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THE MANAGEMENT OF INVASIVE FUNGAL INFECTIONS

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The past decade has revealed the fact that critical patients are at risk for developing invasive fungal infections (IFI). In such context, we have to gather and systematize the necessary tools in order to be able to promptly diagnose this type of infections and to immediately install the necessary and adequate antifungal therapy.

How do we do this?

To begin with, we have to acknowledge the fact that the invasive fungal infections currently represent the third cause [24 – Wisplinghoff] of systemic infections in critical patients. (Fig. 1)

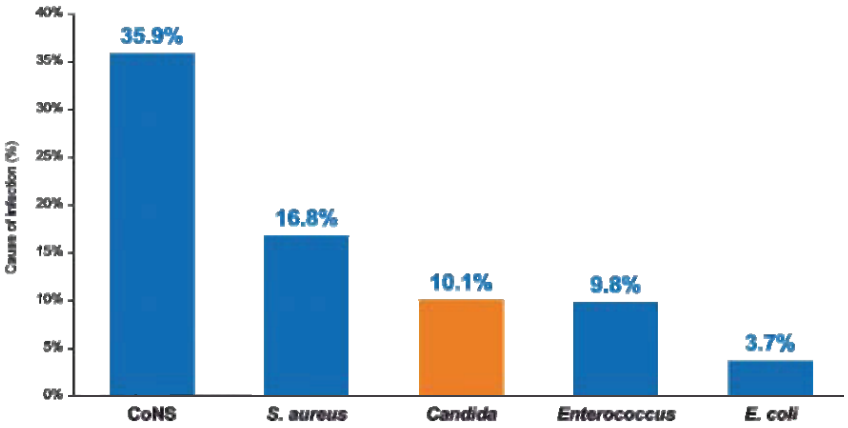

Figure1 The etiology of severe sepsis
Wisplinghoff H. et al. Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24,179 Cases from a Prospective Nationwide Surveillance Study. Clin Infect Dis. 2004;39:309-317

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What induces this kind of infection?

The current data suggest that both *Candida spp.* and *Aspergillus spp.* embody the most important fungi correlated with invasive infections. *Candida spp* seems to be widely represented by the non-albicans species, opposite to the albicans species.

An important study elaborated in our country shows that the incidence of *Candida albicans spp.* comprises 77% while the non-albicans species represent 23%.

An issue of great clinical and therapeutic relevance is the resistance to fluconazole which is 40% in the albicans species and 53% in non-albicans *Candida spp*. Hence, it is strikingly clear that fluconazole is no longer the first line of therapy in IFI. Furthermore we have to keep in mind that *Aspergillus spp*. and of course certain species of non-albicans Candida are naturally non-sensitive to Fluconazole. (Table 1)

INSTITUTION	No.	CA	CA %	C nonA	C nonA %	CA RF	CA RF %	C nonA RF	C nonA RF %
Matei Balș Institute, Bucharest	50*	34	68%	16	32%	10	32%	4	25%
Victor Babeș, Bucharest	56	49	87,5%	7	12,5%	33	67,3%	4*	57%
Infectious diseases, Constanța	7	2	28.5%	5	71.5%	2	100%	5	100%
Infectious diseases, Cluj Napoca	15	11	73,3%	4	26,6%	3	27,3%	2	50%
Victor Babeș, Craiova	25	22	88%	3	12%	0	0%	3	100%
Victor Babeș, Timișoara	13	9	70%	4	30%	3	33.3%	3	75%
Infectious diseases, Brașov	8	7	87%	1	13%	2	29%	0	0%
Total	174	134	77%	40	23%	53	40%	21	53%

Table I. Global results of fungal infections and fluconazole resistance
CA – Candida albicans; C nonA – Candida non-albicans; RF – resistance to fluconazole

Recently, a lot of strategic therapeutic definitions [22, Segal, 2007] connected with the IFI have come up. We presently take into consideration 4 different therapeutic strategies: (table 2)

Strategy	Definition
Prophylaxis	Initiation of antifungal treatment in patients at high risk for IFI
Empirical therapy	Initiation of antifungal treatment or modification of an existing regime in patients with persistent neutropenic fever (with custom duration of 4-7 days) without known source and which do not respond to corresponding antibacterial agents
Preemptive therapy	Initiation of antifungal treatment in patients with persistent neutropenic fever (with custom duration of 4-7 days) *and* laboratory* and radiological** markers indicating IFI
Documented therapy	Initiation of antifungal treatment in patients meeting the EORTC/MSG [5] criteria for probable or confirmed IFI

Table II. Definitions of therapeutic strategies
*Positive testing for Aspergillus galactomannan, PCR or ß-D-glucan
**E.g. the halo sign on CT exam
After Segal BH, et al. Clin Infect Dis 2007; 44: 402–409

- prophylactic strategy
- empirical therapy
- preemptive therapy
- documented therapy

Concomitantly, in 2007, Morrell [19] *et al.* and Kumar [11] *et al.* revealed the fact that the mortality percentage in IFI is directly connected with the span of the delay in initiation of antifungal therapy.

Other important data show that in candidemic patients with septic shock the mortality rate increases by 7,6% per hour of delay in installing the antifungal therapy (fig. 2)

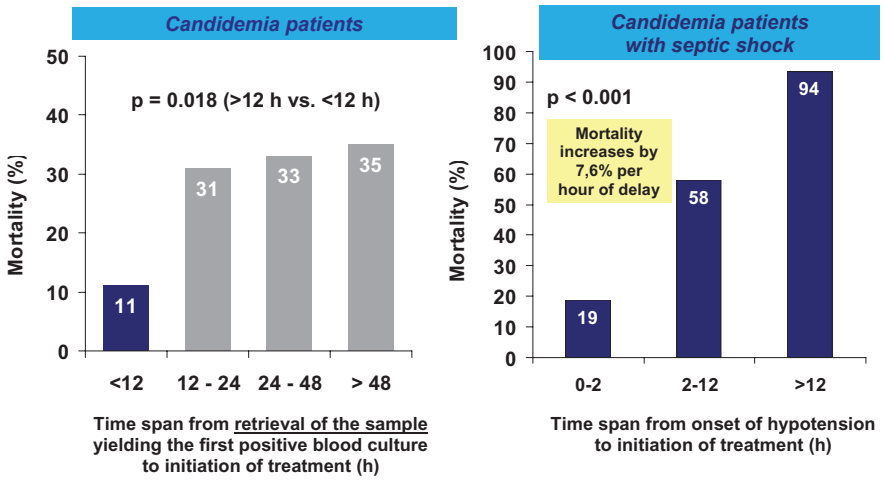

Figure 2. Mortality in candidemic patients stratified according to delay in initiation of treatment
Morrell M et al. Antimicrob Agents Chemother 2005; 49:3640-45. Kumar A et al. ICAAC 2007; poster K-2174

What do we have to do?

We have to install an adequate and optimal antifungal therapy which is supposed to respect 4 different criteria, also know as the 4Ds [10 – J Joseph, 2008]. The 4Ds are represented by: 1. the right **D**rug, 2. right **D**ose, 3. right **D**uration and 4. **D**e-escalation. (fig. 3)

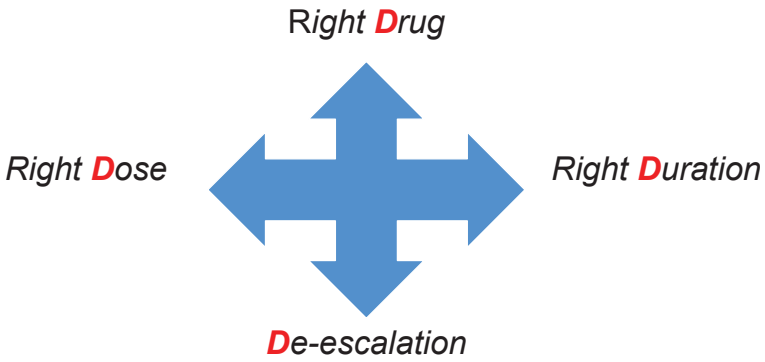

Figure 3. Optimal antifungal therapy respecting the 4Ds principles
J Joseph, KA Rodvold, Expert Opin. Pharmacother. (2008), 9(4): 561-575

In order to be able to de-escalate the systemic antimicotic therapy we can either use Carmeli-like score (fig. 4) which is supposed to stratify the risk of IFI and the possible etiology of such syndromes or we can use the Romanian Antifungal Advisory Board algorithm (fig. 7).

The Carmeli-like risk evaluation score requires answers to three different questions:

- A. Previous contact with the health care department?
- B. Previous therapy with antibacterial and antimicotical drugs during the past 6 months?
- C. Immunologic characteristics of the patient?

The value of the Carmeli-like score can only be 1, 2 or 3, according to highest rated answer.

If the score is "1", the patient answered A1, B1, C1. Score 1 suggests a community-acquired infection.

If the patient scored "2" in at least one question (selecting value "1" for the other questions), the score value will be "2", meaning that the patient developed an infection with a certain level of modified resistance of the fungus. Generally speaking, this kind of infection is known as health care associated infection.

If the patient scored "3" in at least one of the questions, the final score value will be 3, denoting that the patient developed a nosocomial infection (regardless if it's an endogenic of exogenic nosocomial infection). The significance of such a score is that the fungus certainly has a high level of resistance to fluconazole (to standard azole therapy).

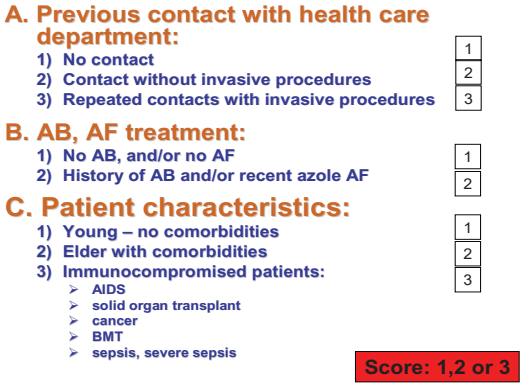

Figure 4. Carmeli-like score – risk stratification
AB – antibiotic, AF – antifungal

Using Carmeli-like risk evaluations we can design the first line of therapy for IFI.

Therefore, in case of Carmeli-like score 1, we can initiate therapy with fluconazole since the score signifies that the patient hasn't recently been in contact with the health care department, has no recent history of antimicotic/antibiotic treatment and has no associated immunodepressive disease.

If the Carmeli-like score is 2, the patient requires de-escalation therapy and in such context we need to start off with either voriconazole, caspofungin, anidulafungin or posaconazole, keeping fluconazole for de-escalation – in a second line of therapy, after receiving the antifungigram results (provided these results show that the fungus is sensitive to fluconazole).

If the Carmeli-like score is 3, we have to define whether the patient is neutropenic or non-neutropenic and we need to start therapy with an echinocandin or voriconazole (see attached algorithm – fig. 5).

If we need to extend the therapeutic strategy, we can use the second therapeutic algorithm and it is evident that if the patient has risk factors for aspergillosis [3 – Cordonnier, 2008], we are required to start with voriconazole [16 – Marchetti 2008]. This attitude is considered to have an A-1 level of evidence strength.

The specific therapeutic attitudes for Carmeli-like scores 2 and 3 could be adjusted according to the presence or absence of previous exposure to azoles. As such, 3 new antifungal drugs need to be employed as first line of therapy: voriconazole, caspofungin and anidulafungin. Therefore voriconazole will be used in circumstances where we expect an IFI with central nervous system (CNS) and lung determination. Caspofungin will be mainly employed in neutropenic patients while anidulafungin will be used in patients with renal and liver failure as well as in patients with comorbities and comedications which might affect CYT P450 activity (fig. 6)

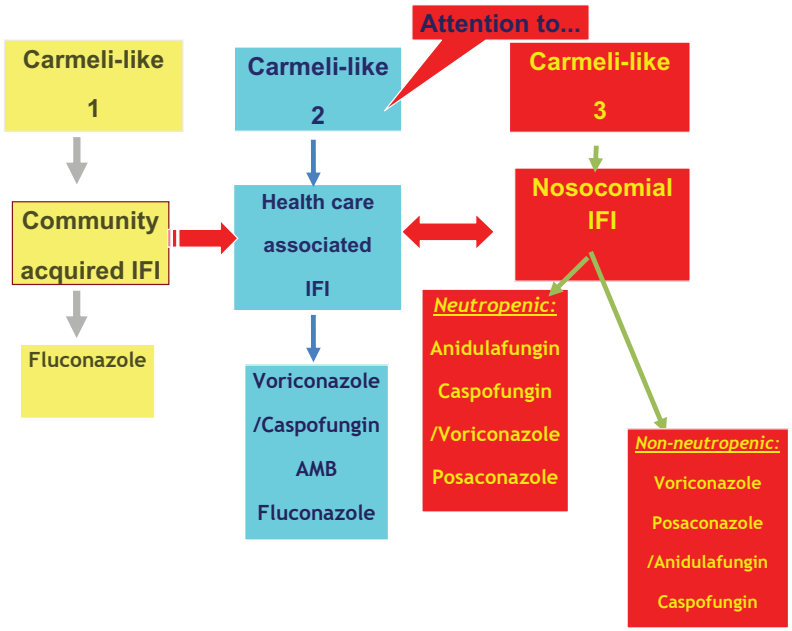

Figure 5. Antifungal systemic therapy according to Carmeli-like score (2)
AMB – amphotericin B, IFI – invasive fungal infections

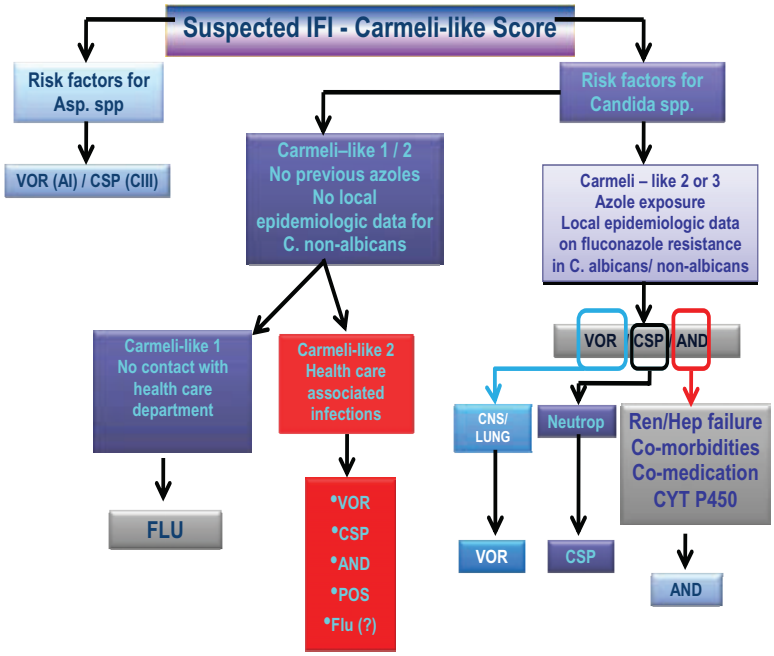

Figure 6. Carmeli-like score extended antifungal therapy algorithm
AND *– anidulafungin,* ***Asp. spp*** *– Aspergillus species,* ***CNS*** *– central nervous system,* ***CSP*** *– caspofungin,* ***Flu*** *– fluconazole,* ***Hep*** *– hepatic,* ***IFI*** *– invasive fungal infection,* ***neutrop*** *– neutropenic,* ***POS*** *– posaconazole,* ***Ren*** *– renal,* ***VOR*** *– voriconazole*

According to the Romanian Antifungal Advisory Board algorithm (fig. 7), the critical patient admitted in ICU with severe sepsis or septic shock or with positive predictive factors for Candida could be enrolled in algorithm number 3.

This attitude is prescribed by the results obtained through different cultures and through paraclinic examinations such as CT or MRI (see algorithm). This algorithm also indicates the right time for stopping antifungal therapy or for switching back to echinocandin according to the de-escalation precept and clinical evolution of the patient under antimicotic therapy.

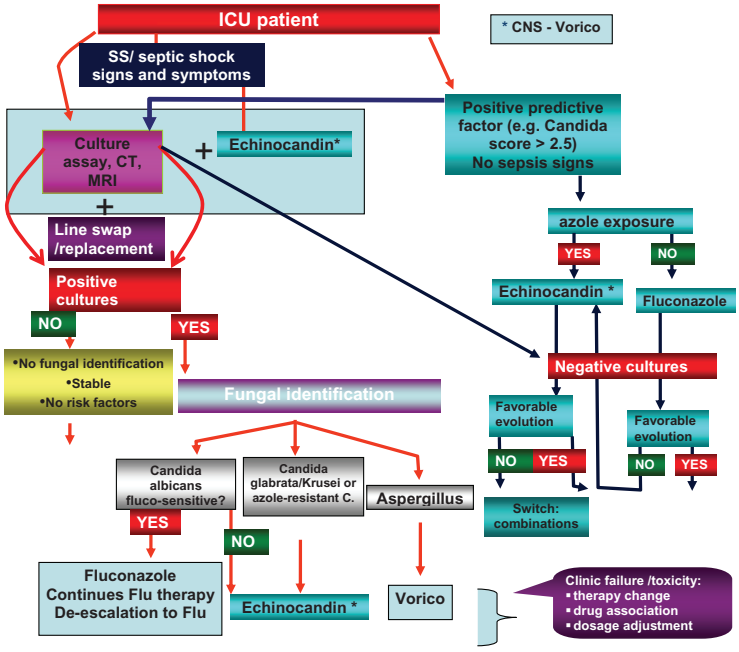

Figure 7. Algorithm of systemic antifungal infection therapy in critical care patients
AFT – antifungal treatment, ***C.*** *– Candida,* ***CNS*** *– central nervous system,* ***Flu*** *– fluconazole,* ***ICU*** *– intensive care unit,* ***Vorico*** *– voriconazole*

Abbreviations: CA – *Candida albicans,* C nonA – *Candida non albicans,* CNS – central nervous system, ICU – intensive care unit, IFI – invasive fungal infections, Flu – fluconazole.

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