ORIGINAL

DIFFERENT PATTERNS OF INAPPROPRIATE ANTIFUNGALS USE IN DAILY PRACTICE: A SINGLE CENTER EXPERIENCE

Briquet Caroline, Martínez-Múgica Barbosa Cristina, Vandercam Bernard, Belkhir Leila, Yombi Jean Cyr

ABSTRACT

The use and cost of antifungal are increasing. There is an urgent need to change prescribing practice.

Objective: Our aim was to identify different patterns of inappropriate antifungal use in daily practice in our center (Cliniques Universitaires St Luc, Brussels).

Setting: A 989 bed teaching hospital in Belgium.

Method: Four point prevalence surveys (PPS) were undertaken prospectively during February, March, August 2014 and March 2015. One infectious disease specialist and two pharmacists assessed the quality of antifungal treatments according to standard guidelines. Antifungal use was evaluated by a modified algorithm used for antimicrobial use evaluation considering indication, dosage and duration of treatment.

Main outcome measure: To assess the quality of use of antifungal agents in terms of indication, choice of molecule, dosage and duration of treatment. Toxicity and potential drug-drug interactions were also evaluated.

Results: 108 antifungal therapies were prescribed to 104 patients during the four PPS. Fifty eight therapies were prophylactic indications (54%). 51.3% of the therapeutic indications were empirical and 21.3% targeted therapies. Fluconazole was the most frequently used drug (61.1%), followed by voriconazole (13%). According to Gyssens algorithm, only 61 prescriptions (56.5%) were judged definitely appropriate. Indications were considered correct in 93.5% (101). In 11.9% of cases the antifungal drug was not chosen correctly. The correct dose of antifungal drugs was prescribed in 75.9%.

Conclusion: These four PPS days identified different patterns of inappropriate antifungal use that should be improved by education and feedback of these results of prescribing habits. This kind of interventions is one of the most successful means of influencing physicians' performance.

Antifungal Therapy – Antimicrobial Stewardship – Audit – Gyssens Algorithm – Point Prevalent Survey (PPS)

Briquet C.*
Martínez-Múgica Barbosa C.‡
Vandercam B.*, †
Belkhir L.*, †
Yombi JC.*, †

* Antimicrobial Management Group. Pharmacy Department.
† Internal Medicine Department, Infectious Diseases.
‡ Hospital Universitario Central de Asturias. Asturias. Spain.
Cliniques Universitaires St Luc. Bruxelles.

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RESUMEN

Tanto el uso como el coste de los antifúngicos han aumentado. Existe una necesidad urgente de cambiar las prácticas de prescripción.

Objetivos: Identificar los patrones de uso inadecuado de antifúngicos en la práctica clínica diaria en el Hospital Cliniques Universitaires de St Luc (Bruselas).

Marco: Un hospital universitario de 989 camas en Bélgica.

Método: Se llevaron a cabo de manera prospectiva cuatro estudios diarios de prevalencia (Point Prevalence Survey; PPS) durante los meses de febrero, marzo y agosto 2014 y marzo 2015. Un especialista en enfermedades infecciosas y dos farmacéuticas clínicas evaluaron la calidad de los tratamientos antifúngicos de acuerdo a las guías estándar. El uso de estos fármacos se evaluó mediante un

algoritmo para la evaluación de antibióticos modificado, teniendo en cuenta la indicación, dosis y duración del tratamiento.

Medida de la variable principal: Evaluar la calidad del uso de agentes antifúngicos en base a la indicación, elección de la molécula, dosis y duración del tratamiento. Se estudiaron también las interacciones potenciales y toxicidad asociada al uso de estos fármacos.

Resultados: Se prescribieron un total de 108 tratamientos antifúngicos durante los cuatro PPS. En total 58 (54%) tenían indicación profiláctica. Entre todas las indicaciones, 21,3% eran tratamientos empíricos, y 21,3% eran dirigidos. Fluconazol fue el fármaco empleado con mayor frecuencia (61,1%), seguido de voriconazol (13%). De acuerdo con el algoritmo de Gyssens modificado, tan solo 61 prescripciones (56,5%) fueron consideradas completamente adecuadas. La indicación fue correcta en el 93,5% (101) de los casos. La elección del antifúngico fue inadecuada en el 11,9% de las prescripciones. En el 75,9% de los casos se empleó una dosis correcta.

Conclusion: Estos cuatro PPS identificaron los patrones de uso inadecuado de antifúngicos, que deberían tratar de mejorarse mediante educación y difusión de estos resultados a los profesionales sanitarios. Este tipo de intervenciones es una de las más exitosas a la hora de influir en los hábitos de prescripción de los médicos.

Terapia antifúngica – Optimización antimicrobiana – Auditoria – Algoritmo de Gyssens – Point Prevalence Survey (PPS)

INTRODUCTION

Antifungal (AF) use has increased during the last decade worldwide,[1] probably due to the high mortality and diagnostic challenges associated with invasive fungal infections. There is a direct correlation between global increase in AF resistance and AF misuse. It is known that AF overuse can lead to increased toxicity, potential drug-drug interactions as well as an increase in healthcare costs.[1] Inappropriate AF use is therefore considered an important health problem nowadays. Antimicrobial stewardship programs whose aim is to optimize antimicrobial therapies evaluating drug selection, indication and dose, route of administration, timing and duration of treatment [2] is a multidisciplinary intervention consisting of specialists in infectious diseases, microbiology and pharmacy working together as a team. The experience with such programs targeting AF treatments is limited. There is still little evidence published despite the few audits of AF drug use demonstrating clear deficiencies in prescribing behavior.[3, 4] Moreover, some published data report containment of costs or even cost savings,[5] with sometimes reduction in resistance and AF expenditure,[6] and improvement in the quality of care.[7, 8] Once a collaborative group is formed, the first step to develop an AF stewardship program is to assess the magnitude of the problem at each center.[9] In order to detect the most important points of misuse, an audit of AF use is recommended.

The aim of this study was to identify different patterns of inappropriate AF use in daily practice in our center. Toxicity and potential drug-drug interactions were also evaluated.

METHOD

An audit was performed on four different dates (February 2014, March 2014, August 2014 and March 2015) to assess the adequacy of AF drug prescription in a 989 bed teaching hospital that encompasses all specialties in Belgium. Any attending physician could prescribe AFs of their choice or one recommended by the infectious diseases team. There are institutional guidelines on AF use developed by the Antimicrobial Management Group (GGA) in collaboration with several medical specialties, based on international evidence-based guidelines,[10] local resistance data, availability and reimbursement of antimicrobial drugs and costs.

In order to evaluate the quality of treatments, each prescription of AF (amphotericin, miconazole, ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, flucytosine, caspofungin and anidulafungin) identified during the four selected dates was reviewed and followed until hospital discharge or end of treatment by two clinical pharmacists and an independent infectious disease specialist according to standard guidelines. The number of AF prescriptions may exceed the number of treated patients since it is possible for patients to be treated with more than one AF agent concomitantly.

Data were collected for those receiving at least one dose of AF on the day of the survey. Data included:

- Patient's characteristics: date of audit, date of birth, sex, date and unit of hospitalization.
- Risk factors for fungal infection at onset of treatment: hematological diseases, transplants, previous fungal infection, cancer, chronic obstructive pulmonary disease and immunosuppression (HIV, immunotherapy, corticotherapy...).
- Patient's infection status: as evidenced by results of abnormal imaging [standard radiograph, CT scan, magnetic resonance imaging (MRI) or others such as bronchoscopy with bronchoalveolar lavage (BAL)], microbiological data (culture date, type, site and re-

TABLE 1. Patients' characteristics and risk factors for fungal infection.

	Total [No. (%)]	*Day 1 [No. (%)]*	*Day 2 [No. (%)]*	*Day 3 [No. (%)]*	*Day 4 [No. (%)]*
No.	104 (100)	24 (23.1)	22 (21.2)	30 (28.8)	28 (26.9)
Sex					
Men	65 (62.5)	14 (58.3)	12 (54.6)	17 (56.7)	22 (78.6)
Women	39 (37.5)	10 (41.7)	10 (45.4)	13 (43.3)	6 (21.4)
Age [Median (range)]	57 (0.7-85.7)	60.9 (1.1-74.5)	56.9 (0.9-82.8)	49.9 (0.8-83.1)	56.1 (9.1-85.7)
Days of hospital stay [Median (range)]	28 (3-208)	32 (14-78)	29 (3-84)	28 (6-208)	26 (3-105)
Hospitalization units					
Medical units	83 (79.8)	19 (79.2)	21 (95.4)	24 (80)	19 (67.9)
Surgical units	11 (10.6)	3 (12.5)	0 (0)	4 (13.3)	4 (14.3)
Intensive care	10 (9.6)	2 (8.3)	1 (4.6)	2 (6.7)	5 (17.9)
Risk factors					
Previous fungal infection	20 (19.2)	3 (12.5)	7 (31.8)	5 (16.7)	5 (17.9)
Transplant	43 (41.3)	8 (33.3)	5 (22.7)	16 (53.3)	14 (50)
HSCT	34 (32.7)	7 (29.2)	5 (22.7)	12 (40)	10 (35.7)
Solid transplant	8 (7.7)	1 (4.2)	0 (0)	3 (10)	4 (14.3)
Hematological diseases	71 (68.3)	20 (83.3)	16 (72.7)	18 (60)	17 (60.7)
Cancer	16 (15.4)	2 (8.3)	4 (18.2)	4 (3.8)	6 (5.8)
Immunosuppression					
Chemotherapy (last month)	66 (63.5)	16 (66.7)	15 (68.2)	17 (56.7)	18 (64.3)
Heavy surgery	12 (11.5)	3 (12.5)	1 (4.6)	5 (16.7)	3 (10.7)
AIDS	3 (2.9)	0 (0)	0 (0)	1 (3.3)	2 (7.1)
COPD	10 (9.6)	2 (8.3)	2 (9.1)	1 (3.3)	5 (17.9)
Immunosuppressive therapy *	39 (37.5)	9 (37.5)	3 (13.6)	16 (53.3)	11 (39.3)
Corticoid treatment **	9 (8.6)	3 (12.5)	1 (4.6)	4 (13.3)	1 (3.6)

*: >90 days; **: >1 mg/kg/day for >3 weeks.
HSCT: Hematopoietic Stem Cell Transplantation; AIDS: Acquired Immune Deficiency Syndrome; COPD: Chronic Obstructive Pulmonary Disease.

sult), clinical criteria (fever, pulmonary symptoms, septic shock, C-reactive protein (CRP), neutropenia) and a history of fungal infections and AF therapy use.
- Infection site: superficial or systemic.
- AF treatment data: agent(s) prescribed, dose, date of initiation and end of treatment, duration of treatment, route of administration (intravenous versus oral), treatment type (labeled as «P» for prophylactic prescriptions; «E» for empirical treatment in the absence of microbiological results; «D» for directed prescription when the pathogen was unknown at the time of prescription but was later identified; or «T» for targeted prescription when treatment was prescribed for a known pathogen) and the main indication for prescribing (probable, proven, or possible invasive aspergillosis, probable or proven invasive candidiasis, superficial candidiasis, febrile neutropenia, primary or secondary —if previous diagnosis of invasive aspergillosis— prophylaxis, digestive decontamination, or other infections).

The five assessment criteria were: indication for AF use (evaluated according to local standard guidelines and international evidence-based guidelines [10] considering local epidemiology of AF resistance and microbiological findings), AF choice (absence of a better alternative), compliance with recommended dosage regimen, loading dose and duration. The appropriateness of AF treatment was determined using a standardized algorithm for antimicrobial drug use evaluation developed by Gyssens, et al,[11] modified for AF use by Raymond, et al,[12] All aspects of AF prescription were systematically evaluated. In each case, the flow chart was followed from top to bottom, stopping when criteria were not met, and assigned to an evaluation category, so the adequacy of AF use was better as Gyssens or Raymond's class decreased:

— Class VI: insufficient or missing data for categorization;
— Class V: inappropriate indication (absence of AF infection or prescription for an infection that does not need AF treatment);
— Class IV: inappropriate AF choice (inappropriate toxicity profile and/or spectrum and/or effectivity);
— Class III: inappropriate dosage (underdose/overdose);
— Class II: inappropriate loading dose;
— Class I: inappropriate timing (short/excessive duration of therapy and switch of administration route when possible);
— Definitely appropriate prescription (all criteria of correct AF use).

An additional evaluation of medical charts was performed, looking for notification of AF use, which is

TABLE 2. Prevalence of AF use in the hospitals during the four days.

	Number of patients in the hospital	*Number of patients with AF*	*% of patients with AF in the hospital*
Day 1	637	24	3.8
Day 2	637	22	3.5
Day 3	542	30	5.5
Day 4	686	28	4.1
Total	2,502	104	4.2

TABLE 3. Prevalence of AF use in the five most users units of hospitalization.

Units	*Day 1 (%)*	*Day 2 (%)*	*Day 3 (%)*	*Day 4 (%)*	*Median (%)*
Hematology transplant unit	83	25	100	100	81
Adult hematology	85	69	82	57	73
Intensive care	14	10	12	19	15
Pediatric hematology	7	24	18	5	13
Infectious units	5	4	10	5	6

recognized as a quality indicator of anti-infective drugs prescribing. Toxicity and potential drug-drug interactions of AF drugs were also analyzed.

The study protocol was approved by the Local Ethics Committee. 2015/23SEP/506.

RESULTS

Patient characteristics. 104 patients received 108 AF prescriptions during the study period (four cumulative days). Most of them had at least one risk factor, immunodeficiency was the most prevalent risk factor. The demographic characteristics of study participants and their risk factors for fungal infection are summarized in Table 1. The median age of patients was 57 years (range: 1-86), 62.5% (No. = 65) were male.

Prevalence of AF use. The prevalence of AF use in hospital is 4.16% (Table 2).

The prevalence is variable depending on the ward where the patients were treated (see Table 3). The main prescribing departments were hematology (No. = 65; 62.5%) and intensive care units (No. = 10; 9.62%).

Patients outcomes. 29 out of 97 patients (30%) died during the study period, 13 (13.4%) in the course of treatment and 5 (5.2%) one month after discontinuation of AF. The aim of the AF treatment was curative in 16 of the 29 dead patients. The causes of mortality were: aspergilloses,[6] invasive candidiasis,[5] and one for cryptococcus neoformans.

Patient infection status. Analysis of the patients' infectious status at the beginning of treatment is summarized in Table 4. Most patients showed clinical criteria of fungal infection (No. = 91; 87.5 %), but only 28 (27%) met microbiological criteria.

Fungal infection was demonstrated in 87.5% (by at least one clinical criteria), in 23.1% (by at least one of imaging procedure), in 27% (by at least one positive microbiological sample) and in 7.7% (by galactomannan).

AF use and diagnoses. Table 5 provides a summary of prescribed AF agents and main indications for therapeutic use. Overall, the most frequent diagnoses were respiratory tract infections (No. = 23, 21.3%), oropharyngeal (No. = 9, 8.3%) and digestive infections (No. = 7, 6.5%). Four patients (3.8%) received a combined therapy of two AF agents. Prophylactic indications («P») accounted for 54% (No. = 58) of all prescriptions: fluconazole (No. = 42; 91.3%) was the AF agent mainly used for primary prophylaxis (No. = 46; 43%), followed by posaconazole (No. = 2; 4.3%), conventional amphotericin (No. = 1; 2.2%) and caspofungin (No. = 1; 2.2%). Treatment for secondary prophylaxis (defined as prophylaxis for a patient with a previous aspergillus infection) was voriconazole in all cases, whereas itraconazole was used for digestive decontamination. 48 (81.3%) out of all patients receiving prophylactic (primary and secondary) treatment were neutropenic (<500 mg/L). In this case, AF therapy was started before neutropenia in 76.9%, in 6.9% the first day of neutropenia and in 17.9% after the neutropenic period. The mean duration for prophylactic treatments was 34 days (range: 5-323).

According to the type of treatment, fluconazole (No. = 9; 39.3%), voriconazole (No. = 7; 30.4%) and caspofungin (No. = 7; 30.4%) were prescribed for empirical treatments («E»). Fluconazole (No. = 3; 75%) was the most used AF for directed prescriptions («D») as well as for targeted treatments (No. = 10; 43.5%). The mean (median of 22 days) duration for therapeutic treatments was 44 days (range: 2-502). The total duration of AF treatment was cal-

TABLE 4. Patients' infectious status at the beginning of the treatment.

	Total [No. (%)]	*Day 1 [No. (%)]*	*Day 2 [No. (%)]*	*Day 3 [No. (%)]*	*Day 4 [No. (%)]*
No.	104 (100)	24 (23.1)	22 (21.2)	30 (28.8)	28 (26.9)
Clinical criteria	91 (87.5)	21 (87.5)	16 (72.7)	28 (93.3)	26 (92.9)
Fever >4 days (despite antibiotic treatment)	43 (41.3)	11 (45.8)	7 (31.8)	9 (30)	16 (57.1)
Pulmonary symptoms	19 (18.3)	5 (20.8)	5 (22.7)	3 (10)	6 (21.4)
Septic shock	10 (9.6)	4 (16.7)	2 (9.1)	3 (10)	1 (3.7)
CRP >5 mg/L	62 (59.6)	11 (45.8)	7 (31.8)	21 (70)	24 (85.7)
Neutropenia <0.5 g/L	59 (56.7)	16 (66.7)	12 (54.6)	15 (50)	16 (57.1)
Infection imaging	24 (23.1)	8 (33.3)	7 (31.8)	5 (16.7)	4 (14.3)
Pathologic radiograph	8 (7.8)	4 (16.7)	2 (9.09)	1 (3.3)	1 (3.6)
Pathologic CT scan	16 (15.4)	4 (16.7)	5 (22.73)	3 (10)	4 (14.3)
Pathologic MRI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Others *	7 (6.7)	2 (8.3)	1 (4.55)	2 (6.7)	2 (7.1)
Microbiological criteria	28 (26.9)	5 (20.8)	6 (27.3)	7 (23.3)	10 (35.7)
Positive cultures	28 (26.9)	5 (20.8)	6 (27.3)	7 (23.3)	10 (35.7)
Positive blood cultures (germs in blood)	4 (14.3)	2 (40)	1 (16.7)	1 (14.3)	0 (0)
Positive urine cultures	1 (3.6)	0 (0)	0 (0)	0 (0)	1 (10)
Liquid bronchial alveolar	3 (10.7)	0 (0)	0 (0)	1 (14.3)	2 (20)
Cerebrospinal fluid	1 (3.6)	0 (0)	0 (0)	1 (14.3)	0 (0)
Pus	6 (21.4)	1 (20)	1 (16.7)	2 (28.6)	2 (20)
Expectorations	4 (14.3)	1 (20)	1 (16.7)	0 (0)	2 (20)
Throat **	1 (3.6)	0 (0)	0 (0)	1 (14.3)	0 (0)
Stools **	8 (28.6)	1 (20)	3 (50)	1 (14.3)	3 (30)
Pathogens isolated					
A. fumigatus	3 (10.7)	0 (0)	0 (0)	0 (0)	3 (30)
C. albicans	8 (28.6)	2 (40)	1 (16.7)	2 (28.6)	3 (30)
C. albicans + C. glabrata	2 (7.1)	0 (0)	1 (16.7)	0 (0)	0 (0)
C. glabrata + C. llusitaniae	1 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)
C. parasilopsis	1 (3.6)	0 (0)	0 (0)	0 (0)	1 (10)
Not identified	11 (39.3)	2 (40)	3 (50)	3 (42.9)	3 (30)
Positive *Aspergillus Ag*	8 (7.7)	2 (8.3)	0 (0)	2 (6.7)	4 (14.3)
2 Ag >0.5	5 (3.8)	0 (0)	0 (0)	2 (6.7)	2 (7.1)
1 Ag >0.7	8 (6.7)	1 (4.2)	0 (0)	2 (6.7)	4 (14.3)
History of AF treatment	42 (40.4)	11 (45.8)	13 (59.1)	9 (30)	9 (32.2)

CRP: C-Reactive Protein; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; Ag: Antigen; *: Bronchoscopy with BAL, gastroscopy; **: Colonization.

culated taking into account the hospitalization as well as the outpatient period.

Appropriateness of AF therapy. Table 6 shows the evaluation of appropriateness of AF use according to separate criteria: indication, choice of AF, correct dosage, loading dosage and duration of treatment.

Fig. 1 shows the evaluation of the appropriateness of AF use according to Gyssens' modified algorithm: cumulative criteria. A total of 61 prescriptions (56.53 %) were definitely appropriate. There were no Class VI prescriptions (insufficient or missing data for categorization). Class V consisted of fluconazole (No. = 4), caspofungin (No. = 2) and itraconazole (No. = 1) treatments prescribed in the absence of risk factors or AF infection; frequently as primary prophylaxis in non-neutropenic patients.

The AF choice was deemed correct in 89 cases (82.4%), but 12 prescriptions (11.1%) of itraconazole (No. = 6; 50%), fluconazole (No. = 3; 25%), caspofungin (No. = 2; 16.7%) and amphotericin (No. = 1; 8.3%) were considered inappropriate; such cases were itraconazole usage for digestive decontaminations mainly, the use of fluconazole or caspofungin for treating aspergillosis, or usage of caspofungin instead of posaconazole as primary prophylaxis for an allogenic bone marrow transplantation (allo-HBMT) patient.

Unnecessary high doses of fluconazole and amphotericin were used twice for treating superficial candidiasis; 200 mg bid instead of QD for fluconazole and doses of 5.25 mg/kg and 4.7 mg/kg of amphotericin, exceeding the recommended 1-3 mg/kg. On the other hand, voriconazole (No. = 2) was underdosed when treating children with probable invasive aspergillosis and fluconazole (No. = 1) for an invasive candidiasis.

There were 14/108 prescriptions (12.9%) with an incorrect loading dose, not prescribed when necessary or administered when not indicated. This mistake was most-

TABLE 5. **AF use and diagnoses.**

	Total [No. (%)]	*Day 1 [No. (%)]*	*Day 2 [No. (%)]*	*Day 3 [No. (%)]*	*Day 4 [No. (%)]*
No.	104 (100)	24 (23.1)	22 (21.2)	30 (28.8)	28 (26.9)
Treatment type					
Prophylactic	58 (53.7)	13 (52)	11 (47.8)	19 (61.3)	15 (51.7)
Directed	4 (3.7)	1 (4)	0 (0)	0 (0)	3 (10.3)
Empirical	23 (21.3)	3 (12)	8 (34.8)	6 (19.3)	6 (20.7)
Targeted	23 (21.3)	8 (32)	4 (17.4)	6 (19.3)	5 (17.2)
Infection					
Proved aspergillosis	8 (7.4)	2 (8)	0 (0)	2 (6.4)	4 (13.8)
Probable aspergillosis	4 (3.7)	2 (8)	2 (8.7)	0 (0)	0 (0)
Possible aspergillosis	8 (7.4)	1 (4)	2 (8.7)	2 (6.5)	3 (10.3)
Proved candidiasis	11 (10.2)	3 (12)	2 (8.7)	4 (12.9)	2 (6.9)
Possible candidiasis	3 (2.8)	0 (0)	1 (4.3)	0 (0)	2 (6.9)
Superficial candidiasis	10 (9.3)	2 (8)	2 (8.7)	4 (12.9)	2 (6.9)
Febrile neutorpenia	3 (2.8)	2 (8)	1 (4.3)	0 (0)	0 (0)
Primary prophylaxis	46 (42.6)	10 (40)	10 (43.5)	14 (45.2)	12 (41.4)
Secondary prophylaxis	2 (1.8)	0 (0)	0 (0)	0 (0)	2 (6.9)
Digestive decontamination	7 (6.5)	1 (4)	1 (4.3)	5 (16.1)	0 (0)
Others (gastroscopy, bronchoscopy)	4 (3.7)	2 (8)	2 (8.7)	0 (0)	0 (0)
Infection site					
Superficial oropharyngeal	9 (8.3)	2 (8)	3 (13)	2 (6.4)	2 (6.9)
Superficial skin	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Systemic central nervous system	3 (2.8)	1 (4)	1 (4.3)	1 (3.2)	0 (0)
Systemic heart	1 (0.9)	0 (0)	0 (0)	0 (0)	1 (3.4)
Systemic digestive	7 (6.5)	3 (12)	1 (4.3)	3 (9.7)	0 (0)
Systemic bone	1 (0.9)	0 (0)	0 (0)	0 (0)	1 (3.4)
Systemic kidney	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Systemic respiratory	23 (21.3)	4 (16)	5 (21.7)	4 (12.9)	10 (34.5)
Systemic blood	5 (4.6)	2 (8)	2 (8.7)	1 (3.2)	0 (0)
Route of administration					
Intravenous	31 (28.7)	9 (36)	8 (34.8)	8 (25.8)	6 (20.7)
Oral	77 (71.3)	16 (64)	15 (65.2)	23 (74.2)	23 (79.3)
AF Agent					
Amphotericin*	5 (4.6)	1 (4)	1 (4.3)	3 (9.7)	0 (0)
Fluconazole	66 (61.1)	18 (72)	12 (52.2)	19 (61.3)	17 (58.6)
Itraconazole	7 (6.5)	1 (4)	1 (4.3)	4 (12.9)	1 (3.4)
Voriconazole	14 (13)	3 (12)	4 (17.4)	1 (3.2)	6 (20.7)
Posaconazole	3 (2.8)	0 (0)	1 (4.3)	2 (6.4)	0 (0)
Caspofungin	10 (9.3)	2 (8)	2 (8.7)	1 (3.2)	5 (17.2)
Anidulafungin	2 (1.8)	0 (0)	1 (4.3)	1 (3.2)	0 (0)
Flucytosine	1 (0.9)	0 (0)	1 (4.3)	0 (0)	0 (0)

* Conventional Amphotericin for prophylactic use (No. = 1), lyposomal amphotericin for treatment use (No. = 4).

ly observed with fluconazole prescriptions (No. = 10), but also with voriconazole (No. = 3), anidulafungin (No. = 1).

Timing was judged inappropriate in 5 cases, all but one affecting fluconazole prescriptions used for primary prophylaxis, which was maintained longer than the neutropenic period.

Switch IV/PO. AF were prescribed intravenously (IV) in 28.7% of cases and orally (PO) in 71.3% during the four day PPS. The switch IV/PO was done correctly in 82% of cases. The correct switch is a switch done on time when it is possible: the oral form exists and criteria for switch are present.[20]

Evaluation of medical charts, drug-interactions and toxicity. As a quality indicator of anti-infective drugs prescribing, the additional evaluation of medical charts revealed that there was a total (45.37%, No. = 49) or partial (only AF: 14.8%, No. = 16; only indication: 4.6%, No. = 5) lack of notification for indications of AF use in 35.2% (No. = 38) of cases.

Potential drug-drug interactions (only moderate and major interactions) were identified in 68.5% (No. = 74) of

TABLE 6. Appropriateness of AF therapy by separated criteria.

Criteria	*Appropriate (%)*	*Inappropiate (%)*
Indications of AF	93.5	–
Choice of AF	88.1	–
Correct dosage	92.1	Overdose: 3.96 Underdose: 3.96
Loading dosage	68.9	–
Duration	81.3	Too long: 14.3 Too short: 4.4

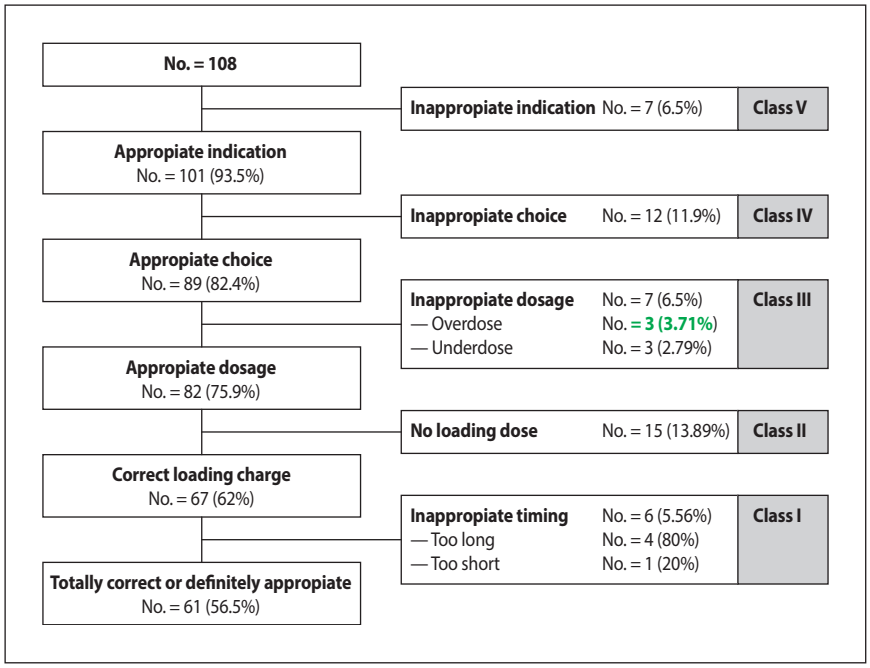

FIG. 1. Appropriateness of AF therapy with cumulative criteria (Gyssens modified algorithm).

all prescriptions, involving mostly azole AFs (No. = 68; 63%). Only anidulafungin and flucytosine were not involved in any interactions. The most frequent interactions were fluconazole with ciprofloxacin (major interaction) and proton pump inhibitors (moderate). It is important to state that AF treatment was concomitantly prescribed with antibiotics in 79.6% of cases.

Hepatic toxicity was observed in 12 patients out of 108 (11.1%), possibly caused by fluconazole in nine cases (75%) and by voriconazole in the remaining three cases (25%).

DISCUSSION

Data collection for the AF use audit was conducted on four separate dates within a single year in order to have a representative sample of prescription writing practices and avoid seasonal bias. The most important finding in our study is that there is a gap in quality of AF prescriptions; only 56.5% of prescriptions met all criteria for adequacy in prescribing. Moreover, lack of notification for indications impairs continuity of care as median percentage reached 64.8% with 45.4% total notification (name of AF + indication)

Adequacy of AF agents (all criteria) was appropriate in 58.3%, similar to other studies with an overall conformity between 54%[13] 58%[17] and 60.5%.[16]

Appropriate indication for AF treatment accounted for 93.5%, which is close to 96.5% published in another study.[17] The choice of AF agent in good indication (two cumulative criteria) was 82.4%. It is better than the results published in studies reporting respectively 75.2%[16] and 62.6%[18] and is close to 89.4% in a study[17] reporting 102 good choice on 114 prescriptions. The dosage was correct in the same proportion (76% in this study vs 77.8%). Fluconazole use, mainly administered orally[15] predominated all indications.[9, 15] The rate of combination therapies among AF prescriptions observed in this study was lower (3.8%) than in other published studies, reporting a rate of combination therapies between 9.4%[16] and 41%,[7] and commonly reported as a cause of misuse.

Regarding the use of AF in children, it was also observed in Gyssens et al. study[12] that voriconazole was

underdosed. The mean duration was found to be too long in prophylactic treatments in non-neutropenic patients, but one of the most common non-conformities generally encountered in other published audits was a too short course of AF for esophageal candidiasis and disseminated infections.[19]

As in other published audits, the main prescribing departments were hematology, medical departments, and intensive care units.[13] Nevertheless, reasons to start AF therapy were different, being targeted therapy [13] or empiric therapy [14] the most common in other studies.

The amount of potential drug-drug interactions identified was high (68.5% of all prescriptions), but overall lower than other interaction rates (77.8%) found in similar studies.[18] Concurrent use of ciprofloxacin and fluconazole may result in an increased risk of QT interval prolongation (major interaction). Concurrent use of fluconazole and omeprazole may result in increased plasma concentrations of omeprazole (moderate). The incidence rate of azoles induced hepatotoxicity (10%) corresponded to that shown in voriconazole and fluconazole information sheet.

Limitations

— More time should have been left between observation days due to long hospital stays and treatment courses.
— Point prevalence survey was chosen because of its simplicity, but it is not as accurate as a daily surveillance.
— According to the AF reimbursement system in Belgium, it would have been interesting to assess the frequency where the choice of the AF drug matched the reimbursement criteria in each specific indication.
— Further analysis should be carried out after implementation of new guidelines or prescribing optimization methods.

Despite these limitations, the presented data and the consequent analysis are a starting point for the implementation of an effective AF stewardship program, and might serve as important reference information for other hospitals with similar settings. CP

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