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# Antifungal stewardship in hematology: reflection of a multidisciplinary group of experts

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1 **Abstract**

2 We present here a practical guide developed by a working group of experts in infectious diseases and  
3 hematology summarizing the different recommendations issued by the different International groups  
4 on antifungals used for hematology patients. In addition, a working group including experts in the  
5 domains of nephrology, hepatology and drugs interactions have reported their different  
6 recommendations when administering antifungals including dose adjustment, monitoring and  
7 management of their side effects. This guide will enable prescribers to have a handy document that  
8 allows a better and optimal use of antifungals in hematology patients taking into account the toxicity  
9 and interactions adjusted to each indication.

10 **Introduction**

11 This paper is the result of the work of a multidisciplinary group of experts in hematology, infectious  
12 diseases, mycology, hepatology, nephrology, intensive care medicine and pharmacists implicated in  
13 the management of invasive fungal infections (IFI) in hematology patients and whose main objective  
14 was to optimize the “stewardship” and “proper use” of antifungals. The group adopted a methodical  
15 approach that consisted in (1) undertaking a comprehensive review of international  
16 recommendations, (2) an in-depth review of all publications, (3) drafting recommendations on the  
17 management of renal or hepatic toxicities, or related to drug interactions, and (4) drafting practical  
18 “summary” modules corresponding to IFI management proposals.

19 A French prospective observational study showed that 44% of hospitalized patients receive  
20 antifungal therapy [1]. In France, the consumption of antifungal agents is generally two times higher  
21 in hematological units than in intensive care units [2]. An analysis done in 2013 has shown that  
22 antifungals have an allocated budget of 177 million Euros, which has been increasing since 2007 [3],  
23 representing the highest budget in hospital anti-infective expenditures [4].

24 **Invasive fungal infections in hematology**

25 IFI patients with a poor prognosis are not always managed in an optimal manner [5-8]. In addition,  
26 there are regular reports of changes occurring in the epidemiology of invasive candidiasis and  
27 aspergillosis, as well as of the emergence of other fungal infections [9, 10].

28 More frequent resistances have been observed for *non-Candida albicans* species [11]. A European  
29 study has shown that candidemias are common hospital infections associated with high mortality of  
30 around 40% for patients with solid tumors or hematological malignancies [12].

31 Regarding invasive aspergillosis, a prospective study included 393 adults, majority with hematological  
32 malignancies, this study showed that 15% presented proven invasive aspergillosis, acute leukemias  
33 and allogeneic Hematopoietic Stem Cell Transplantation (HSCT) were the main IFI risk factors [13].

#### 34 **Watch-points when prescribing antifungal agents**

35 The use of antifungals, whether prophylactic, empiric or curative, requires knowing about their  
36 potential toxicity and the many drug interactions they may have. Two essential organs may be  
37 targeted by toxicity, i.e. the kidneys and liver.

#### 38 **Assessment of renal function**

39 The kidney should be considered from two perspectives. Firstly, the potential impact of pre-existing  
40 renal impairment on the pharmacokinetics of the medicinal products, secondly, the potential renal  
41 toxicity under treatment.

42 Some antifungals require dose adjustments in case of renal impairment and/or may have a direct  
43 renal toxicity of varying degrees through various mechanisms [14-16]. (Table 1)

44 Several formulae can be used to assess renal function. The old Cockcroft-Gault formula should no  
45 longer be used, the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease  
46 Epidemiology Collaboration (CKD-EPI) formulae are both more accurate and were validated with the  
47 new isotope dilution mass spectrometry (IDMS) serum creatinine assay methods [16]. Current  
48 international guidelines recommend using the CKD-EPI formula first [17]. Calculators available on the  
49 Internet and smart phones can be used to perform simultaneous assessments using the three  
50 formulae, making it possible to compare results for a given patient [18].

51 **Assessment of liver function**

52 Considering liver abnormalities, the situation should be assessed as following: 1) liver impairment  
53 must be confirmed by testing the following parameters: transaminases, i.e. alanine transaminase and  
54 aspartate transaminase (ALT, AST), alkaline phosphatase (ALP), total and conjugated bilirubin,  
55 prothrombin rate (PR), international normalized ratio (INR), factor V and Gamma glutamyl  
56 transpeptidase (GGT) and serum albumin; 2) the characteristics of the liver impairment must be  
57 determined as well as whether it is acute or chronic; 3) the severity of the impairment should be  
58 determined.

59 In case of jaundice, a liver ultrasound should be performed. If it is not sufficiently informative, it must  
60 be completed by MRI or a CT scan. As for liver biopsies, they do not yield specific information in the  
61 vast majority of cases of drug-induced liver injury, but remain important when conducted in the  
62 framework of a differential diagnosis (graft *versus* host disease (GVHD), veno-occlusive disease  
63 (VOD)...) )

64 Liver injury is defined by the following criteria:

- 65 - ALT or AST  $\geq$  5 times the upper limit of normal (N)
- 66 - Alkaline phosphatase (ALP)  $\geq$  2 times the upper limit of normal (N)
- 67 - Combination ALT/AST  $\geq$  3 N and total bilirubin  $\geq$  2 N

68 The type of acute liver injury is defined by the ALT/ALP ratio (R) expressed as the number of times  
69 above the upper limit of normal. (Table 2) [19].

70 In case of hepatocellular injury, prescription conditions and antifungal monitoring requirements are  
71 detailed in Table 3.

72 In case of cholestatic liver disease, even in the presence of moderate jaundice, antifungals may still  
73 be prescribed.

74 In terms of severity, liver injury can be considered as detailed in Table 4.

75 In case of chronic hepatitis (>6 months) and steatohepatitis, there is no increased risk of drug-  
76 induced hepatitis, and drug metabolism is not much changed.

77 Regarding the prescription of antifungals in case of severe acute injury with liver insufficiency  
78 (ALT/AST > 10N, bilirubin > 2N, Prothrombin Time, Factor V < 30%, INR > 1.5):

- 79 - Take into account the benefit/risk ratio for any prescription,
- 80 - Select the treatments
- 81 - Prescribe only if the patient's life is at stake.

82 In case of cirrhosis, the risk of severity is evaluated by Child-Pugh scores which were calculated in a  
83 stable situation without any infectious phenomenon and are used as guidelines for the prescription  
84 of medical products (Table 5) [20].

#### 85 **Prescription of antifungals: expert opinion**

86 The main objective of this work was to make the recommendations easier for the clinical practice  
87 while respecting guidelines on "proper use" [21-25].

#### 88 **Prophylactic approach**

89 Antifungal prophylaxis should only be used for patients at high risk of IFI. The target population  
90 includes Acute Leukemia and MDS patients undergoing either intensive chemotherapy or allogeneic  
91 hematopoietic stem cell transplantation (allo-HSCT) either during the early phase or more often  
92 presenting an acute or chronic graft-versus-host disease (GVHD) on immunosuppressive treatment  
93 [26-28].

#### 94 ***Prophylaxis for allogeneic HSCT recipients [28-30]***

95 ●The main risk factors for early aspergillosis (usually defined as occurring within the first 40 days  
96 after allo-HSCT before GVHD) are: active hematological malignancies at the time of transplantation,  
97 AML, advanced age, cord blood transplants, haploidentical transplants, T-cell depleted or CD34  
98 selected grafts, and concerning complications after transplantation: delayed engraftment,  
99 *Pseudomonas aeruginosa*-induced pneumonia or viral respiratory tract infections. The risk appears to  
100 exist even if the transplant is performed in a laminar air flow room (HEPA filtration).

101 We represent an algorithm of the prophylaxis for allogeneic HSCT recipients before engraftment  
102 according to proposal of the group of experts as shown in Figure 1.

103 • GVHD and risk of aspergillosis

104 Not all GVHD patients are at risk of IFI and therefore we suggest prophylaxis to be considered in the  
105 following cases: grade 3-4 acute GVHD, grade 2 acute GVHD receiving high dose corticosteroids (1 to  
106 2 mg/kg/day of methylprednisolone), steroid-resistant acute GVHD, steroid-resistant or steroid-  
107 dependent extensive chronic GVHD, secondary neutropenia, prolonged lymphopenia, viral  
108 respiratory tract infections [26].

109 We represent in Figure 2, an algorithm for the prophylaxis of allo-HSCT recipients, who have  
110 developed GVHD needing immunosuppressive treatment.

111 For GVHD of the gastrointestinal tract or in case of very severe mucositis, intravenous treatment  
112 should be preferred.

113 • Duration of prophylaxis

114 There are no specific recommendations on the duration of prophylaxis, but it should be continued as  
115 long as the risk exists.

116 - If the main risk factor is neutropenia: prophylaxis should be stopped when the absolute  
117 neutrophil count (ANC) remains stable  $> 0.5$  G/L during 3 days.

118 - If the main risk factor is GVHD: prophylaxis should be continued as long as the GVHD is not  
119 controlled and corticosteroid therapy is prescribed at a dose  $\geq 0.5$  mg/kg. In such cases,  
120 prophylaxis can exceed several months and may cause possible toxicity problems, lead to the  
121 emergence of resistance, or increase the costliness of treatment.

### 122 ***Prophylaxis of Acute Leukemia/MDS patients in the induction phase [27]***

123 In these categories of patients we represent an algorithm of prophylaxis according to proposal of the  
124 group of experts as shown in Figure 3.

### 125 **Empirical approach [31]**

126 An empirical approach can be used for the antifungal treatment of patients with neutropenia  
127 (neutrophil count  $<500/\mu\text{L}$ ) who remain febrile after 3-5 days of probabilistic broad spectrum  
128 antibiotics, or who become febrile again on antibiotics after a period of apyrexia.

129 ***Empirical treatment of persistent febrile neutropenia***

130 Treatment is generally initiated at 96 hours, but its timing should be modulated according to the  
131 duration and clinical severity of the neutropenia.

132 Treatment options: liposomal amphotericin B 3 mg/kg/day or caspofungin 70 mg on Day 1, then  
133 50 mg/d thereafter if weight < 50kg and 70 mg if weight > 50 kg.

134 Treatment should be selected taking into account local epidemiology, the risk of emergence of  
135 resistance, the activity spectrum, tolerability and the type of antifungal prophylaxis.

136 ***Empirical treatment of persistent febrile neutropenia following primary prophylaxis***

137 In case of prophylaxis with posaconazole or voriconazole with adequate serum level, isolated fever  
138 and stable clinical condition, treatment is not systematically empirical. Posaconazole or voriconazole  
139 therapy can be continued with an assessment of laboratory parameters and a CT lung scan and then  
140 adapted accordingly.

141 In the case of prophylaxis with posaconazole or voriconazole with inadequate serum level,  
142 prophylaxis should be stopped and empirical treatment initiated.

143 In the case of prophylaxis with fluconazole, prophylaxis should be stopped and empirical treatment  
144 initiated.

145 **Curative approaches [32]**

146 ***Aspergillus infections [21, 33-38]***

147 It is important to document the infection as best as possible from a microbiological perspective.

148 ***First-line treatment of invasive pulmonary aspergillosis (proven, probable or possible)***

149 1<sup>st</sup> choice: voriconazole IV should be the preferred treatment for hospitalized patients, treatment by  
150 the oral route is possible for outpatients:

- 151 - Loading dose on Day 1: 2 x 6 mg/kg.
- 152 - From Day 2: 2 x 4 mg/kg/day.
- 153 - Monitoring of serum levels on Day 3-4.
- 154 - Target residual concentration: 1.5 to 5 mg/L.



155 **Alternative treatments**

156 In case of contraindications to voriconazole:

- 157 - Liposomal amphotericin B: 3 mg/kg/day (off-label use).
- 158 - Amphotericin B phospholipid complex 5 mg/kg/d: less well tolerated by the kidneys and
- 159 generally than liposomal amphotericin B [39].

160 In case of contraindications or intolerance to voriconazole and to lipid formulations of amphotericin

161 B:

- 162 - Isavuconazole IV should be the preferred treatment for hospitalized patients, treatment by
- 163 the oral route is possible for outpatients.

164 Loading dose on Day 1 and Day 2: 200 mg/8h

165 From Day 3: 2 x 4 mg/kg/day

166 Interest of monitoring serum levels under evaluation

167 In case of contraindications to voriconazole, isavuconazole and to lipid formulations of

168 amphotericin B:

- 169 - Intravenous caspofungin (off-label use)

170 70 mg on Day 1, then:

171 70 mg/d from Day 2 if weight > 80kg

172 50 mg/d from Day 2 if weight ≤ 80 kg

173 **Second-line treatment of invasive aspergillosis (in case of 1<sup>st</sup> line treatment impairment)**

174 The parameters to be taken into account to assess treatment impairment (after 8 to 15 days except

175 in case of early clinical deterioration) are as follows:

- 176 - Clinical worsening with no other cause found.
- 177 - Persistence of high galactomannan levels.
- 178 - Increase of inflammatory syndrome with no other identified cause.
- 179 - CT Scan showing worsening.
- 180 - Spreading of infection

181 Algorithms for second line treatment of invasive aspergillosis in case of intolerance or failure are  
182 shown in figures 4 and 5 respectively.

### 183 ***Treatment of aspergillosis emerging during treatment***

- 184 - Prophylaxis with posaconazole or voriconazole with adequate serum level: change of class:  
185 liposomal amphotericin B
- 186 - Prophylaxis with posaconazole with inappropriate serum level: liposomal amphotericin B  
187 (off-label use), voriconazole IV or isavuconazole IV
- 188 - Prophylaxis with voriconazole with inappropriate serum level: absence of sufficient data

### 189 **Invasive candidiasis [40-45]**

#### 190 ***First choice treatment of candidemias***

191 Before the species is identified, treatment should be initiated with an echinocandin.

192 It is important to quickly remove the central venous catheter, and to determine if there is a deep-  
193 seated focus of infection: fundus examination, echocardiography... Any possible colonization (e.g.  
194 with *Candida glabrata*), prophylactic treatment or other antifungal therapy in the past 6 months  
195 (particularly with fluconazole or caspofungin) should be taken into account.

#### 196 ***Alternative treatment***

197 Liposomal amphotericin B.

#### 198 ***Treatment of candidemias after species identification***

199 Ensure the treatment is adequate for the species (for *Candida glabrata*, take into account the  
200 decreased sensitivity to azoles and the growing resistance to echinocandins).

201 An antifungal susceptibility test should be performed for any positive culture.

202 Step-down/oral relay therapy should be considered from Day 7 if possible (depending on the clinical  
203 condition of the patient and the microorganism, it is possible to initiate step-down therapy faster if  
204 the results of the antifungal susceptibility test become available sooner).

205 Duration of treatment: resolution of neutropenia and  $\geq 14$  days after the last positive blood culture  
206 and resolution of clinical symptoms.

207 ***Treatment of candidemias in case of persistent positive blood cultures after catheter removal***

208 Look for a deep-seated focus of infection.

209 Consider changing the treatment.

210 **Mucormycosis [46-49]**

211 First-line treatment: 5 to 10 mg/kg/day liposomal amphotericin B (off label use), step-down therapy  
212 with posaconazole tablets (off label use) if the clinical outcome is satisfactory (with an overlap  $\geq$  5  
213 days and effective serum level)

214 Treatment in case of failure:

- 215 - Posaconazole (off label use) [50]
- 216 - Combination of liposomal amphotericin B + posaconazole or caspofungin (off label use)
- 217 - isavuconazole

218 **Precautions to be taken when monitoring antifungal treatment**

219 **Monitoring of renal toxicity**

220 Antifungals have very different pharmacological properties and renal tolerability is also very different  
221 from one molecule to another.

222 Overall nephrotoxicity is estimated at 66% for amphotericin B, 29% for liposomal amphotericin and  
223 55% for amphotericin B lipid complex [51]. In addition, it is essential to maintain adequate hydration  
224 to improve the renal safety of amphotericin B.

225 Several studies have been performed in hematology to assess the nephrotoxicity of antifungal  
226 molecules used alone or in combination. Azoles and echinocandins are not particularly nephrotoxic  
227 [52, 53]. A prospective study including 250 hematology/oncology patients treated with antifungals  
228 showed that blood creatinine increased in 20% of cases with liposomal amphotericin B, 6% with  
229 voriconazole, 11% with caspofungin and 5% with posaconazole [54].

230 **Monitoring of liver toxicity [55, 56]**

231 ***Occurrence of liver impairment during treatment are detailed in Table 6.***

232 **In case of hepatocellular injury due to antifungal treatment**

233 Transaminases:

- 234 • < 5N: check after a week to determine if levels are increasing, stable or decreasing
- 235 • Between 5-10N: decrease the dose by half and/or check after 3-4 days; if there is a decrease
- 236 in ALT levels, treatment may be continued
- 237 • If levels > 5N for 2 weeks, decrease the dose by half
- 238 • If > 10N or bilirubin > 2N: stop treatment and monitor improvement

239 **In case of cholestatic liver impairment:**

240 Increase in alkaline phosphatase levels:

- 241 - Bilirubin < 2N: check
- 242 - Bilirubin > 2N: stop treatment and monitor improvement.

243 **Drug-drugs interactions**

244 Drug interactions can be pharmacokinetic, interacting on the metabolism or pharmacodynamic,  
245 resulting in the addition of adverse effects [57, 58]. In the event of a toxic reaction or lack of  
246 treatment efficacy, it is recommended to review the mechanisms of actions of the molecules to  
247 understand how they interact so as to know how to proceed. These interactions can affect either the  
248 pharmacokinetics of the azole antifungal and that of the associated drug, or both [57, 58].

249 **Pharmacokinetic interactions**

250 ***Triazoles***

251 Azole antifungals are inhibitors of cytochrome P450 isoenzymes (CYP3A4 for all azoles, CYP2B6 for  
252 voriconazole and isavuconazole, CYP2C9 and CYP2C19 for fluconazole and voriconazole) [57, 59]. In  
253 addition, certain azole antifungal agents are substrates and/or inhibitors of membrane transporters  
254 such as P-glycoprotein or the BCRP (Breast Cancer Resistance Protein) [60]. The molecular  
255 determinants implicated in the mechanisms of azole antifungal drug-drug interactions are  
256 summarized in Table 7. The association of certain molecules with azole antifungals are absolutely  
257 contraindicated (Table 8) [61].

258 ***Echinocandins***

259 Main drug-drug interactions with caspofungin have been identified and are summarized in Table 9  
260 [58]. Concerning the other echinocandins (anidulafungin and micafungin), the potential for drug-drug  
261 interactions is low and they not require dosage adjustments.

#### 262 **Addition of adverse effects**

263 Medicinal products that may increase the risk of adverse effects for patients taking azole antifungals:

- 264 - Potassium-lowering effects: diuretics, corticosteroids, laxatives, immunosuppressive molecules  
265 (sirolimus, everolimus);
- 266 - Risk of peripheral neuropathy: anti-cancer drugs (platinum derivatives, taxanes and vinca  
267 alkaloids), anti-infectious molecules (dapson, nitrofurantoin, metronidazole, pentamidin);
- 268 - Risk of atrial fibrillation (voriconazole): levothyroxine, triptans, NSAIDs, corticosteroids;
- 269 - Risk of optic neuropathy (voriconazole): anti-cancer drugs (cisplatin, fluorouracil, vincristin,  
270 bortezomib), anti-TNF-alpha immunosuppressive molecules, anti-infectious molecules (linezolid),  
271 NSAIDs, amiodarone;
- 272 - Photosensitizing effects (voriconazole): cyclins, fluoroquinolones.

#### 273 **For patients treated with amphotericin B [58]**

- 274 - Nephrotoxic effects: diuretics, angiotensin converting enzyme inhibitors, sartans, aliskiren,  
275 NSAIDs, anti-infectious, anti-cancer drugs, immunosuppressive molecules;
- 276 - Potassium-lowering effects: diuretics, corticosteroids, laxatives, immunosuppressive molecules  
277 (sirolimus, everolimus);
- 278 - Convulsive effects: neuroleptics, sedative H1 antihistamines, antidepressants, tramadol,  
279 quinolones, carbapenems, some anti-cancer drugs;
- 280 - Risk of peripheral neuropathy: anti-cancer drugs (vincristine, bevacizumab), anti-infectious  
281 molecules (nitrofurantoin, metronidazole, pentamidin);
- 282 - Additional risk of anemia: myelotoxic drugs, drugs that decrease iron absorption (PPIs) and those  
283 with an anti-folic effect (methotrexate, antiepileptics).

#### 284 **When used in combination with immunosuppressive therapy**

285 With immunosuppressive molecules (ciclosporin, tacrolimus, sirolimus ...), it is recommended [62]:

286 a) When used in combination with an azole antifungal, to reduce the dosage of the  
287 immunosuppressive molecule and to closely monitor the plasma levels of the immunosuppressant;

288 b) When used in combination with echinocandins:

289 • Ciclosporin increases the plasma concentrations of caspofungin (+ 35% of the AUC)

290 • Caspofungin decreases the plasma concentrations of tacrolimus (C<sub>min</sub> -26%)

291 • Monitoring of blood concentrations of the immunosuppressants and dosages adjustments

292 • Micafungin and anidulafungin have no impact on the plasma concentration of immunosuppressive  
293 molecules and no monitoring is required with their use.

294 c) In case of combination with amphotericin B: addition of nephrotoxic adverse reactions.

295 As there is a lot of information on drug-drug interactions, and many documentary sources are  
296 available, including: Micromedex [63], Multi-Drug Interaction Checker Medscape [64], Drugs.com -  
297 Drug Interaction Guide [65] and Drug Interactions – BNF [66].

298 In conclusion, this work was undertaken to simplify the various recommendations that are available  
299 to prescribers on the use of antifungals while respecting good use and good practice guidelines. It  
300 also summarizes the precautions to be taken to avoid toxicity and drug interactions. Finally, the work  
301 group developed therapeutic strategies presented as decision algorithms adapted to each type of  
302 indication respecting good use guidelines and complying with reference documents and international  
303 recommendations. It should be noted that some of the strategies mentioned do not fall within the  
304 scope of the validated indications of the molecules in their marketing authorizations.

305

306

307 **Conflicts of interest:** None

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**Tables:**

Table 1: potential renal toxicity and antifungal dose adjustments

| <b>Antifungal agent</b>  | <b>Dosage adjustment required in case of renal impairment</b> | <b>Potential renal toxicity</b> |
|--|---|---------------------------------|
| Fluconazole  | Yes   | No                              |
| Itraconazole   | Yes   | Yes                             |
| Ketoconazole   | No  | No                              |
| Posaconazole   | No  | No                              |
| Voriconazole   | No  | Yes                             |
| Anidulafungin  | ND  | ND                              |
| Caspofungin  | No  | Yes                             |
| Micafungin   | ND  | ND                              |
| Flucytosine  | Yes   | No                              |
| Griseofulvin   | No  | No                              |
| Terbinafine  | Yes   | Yes                             |
| Plain amphotericin B   | No  | Yes                             |
| Amphotericin B lipid complexes   | No  | Yes                             |
| Liposomal amphotericin B   | No  | Yes                             |
| <i>ND: No Data</i>   |   |                                 |
| <i>Source: GPR website (www.sitegpr.com), website for healthcare professionals for the Stewardship of Medicinal Product [16]</i> |   |                                 |

Table 2: Definition of liver injury

|                          |                                    |
|--------------------------|------------------------------------|
| Hepatocellular injury    | $R = \text{ALT}/\text{ALP} \geq 5$ |
| Cholestatic liver injury | $R = \text{ALT}/\text{ALP} \leq 2$ |
| Mixed liver injury       | $2 < \text{ALT}/\text{ALP} < 5$    |

Table 3: Prescription conditions and antifungal monitoring requirements in case of hepatocellular injury at time of initiation of antifungal therapy (in case of adverse events or intolerance during antifungal therapy, please refer to alternative treatment section for each category in the text/figure)

| Transaminases                              | Prescription of antifungal agents | Monitoring of liver function |
|--|-----------------------------------|------------------------------|
| < 5N                                       | No restrictions                   | Required                     |
| Between 5 and 10N and bilirubin normal     | Prescription possible             | Frequent                     |
| > 10N or jaundice (Bilirubin >2.5-3 mg/dL) | Prescription limited              | Very frequent                |

Table 4: Types of acute liver injury

|   |          |  |
|---|----------|--|
| 1 | Minimal  | increase in transaminases or ALP with bilirubin <2N and INR <1.5   |
| 2 | Moderate | increase in transaminases or ALP with bilirubin $\geq$ 2N or INR $\geq$ 1.5 or “liver injury” requiring hospitalization          |
| 3 | Severe   | Hepatocellular injury (jaundice + PR < 50%) without encephalopathy   |
| 4 | Serious  | Fulminant liver injury (jaundice + PR/factor V < 50% and encephalopathy) may possibly be an indication for liver transplantation |

Table 5: Adjustment of medicinal prescriptions as a function of the Child-Pugh score

|  |  |
|--|--|
| Child-Pugh A (minimum of 5-6 point)<br>Well stabilized cirrhosis | <ul style="list-style-type: none"><li>• Usually no or little impact</li><li>• Most treatments are authorized at the standard doses</li></ul> |
| Child-Pugh B (7-9 points)<br>Moderately severe                   | <ul style="list-style-type: none"><li>• Dose adjustments required for drugs metabolized by the liver</li></ul>                               |
| Child-Pugh C (10-15 points)<br>Severe impairment                 | <ul style="list-style-type: none"><li>• Limit the prescription of medical products</li><li>• Consider the benefit/risk ratio</li></ul>       |



Table 6: Hepatotoxicity of antifungals

|   |  |
|---|--|
| <p>Azoles:<br/>voriconazole,<br/>posaconazole,<br/>itraconazole,<br/>fluconazole,<br/>isavuconazole</p> | <ul style="list-style-type: none"> <li>•Frequent asymptomatic increase in transaminase levels <math>\geq 3N</math></li> <li>•Rare hepatitis that is rather cholestatic than cytolytic (except fluconazole)</li> <li>•Cross-toxicity: poorly documented, a few cases without cross-toxicity (voriconazole-posaconazole, fluconazole-voriconazole). Therefore, it is possible to prescribe another azole in a positive benefit/risk context</li> </ul> |
| <p>Echinocandins:<br/>caspofungin,<br/>micafungin,<br/>anidulafungin</p>                                | <ul style="list-style-type: none"> <li>•Hepatotoxicity limited to an increase in transaminase levels</li> </ul>  |
| <p>Amphotericin B</p>   | <ul style="list-style-type: none"> <li>•Frequent asymptomatic increase in transaminase or alkaline phosphatase levels</li> <li>•Rare hepatitis</li> </ul>  |
| <p>Flucytosine</p>  | <ul style="list-style-type: none"> <li>•Frequent asymptomatic increase in transaminase or alkaline phosphatase levels</li> <li>•Very rare hepatitis</li> <li>• Extremely rare, severe hepatitis</li> </ul>   |

Table 7: Azole antifungal molecular determinants

BCRP: breast cancer resistance protein; CYP: cytochrome; I: Inhibitor; S: Substrate; NE: Not evaluated; OCT2: organic cation transporter2; P-gp: P-glycoprotein, UDPGT: uridine diphosphoglucuronide

|                              | <b>Itraconazole</b> | <b>Fluconazole</b> | <b>Voriconazole</b> | <b>Posaconazole</b> | <b>Isavuconazole</b> |
|------------------------------|---------------------|--------------------|---------------------|---------------------|----------------------|
| <b>Phase I enzymes</b>       |                     |                    |                     |                     |                      |
| <b>CYP3A4/5</b>              | I S                 | I S                | I S                 | I                   | I S                  |
| <b>CYP2B6</b>                | -                   | -                  | I                   | -                   | I                    |
| <b>CYP2C9</b>                | -                   | I S                | I S                 | -                   | -                    |
| <b>CYP2C19</b>               | -                   | I S                | I S                 | -                   | -                    |
| <b>Phase II enzymes</b>      |                     |                    |                     |                     |                      |
| <b>UDPGT</b>                 | -                   | I                  | -                   | S                   | I                    |
| <b>Membrane transporters</b> |                     |                    |                     |                     |                      |
| <b>P-gp</b>                  | I S                 | S                  | -                   | I S                 | I                    |
| <b>BCRP</b>                  | I                   | -                  | -                   | I                   | I                    |
| <b>OCT2</b>                  | -                   | -                  | -                   | -                   | I                    |

**Table 8: Combinations contraindicated with azole antifungals**

↑: increased plasma concentrations, ↓: decreased plasma concentrations

\* combination with voriconazole not recommended

| <b>Drug</b>  | <b>Antifungal agent</b>                               | <b>Effects of drug exposure</b>   | <b>Clinical consequences</b>   |
|--|---|---|--|
| <b>Amiodarone, cisapride, erythromycin, mizolastine, pimozide, quinidine</b> | Itraconazole, fluconazole, voriconazole, posaconazole | ↑ of the associated medical product   | Risk of ventricular arrhythmias, particularly torsades de pointes                  |
| <b>Ergotamine, dihydroergotamine</b>   | Itraconazole, voriconazole, posaconazole              | ↑ of the rye ergot alkaloid   | Risk of ergotism or of hypertensive crisis   |
| <b>Atorvastatin, simvastatin</b>   | Itraconazole, voriconazole, posaconazole              | ↑ of HMG-CoA reductase  | Rhabdomyolysis   |
| <b>Vincristine</b>   | Itraconazole, voriconazole, posaconazole              | Inhibition of vincristine metabolism through CYP3A4 and its transport by P-gp | Neuropathy, gastrointestinal side effects, electrolyte abnormalities, and seizures |
| <b>Aliskiren</b>   | Itraconazole  | ↑ of aliskiren (nearly 6x)  | Increased risk of adverse effects  |
| <b>Dabigatran</b>  | Itraconazole  | ↑ of dabigatran (more   | Increased risk of bleeding   |

|  |   |  |   |
|--|---|--|---|
|  |   | than double)   |   |
| <b>Domperidone</b>   | Itraconazole<br>fluconazole<br>voriconazole<br>posaconazole | Addition of adverse effects  | Risk of ventricular arrhythmias, particularly torsades de pointes |
| <b>Carbamazepine, phenobarbital, phenytoin*, primidone</b> | Isavuconazole<br>voriconazole                               | ↓ of the azole antifungal due to increased hepatic metabolism by the inducer | Loss of efficacy of the azole antifungal                          |
| <b>Ketoconazole</b>  | Isavuconazole   | ↓ of isavuconazole   | Loss of efficacy of the azole antifungal                          |
| <b>Rifampicin, rifabutin*</b>                              | Isavuconazole<br>voriconazole                               | ↓ of the azole antifungal  | Loss of efficacy of the azole antifungal                          |
| <b>Efavirenz*, etravirine, ritonavir &gt; 200 mgx2/j*</b>  | Isavuconazole<br>voriconazole                               | ↓ of the azole antifungal  | Loss of efficacy of the azole antifungal                          |
| <b>St John's Wort</b>                                      | Isavuconazole<br>voriconazole                               | ↓ of the azole antifungal  | Loss of efficacy of the azole antifungal                          |
| <b>Vardenafil (men &gt; 75 years)</b>                      | Itraconazole  | ↑ of vardenafil  | Risk of severe hypotension  |

Table 9: Drug-drug interactions with echinocandins

|  | <b>Caspofungin</b> | <b>Micafungin</b> | <b>Anidulafungin</b> |
|--|--------------------|-------------------|----------------------|
|--|--------------------|-------------------|----------------------|

|  |   |  |   |
|--|---|--|---|
| <b>Ciclosporin</b>   | AUC of caspofungin<br>↑~35%<br>No dosage<br>adjustments required                                    | None   | AUC ↑~ 22%<br><br>No dosage adjustments<br>required |
| <b>Tacrolimus</b>  | Decrease in the<br>minimum<br>concentration of<br>tacrolimus by 26%:<br>monitoring of<br>tacrolimus | No monitoring  | No monitoring                                       |
| <b>Efavirenz, Nevirapin,<br/>Rifampicin,<br/>Dexamethasone,<br/>Phenytoin,<br/>Carbamazepine</b> | Increase in the dosage<br>of caspofungin to<br>70 mg/d  | No monitoring  | No monitoring                                       |
| <b>Sirolimus, Nifedipin,<br/>Itraconazole,<br/>Amphotericin B</b>                                | No monitoring   | Monitoring of plasma<br>concentrations of<br>these two medicinal<br>products and<br>monitoring of toxicity<br>(risk of increase) | No monitoring                                       |

**Figure legends:**

**Figure 1:** Algorithm of antifungal prophylaxis for allogeneic HSCT recipients before engraftment period.

Aspergillus risk factors include: active hematological malignancies at the time of transplantation, AML, advanced age, cord blood transplants, haploidentical transplants, T-cell depleted or CD34 selected grafts, and concerning complications after transplantation: delayed engraftment, Pseudomonas aeruginosa-induced pneumonia or viral respiratory tract infections.

In case of liver injury, antifungal drugs should be used with caution and under close monitoring, TDM is recommended when possible.

**Figure 2:** Algorithm of antifungal prophylaxis in allogeneic HSCT recipients who have developed GVHD needing immunosuppressive treatment

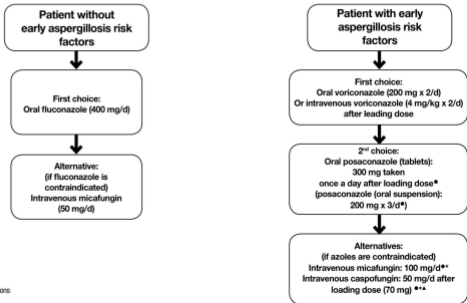
**Figure 3:** Algorithm of antifungal Prophylaxis of AML/MDS patients in the induction phase

**Figure 4:** Algorithm for second line treatment of invasive aspergillosis in case of intolerance

**Figure 5:** Algorithm for second line treatment of invasive aspergillosis in case of failure

# Prophylaxis for allogeneic HSCT recipients

## Period before engraftment



\* Off-label use

\*\*Few data

\*\*\*Risk of emerging infections

# Prophylaxis for allogeneic HSCT recipients

## GVHD

First choice:  
oral posaconazole (tablets): 300 mg taken  
once a day after loading dose  
(posaconazole (oral suspension):  
200 mg x 3/d)



2<sup>nd</sup> choice:  
oral voriconazole (200 mg x 2/d)\*  
or intravenous voriconazole  
(4 mg/kg/ x 2/d) after loading dose\*



Alternatives:  
(if azoles are contraindicated)  
Intravenous micafungin (100 mg/d)\*\*  
Intravenous caspofungin (50 mg/d after  
loading dose (70 mg)\*\*\*)

\* Off-label use

\*\* Few data

\*\*\* Risk of emerging infections



# Prophylaxis of Acute Leukemia / MDS patients

## Intensive induction and consolidation phases

**First choice:**  
oral posaconazole (tablets): 300 mg taken once a day  
after loading dose  
(posaconazole (oral suspension): 200 mg x 3/d)  
until resolution of the aplasia and when a complete  
remission is achieved

### Alternatives:

If high risk of aspergillosis and if  
posacanazole is contraindicated:  
oral voriconazole (200 mg x 2/j)•  
or intravenous voriconazole (4 mg/kg x 2/d)  
after loading dose•

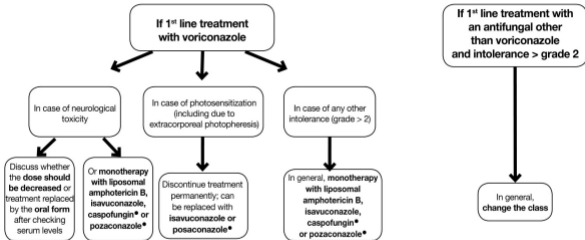
If low risk of aspergillosis, laminar air flow  
environment and based on local  
epidemiology:  
oral fluconazole (400 mg/d)

• Off-label use

## Second line treatment of invasive aspergillosis

### In case of intolerance

In case of intolerance and impairment: see impairment



In all cases, take into account the diagnostic information that is available (species identification, antifungal susceptibility test) and the response to first-line treatment

## Second line treatment of invasive aspergillosis

### In case of failure

