CLINICAL INVESTIGATION

Evaluation of Conformity of a First Prescription of Lipid-Based Formulation of Amphotericin B in a University-Teaching Pediatric Hospital

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OBJECTIVE Invasive fungal infections are an important cause of morbidity and mortality in immunodeficient children. Amphotericin B is an important therapeutic agent for the treatment of invasive fungal infections but is associated with significant toxicities and high acquisition costs. The purpose of this study was to evaluate physician adherence to a local guideline for the use of lipid-based amphotericin B.

METHODS The study was approved through Pharmacology & Therapeutics (P&T) committee activities. A retrospective drug utilization review (DUR) was conducted. All orders written between January 1, 2003, and December 31, 2004, were reviewed. Demographic and descriptive clinical data were collected as well as variables related to the drug order process. Conformity rates were calculated for the primary objective criteria (authorized prescribers – infectious disease members; recommended drug of choice—Abelcet; accepted indications; and presence of underlying conditions).

RESULTS A total of 109 orders for 70 patients were reviewed by a single research assistant for a 2-year period. Global conformity rate for all four criteria was calculated at 7.3%. Non-conformity was mostly associated with the absence of underlying conditions (e.g., prerenal insufficiency or presence of nephrotoxicity due to amphotericin B desoxycholate) in 84.5% of the cases. Infusion-related adverse drug reactions partly explained a switch to a non-formulary lipid-based amphotericin B product. External factors (newly published results since the adoption of the guideline and continuous marketing practices) and internal factors (availability of non-formulary process, inefficient DUR process) could have contributed to non-adherence to a local guideline.

CONCLUSION This study shows low adherence to P&T committee drug guidelines on lipid-based amphotericin B. Continuous and efficient DUR processes should be in place to monitor drug guideline adherence.

KEYWORDS abelcet, ambisome, amphotericin B, drug utilization review, pediatrics

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INTRODUCTION

Optimal medication use in a health center relies on different aspects pertaining to structure (Pharmacology and Therapeutics committee [P&T]), policies (e.g., local guidelines), information systems (e.g., computerized physician order-entry [CPOE]), training (e.g., lectures and presentations) and interventions

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ABBREVIATIONS BMT, bone marrow transplant; CPOE, computerized physician order-entry; DUR, drug utilization review; P&T, Pharmacology and Therapeutics

(e.g., prescription validation process by pharmacists). The goal of this study was to evaluate the conformity of the first prescription of lipid-based amphotericin B according to the local utilization guidelines adopted by the P&T committee of a mother and child university-teaching health center.

Over the last decade, we have noticed an increase in invasive fungal infections within the immunodeficient pediatric population, due to an increase of hospitalizations on hematology-oncology units and of hematopoietic transplants.[1] Amphotericin B is part of standard treatment of most invasive fungal infections in immunodeficient patients.[2,3] Although very effective, amphotericin B nephrotoxicity and infusion-related reactions considerably limit its use. Three lipid-based formulations (Abelcet, Ambisome, Amphotec) were introduced in North America during the last decade, with the purpose of reducing the nephrotoxicity known to conventional amphotericin B desoxycholate (Fungizone).[4] Lipid-based formulations of amphotericin B demonstrated a significantly lower incidence of nephrotoxicity when compared to conventional amphotericin B.[4] However, lipid-based formulations are more costly than conventional amphotericin B,[5] and, to our knowledge, comparative studies of the different lipid-based formulations of amphotericin B in the pediatric population are not available. The only studies evaluating lipid-based formulations of amphotericin B in the pediatric population are non-comparative.[6-8] Only one study conducted in adults demonstrated a higher incidence of nephrotoxicity with Abelcet compared with Ambisome.[9] Other retrospective studies demonstrated similar efficacy and toxicity.[10-13] At the Centre hospitalier universitaire Sainte-Justine, a local guideline regarding the use of lipid-based amphotericin B was adopted in 1998 and remained unchanged until January 2005. This guideline favored the use of Abelcet over Ambisome. However, despite this guideline, we have noticed in the last 3 years an increased use of Ambisome over Abelcet representing respectively 58%, 22%, and 12% of lipid-based amphotericin B dispensed in 2001–2002, 2002–2003 and 2003–2004. The primary objective of this study is to describe the use of lipid-based amphotericin B in a pediatric setting and to evaluate the conformity of the first prescription in regards to the local guideline.

METHODS

The CHU Sainte-Justine is a 500 bed university-teaching health center located in Montréal, Quebec, Canada, with 400 pediatric beds, offering services in areas such as pediatric intensive care, neonatology, hematology-oncology and bone marrow transplant (BMT). The local drug formulary adopted by the P&T committee of the hospital includes two intravenous amphotericin B formulations: Fungizone (amphotericin B desoxycholate), and Abelcet (lipid complex amphotericin B). The use of Abelcet is directed by a drug utilization guideline adopted in June 1998. Liposomal amphotericin B (Ambisome) is not listed on the local formulary and is only available on an "off-formulary" basis, pending a written justification from the prescribing physician and validation of this justification by a pharmacist.

All patients who were prescribed lipid-based amphotericin B between January 1, 2003, and December 31, 2004, were included in the review. Newborn patients (age less than 30 days) were excluded. The charts were selected from the software of the pharmacy system (GesPharRx, version 8.0). Using the patients' computerized pharmacy charts and the paper charts, relevant variables to the study were collected, permitting us to analyze the conformity of the prescription to quality standards. Data were collected by a single person (research assistant & pharmacy intern) during a three-week period, allowing approximately 45 minutes per chart. Five charts were reviewed by a pharmacist in order to verify data collection and application of conformity criteria (Table 1). The study was approved through P&T activities following the principles outlined in the Declaration of Helsinki.

The demographic profile of each patient included number of admissions during the study period, distribution by gender, patient age, weight and height, length of stay per admission, patient care unit upon admission**,** diagnosis upon admission, and percentage of patients who received a BMT within the 12 preceding months. We documented the profile of the first lipid-based amphotericin B prescription when

Table 1. Conformity criteria to the local regulation

Prescribing physician	Restricted to infectious diseases physicians
Indication	Documented systemic fungal infection or strongly suspected fungal infection in an immunodeficient patient
Underlying conditions	Patient suffers from a reversible renal insufficiency before beginning antifungal therapy.* If renal function returns to baseline value during Abelcet treatment, consider resuming amphotericin B desoxycholate
	Treatment with amphotericin B desoxycholate ended in therapeutic failure
	Patient developed clinically significant signs of nephrotoxicity during amphotericin B desoxycholate

** Serum creatinine clearance < 50 mL/min/1.73 m²*

a patient was admitted, with the first prescription defined as the very first order written by an authorized prescribing physician for a given formulation of lipid-based amphotericin B. We did not consider orders related to dosage modification or re-order following an interruption of less than 14 days as first orders**.** We described the formulation of lipid-based amphotericin B that was prescribed, length of validity of the prescription as an indicator of duration of treatment, prescribing physician's service, percentage of prescriptions written after 4 p.m. and during the weekend (Saturday or Sunday), documented indication justifying the prescription, percentage of first prescriptions that were preceded by at least one dose of amphotericin B desoxycholate, mean dose prescribed for the treatment, presence of at least one valid prescription of another nephrotoxic drug (i.e., cyclosporine, tacrolimus, aminoglycoside, diuretic, acyclovir, cisplatin, carboplatin, ifosfamide, methotrexate, or lithium), percentage of prescriptions for a test dose of lipid-based amphotericin B, percentage of prescriptions for one or more pre-medications (i.e., acetaminophen > 10 mg/kg/dose, diphenhydramine > 1 mg/kg/dose, hydrocortisone > 4 mg/kg/dose) or absence of prescription for an adequate pre-medication, and use of concomitant systemic antifungal drugs. We also documented underlying conditions for the first prescription of lipid-based amphotericin B: presence of presumed reversible renal failure before starting the treatment (evaluated as serum creatinine clearance < 50 mL/minute/1.73 m^2) and presence of nephrotoxicity secondary to amphotericin B desoxycholate treatment (also evaluated as a pre-treatment serum creatinine clearance < 50 mL/minute/1.73 m^2).

We documented adverse drug reactions and clinical outcomes after patients received lipid-based amphotericin B. We gathered data on infusion-related reactions, namely medical chart documentation of at least one of the following symptoms: fever, chills, hypotension, nausea or vomiting. We calculated the percentage of prescriptions that led to an increase of more than 1.2-fold, 1.5-fold and 2-fold in the serum creatinine value between the pre-treatment and end-of-treatment values. We also calculated the percentage of prescriptions that led to a decrease in the serum creatinine clearance of more than 25% and 50% between the pre-treatment and end-of-treatment values, using the Schwartz formula (height was unavailable in 8 cases).[14] Finally, we documented clinical outcomes at 60 days following the end of treatment. It was difficult to assess the clinical outcome of a treatment using the pharmacy system, but we attempted to evaluate the outcomes using the following definitions: presumed success, presumed failure, death, and unknown outcome- all these outcomes being mutually exclusive. Presumed success was defined as the documentation of at least one of the following elements: defervescence, or discontinuation of all antifungal treatment without a new antifungal prescription for 60 days following the end of treatment. Presumed failure was defined as the documentation of at least one of the following: new antifungal treatment prescribed within 60 days following the end of treatment, a change in the type of antifungal therapy, or a change in the amphotericin B formulation prescribed (which would then constitute a new prescription in our

definition of the first prescription of lipid-based amphotericin B).

We evaluated the conformity of the first prescription of lipid-based amphotericin B according to the guideline criteria for the utilization of these drugs (Table 1), initially adopted for the use of lipid complex amphotericin B (Abelcet), since liposomal amphotericin B (Ambisome) was not on our hospital's local drug formulary. Prescribing lipid complex amphotericin B is restricted to infectious diseases physicians for the treatment of documented or strongly suspected systemic fungal infections in immunodeficient patients in the following cases: 1) reversible renal failure prior to the start of lipid-based amphotericin B therapy (defined as creatinine clearance < 50 mL/minute/1.73 m^2). If renal function normalizes while undergoing treatment with lipid-based amphotericin B, substituting amphotericin B desoxycholate treatment must be considered; 2) therapeutic failure while receiving amphotericin B desoxycholate; and 3) development of clinically significant signs of nephrotoxicity while undergoing amphotericin B desoxycholate treatment. We evaluated the global conformity to the guideline criteria (prescribing physician, indication, presence of underlying condition, and recommended dosage [5 mg/kg/d]), and also the specific conformity to each criterion. Furthermore, we evaluated the conformity to the prescription of maximal infusion rate (i.e., infusion over at least 2 hours), and the prescription of at least 2 pre-medication drugs (i.e., acetaminophen, diphenhydramine, or hydrocortisone given at usual dosages), for limiting the occurrence of infusion-related reactions.

Data analysis was executed with SPSS version 8.0 (Chicago, IL). Data was analyzed using a Student *t* test for continuous variables and a chi-square test or Fisher exact test for dichotomous variables. $P < .05$ was considered statistically significant.

RESULTS

Seventy-two patients were retrieved from the GesPhaRx 8.0 pharmacy system as having received lipid-based amphotericin B during the study period. Two patients were excluded due to chart unavailability during the data collection period. Table 2 describes the demographic profile of these 70 patients (accounting for a total of 84 admissions during the study period). The majority of the patients were admitted to the hematology-oncology unit (67.1%), and 19 patients had undergone a BMT during the 12 months preceding the onset of treatment. Table 3 shows the profile of the first lipid-based amphotericin B prescription. Seventy-two liposomal amphotericin B prescriptions and 37 lipid complex amphotericin B prescriptions were reviewed, for a total of 109 prescriptions. The length of prescription validity is extremely variable, with an average of 14.3 days and a median of 7 days (range, 1–289 days). Over one-third of the prescriptions (34.9%) were written by a physician who was not authorized to prescribe the drug, according to the prescription guideline for lipid-based amphotericin B. Lipid-based amphotericin B was mostly prescribed to patients with a strongly

Table 2. Patient demographic profile at the time of the first lipid-based amphotericin B prescription

Parameters	Results
Number of patients	70
Number of admissions	84*
Male	36 (51.4%)
Female	34 (48.6%)
Age (yr)†	8.3 ± 6.2
Weight (kg)†	30.8 ± 21.9
Height (cm)†	121.4 ± 33
Patient care unit	
Hematology-oncology	47 (67.1%)
Intensive care	18 (25.7%)
Other	5 (7.1%)
Admitting diagnosis	
ALL	18 (25.7%)
ANL	10 (14.3%)
Neuroblastoma	7 (10%)
Aplastic anemia	6 (8.6%)
Myeloproliferative syndrome	2 (2.9%)
Osteosarcoma	2 (2.9%)
Other, immunodeficient	21 (30%)
Other, non-immunodeficient	4 (5.7%)
BMT in the preceding 12 months	19 (27.1%)
Pre-treatment serum creatinine, mg/L†‡	0.55 ± 0.29

ALL, acute lymphocytic leukemia; ANL, acute non-lymphoblastic leukemia; BMT, bone marrow transplant
** 3 patients had 3 admissions during study period, 8 patients had 2 admissions and 59 patients had 1 admission*
† Mean ± standard deviation
‡ To convert serum creatinine to µmol/L, multiply by 88.4

Table 3. Profile of the first lipid-based amphotericin B prescription

Parameters	Global	ABLC	L-AMB
Number of new prescriptions (n)	109	37	72
Prescriptions in patients with previous BMT	25.6%	27%	25%
Prescribing physician specialty			
Infectious diseases	65.1%	64.9%	65.3%
Hematology-oncology	28.4%	32.4%	26.4%
Other	6.4%	2.7%	8.3%
Prescriptions written after 4:00 p.m. on weekdays, and on weekends (n = 79 with documented time)*	20.3%	19.2%	20.8%
Prescriptions written over the weekend*	23.9%	27%	23.6%
Indications			
Documented systemic fungal infection in an immunodeficient patient	18.3%	16.2%	19.4%
Strongly suspected fungal infection in an immunodeficient patient	74.3 %	83.8%	69.4%
Other†	7.3%	—	11.1%
Dose (mg/kg/d) of lipid-based amphotericin B‡	4.87 ± 1.04	5.0 ± 1.2	4.9 ± 0.9
Prescriptions with ordered rate of infusion	21.1%	40.5%	11.1%
Prescriptions preceded by amphotericin B desoxycholate	14.7%	8.1%	18.1%
Presence of 1 or more nephrotoxic medicines	94.5%	91.9%	95.8%
Prescriptions with ordered test dose	1.8%	0	2.8%
Underlying conditions at time of first prescription			
Documented reversible renal failure prior to treatment (n = 109)*	18.3%	8.1%	23.6%
Reversible renal failure prior to treatment (serum creatinine clearance < 50 mL/min/1.73 m^2) (n = 85 prescriptions not preceded with amphotericin B desoxycholate and with calculable serum creatinine value)*	2.4%	—	3.6%
Amphotericin B desoxycholate nephrotoxicity (creatinine clearance < 50 mL/min/1.73 m^2) (n = 16 prescriptions preceded with amphotericin B desoxycholate therapy)*	12.5%	—	15.4%
Pre-medication			
No suggested pre-medication	8.3%	5.4%	9.7%
At least one suggested pre-medication	91.7%	94.6%	90.3%
At least two suggested pre-medications	43.1%	45.9%	41.7%

ABLC, Abelcet; BMT, bone marrow transplant; L-AMB, liposomal amphotericin B (Ambisome)
** Global number of relevant prescriptions*
† Cutaneous indications (n = 3), craniocerebral trauma (n = 1), home-based therapy (n = 2), other (n = 2)
‡ mean ± standard deviation

suspected but undocumented systemic fungal infection (74.3%, as compared with 18.3% documented infection). A large percentage of patients (94.5%) treated with amphotericin B were concomitantly receiving 1 to 5 nephrotoxic medications. As a result, amphotericin B desoxycholate was used as first-line therapy in only a few patients (14.7%). In 32.2% of cases, we documented the use of at least one other valid prescription for a systemic antifungal agent when lipid-based amphotericin B was first prescribed (fluconazole > caspofungin > fluconazole + caspofungin = voriconazole > itraconazole).

The first lipid-based amphotericin B prescription was justified by the presence of preexisting reversible renal failure as documented in the medical chart in 18.3% of cases, but only in 3.7% of cases according to the calculated serum creatinine clearance. In 2 of 16 cases, appropriate use was justified by nephrotoxicity secondary to the use of amphotericin B desoxycholate (serum creatinine clearance < 50 mL/minute/1.73 m^2). No justification for the use of lipid-based amphotericin B regarding renal function was documented in the medical chart in 87 cases (80%).

Table 4 presents adverse drug reactions and clinical outcomes. Similar infusion-related reactions were noted with lipid complex ampho-

Table 4. Adverse drug reactions and outcomes

Parameters	ABLC (n = 37)	L-AMB (n = 72)
Presence of at least one infusion-related reaction*	1 (2.7%)	1 (1.4%)
Prescriptions associated with an increase in serum creatinine		
≤ 1.2 X baseline value	48.6%	52.8%
1.2 to 1.49 X baseline value	18.9%	20.8%
1.5 to 1.99 X baseline value	16.2%	19.4%
≥ 2 X baseline value	16.2%	6.9%
Decrease in serum creatinine clearance†		
More than 25 % decrease	50%	37.3%
More than 50 % decrease	17.6%	6%
Outcome at 60 days after the end of the lipid-based amphotericin B treatment		
Presumed success (n = 31)	13.5%	36.1%
Presumed failure‡ (n = 44)	73%	23.6%
Death (n = 19)	8.1%	22.2%
Unknown (n = 15)	5.4%	18.1%

ABLC, Abelcet; L-AMB, liposomal amphotericin B

** Fisher exact-test P = .56*

† 8 missing height values, therefore creatinine clearance not calculated

‡ Presumed failure: 9 of these episodes resulted in more than one reason for presumed failure (e.g., change in formulation followed by change in antifungal therapy); thus, the causes for presumed failure are not mutually exclusive

tericin B (2.7%) and liposomal amphotericin B (1.4%). No significant difference was noted between the pre-lipid complex amphotericin B and pre-liposomal amphotericin B serum creatinine clearance values (and between the post-lipid complex amphotericin B and post-liposomal amphotericin B serum creatinine clearance values. No difference was found between lipid complex amphotericin B and liposomal amphotericin B in terms of the percentage of prescriptions that led to a 25% or 50% decrease in the serum creatinine clearance between the pre-treatment and end-of-treatment values. Thirteen formulation changes from lipid complex amphotericin B to liposomal amphotericin B occurred, seemingly justified by infusion-related reaction (n = 2), ease of home-based administration (n = 2), or with no justification retrieved from the medical chart (n = 9). Similarly, 2 patients switched from liposomal amphotericin B to lipid complex amphotericin B due to adverse drug reactions. In 22.9% of cases, patients were treated with at least one other antifungal drug while undergoing lipid-based amphotericin B treatment (fluconazole > caspofungin > voriconazole = itraconazole).

Table 5 shows the conformity profile of the first lipid-based amphotericin B prescription in relation to the utilization guideline currently in use at CHU Sainte-Justine. According to this guideline, lipid complex amphotericin B should be the initial lipid-based formulation of amphotericin B to be used. This decision was made according to available published clinical data at the time of guideline adoption, the lower acquisition cost of lipid complex amphotericin B, and the clinicians' consensus obtained upon the hospital P&T committee evaluation. It can be noted that only 7.3% of all the reviewed prescriptions globally adhered to the established criteria (prescribing physician, indication, presence of underlying conditions and dosage). The guideline did not consider the possibility of changing from one lipid-based formulation to another in case of infusion-related reactions. When considering this condition, the specific conformity rate pertaining to underlying conditions would increase from 16.5% to 41.3%. This would cause the global conformity rate to increase to 24.8%. The guideline did not allow hematology-oncology physicians to prescribe lipid-based amphotericin B to their patients. When considering this condition, the specific conformity rate pertaining to the prescribing physician would increase from 65.1% to 93.6%. This would cause the global conformity rate to increase to 8.3%. If these two criteria were expanded accordingly, global conformity rate would increase from 7.3% to 38.5%. A written request for utilization of liposomal amphoteri-

Table 5. Conformity of the first lipid-based amphotericin B prescription

Parameters	% of Global Conformity
Strict conformity to initial standards	7.3%
Adjusted conformity for inclusion of hematoolgy-oncology physician as authorized prescribing physician	8.3%
Adjusted conformity for inclusion of infusion-related reaction as an underlying condition justifying the use of lipid-based amphotericin B	15.6%
Adjusted conformity for both preceding conditions (hematology-oncology physician and infusion-related reactions)	21.1%
Strict conformity to specific criteria	
Therapeutic indication	92.6%
Underlying conditions (presence of 1 of the 2 possible accepted underlying conditions justifying the use of lipid-based amphotericin B)	16.5%
Prescribed dose within accepted dosage range of 4.8 to 5.2 mg/kg/d	48.6%

cin B on an "off-formulary" basis was completed in only 50% of cases.

DISCUSSION

There are relatively few pertinent published data regarding the use of lipid-based amphotericin B in pediatrics.[6-9,12] Three published prospective studies evaluated the use of one or more lipid-based amphotericin B formulations in a general pediatric population containing a total of 701 pediatric patients, 672 of which were treated with lipid complex amphotericin B and 29 with liposomal amphotericin B.[6,7,9] These studies were primarily interested in evaluating lipid-based amphotericin B efficacy and tolerance. Results differ greatly from one study to another. To our knowledge, only one randomized multicenter study comparing lipid complex amphotericin B to liposomal amphotericin B has been published.[9] However, only 17.2% of the included patients were 16 years of age or younger. In their general population, Wingard et al. reported a higher nephrotoxicity rate (defined as a 2-fold increase in serum creatinine values) than in the above-mentioned pediatric studies.[6,7,10] In the general population, nephrotoxicity was 3 times more likely to occur with lipid complex amphotericin B than with liposomal amphotericin B. However, in the subgroup analysis for patients under the age of 16, no significant increase in serum creatinine values was identified, whether treated with lipid complex amphotericin B or with liposomal amphotericin B.[9] When compared for efficacy, lipid-based formulations of amphotericin B appear to be equivalent.[5,9,10] We are aware of only one published study that reported data on the use of lipid-based amphotericin B according to a local guideline, although another primary objective of the study was to compare nephrotoxicity and efficacy of lipid complex amphotericin B and liposomal amphotericin B.[10] The authors found that nearly 50% of their 67 patients were prescribed lipid-based amphotericin B because of failure to azole antifungal therapy, without any underlying renal dysfunction. They concluded that their guidelines for the use of lipid-based amphotericin B were not followed or strictly enforced. Other studies describing the conformity rate of prescriptions in the context of pre-established guidelines were conducted. Namely, antibiotic use for surgical prophylaxis has been evaluated in a number of studies.[15,16] These studies report variable conformity rates to various published guidelines, ranging from 28%[16] to 65% of the reviewed prescriptions.[15]

Our study describes the profile of 109 lipid-based amphotericin B prescriptions in 70 patients, most of which were admitted on hematology-oncology units, over a period of two years in a tertiary university-teaching health center. The studied population is comparable to those described in other published studies referring to pediatric populations. Since 1997, the addition of a new drug entity to the hospital's local formulary has been regulated by a drug utilization guideline, which has been adopted by the hospital's P&T committee. The guideline is first discussed with the clinician requesting the drug addition, and is then distributed via

a written memo to all the physicians and the pharmacists working in the hospital. Since 2003, the guideline has been available on the hospital's intranet. In many instances, physicians are reminded of the guideline by the pharmacists who attend the medical teams, and who are present on the wards from Monday through Friday until 4 p.m. Incidentally, the presence of a pharmacist can be noted on the three principal units of care pointed by this study (i.e., hematology-oncology unit: 24 beds; BMT unit: 6 beds; pediatric intensive care unit: 24 beds).

When taking into consideration the prescribing physician, indication, underlying conditions and dosage, our study reveals a global conformity rate of 7.3% for lipid-based amphotericin B prescriptions. It can be observed that the "therapeutic indication" criteria are respected in the majority of the cases. The "prescribing physician" criteria are adhered to in almost two-thirds of the cases (65.1%). When not adhered to for that particular criterion, it was mostly when a hematology-oncology physician was acting as attending physician to patients admitted on hematology-oncology units. These physicians are well familiar with aspects relating to systemic fungal infections in immunodeficient hosts. Therefore, globally, the low conformity rate of the prescriptions to the local guideline is mainly due to the absence of documented underlying renal conditions. This finding is similar to the conclusion of the utilization review of lipid-based amphotericin B conducted by Cannon et al.[10]

What could explain the low conformity rate of the first lipid-based amphotericin B prescription to our drug utilization guideline? The guideline was adopted in 1998. The Wingard et al. study was published in 2000, describing a higher incidence of adverse drug reactions and nephrotoxicity with lipid complex amphotericin B than with liposomal amphotericin B in a general population.[9] Although performed mainly on adult patients, this study, combined with other external factors of influence (e.g., medical conferences, consistent marketing strategies developed by pharmaceutical companies, peer influence) may have contributed to the increasing popularity of liposomal amphotericin B among prescribing pediatric physicians and led them to increasingly question the relevance of using amphotericin B desoxycholate or lipid complex amphotericin B as first-line therapy, despite the lack of evidence regarding a possible increase in nephrotoxicity between lipid-based amphotericin B formulations in the pediatric population. Our study, however, does not allow us to evaluate the impact of those external factors. Locally, it is relevant to mention the transfer of license for lipid complex amphotericin B from Liposome Canada to Elan, which led to a limited marketing for lipid complex amphotericin B, while during the same period of time, the marketing for Fujisawa's liposomal amphotericin B was maintained. Nevertheless, no formal request was made to the P&T committee to modify the status of either lipid-based formulation on the hospital's formulary or to allow the local guideline to acknowledge the use of liposomal amphotericin B.

Although our study was not designed to compare the incidence of nephrotoxicity between lipid complex amphotericin B and liposomal amphotericin B, there were no disparities between the two groups on this respect. Our study also reveals a similar incidence of infusion-related reactions between lipid complex amphotericin B compared with liposomal amphotericin B, although suboptimal premedication was noted in over one-half of the patients. Our study was not designed to evaluate incidence of adverse drug reactions. It is important to note that justifications regarding the change of therapy from lipid complex amphotericin B to liposomal amphotericin B were poorly documented in the medical charts. Data collection showed some confusion in the different terms for amphotericin B prescriptions. The use of generic denomination is included in the hospital's regulation for issues of prescriptions. Thus, according to this rule, one would think that it would first favor lipid complex amphotericin B, the only lipid formulation included on the list. However, this was not the case, implying that most prescriptions were written using the commercial name instead of the generic name.

Considering that a drug utilization guideline requires a pharmacist to validate prescriptions prior to starting therapy in our hospital, how can we explain the limited impact of the pharmacists' regulation on upholding prescription conformity to the lipid-based amphotericin B

guideline? Although relevant patients were treated on three main care units, prescriptions are discussed on the ward during medical rounds, but interpreted at the main pharmacy by the staffing pharmacists. Of the 79 prescriptions that listed the exact time they were written, 15 ordered a change in the formulation (generally from lipid complex amphotericin B to liposomal amphotericin B, n = 13); 11 of these 15 changes were ordered after 4 p.m., and 4 changes were ordered over the weekend. At these particular times, the pharmacist on duty at the main pharmacy is usually not a member of the patient care units targeted by this study, therefore, limiting the intervention to obtaining a written "off-formulary" utilization request signed by the prescribing physician. In many cases (27.5%), it was not possible to evaluate this aspect due to the omission of prescription time. Our study demonstrates that implementing drug utilization guidelines may have a very limited impact if there is a possibility to use drugs not included on the formulary. In our study, non-conformity was shown to be mostly due to the absence of underlying conditions justifying the use of lipid-based amphotericin B. Attending pharmacists on the wards and staffing pharmacists should have made sure these conditions were fulfilled before the lipid-based amphotericin B was administered. It is not clear why this was not consistently done, but one reason might be that, with the increase in clinical activities, pharmacists get exposed to some influential factors, such as opinion leaders' preferences for lipid-based formulations. DUR activities, historically vested in pharmacists, have also been reduced over the years due to the introduction of pharmaceutical care and reallocation of resources to other clinical activities; a DUR generally requires a considerable amount of time and effort due to the its complex systematic methodology. Our study reveals the importance of conducting DUR on a regular basis with a more timely approach. Following that study, our research unit in clinical practice has adopted a DUR method that relies on a limited amount of criteria (n < 5–10), a limited sample size of patients (n = 30) and a limited period of time for data collection, analysis, report and feedback (30 days) in order to facilitate the process and to provide clinicians with timely results that could influence practice to a greater extent.

Even though our study was not conducted to evaluate the clinical impact of the lipid-based amphotericin B formulations, we attempted to measure the outcomes of therapy. For example, because "presumed failure" included changes in lipid-based formulations, we noted a higher "presumed failure" rate with lipid complex amphotericin B than with liposomal amphotericin B. If we do not consider the 15 formulation changes as failures, the presumed failure rate would be 43.2 % for lipid complex amphotericin B and of 32.9% for liposomal amphotericin B (compared with 73.0% and 23.6%, respectively, if the "presumed failure" criteria are analyzed as per the initial protocol).

Kuti et al. conducted a comparative cost analysis of two lipid-based formulations of amphotericin B– lipid complex amphotericin B and liposomal amphotericin B.[5] These two agents were compared with respect to acquisition cost, antifungal treatment-associated and hospitalization-associated costs. The authors concluded that the cost difference is primarily due to the acquisition costs and that the treatment-related added costs are similar for both formulations. According to the prices paid by our hospital over the study period ($215.55 Canadian dollars for a 50 mg vial of liposomal amphotericin B and $198.40 Canadian dollars for a 100 mg vial of lipid complex amphotericin B), we calculated an overall cost of $1,084,641 Canadian dollars (i.e., $988,367 Canadian dollars for liposomal amphotericin B and $96,274 Canadian dollars for lipid complex amphotericin B). Assuming that all of the 109 prescriptions had been made for lipid complex amphotericin B as directed by the local guideline, the total cost would have been $551,772 Canadian dollars, therefore, saving $532,869 Canadian dollars over the two-year period. Hence, it is reasonable to question the quasi-systematic use of liposomal amphotericin B, which was 200% more costly than lipid complex amphotericin B, knowing that infusion-related reactions with lipid complex amphotericin B are provisional and can usually be minimized by adequate pre-medication. In our study, less than 50% of the patients undergoing lipid complex amphotericin B treatment received optimal pre-medication; however, infusion-related reactions (fever, chills) were comparable

for lipid complex amphotericin B (2.7%) and liposomal amphotericin B (1.4%) (P = .56). When considering the large cost difference between the two formulations during the study period and the similar efficacy and tolerability by published data, it appears reasonable to consider that lipid complex amphotericin B, along with adequate pre-medication, should have remained the first choice of treatment in our population, when conventional amphotericin B treatment did not constitute an acceptable option (e.g., in case of altered renal function). In January 2005, Fujisawa offered our purchase group a 50% reduction in price for its liposomal amphotericin B, which would cancel the incurred gap made in 2003–2004.

In summary, this study describes a low conformity rate to the drug utilization guideline adopted by a pediatric university-teaching health center for the first lipid-based amphotericin B prescription. The P&T committee of a health care center must put in place drug utilization guidelines for the drugs that are included in the hospital's formulary. Our study stresses the need for conducting efficient DUR, based on a limited number of criteria, which can be achieved using a minimal amount of information, in order to provide clinicians with punctual information describing the use or misuse of medications. Although pharmaceutical care constitutes an important development of the last decade, interest and resources must still be granted to DUR activities, so that drug utilization guidelines evolve in conjunction with local clinical practices.

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