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

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Abstract

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

Introduction

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

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

Invasive fungal infections in hematology

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

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

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

Watch-points when prescribing antifungal agents

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

Assessment of renal function

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

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

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

Assessment of liver function

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

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

Liver injury is defined by the following criteria:

- ALT or AST ≥ 5 times the upper limit of normal (N)
- Alkaline phosphatase (ALP) ≥ 2 times the upper limit of normal (N)
- Combination ALT/AST ≥ 3 N and total bilirubin ≥ 2 N

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

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

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

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

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

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

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

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

Prescription of antifungals: expert opinion

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

Prophylactic approach

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

Prophylaxis for allogeneic HSCT recipients [28-30]

●The main risk factors for early aspergillosis (usually defined as occurring within the first 40 days after allo-HSCT before GVHD) are: 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. The risk appears to exist even if the transplant is performed in a laminar air flow room (HEPA filtration).

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

● GVHD and risk of aspergillosis

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

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

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

● Duration of prophylaxis

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

- If the main risk factor is neutropenia: prophylaxis should be stopped when the absolute neutrophil count (ANC) remains stable > 0.5 G/L during 3 days.
- If the main risk factor is GVHD: prophylaxis should be continued as long as the GVHD is not controlled and corticosteroid therapy is prescribed at a dose ≥ 0.5 mg/kg. In such cases, prophylaxis can exceed several months and may cause possible toxicity problems, lead to the emergence of resistance, or increase the costliness of treatment.

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

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

Empirical approach [31]

An empirical approach can be used for the antifungal treatment of patients with neutropenia (neutrophil count <500/µL) who remain febrile after 3-5 days of probabilistic broad spectrum antibiotics, or who become febrile again on antibiotics after a period of apyrexia.

Empirical treatment of persistent febrile neutropenia

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

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

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

Empirical treatment of persistent febrile neutropenia following primary prophylaxis

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

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

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

Curative approaches [32]

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

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

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

1st choice: voriconazole IV should be the preferred treatment for hospitalized patients, treatment by the oral route is possible for outpatients:

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

Alternative treatments

In case of contraindications to voriconazole:

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

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

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

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

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

  Interest of monitoring serum levels under evaluation

In case of contraindications to voriconazole, isavuconazole and to lipid formulations of amphotericin B:

- Intravenous caspofungin (off-label use)

  70 mg on Day 1, then:

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

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

Second-line treatment of invasive aspergillosis (in case of 1st line treatment impairment)

The parameters to be taken into account to assess treatment impairment (after 8 to 15 days except in case of early clinical deterioration) are as follows:

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

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

Treatment of aspergillosis emerging during treatment

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

Invasive candidiasis [40-45]

First choice treatment of candidemias

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

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

Alternative treatment

Liposomal amphotericin B.

Treatment of candidemias after species identification

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

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

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

Duration of treatment: resolution of neutropenia and ≥ 14 days after the last positive blood culture and resolution of clinical symptoms.

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

Look for a deep-seated focus of infection.

Consider changing the treatment.

Mucormycosis [46-49]

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

Treatment in case of failure:

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

<u>Precautions to be taken when monitoring antifungal treatment</u>

Monitoring of renal toxicity

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

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

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

Monitoring of liver toxicity [55, 56]

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

In case of hepatocellular injury due to antifungal treatment

Transaminases:

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

In case of cholestatic liver impairment:

Increase in alkaline phosphatase levels:

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

Drug-drugs interactions

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

Pharmacokinetic interactions

Triazoles

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

Echinocandins

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

Addition of adverse effects

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

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

For patients treated with amphotericin B [58]

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

When used in combination with immunosuppressive therapy

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

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

b) When used in combination with echinocandins:

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

• Caspofungin decreases the plasma concentrations of tacrolimus (Cmin -26%)

• Monitoring of blood concentrations of the immunosuppressants and dosages adjustments

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

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

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

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

Conflicts of interest: None

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Tables:

Table 1: potential renal toxicity and antifungal dose adjustments

Antifungal agent	**Dosage adjustment required in case of renal impairment**	**Potential renal toxicity**
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

ND: No Data

Source: GPR website (www.sitegpr.com), website for healthcare professionals for the Stewardship of Medicinal Product [16]

Table 2: Definition of liver injury

Hepatocellular injury	R = ALT/ALP≥ 5
Cholestatic liver injury	R = ALT/ALP≤ 2
Mixed liver injury	2 < ALT/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 ≥ 2N or INR ≥ 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) Well stabilized cirrhosis	• Usually no or little impact • Most treatments are authorized at the standard doses
Child-Pugh B (7-9 points) Moderately severe	• Dose adjustments required for drugs metabolized by the liver
Child-Pugh C (10-15 points) Severe impairment	• Limit the prescription of medical products • Consider the benefit/risk ratio

Table 6: Hepatotoxicity of antifungals

Azoles: voriconazole, posaconazole, itraconazole, fluconazole, isavuconazole	•Frequent asymptomatic increase in transaminase levels ≥ 3N •Rare hepatitis that is rather cholestatic than cytolytic (except fluconazole) •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
Echinocandins: caspofungin, micafungin, anidulafungin	•Hepatotoxicity limited to an increase in transaminase levels
Amphotericin B	•Frequent asymptomatic increase in transaminase or alkaline phosphatase levels •Rare hepatitis
Flucytosine	•Frequent asymptomatic increase in transaminase or alkaline phosphatase levels •Very rare hepatitis • Extremely rare, severe hepatitis

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

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

Table 8: Combinations contraindicated with azole antifungals

↑: increased plasma concentrations, ↓: decreased plasma concentrations

* combination with voriconazole not recommended

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

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

Table 9: Drug-drug interactions with echinocandins

	Caspofungin	**Micafungin**	**Anidulafungin**

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

Patient without early aspergillosis risk factors

↓

First choice:
Oral fluconazole (400 mg/d)

↓

Alternative:
(if fluconazole is contraindicated)
Intravenous micafungin (50 mg/d)

Patient with early aspergillosis risk factors

↓

First choice:
Oral voriconazole (200 mg x 2/d)
Or intravenous voriconazole (4 mg/kg x 2/d) after leading dose

↓

2nd choice:
Oral posaconazole (tablets): 300 mg taken once a day after loading dose•
(posaconazole (oral suspension): 200 mg x 3/d•)

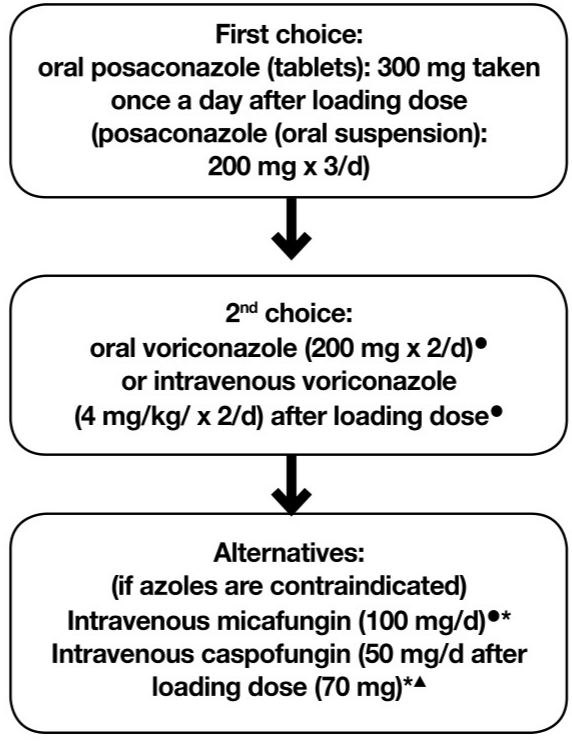
↓

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 for allogeneic HSCT recipients

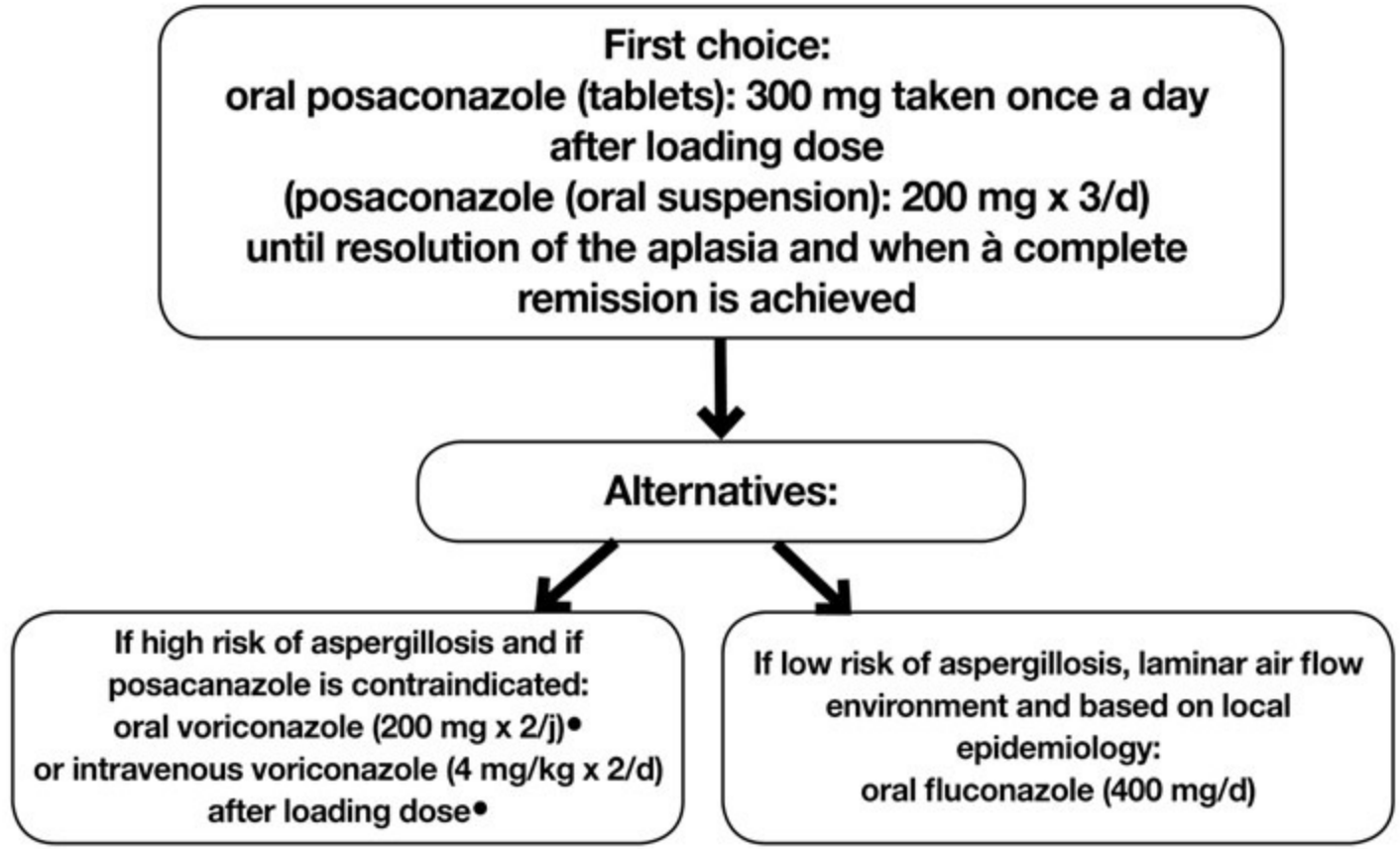
GVHD



• Off-label use
*Few data
▲Risk of emerging infections

Prophylaxis of Acute Leukemia / MDS patients

Intensive induction and consolidation phases



• Off-label use

Second line treatment of invasive aspergillosis

In case of intolerance

In case of intolerance and impairment: see impairment

If 1st line treatment with voriconazole

- In case of neurological toxicity
  - Discuss whether the **dose should be decreased** or treatment replaced by the **oral form** after checking serum levels
  - Or **monotherapy with liposomal amphotericin B, isavuconazole, caspofungin• or pozaconazole•**
- In case of photosensitization (including due to extracorporeal photopheresis)
  - Discontinue treatment permanently; can be replaced with **isavuconazole or posaconazole•**
- In case of any other intolerance (grade > 2)
  - In general, **monotherapy with liposomal amphotericin B, isavuconazole, caspofungin• or pozaconazole•**

If 1st line treatment with an antifungal other than voriconazole and intolerance > grade 2

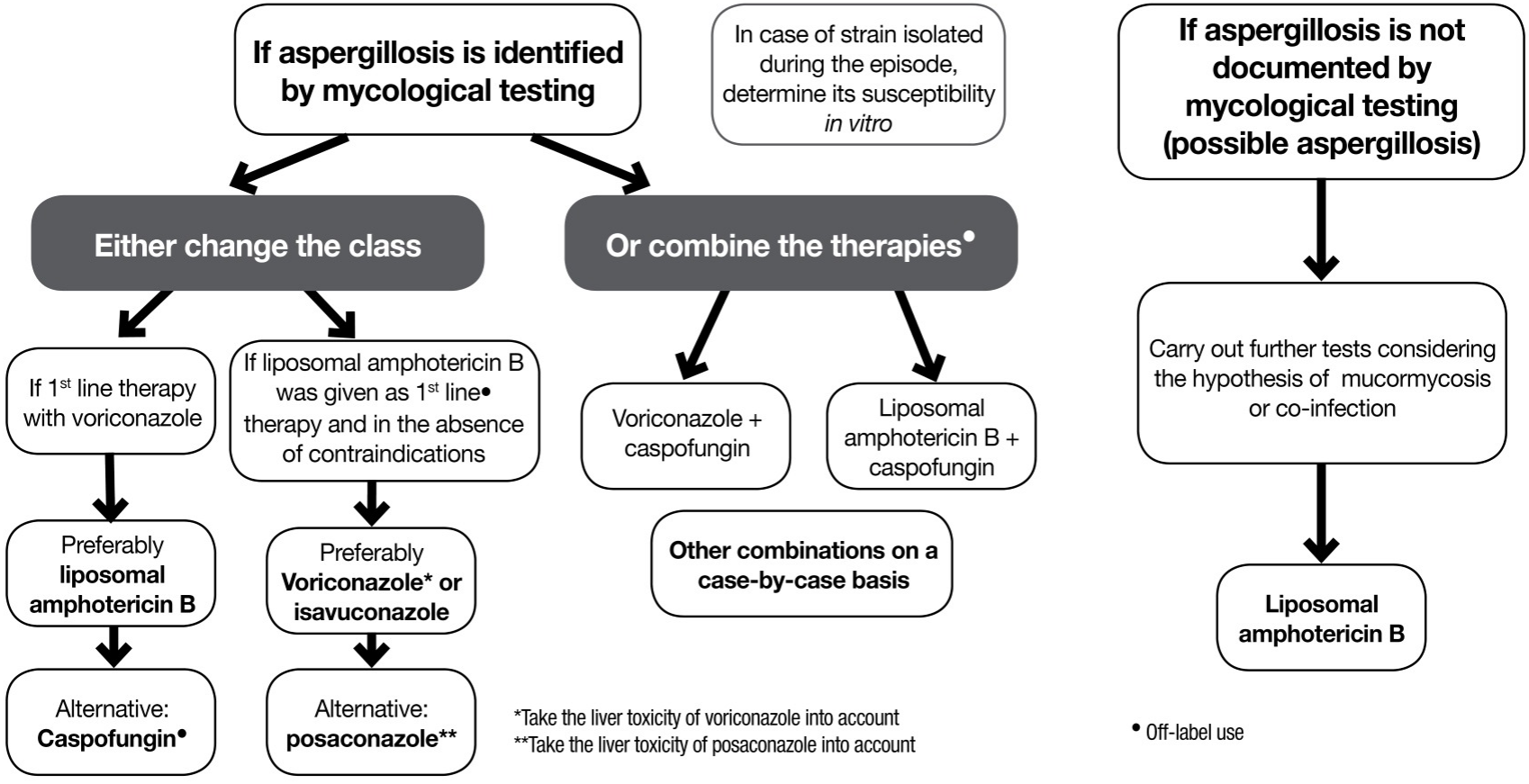
- In general, **change the class**

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

• Off-label use

Second line treatment of invasive aspergillosis

In case of failure



*Take the liver toxicity of voriconazole into account
**Take the liver toxicity of posaconazole into account

• Off-label use