

# DESCRIPTIVE ANALYSIS OF ANTIFUNGALS USE IN FIVE UNIVERSITY TEACHING HOSPITALS IN QUEBEC

MC. Michel<sup>1</sup> ▪ F. Varin<sup>2</sup> ▪ L. Deschênes<sup>1</sup> ▪ C. Guévremont<sup>3</sup> ▪ G. Bérard<sup>4</sup> ▪ N. Marcotte<sup>1</sup> ▪ E. Pelletier<sup>5</sup> ▪ R. Rajan<sup>3</sup> ▪ P. Farand<sup>4</sup> ▪ D. Froment<sup>2</sup> ▪ P. Ovetchkine<sup>5</sup>

1- CHU de Québec-UL, Québec, Qc, Canada; 2- Centre hospitalier de l'Université de Montréal, Montréal, Qc, Canada; 3- McGill University Health Center, Montréal, Qc, Canada; 4- Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Qc, Canada; 5- Centre hospitalier universitaire Sainte-Justine, Montréal, Qc, Canada; 1-5: Programme de Gestion Thérapeutique des Médicaments (PGTM), Qc, Canada

## Abstract

**Background:** The Programme de gestion thérapeutique des médicaments (PGTM) (a therapeutic drug management program) performed a descriptive analysis to identify the indications for which selected antifungals were prescribed in the five Quebec university teaching hospitals.

**Methods:** Retrospective analysis of adult patients who received selected antifungals between April 1<sup>st</sup> 2014 and March 31<sup>st</sup> 2015 (liposomal amphotericin B, anidulafungin, caspofungin, micafungin, posaconazole, voriconazole). Fluconazole and itraconazole were excluded from the study unless they were administered prior to or concurrent with the antifungal drug being studied. This situation was considered in the analysis.

**Results:** A total of 1086 antifungals were prescribed to 604 adult patients for prophylaxis or treatment. Among these patients, a total of 104 aspergillosis, 99 candidiasis and 100 febrile neutropenia episodes were reported. Posaconazole (72%) represents the most frequent antifungal administered for prophylaxis. For the management of aspergillosis and candidiasis infections, voriconazole (77%) and echinocandins (80%) are respectively the most commonly prescribed treatments. Echinocandins (68%) are also frequently utilized for episodes of febrile neutropenia. However, in 25 patients (17%) receiving prophylaxis, 101 (39%) receiving empiric treatment, 5 (4%) being treated for aspergillosis and 40 (53%) patients being treated for candidiasis infection, the choices of antifungals were not consistent with available guidelines at the time of data collection. Finally, it should be noted that 40 patients (53%) were prescribed caspofungin as first line candidiasis treatment without initially receiving fluconazole or amphotericin B.

**Conclusion:** Further analysis to better understand the underlying reasons for the extensive use of echinocandins should be performed. In order to promote the optimal use of antifungal agents and improve the quality of care, the PGTM plans to develop local guidelines and algorithms for the treatment and prophylaxis of fungal infections. Broad dissemination of this information to health care professionals will be a priority.

## INTRODUCTION

- Antifungals are frequently used in the prophylaxis and treatment of adult fungal infections in Quebec's university teaching hospitals;
- The optimal use of antifungal agents is a challenge considering their efficacy and safety profiles;
- Antifungal costs account for a substantial portion of hospital budgets. It is therefore important to ensure that they are used wisely;
- The Programme de gestion thérapeutique des médicaments (a therapeutic drug management program) performed a descriptive analysis to identify the indications for which the selected antifungals are prescribed in the five university teaching hospitals in Quebec, and to provide an overview of their use.

## METHODS

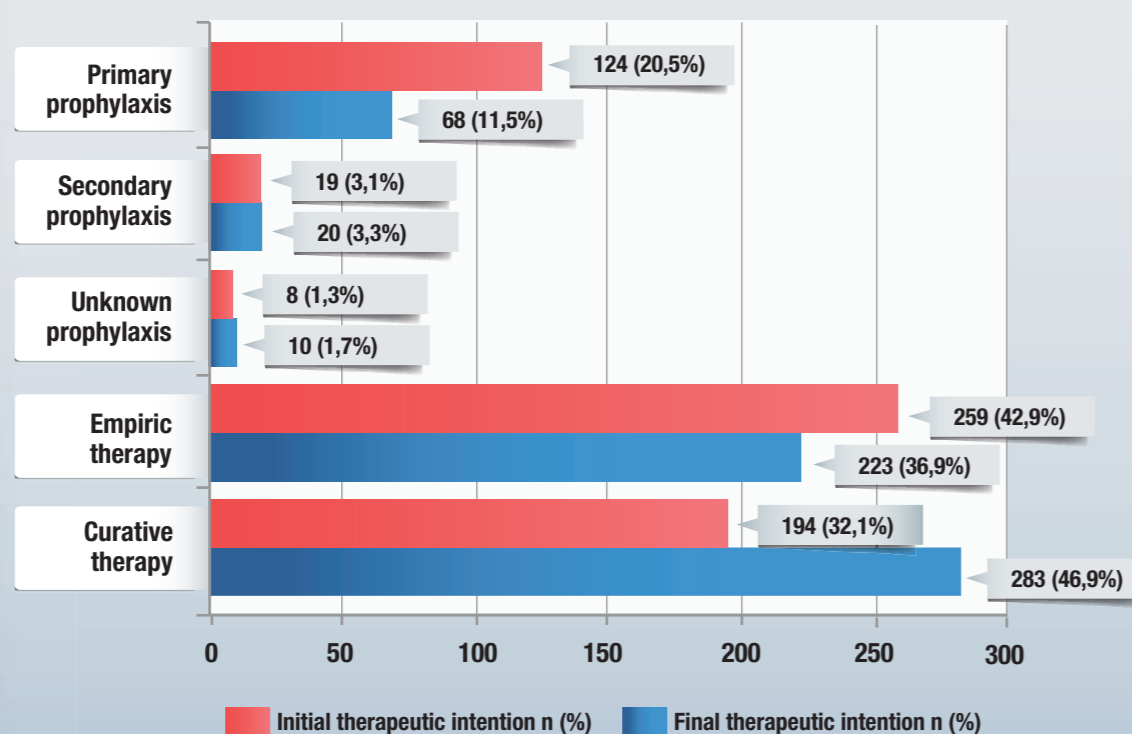
- Retrospective descriptive analysis;
- The required information was gathered from patients' charts;
- Inclusion criteria:**
  - adult patients who received selected antifungals between April 1<sup>st</sup> 2014 and March 31<sup>st</sup> 2015;
  - Selected antifungals: liposomal amphotericin B, anidulafungin, caspofungin, micafungin, posaconazole, voriconazole. *Fluconazole and itraconazole were excluded from the study unless they were administered prior or concurrently to the antifungal drug being studied. This situation was considered in the analysis.*
- Exclusion criterion:**
  - Antifungals prescribed by a route of administration other than orally or parenterally.
- A random sampling procedure was used when required to include a maximum of 50 patients for each antifungal, in each university teaching hospital. A sampling procedure was conducted if necessary (with a random Excel formula).

## RESULTS

**Table 1. Patients baseline characteristics (N=604)**

Characteristic	n (%)
Age (median; standard deviation)	58 (61;15)
Sex (men)	343 (58%)
Weight Kg (median; standard deviation)	72 (70;16)
Antifungal allergy	11 (1.8%)
<b>Clinical condition</b>	
Acute myeloid leukemia (AML) induction	111 (18.4%)
Stem cell transplantation (SCT) & Bone marrow transplantation (BMT)	102 (16.7%)
Solid organ graft	70 (11.6%)
Lymphoma	53 (8.8%)
Acute myeloid leukemia consolidation	39 (6.5%)
Graft versus host disease (GvHD)	38 (6.3%)
Chronic leukemia	14 (2.3%)
Acute lymphocytic leukemia (ALL)	13 (2.2%)
Myeloma	10 (1.7%)
Other cancer	113 (18.7%)
Human immunodeficiency virus	12 (2.0%)
Diabetes	153 (25.3%)
Cystic fibrosis	16 (2.6%)
Intestinal disease	50 (8.3%)
<b>Comorbidity</b>	
Neutropenia	186 (30.6%)
Hemodynamic instability	103 (17.1%)
Hepatic impairment	102 (16.9%)
<b>Renal Function (creatinin clearance)</b>	
≥ 60 ml/min	389 (64.4%)
30-59 ml/min	136 (22.5%)
0-29 ml/min	79 (13.1%)
<b>Care units</b>	
Intensive care units	234 (38.7%)
Other care units	370 (61.3%)
<b>Mortality</b>	
End of study	213 (35.3%)
During antifungal treatment	165 (27.3%)

**Figure 1. Initial vs final therapeutic intention (N=604)**



**Table 2. Criteria at the initiation of the antifungal (N=604)**

Criteria n	Liposomal Amphotericin B n = 48	Anidulafungin n = 3	Caspofungin n = 247	Micafungin n = 40	Posaconazole n = 125	Voriconazole n = 141
Neutropenia n = 186	7 (14.6%)	0	55 (22.3%)	15 (37.5%)	80 (64%)	29 (20.6%)
Febrile neutropenia n = 100	4 (8.3%)	0	42 (17%)	15 (37.5%)	19 (15.2%)	20 (14.2%)
Fever n = 228	16 (33.3%)	0	122 (49.4%)	25 (62.5%)	24 (19.2%)	41 (29.1%)
Fever (without any other criteria) n = 60	8 (16.7%)	0	32 (13%)	6 (15%)	2 (1.6%)	12 (8.5%)
Galactomannan (positive)* n = 33	1 (2.1%)	0	7 (2.8%)	0	1 (0.8%)	24 (17%)
Imaging (positive)* n = 64	6 (12.5%)	0	18 (7.3%)	0	3 (2.4%)	37 (26.2%)
Culture (positive)* n = 162	22 (45.8%)	1 (33.3%)	82 (33.2%)	10 (25%)	6 (4.8%)	41 (29.1%)
Others n = 74	11 (22.9%)	1 (33.3%)	41 (16.6%)	5 (12.5%)	1 (0.8%)	15 (10.6%)

\*: positive before the initiation of the antifungal agent  
%: based on each antifungal

**Table 3. Prophylaxis or treatment at the initiation of the antifungal (N=604)**

	Liposomal Amphotericin B n = 48	Anidulafungin n = 3	Caspofungin n = 247	Micafungin n = 40	Posaconazole n = 125	Voriconazole n = 141
Prophylaxis (n=151)	2 (1.3%)	1 (0.7%)	19 (12.6%)	0	108 (71.5%)	21 (13.9%)
Empiric therapy (n=259)	24 (9.3%)	2 (0.8%)	141 (54.4%)	30 (11.6%)	8 (3.1%)	54 (20.8%)
Curative therapy (n=194)	22 (11.3%)	0	87 (44.8%)	10 (5.2%)	9 (4.6%)	66 (34%)

**Table 4. Curative or empiric therapy at the initiation of the antifungal for specific diagnoses (N=327)**

	Liposomal Amphotericin B n = 48	Anidulafungin n = 3	Caspofungin n = 247	Micafungin n = 40	Posaconazole n = 125	Voriconazole n = 141
Aspergillosis (n=103)	5 (5C ; 0E)	0	15 (8C ; 7E)	1 (0C ; 1E)	3 (3C ; 0E)	79 (53C ; 26E)
Candidiasis (n=99)	4 (3C ; 1E)	0	66 (48C ; 18E)	13 (8C ; 5E)	3 (3C ; 0E)	13 (13C ; 0E)
Febrile neutropenia (n=100)	4 (0C ; 4E)	0	42 (36E)*	15 (0C ; 15E)	19 (0C ; 4E)*	20 (0C ; 16E)*

C: curative therapy; E: empiric therapy; \*: one missing patient received a prophylaxis  
\*: some patients are missing because they had a febrile neutropenia with a diagnosis of candidiasis or aspergillosis for which they received a treatment.

**Table 5. Posaconazole prophylaxis vs clinical conditions**

	AML induction	AML consolidation	MDS	GvHD	BMT/SCT	ALL	Others
Primary prophylaxis n = 95*	65	10	6	12	34	3	2
Secondary prophylaxis n = 8*	4	4	0	4	5	0	1
Unknown prophylaxis n = 5*	1	1	0	2	4	1	1

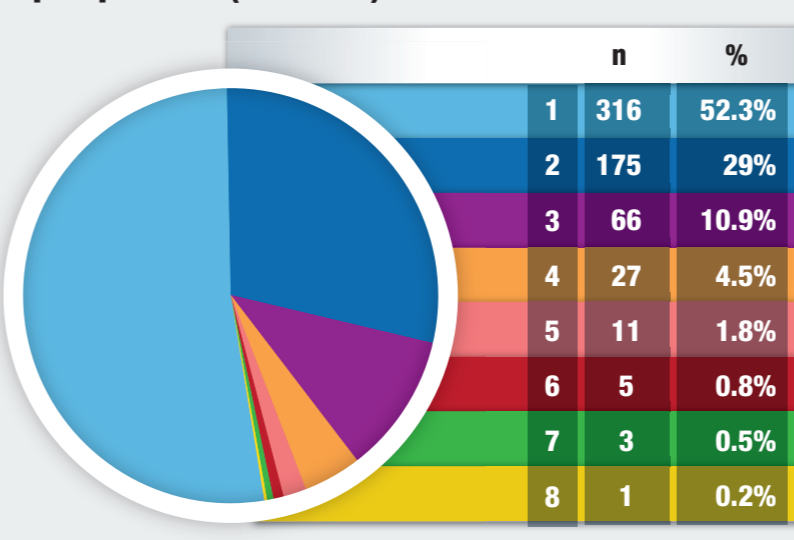
\*: more than one clinical condition is possible for each patient

**Table 6. Initial vs final therapeutic intention for specific diagnoses**

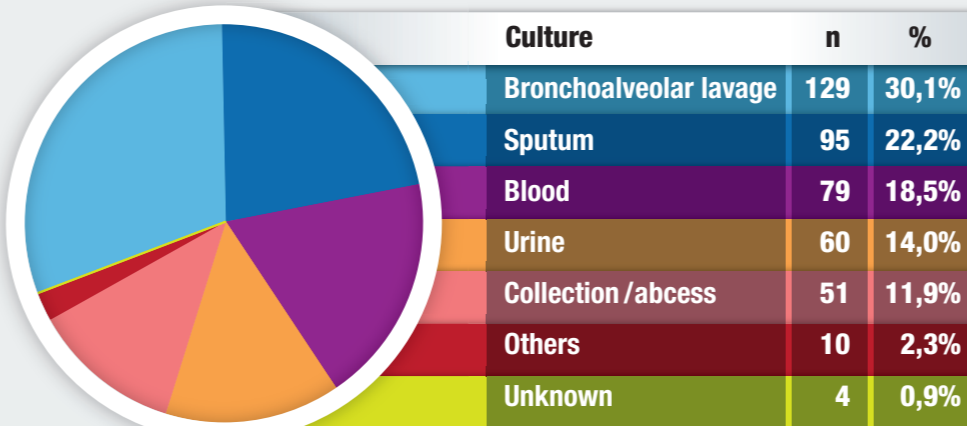
	Initial (N=327)			Final (N=346)		
	n	Prophylaxis	Treatment	n	Prophylaxis	Treatment
Aspergillosis	104	1	103 (69C ; 34E)	94	2	92 (83C ; 9E)
Candidiasis	99	0	99 (76C ; 23E)	133	0	133 (127C ; 6E)
Febrile neutropenia	100	15*	85 (75E)**	112	10	102** (84E)

C: curative therapy; E: empiric therapy  
\*: these patients received antifungal prophylaxis during hospitalization prior to the episode of febrile neutropenia  
\*\*: 10 (initial) or 18 (final) patients with a diagnosis of aspergillosis or candidiasis with a febrile neutropenia. These patients needed curative therapy.

**Figure 2. Total antifungal agents prescribed per patient (N=1086)**



**Figure 4. Site of the biological culture (N=428)**



Note : 38% patients had a culture

**Table 7. Justifications for switching antifungal therapy (N=564)**

	n	%
Inadequate clinical response	143	25.4%
Culture results	133	23.6%
Combination	57	10.1%
Switching to oral route*	48	8.5%
Side effects	44	7.8%
NPO patient	15	2.7%
Drug Interaction	14	2.5%
Renal Failure	7	1.2%
Unknown	32	5.7%
Other	71	12.6%

\*: 36% of patients who left the hospital on an oral antifungal received an IV antifungal until discharge from hospital.

**Table 10. Curative or empiric therapy for final specific diagnoses (last antifungal prescribed) (N=346)**

	Liposomal Amphotericin B		Anidulafungin		Caspofungin		Micafungin		Posaconazole		Voriconazole		Fluconazole	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E
Aspergillosis n = 92	1	0	0	0	9	1	1	0	8	1	64	7	0	0
Systemic candidiasis** n = 133	10*	0	0	1	61	3	15	1	5*	0	26	2	10	0
Febrile neutropenia n = 84	0	3	0	1	0	27	0	6	0	26	0	21	0	0

C: curative therapy; E: empiric therapy  
\*: combination  
\*\* catheter associated candidiasis: n=8

## LIMITS

- Retrospective data collection
- Fluconazole and itraconazole exclusion
- Limited number of patients
- Publication of new guidelines during the study period

## DISCUSSION/CONCLUSION

- Posaconazole is the most frequently prescribed antifungal agent (72%) for prophylaxis. All other agents are primarily used for treatment;
- Voriconazole (77%) is the most frequently prescribed antifungal agent for aspergillosis (empiric or curative therapy);
- Echinocandins are the most frequently prescribed antifungal agents (80%) for candidiasis (empiric or curative therapy);
- Echinocandins are the most frequently prescribed agents (68%) for empiric therapy of febrile neutropenia;
- According to the guidelines, many patients received an antifungal agent without a clear indication written in the patient's chart:
  - Prophylaxis: 17%
  - Empiric therapy: 44%
  - Aspergillosis curative therapy: 7%
- According to Quebec provincial guidelines, a deviation of 53% was observed for candidiasis treatment (no fluconazole or amphotericin B beforehand).

## RECOMMENDATIONS

- Based on the main published guidelines, develop and disseminate common antifungal utilization criteria and algorithms to all five university teaching hospitals. Priority should be given for candidiasis and empiric therapy;
- Conduct a further study to assess clinicians' adherence to these recommendations;
- Ensure that posaconazole as primary prophylaxis is the appropriate choice;
- Ensure that combinations of antifungals are warranted;
- Remind clinicians to switch from parenteral to oral administration as soon as the patient's clinical condition permits;
- Improve documentation in patient's chart by providing details in the progress notes.

