Invasive fungal infections

Invasive fungal infections are a feared complication in hematooncological, immunosuppressed and resuscitation patients. Patients with allogeneic bone marrow transplant and patients with acute leukemia are most at risk.

The most common fungal invasive infection is undoubtedly *'candidiasis'*, especially *Candida albicans*, which is still well susceptible to fluconazole. However, the increasing incidence of candidiasis with significant resistance to fluconazole is a warning sign. *C. glabrata* and *C. krusei*. While *C. glabrata* is about 30% resistant to fluconazole strains, *C. krusei* is almost always resistant.

The incidence of invasive infections caused by fibrous fungi is increasing, especially at hematooncological workplaces. The vast majority are invasive *'aspergillosis'*. The incidence of infections caused by other filamentous fungi, especially invasive zygomycosis (*Mucor spp., Rhizomucor spp., Rhizopus spp.*) and invasive fusariosis (*Fusarium spp.*), is low, but in recent years has increased especially in large transplant centers.

For many years, "amphotericin-B" was the only drug available to treat these infections. However, in the early 1990s, a new class of azole antifungals entered the market - "fluconazole" and then itraconazole. A novelty was the incorporation of amphotericin-B into lipid carriers in order to reduce the toxicity of the parent molecule. After the year 2000, the development of new drugs accelerated even more, and *azoles of II generation* were approved for use and a brand new drug group,' *echinocandins'* (already 3 representatives). Many new drugs are less toxic than the original conventional amphotericin B (C-AMB) molecule, and some of them are (in some cases) more effective.

Antifungals

🔎 *For more information see Antifungals.*

- Most of them interfere with the synthesis or integrity of ergosterol in the cell membrane of fungal pathogens or interfere with the formation of their cell wall.
- According to the mechanism of action, we divide antifungals into: polyenes, azoles, echinocandins and others (the last group includes practically only flucytosine, now used exceptionally in the combined treatment of cryptococcal infection with C-AMB)

Polyenes

Amphotericin-B and its lipid forms have a broad spectrum of action. The mechanism of their action lies in the binding to the ergosterol (cholesterol-like sterol) of the cell membrane of the fungal cell with consequent damage to its integrity. The result is leakage of intracellular contents and lysis of the cell.

Amphotericin-B deoxycholate

- Until recently, due to its broad-spectrum and fungicidal effect, it has become the gold standard in the treatment of infections caused by candida, cryptococci and fibrous fungi;
- intravenous administration only;
- toxicity - nephrotoxicity, infusion-related toxicity, ion imbalance.
  - C-AMB infusion reactions (chills, shivers, fever, bronchospasm and hypotension) occur in up to 50-60% of patients. Occurrence of this reaction can be reduced significantly by a sufficiently enough long time of application of the infusion (at least 4-6 hours, even 24 hours) and especially by premedication, which precedes the actual administration of C-AMB (antipyretic, possibly in combination with hydrocortisone and antihistamine).
  - However, the most serious side effects of C-AMB are *nephrotoxicity and ion loss* (especially potassium and magnesium), which excel at up to 80%.
  - All side effects can be significantly reduced - C-AMB should not be used in patients with pre-existing renal impairment or at the same time as other drugs with renal toxicity; it is necessary to maintain sufficient diuresis (up to 4 l per day), which usually requires central vein cannylation with monitoring of the central venous pressure during intensive intravenous hydration. ** It is necessary to intensively substitute the loss of ions, especially potassium, again mostly in the form of a continuous infusion of concentrated potassium preparation, or magnesium, via the central vein.
  - C-AMB administration by continuous 24-hour infusion also provides some reduction in nephrotoxicity. The cumulative dose of C-AMB 4 g should also not be exceeded (renal damage when this dose is exceeded is usually irreversible).

Amphotericins-B on a fat carrier

- Liposomal amphotericin-B (L-AMB, Ambisome - not registered in the Czech Republic), amphotericin-B lipid complex (ABLC, Abelcet) and amphotericin-B colloidal dispersions (ABCD, Amphocil) - have not yet shown advantages in the treatment of IFI over C-AMB .
- These products have several undeniable advantages - a significant *'reduction in nephrotoxicity'*. However, despite the reduction of the risk of renal impairment, renal toxicity is not zero and ranges (depending on the definition of nephrotoxicity) from 10 to 30%.
- Another advantage is' *better penetration* into some tissues. Compared to C-AMB, practically all of them achieve higher concentrations in the liver and spleen, L-AMB also in brain tissue and ABLC in the lungs.

- A certain disadvantage of amphotericin on lipid carriers is mainly their many times higher price compared to C-AMB.

Azoles

- The most common products used in the treatment of mycoses.
- The mechanism of action is inhibition of cytochrome P-450-dependent synthesis of ergosterol, which is an essential component of the cell wall of fungi.
- The first group of azoles - imidazoles (ketoconazole, clotrimazole, miconazole) is usually used to treat superficial fungal infections;
- the second group of azoles - triazoles (fluconazole, itraconazole, voriconazole, posaconazole) is intended for the treatment of both superficial and systemic fungal diseases.

First generation of triazoles (fluconazole, itraconazole)

Fluconazole (Diflucan, Mycomax)

- It acts on candida and cryptococci strains, but has no effect on filamentous fungi;
- triazole with excellent absorption and, unlike other drugs in this group, is mainly excreted by the kidneys;
- the main advantage is high security and minimal risk of interactions;
- available in both oral and intravenous form;
- However, the massive spread of this drug has led to an increase in the number of isolates primarily (*C. krusei*) or secondary resistant (*C. glabrata*) in the population.

Itraconazole (Sporanox)

- The intravenous form contains the vehicle SBECD (sulfo-butyl-ether-cyclodextrin), which increases the solubility of the drug in water;
- The oral form is available in capsule and solution form, but in both cases the main problem is very limited absorption capacity. The capsules have a lower bioavailability, moreover significantly affected by food intake. The above-mentioned oral solution has a slightly better pharmacokinetic profile. Insufficient absorption of oral itraconazole, together with the risk of numerous drug interactions, causes significant intra- and inter-individual variability in plasma drug concentrations. To ensure that effective serum concentrations are achieved and, conversely, to avoid the risk of high concentrations that may be associated with adverse reactions, measurement of plasma drug concentrations with respect to target concentrations of 500-2000 ng / ml is generally recommended.

Second generation of triazoles

Voriconazole (Vfend) and posaconazole (Noxafil) represent the second generation of triazoles with a broad spectrum of action on candida, *Cryptococcus neoformans* and filamentous fungi, including *Aspergillus spp.* , *Scedosporium spp.* And *Fusarium* spp . Voriconazole is also effective on fluconazole-resistant candida, although cross-resistance strains can already be observed. * both in the form of oral tablets and solutions with very good bioavailability and in the form of intravenous infusion (again using the SBECD carrier);

- it is absorbed very well, however, its absorption may be impaired in various abnormalities of the gastrointestinal tract. In addition, as with itraconazole, cytochrome P-450 induces the intensity of antifungal metabolism in various drug interactions. Thus, voriconazole also has a relatively large intra- and inter-individual variability in plasma drug concentrations. Monitoring of these concentrations is therefore increasingly recommended, especially during the treatment of life-threatening infections. Target concentrations are then recommended in the range of 1.0-2.0 to 4.0 mg / ml.

The broadest spectrum of azole antifungals currently has "posaconazole". Cross-resistance with fluconazole in yeast is uncommon and, in addition, it is the only azole with a clinical effect on zygomycetes.

- currently only available as an oral solution;
- its absorption is much more variable than that of voriconazole and improves significantly with food. If the administration of a sufficient amount of food is not possible, then it is recommended to divide the daily dose into several parts;
- drug interactions via cytochrome P-450 are minimal with posaconazole, but it is the uncertainty in sufficient drug absorption on the one hand and the relationship between the effect of invasive aspergillosis treatment and the achieved plasma concentration on the other hand that many authors also recommend measuring plasma concentrations of this drug (triazole).

Side effects of triazoles

- In general, azoles are a safe group of antifungals, even when used for a longer period of time.
- All triazoles can cause *hepatotoxicity* ', which usually takes place under the manifestation of elevated transaminase elevations and only exceptionally requires discontinuation of the drug.
- The intravenous form of itraconazole and voriconazole is contraindicated due to renal impairment due to the risk of SBECD accumulation.
- One of the most significant disadvantages of triazoles is that they are metabolised by the hepatic cytochrome P-450 (CYP) system - especially CYP2C9, CYP2C19 and CYP3A4. The genetic activity of these enzymatic systems, as well as the effect of other drugs that induce CYP or its substrates, may lead to effects on plasma concentrations and thus to reduced efficacy or increased toxicity of triazole antifungals. In contrast, triazoles

are inhibitors of CYP and therefore lead to increased concentrations of drugs metabolised by this system.
- Unfortunately, one of the most important drug groups used in patients at risk for IFI are immunosuppressants (but also a number of other drugs such as carbamazepine, barbiturates, rifampicin and others). Co-administration of some triazoles with certain immunosuppressants is often contraindicated (eg sirolimus with voriconazole), or at least must be associated with the measurement of plasma concentrations of these drugs. The highest risk of a "bi-directional" drug interaction is found for triazoles with itraconazole and voriconazole, and significantly lower for posaconazole and fluconazole.

Echinocandins

- The site of action is the cell wall. By inhibiting the enzyme 1,3-β-D synthetase, they block the production of 1,3-β-D glucan, one of the cornerstones of the cell wall. Under the influence of echinocandins, there is a significant disruption of the forming cell wall of fungi and subsequent osmotic lysis of the fungal cell. The fact that the target site of action of echinocandins is not present in the mammalian cell explains the minimal toxicity of this drug class.
- There are currently three echinocandins available: caspofungin (Cancidas), anidulafungin (Ecalta) and micafungin (Mycamine). All are effective against candida and aspergillus strains and, conversely, are ineffective in infections caused by "Cryptococcus neoformans" and filamentous fungi other than Aspergillus spp.
- Intravenous administration only;
- they penetrate the tissues very well, with the exception of cerebrospinal fluid, where the penetration is low due to the high binding to plasma proteins.
- Their administration is associated with minimal toxicity, and since they are not metabolised by cytochrome P-450, they also have very few drug interactions.
    - The exception is ciclosporin - elevated liver enzymes may occur when caspofungin and micafungin are co-administered.
- In case of renal failure, it is not necessary to reduce the dose of echinocandins, in case of more severe hepatic impairment, a lower dose is recommended only for caspofungin.

Other drugs

The use of other drugs in the treatment of IFIs in cancer patients is practically limited to "flucytosine".

- Part of the combined treatment of cryptococcal meningitis;
- belongs to antimetabolites;
- after entering the cell, it is metabolized to 5-fluorouracil and is subsequently incorporated into fungal RNA. The result is a disruption of RNA / DNA synthesis and its extinction;
- in oral and intravenous form;
- has very good pharmacokinetics, including excellent cerebrospinal fluid penetration. Its main limitation is the narrow spectrum of action (only yeasts and cryptococci), and above all the very rapid development of acquired resistance. Therefore, it is only used in combination antifungal therapy.
- Today, its only indication is the use of *'in combination with C-AMB in the treatment of' 'cryptococcal meningitis*.

Treatment of invasive candidiasis

It is essential for the successful treatment of invasive candidiasis (IC) that treatment is initiated as soon as possible from the moment of a positive culture test for Candida spp. from a primarily sterile site.

The choice of antifungals in the treatment of IC is a two-step process. At the first moment, the clinician is informed about the presence of yeast in the blood culture or primarily sterile material. Only after a few days comes information about the exact identification, possibly susceptibility to antifungals.

In regard to the available antifungals, fluconazole, amphotericin-B deoxycholate (and its lipid forms), voriconazole, and all three echinocandins demonstrated efficacy in the treatment of IC in a well-designed randomized study. (There is still no relevant data on the use of itraconazole and posaconazole in the treatment of IC.)

However, these findings apply to regular patients without neutropenia. There are significantly fewer reports to the effectiveness of individual drugs in patients with neutropenia. In the large studies mentioned above, these patients were mostly excluded or formed only a very small part of the cohort. For these reasons, it is very difficult to decide whether the same recommendations can be applied to patients with neutropenia.

Initial treatment of invasive candidiasis (before the result of strain identification is available)

1. Patients without neutropenia.

- The drug of choice is "fluconazole" at a dose of 400-800 mg / day or "echinocandins" (caspofungin 70 mg / day on day 1 followed by 50 mg / day; anidulafungin 200 mg / day 1). day followed by 100 mg / day; micafungin 100 mg / day) or "amphotericin-B deoxycholate" in an amount of 0.6 mg / kg / day.
- Fluconazole is preferred in patients who are not in critical condition and have not received azole prophylaxis;
- echinocandins, on the other hand, in patients who are in critical condition (especially with multiorgan failure) or who have had azole prophylaxis before the infection developed.
- If these patients do not have impaired renal function, amphotericin-B deoxycholate or its lipid forms can also

be chosen.

1. Patients with neutropenia.

In these patients, especially if azole prophylaxis has been used (which is very common here) or if the patient is colonized with *C . glabrata* and *C.krusei* strains, fluconazole is not a suitable as a initial treatment. Therefore, echinocandins or amphotericin-B deoxycholate are recommended as an initial treatment at the doses mentioned above until the definitive determination of the yeast strain.

- Echinocandins are again recommended especially in individuals with neutropenia and organ damage, especially with impaired renal function, due to their minimal side effects.
- Lipid forms of amphotericin-B can also be considered in isolated renal impairment, but always with the knowledge that their nephrotoxicity, unlike echinocandins, is not zero.
- On the other hand, it should be borne in mind that there are only a small number of patients with neutropenia in studies demonstrating the efficacy of individual echinocandins. For these reasons, although a similar effect of the entire drug class can be expected, anidulafungin is not officially indicated in the treatment of IC in neutropenic individuals.

Treatment of invasive candidiasis after candida strain identification

- In infection caused by *C. Erosocandins or amphotericin-B deoxycholate (or its lipid forms) are the drug of choice. Consequently, if the strain is sensitive to voriconazole in vitro, this triazole can also be used.*
- If it is an infection caused by *C. glabrata* and antifungal susceptibility has not been tested, treatment with *echinocandin 'or amphotericin-B deoxycholate'* (possibly its lipid forms) is again indicated. If this yeast is sensitive to fluconazole or voriconazole in vitro, then it is possible to change the treatment to these triazoles, especially in a patient with stable condition.
- For infections caused by C. parapsilosis, fluconazole or amphotericin-B deoxycholate (or its lipid forms) are the drugs of choice. This is because the use of echinocandins is not recommended in case of infection caused by this species due to the reduced in vitro sensitivity.

Other recommendations

Venous catheter removal.

In all non-hematological patients with candidiasis, replacement of the central venous catheter (CVC) as a possible primary source of candida infection is always recommended. In hematooncological patients, damage to the gastrointestinal tract by anti-tumor treatment and subsequent penetration of colonizing candidates into the circulation may also be a source of infection. The strength of the evidence for the removal of the CVC is therefore less here. Nevertheless, due to the risk of subsequent catheter settlement, it is generally recommended to remove it. Optimal duration of treatment. The standard duration of treatment of the absolutely most common form of IC - candidiasis - is 14 days from the last positive blood culture with evidence of 'Candida spp.' 'And the simultaneous disappearance of clinical signs of infection. In addition, in haemato-oncology patients, resolution of neutropenia is required prior to discontinuation of treatment.

In the case of an organ disease caused by a yeast infection, the treatment is terminated only after the complete disappearance of the microbiological, radiological and clinical signs of the disease.

Importance of in vitro antifungal susceptibility testing.

Although the results of studies examining the relationship between the in vitro susceptibility of yeast strains and the clinical effect of the drug in vivo are inconclusive, this testing is generally recommended (especially given the risk of non-albicans candida resistance to azole antifungals).

In vitro susceptibility testing can help explain the lack of effect of the initially selected antifungal and facilitate the choice of targeted antifungal therapy. Furthermore, in vitro susceptibility testing (Figure 1) allows a possible modification of intravenous antifungal therapy with oral azole therapy in patients who are found to have improved clinical course but the treatment has not yet reached the recommended duration.

Treatment of invasive aspergillosis

Drugs that act on aspergillus strains include amphotericin-B and its lipid-bearing forms, itraconazole, voriconazole, posaconazole, and echinocandins. So far, only five randomized studies have been performed in the primary treatment of the most common invasive mycosis in hematooncological patients - invasive aspergillosis (IA). Thus, most of the information on IA treatment (both primary and rescue) comes from non-randomized cohorts of patients and from retrospective analyzes.

Primary treatment of invasive aspergillosis

- Until recently, amphotericin-B deoxycholate was the gold standard in the treatment of IA at a dose of 1.0-1.25 mg / kg / day. However, this treatment was successful in up to a third of patients, and in addition, C-AMB, which was often long-term in the IA indication, was associated with a high risk of nephrotoxicity.
- Since 2002, after the publication of Herbrecht et al. *voriconazole* 'has become the standard in primary treatment. Voriconazole has not only shown greater efficacy than C-AMB in this indication (53% vs. 32%), but has also been associated with a lower risk of nephrotoxicity and might be changed to oral form after initial intravenous treatment. There is not yet enough information on whether it is possible to start treatment

immediately with the oral form of the drug, and therefore it is still recommended to start with the intravenous form initially. Due to the correlation between plasma drug concentrations and the effect of IA treatment, the need to monitor plasma drug concentrations and possible dose adjustments according to the outcome is pointed out increasingly. Although such a procedure is not common yet, it may further increase the likelihood of success in treating this life-threatening infection.
- Voriconazole is also the drug of choice in case of disseminating IA to the CNS. In a study by Schwartz et al. treatment response in this case was achieved in 35% of patients.
- If voriconazole is contraindicated, the alternative in primary treatment of IA is liposomal amphotericin-B (L-AMB), which is not available in the Czech Republic, or amphotericin-B lipid complex (ABLC) .24 Their effectiveness in this indication was 50%. ,47% respectively. On the contrary, the third amphotericin on a lipid carrier - amphotericin-B colloidal dispersion - is generally not recommended in this case, especially in regard to the results of the work of Bowden et al.
- Information on the use of echinocandins as monotherapy in the initial treatment of IA is limited and is not the drug of choice in this case. In the recently published work of Viscoli et al. Caspofungin has shown limited efficacy in primary treatment of IA (33%).
- Exceptions are patients with multiorgan involvement - here caspofungin (or other echinocandins in the future) may be practically the only antifungal that can be used due to its high safety.
- Reports on other echinocandins are scarce. This is very similar for itraconazole and posaconazole, where data lack completely. Therefore, these drugs cannot be recommended in the primary treatment of IA.
- Although there are increasing reports in the literature about the use of combination antifungal therapy (especially voriconazole, posaconazole or lipid amphotericins with echinocandins) in primary treatment of IA and these reports are often very encouraging, such a procedure is not yet generally accepted.

Rescue therapy of invasive aspergillosis

The choice of antifungals in case of failure of primary treatment is complicated. Virtually all information on the effectiveness of individual drugs in this case come only from non-comparative or retrospective analyzes. In addition, there is still a lack of broader information on the most appropriate treatment in case of voriconazole failure as a first-line antifungal agent. The only available data are on the use of voriconazole, posaconazole, L-AMB, ABLC, ABCD, caspofungin and micafungin in rescue treatment and the efficacy of these drugs is between 30 and 50%. For patients with IA who are primarily resistant or intolerant to basic treatment, there is (unlike primary treatment) much more information about the possibility of combination antifungal treatment. Combinations of mainly second-generation triazoles with echinocandins (possibly amphotericins on lipid carriers with echinocandins) are already an option in this case, and some works even point to an extension of the survival period of patients treated this way.

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