Research Paper

Evaluation of treatment of invasive fungal infections

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ABSTRACT

Objective: To identify the risk factors associated with invasive fungal infections (IFI) in immunocompromised patients (IP), and monitor antifungal therapy appropriateness and costs. **Materials and Methods:** The 1-year observational retrospective study was performed on 101 IP, who received antifungal intravenous therapy with fluconazole (F), liposomal amphotericin-B (A), caspofungin (C), itraconazole (I) for ≥4 days. Patient therapy was divided into three groups: Prophylactic, empirical, and target. Immunosuppressive therapy (IT), total parenteral nutrition (TPN), dialysis, central line, steroid therapy, stent use, neutropenia, and mechanical ventilation were evaluated. Variables were therapy duration, defined daily dose (DDD) consumption, DDD average cost. **Results:** Main risk factors were central line (65.3%), TPN (56.4%), dialysis (46.5%), IT (42.6%), mechanical ventilation (32.7%), neutropenia (24.8%), steroid therapy (23.8%), and stent use (14.9%). Average duration of prophylaxis was 7 days; F (61%), A (26%), and C (13%) were used. Average duration of empirical therapy was 8 days; F (52.9%), A (26.5%), C (8.8%), I (2.9%), and in association A + C, A + F, C + F (8.9%) were used. Average duration of target therapy was 9 days; F (40.4%), A (23.1%), C (15.4%), I (7.7%), and in association A + C, A + F, C + F (13.4%) were used. DDD consumption and DDD average-cost were: C 50 mg vial: 273 DDD, €381.1; C 70 mg vial: 33.6 DDD, €389.6; F 200 mg vial: 768 DDD, €11.8; F 100 mg vial: 89 DDD, €10.6; I 250 mg vials: 62.5 DDD, €68.8; and A 50 mg vial: 2200 DDD, €93.4; respectively. **Conclusions:** Data showed an appropriate use of antifungals. Best alternative therapy (cheaper antifungal drug) was prescribed for most patients. The high cost of A and C was justified by IFI resolution.

Key words: Costs, defined daily dose, invasive fungal infections, prescriptive appropriateness, risk factors

INTRODUCTION

Invasive fungal infections (IFI) are an important cause of morbidity and mortality in seriously immunosuppressed and immunocompromised patients.[1-4] Given the limited clinical manifestations and the risk of multiresistant strains developing, there are still many difficulties in preventing, diagnosing, and treating invasive mycoses.

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Candida and Aspergillus are the main species responsible for IFI.[5] There are currently few available systemic antimycotic drugs; therefore it is important to enforce a sound therapy limiting resistance as much as possible and at the same time fighting these infections. Developing antifungal drugs with improved tolerance and/or specificity, but with very high costs (liposomal amphotericin B, caspofungin) has improved effective treatment and increased hospitals' pharmaceutical expenditure.

A clinical pharmacist on the unit can be essential to monitor these therapies in terms of appropriateness of prescription, and to rationalize the use of these highly expensive drugs.

This retrospective study done at Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT) in Palermo, has the goal to:

- Identify major risk factors of IFI development in patients at risk of immunocompromisation from major surgery,

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immunosuppressive therapy for replacement surgery or severe disease, or undergoing systemic antifungal therapy; over a period of 12 months[6-8]
- Monitor the appropriateness of prescription of empirical, prophylactic, and target therapies in compliance with the Infectious Diseases Society of America (IDSA)[9,10] and European Organization for Research and Treatment of Cancer (EORTC) guidelines
- Assess adherence to microbiology outcomes in case of target therapy
- Monitor consumption to rationalize costs of more expensive antimycotic drugs.

MATERIALS AND METHODS

The 1-year observational retrospective study was performed at ISMETT, a 78-bed transplant center in Palermo, Italy, reviewing the electronic medical records and antimycograms of all patients undergoing systemic antifungal therapy.

Analysis criteria were based on the clinical profile of the patients indicated below, monitoring consumption of fluconazole (F), liposomal amphotericin B (A), caspofungin (C), and itraconazole (I) in prophylactic, empirical, and target therapy; and also on compliance with microbiology results in cases of ascertained infections.

The study included solid organ transplant recipients (liver, kidneys, heart, and lung), patients who underwent cardiac and abdominal surgery, and patients with serious internist diseases (carcinoma, cirrhosis, short bowel syndrome, cardiac decompensation, and respiratory failure) admitted in the intensive care unit (ICU) and inpatient units. Inclusion criteria were the presence of at least one risk factor and an empirical, prophylactic, and target therapy lasting 4 days or more.

Individuals reporting at least one of the following factors according to IDSA classification were considered at risk of developing IFI: Patients with a central line in place, on total parenteral nutrition (TPN), on dialysis, with a stent or other prosthesis device, on immunosuppressive and steroids therapy, or mechanical ventilation.

We also performed a cost analysis (%) and a review of DDD antimycotic drug consumption for prophylactic, empirical, and target therapies.

For each antimycotic drug and for every therapeutic regimen enforced in the period under consideration, we reviewed:
- Number of patients undergoing (prophylactic, empirical, target) therapy to assess IFI incidence in the population at risk
- Average length of therapy (days)
- Total expenditure (in Euro) and average cost (in DDD) for each antimycotic drug utilized (all drug costs were considered without value added tax (VAT)
- Average cost per patient based on average number of days of therapy (in Euro).

RESULTS

The sample included 101 patients on systemic antifungal therapy of which 17 were children (average age: 7-year-old (yo)], 52 men (average age: 53 yo), and 32 women (average age: 57 yo).

Of the 101 patients, 43 underwent a solid organ transplant (six heart, seven lung, four kidney, 24 liver, and two liver and kidney combined); eight suffered respiratory failure, five cardiac decompensation, one chronic ischemic cardiomiopathy, six underwent cardiac surgery (one mitral valve repair, one mitral prosthesis implant, four aortic valve replacement); 13 were affected by neoplasia (two stomach adenocarcinoma, six cholangiocarcinoma, two hepatocarcinoma, two pancreas neoplasia, and one nephroblastoma); four were affected by short bowel syndrome, seven liver cirrhosis, three liver failure, two renal failure, two liver resections, four bowel resection; while four had undergone various abdominal surgery interventions.

Risk factors

The average number of risk factors in the sample is three.

Risk factors encountered were: 42.6% immunosuppressive therapy, 56.4% TPN, 46.5% dialysis, 65.3% central line, 23.8% steroid therapy, 14.9% valves-stent-medical devices, 24.8% neutropenia, and 32.7% mechanical ventilation.

Therapies

13.9% of patients ($n = 14$) only received prophylactic therapy with an average duration of 7 days; 33.7% ($n = 34$) received only empirical therapy with an average duration of 8 days, and 33.7% ($n = 34$) received only target therapy with an average length of 9 days.

For 3% ($n = 3$) of patients it was deemed appropriate to perform a prophylactic therapy followed by an empirical therapy, for 9.9% ($n = 10$) empirical therapy followed by target therapy, for 5% ($n = 5$) prophylactic followed by target therapy, and for 1% ($n = 1$) prophylactic therapy followed by empirical and then by target therapy.

Prophylactic therapy

The first choice of drug for prophylactic therapy was F 61% ($n = 14$), followed by A 26% ($n = 6$), and C 13% ($n = 3$).

Empirical therapy

The first choice of antifungal was F 52.9% ($n = 18$), followed by A 26.5% ($n = 9$), C 8.8% ($n = 3$), and I 2.9% ($n = 1$). Only

in 2.9% of cases we performed a combined therapy with two active principles (A + C, A + F, C + F).

Target therapy

In the 50 target antimycotic drug prescriptions, the most commonly-used medication was F 40.4% ($n = 21$), followed by A 23.1% ($n = 12$), C 15.4% ($n = 8$), and I 7.7% ($n = 2$). In the other cases, it was necessary to resort to a combined regimen of antifungals (A + C, A + F, C + F, A + I).

Four deaths occurred during target treatment: Two patients showed infections from *Candida glabrata* and *C. albicans* in several microbiology cultures, one from *Geotricum capitatum* encountered in the blood culture and one from *Aspergillus fumigatus* seen in the bronchial culture.

An additional three patients died a few days after the end of the target treatment. Microbiology results showed *C. glabrata* colonies present after the therapy. Of the seven deceased patients, four of them were under treatment with A, two with C, and one with F. As shown by microbiology results, the antimycotic drug regimen established in these patients failed to eradicate the infection thus possibly contributing to their death.

The isolated fungal species were: Candida 90.1%, Aspergillus 6.7%, Cryptococcal 1.7%, Geotrichum 1.7%. The antifungal target prescription rate [Figure 1] for each isolated fungal species was: *C. albicans* F 22 patients, A seven patients, C five patients; *C. glabrata* F two patients, A seven patients, C seven patients, I three patients; *C. krusei* F one patient; *A. niger* A one patient; *A. terreus* A two patients; *A. pneumonia* A one patient; *Cryptococcal neoformas* A one patient; Geotrichum F one patient.

During the study period IFI's incidence in the population with major risks (reviewed sample: 101 patients) was 49.5 and 3.8% in the overall hospital population (2,632 patients), respectively.

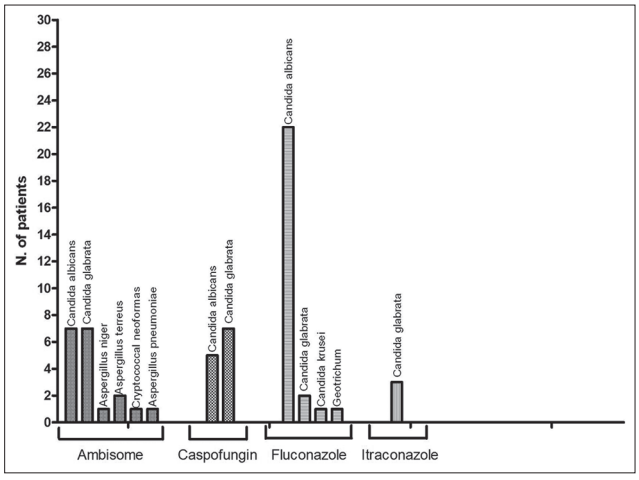

Figure 1: Antifungal prescription rate for each isolated fungal species

The average durations of the three therapeutic regimes for each antimycotic drug reviewed were.

A: Prophylactic and empirical therapy 7 days and target therapy 10 days; C: Prophylactic therapy 7 days, empirical therapy 8.5 days, and target therapy 8 days; F: Prophylactic therapy 6 days, empirical therapy 8 days, and target therapy 9 days; I: Empirical therapy 4 days and target therapy 8 days.

Cost analysis

A [Table 1]: Costs were calculated based on daily doses (mg/kg body weight) prescribed per patient. For prophylactic therapy costs were approximately €670 for one 250 mg/day dose (median), corresponding to 3.6 mg/kg/day (median) for average body weight of 58 kg; average cost per patient for 7 days of treatment was €6961.7.

For empirical and target therapies, costs were approximately €540 for one 200 mg/day dose (median), corresponding to 3.3 mg/kg/day (median) for average body weight of 54 kg for empirical therapy and 56 kg for target therapy. Average cost per patient for 7 days of empirical therapy was €3870.1, while for 10 days of target therapy it was €5471.5.

C [Table 2]: Costs per patient were calculated considering a 70 mg/day loading dose and a 50 mg/day maintenance dose. For prophylaxis therapy the cost was €2815 for 7 days, for empirical therapy it was €4083.2 for 8.5 days, and for target therapy €5420.7 for 8 days.

F [Table 3]: This was the most commonly prescribed antifungal drug for all treatments. The average cost per patient in prophylaxis for 6 days of therapy was €120.3, for empirical therapy €150.7 for 8 days, and for target therapy €169.3 for 9 days.

[Table 4]: Only one patient received a 4-day empirical treatment with an average cost of €345; three patients received

Table 1: Ambisome® cost analysis

Therapy	Liposomal amphotericin-B			
	Patients (*n*)	Average days of therapy	Total cost (Euro)	Average cost/patient (Euro)
Prophylactic	6	7	41,770	6961.7
Empirical	14	7	54,181	3870.1
Target	20	10	109,429	5471.5

Table 2: Caspofungin cost analysis

Therapy	Casponfungin			
	Patients (*n*)	Average days of therapy	Total cost (Euro)	Average cost/patient (Euro)
Prophylactic	4	7	11,260	2815
Empirical	10	8.5	40,832.25	4083.2
Target	12	8	65,048.25	5420.7

target therapy against *C. glabrata* for 8 days with an average cost per patient of €1318.6. No patient enrolled in the study received prophylaxis with I.

The total expenditure for the period under consideration for all utilized antimycotic drugs was: A 61% for 40 patients, C 34.8% for 26 patients, F 3% for 66 patients, and I 1.3% for four patients.

The total expenditure over 1 year for each antifungal with reference to a "*n*" number of patients who received prophylactic treatment was: A €41,770 for 6 patients, C € 11,260 for four patients, F €1,684 for 14 patients; empiric treatment was: A €54,181 for 14 patients, C €42,547 for ten patients, F €3,917 for 26 patients, I €345 for one patient; and target treatment was: A €109,429 for 20 patients, C €63,333 for 12 patients, F €4,403 for 26 patients and I €3,956 for three patients [Figure 2].

Intravenous (I.V.) antifungal consumption reviewed in terms of DDD in the period under consideration [Table 5] was: C 50 mg vial 273 DDD, C 70 mg vial 33.6 DDD, F 200 mg vial 768 DDD, F 100 mg vial 89 DDD, I 250 mg vial 62.5 DDD, and A 50 mg vial 2,200 DDD.

The DDD average cost shows the total expenditure divided for the total doses consumed and, on average, the cost of one day of therapy: C 50 mg vial €381.1, C 70 mg vial €389.6, F 200 mg vial €11.8, F 100 mg vial €10.6, I 250 mg vial € 68.8, and A 50 mg vial €93.4.

DISCUSSION

Today a timely and reliable diagnosis of IFI is still hard to perform as IFI tends to manifest itself as an undifferentiated clinical syndrome. IFI have a different incidence according to the patient and graft:[11,12] Candida, for example, often infects the liver and kidneys of patients who received these grafts and the cardiac valves, while Aspergillus is mostly responsible for lung infections.[4,13,14]

Prophylaxis should be started before the symptoms.[15] It is essential to treat transplant recipients and patients more at risk and customize therapy based on their clinical conditions.

If a patient reports clinical signs of infection (e.g., antibiotic-resistant fever, failure to identify the pathogenic agent, and no radiology evidence), the plan of therapy should involve starting an empirical antimycotic therapy followed by a target therapy with

Table 3: Fluconazole cost analysis

Therapy	Fluconazole			
	Patients (*n*)	Average days of therapy	Total cost (Euro)	Average cost/patient (Euro)
Prophylactic	14	6	1,684	120.3
Empirical	26	8	3,918.8	150.7
Target	26	9	4,403	169.3

Table 4: Itraconazole cost analysis

Therapy	Itraconazole			
	Patients (*n*)	Average days of therapy	Total cost (Euro)	Average cost/patient (Euro)
Prophylactic	0	0	0	0
Empirical	1	4	345	345
Target	3	8	3,956	1,318.6

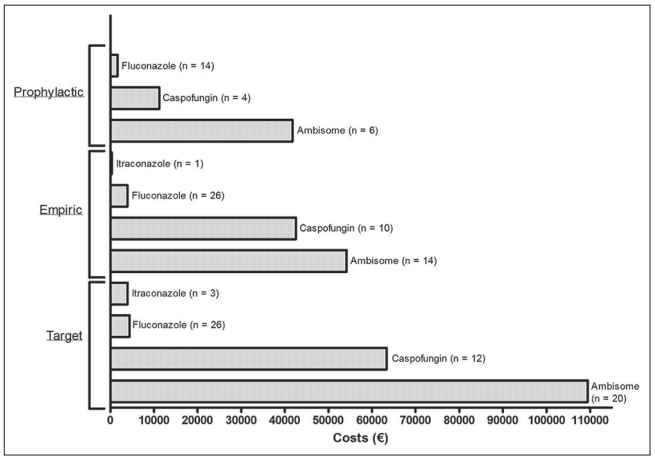

Figure 2: Expenditure (€) over 1 year for each antifungal with reference to a "*n*" number of patients who received prophylactic, empirical, and target treatment

Table 5: DDD and average cost of DDD of intravenous antifungals reviewed in study period

Product	Grams/ unit dose	Unit doses/ package	Antifungal	ATC code	Administration route	DDD (WHO 2008) U	DDD/ package	Packages	Grams	DDD	Total cost (Euro)	DDD average cost (Euro)
Cancidas®	0.05	1	Caspofungin	J02AX04	P	0.05 g	1.0	273	13.7	273.0	104,051.2	381.1
Cancidas®	0.07	1	Caspofungin	J02AX04	P	0.05 g	1.4	24	1.7	33.6	13,089.3	389.6
Diflucan®	0.2	1	Fluconazole	J02AC01	P	0.2 g	1.0	768	153.6	768.0	9,062.4	11.8
Diflucan®	0.1	1	Fluconazole	J02AC01	P	0.2 g	0.5	178	17.8	89.0	943.4	10.6
Sporanox®	0.25	1	Itraconazole	J02AC02	P	0.2 g	1.3	50	12.5	62.5	4301	68.8
Ambisome®	0.05	10	Amphotericin	J02AA01	P	0.035 g	14.3	154	77.0	2,200	205,380	93.4

DDD=Defined daily dose, ATC=Anatomical therapeutic chemical classification.

antifungals to which the pathogenic microorganism, according to the antimycogram, is sensible to, and if there are compatible radiology evidences.[15-17] The most commonly-isolated species in this study were Candida and Aspergillus.

As can be detected from the results of the reviewed population, immunosuppressive therapy is one of the major risk factors, immediately after the central lines and TPN. The TPN lipid component does favor microbial development and proliferation. Although encountered in a lower percentage, other risk factors included mechanical ventilation, neutropenia, steroid therapy, and placement of stents and other devices.

Prescriptions that are based on microbiology outcomes, involved switching empirical therapy to target therapy and were considered appropriate. Of the ten patients who received empirical therapy followed by target therapy, five received the same antimycotic drug for both therapeutic regimes, three were administered a different antimycotic (changing the medication from empirical to target therapy was justified by the antifungal's specific action against isolated species), two received a combination of two antimycotic drugs (A + F) in their target therapy due to persisting infection of multiple fungal species. Assessing patients who underwent a prophylactic treatment followed by a target therapy showed two patients under prophylaxis with F had to undergo one target treatment with I against *C. glabrata* and one with A against *A. niger*. Failure to succeed of the prophylaxis with F in these two patients was due to resistance to F of these two fungal species.

The assessment of the target therapies showed the physicians' approach, following the IDSA guidelines, when treating *C. albicans* infections initially resolved to using F; and then as a second choice, A. In the case of isolation of *C. glabrata*, a fungal species that has developed resistance to F, the drugs of choice were A and C. Target treatment against *A. niger* was performed with A only.

IFI are difficult to treat and often require long-term therapies. With soaring costs of antimycotic treatments and hospital stay,[18] The need was therefore stressed to assess the appropriateness of prescriptions, identifying any use not compliant with international guidelines and/or therapeutic indications, and monitor consumption of particularly expensive antifungals expressing them in terms of DDD. The world Health Organization's (WHO's) definition of DDD is "the assumed average maintenance dose per day of a drug used for its main indication in adults".[19] The DDD should therefore be considered only as a technical tool, an indicator of consumption, to measure drug prescriptions.

In the scope of every A and C therapeutic regimen, being the most expensive, two antifungals showed a DDD average cost higher than the one for treatment with F, despite the number of patients treated with this azole was almost 50% more compared to A and C.

F was always the first choice drug in all three therapeutic regimens. Treating *C. albicans* infections we encountered an overall good outcome rate using any of the four antimycotics reviewed indifferently. This caused physicians to pick the less expensive alternative preferring F to the more expensive antifungals.

The use of I, given its higher cost and wider spectrum compared to F, was limited to cases of F-resistance. The pharmacology treatment using A, C, and F in seven out of 50 patients undergoing target therapy was unable to eradicate the mycotic infection, resulting as ineffective. The persistence of such infections in these patients, already heavily compromised, may have contributed to their death.

An analysis of the medical records and antimycograms showed the antimycotic drugs reviewed were used appropriately in the ascertained IFI, in compliance with the IDSA guidelines.

Prescriptions that upon an initial analysis of the microbiology reports appeared inappropriate and not supported by evidence in literature, were subsequently supported by an infectivologist for the heavily compromised patients.

Examples of prescriptions not entirely compliant with the guidelines included:

- Choice of drug not tested in antibiogram, but assumed to be effective based on scientific data (7%)
- Association of two drugs despite antimycogram showed resistance to one of the two (e.g., A + C in invasive aspergillosis or candidiasis, A + F); 4% of target therapies.

The resolution of fungal infections in several patients as per the negative outcomes of microbiology results (no mycotic growth) for posttransplant cultures supported the high costs of A and C.

It should be noted, we did encounter a certain degree of attention among the medical staff, supported by clinical pharmacists, while prescribing, whenever possible, the less expensive antifungals, seeking the best alternative treatment for the highest number of patients.

CONCLUSIONS

Foreseeing the success of IFI treatment is often difficult given the fact that several issues are involved, either related to fungal strain, or to the drug of choice, or to the host.

Monitoring and assessing the appropriateness of the prescription is an essential tool to rationalize the use of

antimicrobials, to control and prevent hospital-acquired fungal infections, and to limit the onset of microbial resistance. In this scope, the support of a clinical pharmacist performing a clinical, therapeutic, and pharmacoeconomic analysis becomes essential. With a similar approach and guaranteeing compliance with the standard guidelines, it will be possible to provide a better quality and customized therapy, while at the same rationalizing resources for these highly expensive antifungal treatments.

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