI incidence rate in France is 5.3% among all immunocompromised  
27 children, 7.0% in children with a relapsing acute lymphoblastic leukaemia (ALL), and up to 12.9% in  
28 children with acute myeloid leukaemia (AML) [1]. The IFI-related mortality rate is as high as 33% in  
29 children with acute leukaemia (AL) in recent studies [2,3].

30 International guidelines recommend a monotherapy as first line treatment for most IFI (mold  
31 or yeast) [4–8]. Since very few randomised studies on antifungal therapy have been conducted in  
32 children, paediatric guidelines are mainly derived from those for adult patients. These infections are  
33 difficult to diagnose [9] and to treat, as they usually require prolonged antifungal therapy. New  
34 therapeutic approaches have been explored, including antifungal combination therapy (ACT),  
35 advocated in international guidelines as salvage therapy for some IFI. ACT presents some benefits  
36 like widening the spectrum and minimizing the risk of resistance [10,11], but since limited clinical  
37 data is available, even in adults, its use is still controversial. Data is even more scarce in children as  
38 few studies have documented the feasibility, safety and efficacy of such combinations in  
39 immunocompromised children [12–14]. The response rates are generally good but vary between  
40 studies.

41 We aimed to describe, among children treated in our department for haematological  
42 diseases or solid tumours, the situations in which a combination of systemic antifungal agents was  
43 used, the clinical and microbiological characteristics as well as the evolution of the IFI involved, and  
44 the safety of these treatments.

45

46 **Materials and methods**

47 The Paediatric Haemato-Oncology Department at Armand Trousseau Hospital treats children  
48 and adolescents with haematological malignancies, aplastic anaemia, or solid tumours (except for  
49 brain tumours and retinoblastomas). In addition to conventional chemotherapy, treatments may  
50 include immunotherapy, high-dose chemotherapy with autologous haematopoietic stem cell  
51 transplantation (HSCT). If necessary, allogeneic HSCT are performed at another centre. Using our  
52 prescription software, we retrospectively searched for hospital stays between 1<sup>st</sup> January 2017 and  
53 31<sup>st</sup> December 2020 during which at least 1 systemic antifungal was administered to the patient. All  
54 screened patients were aged 0 to 18 years, and were treated either exclusively in our unit, or in both  
55 our department and the intensive care unit (ICU) of the Armand Trousseau hospital for a variable  
56 duration. We then included hospital stays during which a combination of at least 2 antifungal agents  
57 was prescribed for at least 48 hours. For a same patient, 2 ACT were recorded as 2 separate cases, if

58 they were administered during different hospital stays for 2 different IFI episodes and spaced by a  
59 monotherapy or no antifungal treatment.

60 IFI were classified as proven, probable or possible, according to the revised definitions of the  
61 European Organisation for Research and Treatment of Cancer (EORTC) and the Mycosis Study Group  
62 (MSG) [9]. The clinical severity of these infections was assessed according to the 2005 consensus  
63 conference [15] and classified into 3 categories: sepsis, severe sepsis and septic shock. The serum  
64 Beta-D-Glucan (BDG) assay (Fungitell, Cape Code) was considered positive if results were equal to or  
65 greater than 80 pg/mL. A serum galactomannan index (Platelia, Biorad) of 0.5 or higher was  
66 considered positive. Quantitative PCR for *Aspergillus fumigatus* (Mycogenie *Aspergillus fumigatus*,  
67 Ademtech) was reported as positive if the Cp was below 40. In-house pan-Mucorales qPCR [16] was  
68 realized if needed. Response to treatment at 12 weeks for proven and probable IFI was reported in 3  
69 categories, as defined by the EORTC/MSG 2008 consensus criteria: complete response, partial  
70 response or failure [17]. Only complete and partial responses were considered favourable. The 12-  
71 week survival rate was also calculated. The toxicity of antifungal agents was assessed and classified  
72 according to the Common Terminology Criteria for Adverse Events (CTCAE) 4<sup>th</sup> version [18].

73

#### 74 **Statistical analysis**

75 Categorical variables are analysed comparing frequency and percentage, and continuous  
76 variables as median and range.

77

#### 78 **Results**

79 Over a 4-year period, between January 1st 2017 and December 31st 2020, our department  
80 recorded 3136 hospital stays (corresponding to 772 patients). Systemic antifungal therapy was  
81 prescribed in 406 hospital stays (239 patients). We isolated 16 hospital stays (corresponding to 16 IFI  
82 cases in 14 patients) during which an ACT was prescribed for at least 48h hours (figure 1). ACT  
83 represent 3.9% of systemic antifungal prescriptions in our department, and concern 5.9% of patients  
84 for whom antifungal treatment is indicated.

85 Patients' characteristics at ACT initiation are described in table 1. Most patients suffered  
86 from an AL: lymphoblastic in 8 patients (57.1%) and myeloid in 4 (28.6%). The majority (n=10; 71.4%)  
87 was treated for a relapse at ACT initiation. In all but 1 IFI case, patients were neutropenic (with a  
88 polynuclear neutrophil count below 0.5 G/L), with a median neutropenia duration of 22.5 days (7 –  
89 85). The median time to neutrophil recovery after ACT initiation was 7 days (0 – 26). In 5 cases they  
90 received at least 21 days of corticosteroids therapy at a dose of 0,3 mg per kg per day or more,  
91 within 60 days before IFI occurrence. In all cases, patients received at least 1 systemic antibiotic  
92 within the week before ACT initiation.

93 At the onset of IFI symptoms, 3 patients were receiving an antifungal prophylaxis. Two  
94 patients had a previous history of invasive aspergillosis (1 probable pulmonary and 1 proven  
95 cerebral) and were treated with voriconazole as secondary prophylaxis when they presented a new  
96 IFI episode: a proven cutaneous aspergillosis and a probable pulmonary aspergillosis respectively).  
97 The third patient received posaconazole as primary prophylaxis and developed a possible IFI.

98 At ACT initiation, in 13 cases (81.3%) patients were receiving an antifungal monotherapy, as  
99 empiric treatment for prolonged febrile neutropenia in 9 cases (56.2%) and curative treatment for  
100 isolated fungal pathogens in 4 cases (25%). The median duration for prior antifungal monotherapy  
101 was 24 days (2 – 57). For the other 3 cases (18.8%), the ACT was directly initiated, without prior  
102 antifungal treatment. These 3 cases correspond to critical IFI: 1 case of proven invasive candidiasis  
103 due to *Candida tropicalis* with candidemia and liver, spleen and kidney lesions; 1 case of proven  
104 mucormycosis with cerebral, lung and gastric lesions, presenting with a perforated stomach; and 1  
105 case of possible IFI with a severe initial presentation.

106 IFI severity, classification and biological characteristics are described in table 2. At the onset  
107 of IFI, all patients reported fever, which lasted for a median time of 5.5 days (1 – 22). Other clinical  
108 signs varied according to the IFI localisation. Because of severe organ failure or worsening clinical  
109 signs, an admission in the ICU department was required in 7 cases (43.8%).

110 Beta-D-Glucan (BDG) were positive in 6 cases (37.5%): 3 invasive aspergillosis, 2 chronic  
111 disseminated candidiasis and 1 possible IFI. Seric Galactomannan (GM) antigen was positive in 4  
112 cases (25 %), all of which were proven invasive aspergillosis. A bronchoalveolar lavage was  
113 performed in 5 cases; GM antigen on BAL came back positive in 2 cases. The specific *A. fumigatus*  
114 blood PCR was positive in 5 (55.6%) of the 9 invasive aspergillosis cases.

115 Among the 9 proven IFI, 7 (77.8%) were diagnosed or confirmed by histological analysis,  
116 microscopic direct examination or culture of a sterile tissue sampling. 6 were aspergillosis (5 *A.*  
117 *fumigatus* and 1 *A. parasiticus*) and 1 was a mucormycosis. The 2 others proven IFI had positive blood  
118 culture (1 *C. tropicalis* and 1 *Geotrichum capitatum*).

119 The outcome at 12 weeks of the reported proven or probable IFI (n=13) was favourable in  
120 most cases: 8 cases (61.5%) achieving a complete response, 4 (30.8%) achieving a partial response.  
121 Surgery to remove infected tissues was performed in 4 cases of invasive aspergillosis, and for the  
122 mucormycosis stomach infection. Twelve weeks after diagnosis of proven or probable IFI, in 12 out of  
123 13 cases (92.3%), patients were alive. One IFI-related death was attributed to the disseminated  
124 mucormycosis infection with lesions to the brain, lung and stomach.

125 Antifungal combinations are described in table 3. ACT was prescribed as a bitherapy in 13  
126 cases (81.2%), including 9 single courses and 4 successive courses; and as a tritherapy (n=3; 18.8%). A  
127 combination of three antifungal agents was reported in 3 IFI cases: a cerebral aspergillosis, a

128 disseminated mucormycosis and a disseminated *Geotrichum capitatum* infection. The most used  
129 antifungal agents were liposomal amphotericin B (n=13; 81.3% of ACT), caspofungin (n=12; 75%) and  
130 voriconazole (n=9; 56.3%). Liposomal amphotericin B was mostly combined with caspofungin (n=7)  
131 and with voriconazole (n=5). Caspofungin was mainly combined with an azole: voriconazole (n=5),  
132 posaconazole (n=2) and fluconazole (n=1). The median duration of ACT was 18.5 days (5 – 97). Main  
133 reported reasons for using an ACT were the IFI initial severity, an uncontrolled clinical status  
134 (including persistent fever) and/or worsening or emerging radiological lesions despite initial  
135 antifungal monotherapy.

136  
137 Adverse events (AE) were reported in 10 cases (62.5%) (table 4). We observed mainly  
138 hypokalaemia (n=9) and serum creatinine elevation (n=2) when using liposomal amphotericin B; and  
139 perturbations in the liver features (n=4) when using voriconazole. In 4 cases, because of an AE, the  
140 suspected antifungal agent was discontinued or replaced by another. Regarding serum creatinine  
141 elevation, in the 2 reported cases, patients were also receiving vancomycin, and both vancomycin  
142 and liposomal amphotericin B were discontinued as soon as this AE was recorded. Both patients  
143 recovered their baseline serum creatinine level after a few days of intravenous hydration.

144

## 145 **Discussion**

146 Despite improved chemotherapy protocols and increased survival rates in children treated  
147 for malignancy [19], IFI remain a significant cause of morbidity and mortality, particularly in children  
148 with AL. Paediatric haemato-oncology units are facing an increasing incidence of emerging  
149 pathogens (as *Geotrichum sp.* or mucormycosis invasive infections) [1]. New antifungal therapies and  
150 new approaches for the treatment of IFI are needed for these difficult-to-manage infections. ACT  
151 could be an interesting option, with multiple objectives: to broaden the spectrum of antifungal  
152 therapy (species identification may be difficult to obtain, or delayed compare to the onset of  
153 symptoms), to take advantage of the synergistic activity between specific antifungal agents and to  
154 reduce the risk of resistance emergence. However, paediatric data on this strategy are scarce [12,13].  
155 With this study, we provide additional information on the real-life prescribing practices of ACT, and  
156 on the clinical, biological and microbiological characteristics of IFI for which an ACT was used, in a  
157 department managing both haematological malignancies and solid cancers in children. All patients  
158 included were treated for haematological disease (13 leukaemia and 1 aplastic anaemia), and all had  
159 one or more classic risk factors for IFI: relapsed or refractory disease, prolonged and profound  
160 neutropenia, and use of corticosteroids in the weeks preceding IFI. We did not identify any patients  
161 treated for solid cancer who received ACT, highlighting the lower risk of severe IFI in these patients.

162 Our results show that very few patients received an ACT over a 4-year period in our  
163 department as it concerns about 6% of patients for whom antifungal treatment is indicated, and  
164 represents less than 4% of systemic antifungal prescriptions in our department. The use of an ACT is  
165 relatively marginal compared to the prescriptions of antifungal monotherapy. Our practice was in  
166 line with international recommendations as in 13 (81.3%) cases of IFI, a monotherapy was prescribed  
167 as first-line treatment. In only 3 cases, the ACT was started as initial therapy, contrary to current  
168 recommendations. The immediately severe presentation of these cases and the initial lack of  
169 diagnosis of the involved pathogen may have led physicians to prescribe an ACT as first-line  
170 treatment. In all our IFI cases treated with ACT, patients presented with either immediate life-  
171 threatening symptoms or subsequent worsening signs, leading in 7 (43.8%) cases to an admission in  
172 the ICU. One death occurred. Admittedly, international guidelines do not advocate for antifungal  
173 combinations in the treatment of IFI and a monotherapy should be prescribed. But in a limited  
174 number of children presenting particularly severe IFI, with uncontrolled clinical and/or radiological  
175 signs despite initial monotherapy, an ACT might be considered by physicians. The total length of  
176 antifungal therapy for probable and proven IFI in our cohort was in most cases longer than the  
177 recommended durations. However, for invasive aspergillosis, it is specified in the guidelines that the  
178 minimum treatment duration is 6 to 12 weeks, dependent of the degree and duration of  
179 immunosuppression [6]. The need to resume chemotherapy leading to further neutropenia and  
180 immunosuppression might have led physicians to extend antifungal therapy duration, because of the  
181 risk of IFI recurrence in these situations [20].

182 The potential synergy between the antifungal agents administered in combination deserves  
183 discussion. Synergy between caspofungin and voriconazole has been found in vitro [21,22] and these  
184 results have been subsequently confirmed by some clinical studies [13,23]. This synergy can be partly  
185 explained by the fact that echinocandins and azoles target 2 different components of the fungal cell  
186 wall. Echinocandins, such as caspofungin, inhibit the synthesis of 1,3- $\beta$ -D-glucan in the fungal cell  
187 wall, while azoles inhibit 14- $\alpha$ -demethylase which suppresses ergosterol synthesis. The same  
188 explanation can be applied to the combination of caspofungin and liposomal amphotericin B. The  
189 latter binds to ergosterol, prevents it from integrating into the fungal membrane, which makes the  
190 membrane permeable, leading to cell lysis. On the contrary, there is still some doubt about a possible  
191 antagonistic effect in vitro and in vivo between liposomal amphotericin B and azoles [10,11,21]. Qiu  
192 et al [12] found a significantly lower response rate in patients treated with a combination of  
193 voriconazole and amphotericin B compared to those treated with a caspofungin-based combination.  
194 In our study, ACT based on liposomal amphotericin B and voriconazole were used as initial bitherapy  
195 in 3 cases. The retrospective nature of our study did not allow us to determine the reasons for this



196 choice (relay before continuation of voriconazole alone, waiting for effective serum levels, or other  
197 reason), but the response was favourable at 12 weeks in each of these cases.

198         Regarding the safety of ACT, in a prospective multicentre cohort of invasive mold infections  
199 in 131 children, Wattier et al [24] found an increased risk of AE with ACT as compared to  
200 monotherapy. In our study, an AE was reported in 10 cases (62.5%) and led to the discontinuation of  
201 the suspected antifungal agent in 4 cases. No permanent organ damage related to an AE was  
202 reported. The other AE described here were minor, transient and easily managed.

203         In terms of efficiency, in the analysis reported by Wattier et al, 33 out of 131 patients (25%)  
204 received an initial combination therapy for a mold infection and 70 patients (53%) received a  
205 combination therapy within 12 week after diagnosis, but no significant association was found  
206 between combination therapy and treatment outcome [24]. However, in this cohort, clinical  
207 indications of ACT were not detailed. Other non-comparative studies have found satisfactory results  
208 concerning efficiency. Qiu et al [12] reported the use of ACT after allogeneic HSCT in 95 children with  
209 haematological disorders and found an overall response rate for proven or probable IFI of 77.9%.  
210 This response rate depended on the type of combination used, caspofungin with voriconazole or  
211 liposomal amphotericin B being the most effective combinations. Lee et al [13] studied caspofungin  
212 and voriconazole combination in 22 patients with acute leukaemia with an overall response rate of  
213 90.9% and a complete response rate of 86.3%. The main weakness of our study is its retrospective  
214 nature, which did not allow us to precisely evaluate the causes of treatment changes, and to perform  
215 full pharmacokinetics analysis. Furthermore, the aim of our work, which was non-randomised, was  
216 not to demonstrate the efficiency of ACT, and the small number of cases included does not allow any  
217 definitive conclusions to be drawn. However, despite the severity of these IFI at the time of ACT  
218 initiation, we report a good response at 12 weeks for proven or probable IFI with 8 complete  
219 responses (61.5%), 4 partial responses (30.8%) and only 1 IFI-related death. This response rate of  
220 92.3% encourages further work on ACT in paediatric patients at high risk of severe forms, through  
221 prospective, randomised and multi-centre studies.

222

## 223 **Conclusion**

224         While international guidelines recommend a first-line monotherapy for the treatment of IFI  
225 in patients with haematological malignancies, the use of ACT in our paediatric haematology-oncology  
226 department is rare and concerned the most severe cases and/or those not responding to the first-  
227 line treatment. Our practices are therefore mostly in line with these recommendations. The  
228 acceptable safety of these ACT and the satisfactory efficiency found in this retrospective study  
229 support new prospective trials on these combinations.

230

231 **Declarations of Competing Interest:** None.

232

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234 commercial, or not-for-profit sectors.

235

236 **Ethics:** Our study falls within the framework of retrospective single-centre observational studies  
237 based on data that do not involve the human person. In accordance with French law, this study does  
238 not require written consent from patients or their legal representatives. A declaration to the  
239 Commission Nationale de l'Informatique et des Libertés (CNIL) (form MR-004) and a registration in  
240 the register of treatments of the Assistance Publique-Hôpitaux de Paris (APHP) have been carried out  
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325 **Figure 1.**

326 Flow chart

327 **Table 1**

328 Patient's characteristics at initiation of antifungal combination therapy.

<b>Parameters</b>	<b>Total patients (n=14)</b>
Median age – years [min – max]	9.6 [1.1 – 16.7]
Gender (M/F)	6 / 8
Underlying disease	
ALL	8 (57.1 %)
AML	4 (28.6 %)
Biphenotypic AL	1 (7.1 %)
Aplastic anaemia	1 (7.1 %)
Disease status at first ACT initiation	
Complete remission	4 (28.6 %)
Relapse or refractory disease	10 (71.4 %)

329

330 M: male; F: female; ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; AL: acute leukaemia;

331 ACT: antifungal combination therapy

332 **Table 2**

333 Clinical and biological characteristics of invasive fungal infections at the initiation of antifungal

Characteristics	Total IFI cases (n=16)
<i>Clinical severity</i>	
Sepsis	9 (56.3%)
Severe sepsis	4 (25%)
Septic shock	3 (18.7%)
<i>IFI classification</i>	
<b>Proven</b>	<b>9 (56.3%)</b>
Invasive aspergillosis	6
<i>Candida tropicalis</i> fungemia and chronic disseminated candidiasis	1
Invasive mucormycosis	1
<i>Geotrichum capitatum</i> fungemia	1
<b>Probable</b>	<b>4 (25%)</b>
Probable invasive aspergillosis	3
Probable chronic disseminated candidiasis	1
<b>Possible</b>	<b>3 (18.7%)</b>
<i>Fungal biomarkers</i>	
Positive BDG	6 (37.5%)
Median maximal BDG level – pg/mL [min – max]	491.5 [126 - 500]
Positive serum Galactomannan antigen	4 (25%)
Positive <i>Aspergillus fumigatus</i> blood PCR	5 (31.3%)
Positive Mucorales blood PCR	1 (6.3%)
<i>Other biological results</i>	
Median maximal CRP level – mg/L [min – max]	228 [10 - 451]
Median maximal PCT level * – ng/mL [min – max]	3.15 [0.32 - 25.6]
Median maximal fibrinogen level – g/L [min – max]	5.41 [2.62 - 10]

334 combination therapy.

335

336

337 IFI: invasive fungal infection; BDG: beta-D-glucan; PCR: polymerase chain reaction; CRP: C-reactive protein; PCT:  
338 procalcitonin

339 \* PCT was documented in only 9 patients



340 **Table 3**

341 Composition and duration of antifungal combination therapy for each invasive fungal infection.

Administrated antifungal agents	Diagnosed IFI	Combination duration (days)
<i>Bitherapy: single course</i>		
L-AMB + CAS	Probable pulmonary IA	5
L-AMB + CAS	Probable pulmonary IA	5
L-AMB + CAS	Possible IFI	7
L-AMB + VOR	Proven pulmonary IA	73
L-AMB + VOR	Proven cutaneous and pulmonary IA	5
L-AMB + VOR	Proven pulmonary IA	21
CAS + VOR	Probable CDC	7
CAS + VOR	Possible IFI	17
CAS + POS	Possible IFI	6
<i>Bitherapy: successive courses</i>		
L-AMB + CAS fol. by CAS + POS	Probable pulmonary IA	60 (31 then 29)
L-AMB + CAS fol. by CAS + VOR	Proven pulmonary IA	15 (5 then 10)
CAS + FLU fol. by CAS + L-AMB	Proven <i>C. tropicalis</i> fungemia	33 (12 then 21)
CAS + VOR fol. by VOR + L-AMB	Proven sinus IA	29 (26 then 3)
<i>Tritherapy</i>		
L-AMB + CAS + VOR fol. by CAS + VOR	Proven cerebral and pulmonary IA	97 (23 then 74)
L-AMB + CAS fol. by L-AMB + CAS + POS	Proven IM	20 (15 then 5)
L-AMB + 5-FC + VOR fol. by L-AMB + VOR	Proven <i>G. capitatum</i> fungemia	29 (7 then 22)

342

343 IFI: invasive fungal infection; IA: invasive aspergillosis; CDC: chronic disseminated candidiasis; IM: invasive  
 344 mucormycosis; L-AMB: liposomal amphotericin B; CAS: caspofungin; VOR: voriconazole; POS: posaconazole;  
 345 FLU: fluconazole; 5-FC: 5-Fluorocytosine; fol.: followed

346 **Table 4**

347 Adverse events.

Reported AE*		Antifungal combination	AE's grade**	Treatment	Antifungal agent discontinued
HypoK	Isolated	L-AMB + CAS	HypoK: 2	Potassium supplementation	No
		L-AMB + CAS + VOR	HypoK: 2		No
		L-AMB + VOR + 5-FC	HypoK: 2		No
		CAS + FLU followed by CAS + L-AMB	HypoK: 3		No
		L-AMB + CAS	HypoK: 4		Yes (L-AMB)
		L-AMB + CAS + POS	HypoK: 4		No (IFI-related death)
	Associated with increased CL	L-AMB + VOR followed by CAS + VOR	HypoK: 2 CL: 2	Potassium supplementation and IV hydration	Yes (L-AMB)
		L-AMB + CAS followed by CAS + POS	HypoK: 3 CL: 2		Yes (L-AMB)
	Associated with disrupted LF	L-AMB + VOR	HypoK: 2 LF: 2	Potassium supplementation	No
	Isolated disrupted LF	CAS + VOR	LF: 2	None	Yes (VOR)

348

349 \*Adverse events were reported in 10 (62.5%) of the 16 total cases

350 \*\*Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0

351 AE: adverse events; HypoK: hypokalaemia; CL: creatinine levels; LF: liver features; L-AMB: liposomal

352 amphotericin B; CAS: caspofungin; VOR: voriconazole; POS: posaconazole; FLU: fluconazole; 5-FC: 5-

353 fluorocytosine; IV: intravenous

From January 1st 2017 to December 31st 2020:  
3136 hospital stays (772 patients) in total

Systemic antifungal agents administrated:  
406 hospital stays (239 patients)

390 hospital stays (225 patients) excluded:  
- 383 antifungal monotherapy  
- 7 antifungal combination therapy for less than 48 hours

Antifungal combination therapy prescription for at least 48 hours:  
16 hospital stays (14 patients)

