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Outpatient parenteral antifungal therapy (OPAT) for invasive fungal infections with intermittent dosing of liposomal amphotericin B

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Abstract

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). All adult patients treated with LAmB with a 2 or 3 times weekly administration via the outpatient departments in four academic tertiary care centers 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. In total, 18 patients were included. The most frequently used regimen (67%) was 5 mg/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 favorable 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 one patient only. The 100-day mortality and 1-year mortality after initiation of OPAT were 0% and 6%, respectively. 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.

Key words: Invasive fungal infection, liposomal amphotericin B, outpatient parenteral antibiotic treatment, triazole resistance, antifungal stewardship.

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 favorable adverse event profile compared to conventional formulations of amphotericin B and it is rarely associated with renal toxicity.[4,5] Nevertheless, 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, for example, *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 dismissal from the hospital during intravenous treatment; however, often the treatment duration is long and exceeds the period of necessity of hospitalization for clinical reasons.[1,2] The practical limitations of daily intravenous treatment are evident. Reduction of duration of hospital stay would be favorable 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 in 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 multicenter 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 centers 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 and 10 mg/kg. The choice to start treating with intermittent therapy with LAmB was made according to the clinical judgment 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 2 weeks.

Nephrotoxicity was defined as a >1.5 times increase of baseline serum creatinine levels resulting in an eGFR of <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 symptoms 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 were 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 data set. Kaplan-Meier curves of survival during OPAT with LAmB were constructed. The analyses were performed using STATA v. 16 (Statacorp, College Station, TX, 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 2 or 3 times a week. Triazole resistance, demonstrated by either polymerase chain reaction (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 the median age was 60 years. Fourteen patients (78%) had a hematological 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. (three patients), *Fusarium* spp. (two patients), and a combination of both *Aspergillus* and *Mucor* (one 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 3 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 data set had normalized renal functions after decreasing of dosage or cessation of LAmB therapy. Severe hypokalaemia (<2.5 mmol/l) was not observed during treatment with LAmB in an intermittent scheme. Oral substitution of potassium had been applied in two cases. Potassium levels raised to normal levels during treatment in one of these patients and soon after the end of intermittent treatment in the other patient.

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 out of 18 patients, 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 three patients). Readmission to the hospital was necessary due to factors related to the infection (three patients) or to LAmB-related nephrotoxicity (one patient). Figure 1 shows the survival rates of all patients in a Kaplan Meier analysis since start of OPAT. Figure 2 shows the time until resolution of infection. Figure 3 shows the time until nephrotoxicity occurred during intermittent treatment.

Table 1. Patient characteristics.

Total number of patients	18
Patient characteristics	
Sex, male (%)	9 (50)
Age, median (range)	60 (18–78)
Underlying predisposing disease, number of patients (%)	
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 patients (%)*	
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 patients (%)	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	10 (56)
Of which	
– 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)
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 patients (%)	7 (39)
100-day mortality after start of OPAT, number of patients (%)	0 (0)
1-year mortality after start of OPAT number of patients (%)	1 (6)
Resolution of infection,‡ number of patients (%)	13 (72)

ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CGD, chronic granulomatous disease; CLL, chronic lymphatic leukemia; COPD, chronic obstructive pulmonary disease; CT, computed tomography; HSCT, hematopoietic stem cell transplantation; IA, invasive aspergillosis; LAmB, liposomal amphotericin B; MDS-RAEB2, myelodysplastic syndrome with refractory anemia with excess blasts-2; PCR, polymerase chain reaction.

*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 <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: two patients treated with 6 mg/kg 3 times weekly and one patient treated with 5 mg/kg 3 times/week were switched to 3 mg/kg 3 times weekly. Of two patients treated with 3 mg/kg 3 times/week, one was switched to 3 mg/kg 2 times/week and one patient was switched to 2 mg/kg 3 times/week. Kidney function normalized in all five patients.

‡Resolution of infection defined as clinically observed absence of symptoms 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. CT, computed tomography; OPAT, outpatient antifungal therapy.

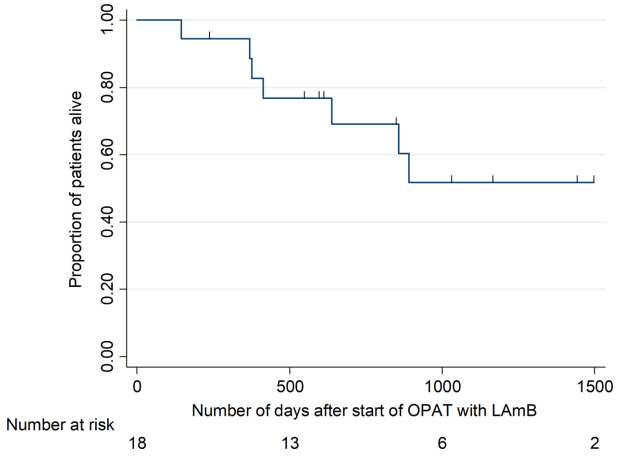

Figure 1. Overall survival from start of intermittent treatment. Censored cases were lost to follow-up. LAmB, liposomal amphotericin B; OPAT, outpatient antifungal therapy.

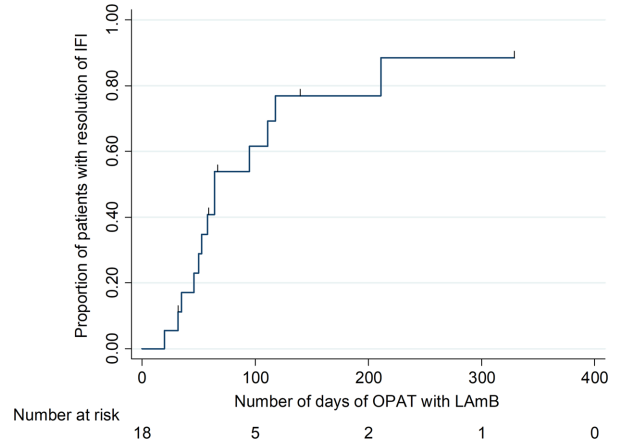

Figure 2. Time to resolution of IFI after start of intermittent therapy. Censored cases stopped intermittent treatment before resolution of infection. Resolution of IFI was defined as clinically observed absence of symptoms that are likely to be caused by IFI in combination with findings concordant with resolution of IFI on high-resolution CT scan. IFI, invasive fungal infection; LAmB, liposomal amphotericin B; OPAT, outpatient antifungal therapy.

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

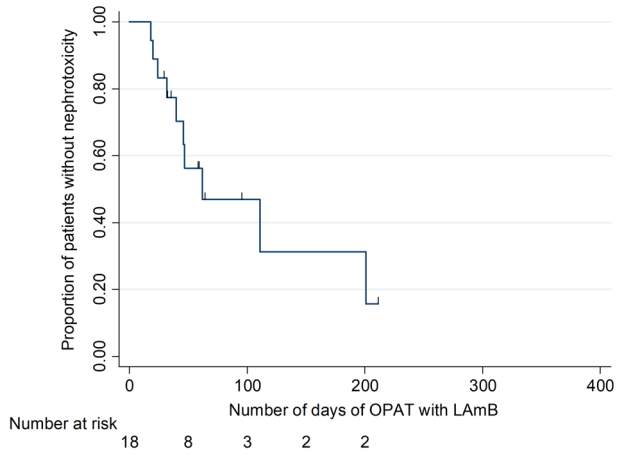

Figure 3. Occurrence of nephrotoxicity from start of intermittent treatment. Censored cases stopped intermittent treatment before nephrotoxicity occurred. Nephrotoxicity was defined as a >1.5 times increase of baseline serum creatinine levels resulting in an eGFR of < 40 ml/min/1.73 m^2 during treatment 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. LAmB, liposomal amphotericin B; OPAT, outpatient antifungal therapy.

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 program 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, that is, 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 favorable 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.

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 warranted.

Contributions

R.P., A.S., and R.D. performed the data collection. R.P. wrote the first draft of the manuscript. R.P., J.W., and M.B. were involved in the concept and design of the study. M.B., B.R., R.B., and I.S. acted as local main investigators in their respective centers and provided the data. Analyses were performed by R.P. in collaboration with M.B. All authors critically revised all drafts of the paper and approved the final version.

Declaration of interest

A.S. reports nonfinancial support from Abvie, Roche, Pfizer, and Gilead, outside the submitted work. R.V.D. reports nonfinancial support from Pfizer, Inc., nonfinancial support from Gilead Sciences, outside the submitted work. I.S. reports nonfinancial support from Pfizer, personal fees from Pfizer, outside the submitted work. R.J.B. reports grants, consultation, and speaker fees from Gilead, MSD, F2g, Amplyx, and Pfizer during the conduct of the study, outside the submitted work. All other authors report no conflicts of interest. All of the authors are responsible for the content and the writing of the paper.

References

1. Patterson TF, Thompson GR, Denning DW et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 63: e1–e60.
2. Panackal AA, Bennett JE, Williamson PR. Treatment options in invasive aspergillosis. *Curr Treat Options Infect Dis*. 2014; 6: 309–325.
3. Girmenia C, Iori AP. An update on the safety and interactions of antifungal drugs in stem cell transplant recipients. *Expert Opin Drug Saf*. 2017; 16: 329–339.
4. Herbrecht R, Denning DW, Patterson TF et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002; 347: 408–415.
5. Herbrecht R, Patterson TF, Slavin MA et al. Application of the 2008 definitions for invasive fungal diseases to the trial comparing voriconazole versus amphotericin B for therapy of invasive aspergillosis: a collaborative study of the Mycoses Study Group (MSG 05) and the European Organization for Research and Treatment of Cancer Infectious Diseases Group. *Clin Infect Dis*. 2015; 60: 713–720.
6. Vermeulen E, Lagrou K, Verweij PE. Azole resistance in *Aspergillus fumigatus*. *Curr Opin Infect Dis*. 2013; 26: 493–500.
7. van der Linden JWM, Arendrup MC, Warris A et al. Prospective multicenter international surveillance of azole resistance in *Aspergillus fumigatus*. *Emerg Infect Dis*. 2015; 21: 1041–1044.
8. Chowdhary A, Sharma C, Kathuria S, Hagen F, Meis JF. Prevalence and mechanism of triazole resistance in *Aspergillus fumigatus* in a referral chest hospital

in Delhi, India and an update of the situation in Asia. *Front Microbiol*. 2015; 6: 428.
9. Steinmann J, Hamprecht A, Vehreschild MJGT et al. Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany. *J Antimicrob Chemother*. 2015; 70: 1522–1526.
10. Seyedmousavi S, Hashemi SJ, Zibafar E et al. Azole-resistant *Aspergillus fumigatus*, Iran. *Emerg Infect Dis*. 2013; 19: 832–834.
11. Lestrade PPA, Meis JF, Melchers WJG, Verweij PE. Triazole resistance in *Aspergillus fumigatus*: recent insights and challenges for patient management. *Clin Microbiol Infect*. 2019; 25: 799–806.
12. Verweij PE, Ananda-Rajah M, Andes D et al. International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. *Drug Resist Updat*. 2015; 21: 30–40.
13. Nucci M, Anaissie EJ, Queiroz-Telles F et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. *Cancer*. 2003; 98: 315–319.
14. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J, Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis*. 2009; 48: 1743–1751.
15. Bernard L, El-hajj, Pron B et al. Outpatient parenteral antimicrobial therapy (OPAT) for the treatment of osteomyelitis: evaluation of efficacy, tolerance and cost. *J Clin Pharm Ther*. 2001; 26: 445–451.
16. Keller SC, Williams D, Gavgani M et al. Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2018; 66: 11–19.
17. Muldoon EG, Switkowski K, Tice A, Snydman DR, Allison GM. A national survey of infectious disease practitioners on their use of outpatient parenteral antimicrobial therapy (OPAT). *Infect Dis (Lond)*. 2015; 47: 39–45.
18. Lehrnbecher T, Bochennek K, Klingebiel T, Gastine S, Hempel G, Groll AH. Extended dosing regimens for fungal prophylaxis. *Clin Microbiol Rev*. 2019; 32: e00010–19.
19. Adler-Moore J, Lewis RE, Brüggemann RJM, Rijnders BJA, Groll AH, Walsh TJ. Preclinical safety, tolerability, pharmacokinetics, pharmacodynamics, and antifungal activity of liposomal amphotericin B. *Clin Infect Dis*. 2019; 68: S244–S259.
20. Groll AH, Rijnders BJA, Walsh TJ, Adler-Moore J, Lewis RE, Brüggemann RJM. Clinical pharmacokinetics, pharmacodynamics, safety and efficacy of liposomal amphotericin B. *Clin Infect Dis*. 2019; 68: S260–S274.
21. [Web page] 11 may 2019]; Available at: https://www.astellas.us/docs/ambisome.pdf.
22. Walsh TJ, Lewis RE, Adler-Moore J. Pharmacology of liposomal amphotericin B: an introduction to preclinical and clinical advances for treatment of life-threatening invasive fungal infections. *Clin Infect Dis*. 2019; 68: S241–S274.
23. Adler-Moore JP, Olson JA, Proffitt RT. Alternative dosing regimens of liposomal amphotericin B (AmBisome) effective in treating murine systemic candidiasis. *J Antimicrob Chemother*. 2004; 54: 1096–1102.
24. Smith PJ, Olson JA, Constable D, Schwartz J, Proffitt RT, Adler-Moore JP. Effects of dosing regimen on accumulation, retention and prophylactic efficacy of liposomal amphotericin B. *J Antimicrob Chemother*. 2007; 59: 941–951.
25. Stone NR, Bicanic T, Salim R, Hope W. Liposomal amphotericin B (AmBisome[R]): a review of the pharmacokinetics, pharmacodynamics, clinical experience and future directions. *Drugs*. 2016; 76: 485–500.
26. Cordonnier C, Mohty M, Faucher C et al. Safety of a weekly high dose of liposomal amphotericin B for prophylaxis of invasive fungal infection in immunocompromised patients: PROPHYSOME Study. *Int J Antimicrob Agents*. 2008; 31: 135–141.
27. Malani PN, DePestel DD, Riddell J, Bickley S, Klein LR, Kauffman CA. Experience with community-based amphotericin B infusion therapy. *Pharmacotherapy*. 2005; 25: 690–697.
28. Official website of the Dutch Belgian Mycoses Study Group. Available at: https://dbmsg.nl/.
29. De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; 46: 1813–1821.
30. Verweij PE, Snelders E, Kema GHj, Mellado E, Melchers WJG. Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use? *Lancet Infect Dis*. 2009; 9: 789–795.
31. Jensen RH, Hagen F, Astvad KMT, Tyron A, Meis JF, Arendrup MC. Azole-resistant *Aspergillus fumigatus* in Denmark: a laboratory-based study on resistance mechanisms and genotypes. *Clin Microbiol Infect*. 2016; 22: 570.e1–9.
32. van de Peppel RJ, van der Beek MT, Visser LG, de Boer MGJ, Wallinga J. Managing invasive aspergillosis in haematological patients in the era of resistance polymerase chain reaction and increasing triazole resistance: a modelling study of different strategies. *Int J Antimicrob Agents*. 2019; 53: 284–293.
33. Giannella M, Ercolani G, Cristini F et al. High-dose weekly liposomal amphotericin B antifungal prophylaxis in patients undergoing liver transplantation. *Transplantation*. 2015; 99: 848–854.
34. Moreau P, Milpied N, Fayette N, Ramée J-F, Harousseau JL, Reduced renal toxicity and improved clinical tolerance of amphotericin B mixed with intralipid compared with conventional amphotericin B in neotropenic patients. *J Antimicrob Chemother*. 1992; 30: 535–541.
35. Schoffski P, Freund M, Wunder R et al. Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study. *BMJ*. 1998; 317: 379–384.
36. Sorkine P, Nagar H, Weinbroum A et al. Administration of amphotericin B in lipid emulsion decreases nephrotoxicity. *Crit Care Med*. 1996; 24: 1311–1315.
37. Kato H, Hagihara M, Yamagishi Y et al. The evaluation of frequency of nephrotoxicity caused by liposomal amphotericin B. *J Infect Chemother*. 2018; 24: 725–728.
38. Steimbach LM, Tonin FS, Virtuoso S et al. Efficacy and safety of amphotericin B lipid-based formulations: a systematic review and meta-analysis. *Mycoses*. 2017; 60: 146–154.
39. Tonin FS, Steimbach LM, Borba HH et al. Efficacy and safety of amphotericin B formulations: a network meta-analysis and a multicriteria decision analysis. *J Pharm Pharmacol*. 2017; 69: 1672–1683.
40. Personett HA, Kayhart BM, Barreto EF et al. Renal recovery following liposomal amphotericin B-Induced nephrotoxicity. *Int J Nephrol*. 2019; 2019: 8629891.
41. Norton K, Ingram PR, Heath CH, Manning L. Risk factors for nephrotoxicity in patients receiving outpatient continuous infusions of vancomycin in an Australian tertiary hospital. *J Antimicrob Chemother*. 2014; 69: 805–808.
42. Ingram PR, Lye DC, Fisher DA, Goh W-P, Tam VH. Nephrotoxicity of continuous versus intermittent infusion of vancomycin in outpatient parenteral antimicrobial therapy. *Int J Antimicrob Agents*. 2009; 34: 570–574.
43. Norris AH, Shrestha NK, Allison GM et al. 2018 Infectious Diseases Society of America clinical practice guideline for the management of outpatient parenteral antimicrobial therapy. *Clin Infect Dis*. 2019; 68: 1–4.