Outpatient Parenteral Antifungal Therapy (OPAT) for Invasive Fungal Infections with intermittent dosing of Liposomal Amphotericin B.

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Alle wegen leiden naar Rome maar de weg tussen Antwerpen en Rotterdam is bezaaid met ontelbare obstakels wegens een falend openbaar vervoer. Brompton-gerelateerd reisadvies kan worden bekomen bij Rijnders & Schauwvlieghe Travel Agency.

ABSTRACT

Background

Triazole resistant *A. fumigatus* has been documented in many parts of the world. In the Netherlands, incidence is now above 10% and results in the need for long-term parenteral therapy with liposomal amphotericin B (LAmB). The long terminal half-life of LAmB suggests that intermittent dosing could be effective, making the application of outpatient antifungal therapy (OPAT) possible. Here, we report our experience with the use of OPAT for Invasive Fungal Infections (IFI).

Methods

All adult patients treated with LAmB with a 2 or 3 times weekly administration via the outpatient departments in four academic tertiary care centres in the Netherlands and Belgium since January 2010 were included in our analysis. Patient characteristics were collected, as well as information about diagnostics, therapy dose and duration, toxicity, treatment history and outcome of the IFI.

Results

In total, 18 patients were included. The most frequently used regimen (67%) was 5mg/kg 3 times weekly. A partial response to the daily treatment prior to discharge was confirmed by CT-scan in 17 (94%) of patients. A favourable outcome was achieved in 13 (72%) patients. Decrease in renal function occurred in 10 (56%) cases but was reversible in all and was treatment limiting in 1 patient only. 100-day mortality and 1-year mortality after initiation of OPAT were 0% and 6%, respectively.

Conclusions

In a selected population, and after confirmation of initial response to treatment, our data support the use of OPAT with LAmB for treatment of IFI in an intermittent dosing regimen.

BACKGROUND

Invasive Fungal Infections (IFI) are often life-threatening and occur predominantly in immunocompromised patients. After surviving the initial phase of infection, prolonged treatment with an antifungal agent is often necessary to ensure complete resolution (1, 2). Unfortunately, the different antifungal drugs in the current medical armamentarium all have shortcomings when used for a prolonged period of time (3). For invasive aspergillosis (IA) voriconazole became the first-choice treatment after an improved survival was documented over conventional amphotericin B (cAmB). Furthermore, voriconazole has a favourable adverse event profile compared to conventional formulations of amphotericin B and it is rarely associated with renal toxicity (4, 5). Nonetheless, no direct comparison between voriconazole and the more well-tolerated liposomal amphotericin B (LAmB) has been made. In recent years, increasing rates of triazole resistant *Aspergillus* fumigatus in particular in Europe but also in other continents have become a major concern (6-10). This has led to a renewed incentive to reconsider therapeutic strategies using LAmB (11, 12). For many IFI caused by non-Aspergillus fungi, e.g. *Mucorales* spp., LAmB already is the preferred first-line treatment (13, 14). Therefore, treatment with LAmB is increasingly indicated and sometimes even the last resort in the management of invasive fungal disease.

LAmB is solely administered in an intravenous formulation. Both safety concerns and logistical reasons prevent dismission from the hospital during intravenous treatment; however, often the treatment duration is long and exceeds the period of necessity of hospitalisation for clinical reasons (1, 2). The practical limitations of daily intravenous treatment are evident. Reduction of duration of hospital stay would be favourable when considering both patient quality of life as well as economic costs. Furthermore, continued daily intravenous administration will lead to high cumulative dosages, associated with a higher rate of adverse events. As an alternative, we have started to apply Outpatient Antifungal Therapy (OPAT) with LAmB. OPAT has been implemented successfully in the past with various antibiotics. In bacterial infections, increasing antimicrobial resistance rates have made prolonged intravenous treatment with reserve antibiotics necessary. For example, the increasing rate of Methicillin Resistant *Staphylococcus aureus* has been an important reason to apply prolonged OPAT with vancomycin (15-17). With LAmB, outpatient use has recently been implemented in a prophylactic setting (18).

Two recent reviews of the pharmacokinetic properties of LAmB strengthen the hypothesis that LAmB can effectively be applied as OPAT (19, 20). LAmB has a relatively short elimination half-life of 7 hours shortly after initiation of therapy, which increases to over 100 hours after prolonged use. This phenomenon is attributed to accumulation in tissues and slow redistribution (21, 22). When these pharmacokinetic properties of

LAmB are taken into account, (23-25), it can be expected that a therapeutic concentration can be attained is a less frequent dosing scheme. Moreover, it may be possible to (partially) avoid nephrotoxicity if the total dose of LAmB is spread over multiple days (25, 26). Nephrotoxicity however remains an important caveat in the application of OPAT with LAmB, as mentioned in pharmacological review papers and in previous experimental experience (19, 20, 22, 27).

For those in need of prolonged antifungal treatment, step-down therapy to intermittent dosing in the context of outpatient treatment could offer similar efficacy with the potential of improved safety. An intermittent dosing strategy is occasionally applied in several hospitals in the Netherlands and Belgium. In this study, we are introducing the concept of treatment of IFI with intermittent LAmB dosing as OPAT.

METHODS

Study Setting and patient population

A multi-centre retrospective cohort study was conducted within the Netherlands and Belgium. Hospitals that participate in the Dutch-Belgian Mycoses study group (DB-MSG) (28), a consortium committed to the clinical research of IFI, were sent an inquiry about their experience in the application of OPAT with LAmB in the past 10 years. Of the 11 medical centers that participate in the DB-MSG, four responded that they had applied OPAT with LAmB in recent years. OPAT was applied at the home of the patient or within the hospital outpatient department. All adult patients treated with LAmB with a less frequently than daily administration via the outpatient departments of Leiden University Medical Center, Erasmus MC Rotterdam, Radboud University Medical Center Nijmegen, and the University Hospitals Leuven since January 2012 were included. These centres are all tertiary care university hospitals and engaged in extensive solid organ and hematopoietic stem cell transplantation programs.

Study protocols and definitions

No uniform protocols for the start of intermittent therapy with LAmB were present. Typically for *Aspergillus* disease, a 3 mg/kg dose was started. For *Mucor* species a typical dose was between 5-10 mg/kg. The choice to start treating with intermittent therapy with LAmB was made according to the clinical judgement of the treating physician usually based on imaging and clinical course. Patients that were started on OPAT with LAmB were closely monitored for the occurrence of nephrotoxicity and most patients received the drugs in the outpatient department of the hospital. In the first month, all patients had at least a weekly monitoring of electrolyte and kidney function. In the subsequent weeks, monitoring occurred at least once every two weeks.

Nephrotoxicity was defined as a >1.5 times increase of baseline serum creatinine levels resulting in an eGFR of less than 40 ml/min/1.73 m^2 during treatment or as electrolyte disorders suspected to be the result of renal damage and requiring cessation of treatment with LAmB at the discretion of the treating physician. Resolution of IFI was defined as clinically observed absence of complaints that are likely to be caused by IFI in combination with findings concordant with resolution of IFI on high-resolution CT-scan and the absence of the need to restart antifungal therapy within 6 months.

Data collection

At the participating sites, lists of patients that received LAmB as an outpatient were provided by the hospital pharmacy. Based on these lists, the electronic medical records were examined to ensure eligibility for inclusion in our study. The only inclusion criterion was at least 2 weeks of intermittent treatment outside of the hospital with LAmB for an invasive fungal infection meeting the diagnostic criteria of the revised (2008) EORTC/MSG definitions for invasive fungal disease (29).

After retrieval of all relevant information, the data of all participants was pseudonymized. Patient characteristics including age, diagnosis of immunocompromising disease, diagnosis of IFI, comorbidity and immune status were collected, as well as information about performed diagnostics, dosage of therapy, duration of therapy, treatment history, switch of antifungal therapy, renal function and outcome of the IFI. The latter three variables were considered the primary study outcomes to assess the safety and efficacy of this strategy. IFI were classified according to the 2008 revised European Organisation for Research and Treatment of Cancer – Mycoses Study Group criteria for the classification of IFI (29).

Analyses

Descriptive statistics of clinical variables of patients were calculated using the complete dataset. Kaplan Meier curves of survival during OPAT with LAmB were constructed. The analyses were performed using STATA v 16 (Statacorp, College Station, Texas, USA).

Ethics

The study was reviewed by the institutional review board of the LUMC Leiden in the Netherlands, which confirmed that the study did not fall under the Dutch law on research on human subjects. The institutional review board from UZ/KU Leuven in Belgium approved the study. Data were processed after pseudonymization by the local investigators and in accordance with Personal Data Protection Acts of the respective countries.

RESULTS

Between January 1st 2010 and September 1st 2018, a total of 18 adult patients received LAmB as an outpatient in a dosing frequency of two or three times a week. Triazole resistance, demonstrated by either PCR or culture, has been the most common reason (in 10 cases) to choose treatment with LAmB instead of voriconazole in the patients with Invasive Aspergillosis. Of all patients, nine (50%) were male and median age was 60 years. Fourteen patients (78%) had a haematological malignancy as underlying predisposing disease. Other underlying diseases were Chronic obstructive Pulmonary Disease (COPD), Sickle Cell disease and Chronic Granulomatous Disease (CGD). Suspected causative agents of IFI were *Aspergillus* spp. (12 patients), *Mucorales* spp. (3 patients), *Fusarium* spp. (2 patients) and a combination of both Aspergillus and Mucor (1 patient). Table 1 summarizes the descriptive characteristics of the study cohort. A response to treatment prior to discharge and start of OPAT with LAmB was confirmed by CT-scan in 17 patients. For the remaining patient, clinical improvement had been the reason to proceed with OPAT. Patients switched from daily treatment as an inpatient to intermittent OPAT with LAmB after a median of 56 days (range 14-193 days). Median dosage of liposomal amphotericin B was 3 mg/kg, administered three times each week. Some patients switched drug dosage and/or frequency as detailed in the legend. None of the patients received combination therapy. Resolution of infection was finally achieved in 13 patients. The remaining patients were readmitted to the hospital, switched to another antifungal, died or were lost to follow-up.

Nephrotoxicity during OPAT occurred in 10 cases, of which in only one case treatment needed to be switched to another antifungal agent (posaconazole, after establishing intermediate sensitivity).

All patients in our dataset had normalised renal functions after decreasing of dosage or cessation of LAmB therapy. Severe hypokalaemia (less than 2.5 mmol/litre) was not observed during treatment with LAmB in an intermittent scheme. No intravenous or oral substitution of potassium was has been applied.

For the remaining cases, the treating physician opted for a dose reduction (four cases) or, after establishing a sufficient treatment response, for the cessation of antifungal therapy (five cases). The 100-day mortality and 1-year mortality were 0 and 1 patients out of 18 respectively. All-cause mortality until the end of follow-up was 39% but was related to the underlying immunocompromising disease. In all cases treated for invasive aspergillosis, the reason to treat with LAmB was triazole resistance (demonstrated in 10 patients, presumed in 3 patients). Readmission to the hospital was necessary due to factors related to the infection (3 patients) or to LAmB-related nephrotoxicity (1 patient). Figure 1a shows the survival rates of all patients in a Kaplan Meier analysis since start of OPAT. Figure 1b shows the time until resolution of infection. Figure 1c shows the time until nephrotoxicity occurred during intermittent treatment.

Total number of patients	18
Patient Characteristics	
Sex, male (%)	9 (50)
Age, median (range)	60 (18-78)
Underlying predisposing disease, number of pts. (%)	
ALL	6 (33)
AML/MDS-RAEB2	4 (22)
CLL	3 (17)
COPD	2 (11)
Aplastic Anemia	1 (6)
CGD	1 (6)
Sickle Cell Disease	1 (6)
Prior allogeneic HSCT for any underlying disease	8 (44)
Invasive Fungal Infection, number of pts. (%)*	
Aspergillosis	13 (72)
Mucormycosis	3 (17)
Fusariosis	2 (11)
Cryptococcosis	1 (6)
Reason to treat Invasive Aspergillosis with LAmB, Number of patients (% of patients with IA)	
Triazole resistance identified with culture or PCR	10 (77)
Resistance presumed because IA occurred despite adequate prophylaxis with a triazole	2 (15)
Resistance presumed because IA showed progression despite adequate treatment with a triazole	1 (8)
Treatment	
Dosage in mg/kg and frequency in times/week†, number of patients treated with the regimen at any point	
2 mg/kg 3 times/week	1
3 mg/kg 2 times/week	1
3 mg/kg 3 times/week	12
5 mg/kg 3 times/week	2
6 mg/kg 3 times/week	5
10 mg/kg 2 times/week	2
Response to treatment confirmed by CT before start of intermittent therapy, number of pts (%)	17 (94)
Number of days between date of diagnosis and start of intermittent therapy, median number of days (range)	56 (14-193)
Nephrotoxicity^, number of patients (%)	
Occurrence of nephrotoxicity at some point during intermittent LAmB treatment Of which	10 (56)
- resulting in switch to other antifungal agent	1 (10)
- resulting in cessation of antifungal treatment (because of concurrent sufficient clinical and radiological response to treatment)	4 (40)
- resulting in dose or frequency reduction–	5 (50)

Table 1: Patient characteristics
Legend: On next page

Legend: LAmB denotes liposomal amphotericin B, ALL Acute Lymphoid Leukaemia, AML Acute Myeloid Leukaemia, MDS-RAEB2 Myelodysplastic Syndrome with Refractory Anaemia with Excess Blasts-2, CLL Chronic Lymphatic Leukaemia, HSCT hematopoietic stem cell transplantation, CT Computed tomography, COPD Chronic Obstructive Pulmonary Disease, PCR Polymerase Chain Reaction, CGD chronic granulomatous disease, IA invasive Aspergillosis. * Numbers add up to more than 100% due to one patient suffering from an infection caused by both Mucor and Aspergillus. ^Nephrotoxicity defined as either serious electrolyte disturbances necessitating treatment cessation at the discretion of the treating clinician or at least 50% increase of creatinine levels resulting in a eGFR of less than 40 ml/min. †Numbers add up to more than 100% because of 5 patients with dose alterations during the study period. ~ Dose reductions were as follows: 2 patients treated with 6 mg/kg 3 times weekly and 1 patient treated with 5 mg/kg 3 times/week were switched to 3 mg/kg 3 times weekly. Of 2 patients treated with 3mg/kg 3 times/week, one was switched to 3mg/kg 2 times/week and 1 patient was switched to 2mg/kg 3 times/week. Kidney function normalised in all 5 patients. ‡ Resolution of infection defined as clinically observed absence of complaints that are likely to be caused by Invasive Fungal Infection in combination with clinically irrelevant or absent abnormalities concordant with Invasive Fungal Infection on High-resolution CT-scan.

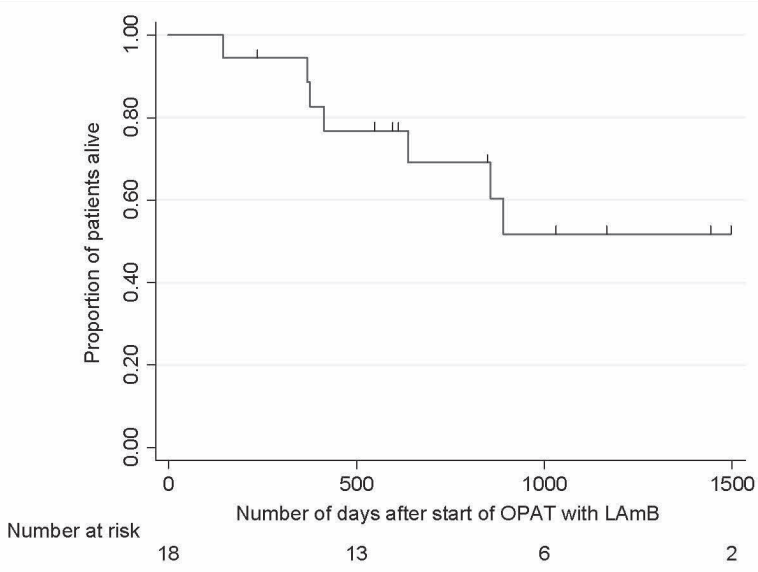

Figure 1A: Overall survival from start of intermittent treatment
Legend: OPAT denotes outpatient antifungal therapy, LAmB liposomal amphotericin B. Censored cases were lost to follow up.

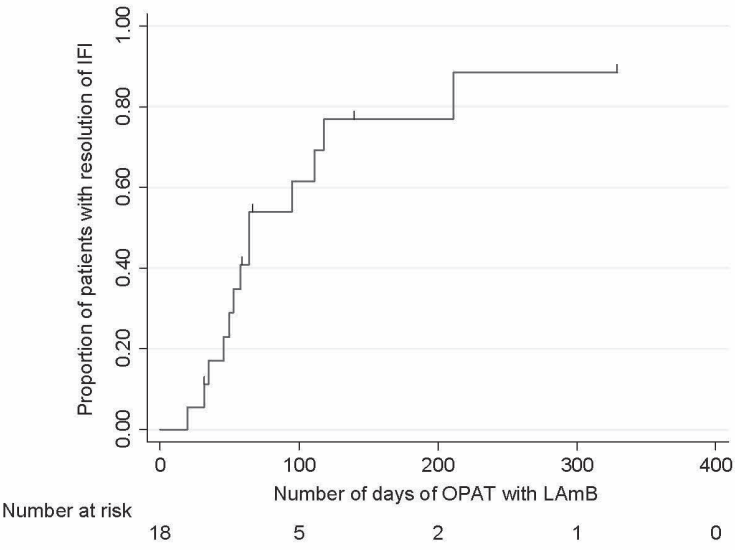

Figure 1B: Time to resolution of IFI after start of intermittent therapy.
Legend: IFI denotes invasive fungal infection, OPAT denotes outpatient antifungal therapy, LAmB liposomal amphotericin B. Censored cases stopped intermittent treatment before resolution of infection. Resolution of IFI was defined as clinically observed absence of complaints that are likely to be caused by IFI in combination with findings concordant with resolution of IFI on High-resolution CT-scan.

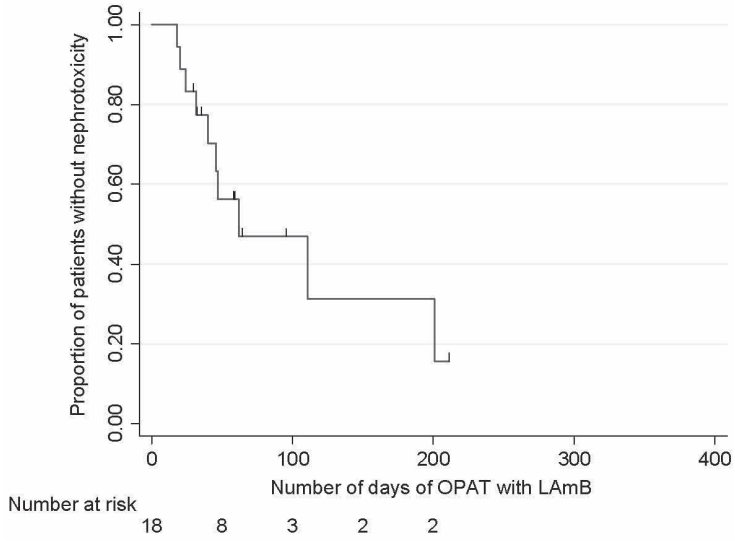

Figure 1C: Occurrence of nephrotoxicity from start of intermittent treatment
Legend: OPAT denotes outpatient antifungal therapy, LAmB liposomal amphotericin B. Censored cases stopped intermittent treatment before nephrotoxicity occurred. Nephrotoxicity was defined as a >1.5 times increase of baseline serum creatinine levels resulting in an eGFR of less than 40 ml/min/1.73 m^2 during treatment or as electrolyte disorders suspected to be the result of renal damage and requiring cessation of treatment with LAmB at the discretion of the treating clinician.

Outcome	N=18
Median number of days of follow-up, median (range)	741 (145-2543)
All-cause mortality at end of follow-up, number of pts (%)	7 (39)
100 day mortality after start of OPAT, number of pts (%)	0 (0)
1 year mortality after start of OPAT number of pts (%)	1 (6)
Resolution of infection‡, number of pts (%)	13 (72)

Table 2: Outcomes
Legend: ‡ Resolution of infection defined as clinically observed absence of complaints that are likely to be caused by Invasive Fungal Infection in combination with clinically irrelevant or absent abnormalities concordant with Invasive Fungal Infection on High-resolution CT-scan.

DISCUSSION

This study shows that the use of OPAT with LAmB in a 2 or 3 times weekly dosing scheme results in high rates of therapy response in a selected patient population and after confirmation of an initial response to daily IV therapy with LAmB. However, safety issues did arise, resulting in mostly reversible nephrotoxicity and in some cases infection or therapy-related readmission to the hospital.

The majority of patients in this study needed prolonged use of LAmB for the treatment of triazole resistant *A. fumigatus* infections. After the first reports of voriconazole resistant A. fumigatus appeared in 2009 from the Netherlands (30), triazole resistance has now extensively been reported in many regions all over the world (7, 11). Although the prevalence is low in some regions, the rates have been steadily increasing in others (7, 31). The high rates of triazole resistance also impact decision making in patients for whom susceptibility testing is not possible. In many cases, the clinician may fear presence of resistance in case of worsening of clinical or diagnostic parameters after treatment with a triazole even with negative or absent resistance tests. Because of difficulty in establishing triazole-resistance or sensitivity, the clinical suspicion of resistance is becoming an important reason to abstain from further treatment with triazoles and opting for LAmB instead. Fortunately, more possibilities to detect resistance have become available. The impact of resistance testing of invasive aspergillosis using PCR is expected to more effectively guide the clinician in the optimal choice of therapy (32) and is being evaluated in a prospective multicentre study in the Netherlands and Belgium (NCT03121235).

Renal toxicity

Since the introduction of (conventional) amphotericin B as treatment of fungal infections, nephrotoxicity has been a major concern. Nevertheless, nephrotoxicity has significantly decreased after the introduction of the liposomal formulation of amphotericin B (33-36). In particular, patients that need prolonged therapy and are exposed to

high doses over a prolonged period of time are vulnerable for the development of renal adverse events. A decrease in dosage could also be beneficial in mitigating the drug-related renal toxicity. However, nephrotoxicity occurring at the end of the anticipated therapy period has been a reason to stop antifungal treatment prematurely and instead evaluate the natural course of the disease. Importantly, the associated nephrotoxicity was reversible in the majority of cases after cessation of therapy or dose alteration. The occurrence and time course of nephrotoxicity did differ from literature describing patients with daily dosing (37-39). Additionally, some experience in the assessment of the safety of the use of LAmB in an outpatient setting is previously described by Malani et al in 2005 (27). The authors of this study also found high rates of nephrotoxicity; the results are nonetheless not directly comparable due to their inclusion of application of non-lipid formulations of amphotericin B. The mentioned literature reports generally lower rates of reversibility of nephrotoxicity and shorter duration until occurrence of nephrotoxicity. However, a recent study also reports a high rate of reversibility of nephrotoxicity after use of LAmB (40). Possibly, our data supports the theory that nephrotoxicity occurs later and has a higher probability to be reversible when applying LAmB in an intermittent dosing schedule.

Application of OPAT strategies are slowly expanding within the field of infectious diseases and are being implemented in regular practice. Similar to LAmB, intravenous vancomycin therapy is also associated with renal toxicity but has nonetheless been successfully implemented in an OPAT programme for many years now (16, 17). Despite early reluctance, the expected logistic and toxicity-related disadvantages (41, 42) are outweighed by the advantages of a decrease in hospital stay with similar therapeutic effectiveness thanks to the implementation of monitoring of toxicity and therapeutic drug monitoring (15, 17, 43).

Study strengths and limitations.

Despite a nation-wide inquiry, only a small subset of adult patients treated for IFI have been identified. The means by which these patients have been selected to undergo OPAT is inherently biased, i.e. the decision of the clinician to apply this therapeutic strategy has been dependent on many factors, both known and unknown. Since no guideline refers to or advises OPAT with LAmB, and due to lack of supportive literature, physicians may only have elected this approach in specific situations. Additionally, lack of existing intra- or extramural infrastructure to apply OPAT could be a limiting factor. Due to this selection, presumably patients with a relatively favourable prognosis with regard to the IFI were included in our study. Also, the heterogeneity of both the patient population and the different dosings that have been used make it difficult to draw any hard conclusions about efficacy and tolerability. As it is impossible to adjust for all of these factors, the results of our study cannot be directly compared with other cohorts

of patients with IFI. However, the baseline variables that have been presented, summarize the most important characteristics, possibly contributing to identifying potentially eligible patients for this treatment strategy. Only patients with an initial response to therapy with LAmB showing no or only mild prior adverse events related to LAmB use were subjected to this strategy. Hence, the involved physicians balanced the risks of inadequate treatment of invasive fungal disease against the advantages of treatment in the outpatient setting. For future adaptation of this strategy, it is important for the clinician to weigh these factors before deciding on applying OPAT with LAmB.

SUMMARY AND CONCLUSIONS

After documentation of an initial treatment response and in a selected patient group, intermittent therapy with LAmB in the outpatient setting appeared to be a valuable treatment option for IFI. Frequent monitoring of renal function and potassium levels, for example once every week, is strongly recommended for early recognition of nephrotoxicity, as it can also occur during prolonged OPAT. This treatment strategy is expected to provide advantages in costs, decrease of hospital-associated infections and patient's quality of life. Further research will be necessary to expand upon the possibilities that this treatment strategy offers. The identification of eligible patient populations that would most benefit from this strategy as well as further study of the toxicity concerns in this setting, are warrented.

Contributions

RP, AS and RD performed the data collection. RP wrote the first draft of the manuscript. RP, JW and MB were involved in the concept and design of the study. MB, BR, RB and IS acted as local main investigators in their respective centers and provided the data. Analyses were performed by RP in collaboration with MB. All authors critically revised all drafts of the manuscripts and approved the final version.

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