Adherence to recommendations for the use of antifungal agents in a tertiary care hospital

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Objecitves: The aim of our study was to assess the adherence to labelling and international guidelines for antifungal prescribing.

Methods: A retrospective study was performed in intensive care units in addition to the oncology and haematology department, which covered 70% of antifungal consumption at Hautepierre Hospital, Strasbourg, France. On reviewing medical charts, the antifungal prescription was examined in relation to the recommendations of indication, dosage, risk of drug–drug interactions and, where appropriate, antifungal susceptibility testing. Treatments were considered appropriate, inappropriate or debatable.

Results: Between January and April 2007, 199 treatments were given for 179 different episodes in 133 adult patients. Treatments were prescribed for pre-emptive or targeted therapy (n=90, with 60 for candidiasis, 26 for aspergillosis and 4 for other mould diseases), empirical therapy (n=17) and primary (n=81) or secondary (n=11) prophylaxis. Fluconazole accounted for 67% of prescriptions, followed by voriconazole (19%), caspofungin (10%), posaconazole (2%), conventional or liposomal amphotericin B (2%), itraconazole (<1%) and terbinafine (<1%). Indication and dosage were found to be appropriate in 65% and 62% of cases, inappropriate in 22% and 21%, and debatable in 13% and 17%, respectively. The overall (by combining all assessment criteria) rate of inappropriate use was 40%. The overall survival rate at 12 weeks was highest in patients receiving appropriate therapy (81% versus 72% and 68% in the debatable and inappropriate therapy groups, respectively), with between-group differences not being significant (P=0.49).

Conclusions: Our evaluation revealed a high proportion of inappropriate or debatable use of antifungal agents, while highlighting significant issues, such as inadequate dosage or indications.

Keywords: aspergillosis, candidiasis, guidelines, invasive fungal infections, antifungal therapy

Introduction

Over the last decade, several new antifungal agents active against invasive fungal diseases have been developed, including lipid formulations of amphotericin B, newer azoles and echinocandins. These agents differ in terms of their spectrum of action, clinical efficacy, tolerance, potential drug–drug interactions and route of administration. The availability of these new agents has important implications on patient care. Overall, both safety and efficacy have been improved, with the availability of more agents facilitating the use of new strategies, such as prophylactic, empirical, pre-emptive and targeted therapy. In order to help clinicians use antifungal agents properly, international guidelines have been developed for the treatment of the most common invasive fungal diseases.1–9

With the availability of a greater number of antifungal agents, antifungal treatment is not always optimally prescribed. The inappropriate use of antifungal agents may lead to a variety of adverse outcomes, including unnecessary exposure to medications, persistent infections, increased costs and overall increase
in antifungal resistance. Few studies have assessed the appropriateness of antifungal use in the setting of new agents. Therefore, we undertook a retrospective study of systematic antifungal use in medical and surgical intensive care units in addition to an oncology, haematology and haematopoietic stem cell transplantation (HSCT) department in a tertiary care hospital in Strasbourg, France. The study aimed to assess whether the treatment of invasive fungal diseases in Hautepierre Hospital adhered to labelling and international guidelines of the Infectious Diseases Society of America (IDSA) and European Conference on Infections in Leukemia (ECIL). We carried out a comprehensive evaluation of systemic antifungal therapy in clinical practice in order to determine whether adherence to recommendations was associated with improved clinical outcome.

Patients and methods

Our retrospective study was performed on adult patients in the medical intensive care unit (27 beds), surgical intensive care unit (18 beds) and oncology and haematology department (76 beds, including a 30 bed unit with high-efficiency particulate air (HEPA)-filtered air and positive air pressure, and a 5 bed unit with laminar air flow rooms for myeloblastic antileukemic HSCT). These departments covered 70% of antifungal consumption at Hautepierre Hospital, Strasbourg, a tertiary care 1021 bed hospital. A list of all patients aged ≥18 years who were prescribed a systemic antifungal agent between January and April 2007 was obtained from the inpatient pharmacy database. All consecutive inpatients who were given a systemic antifungal agent (amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B lipid complex, fluconazole, oral itraconazole, voriconazole, posaconazole, caspofungin, terbinafine and fluconosine) were included in the study. Micafungin and anidulafungin were not available in Hautepierre Hospital at the time of the study, while amphotericin B colloidal dispersion and intravenous itraconazole were not marketed in France. Patients receiving topical antifungal drugs or treatments for skin or nail fungal infections were excluded from the study. The Quality Control Board of the University Hospital of Strasbourg approved the study.

Data collection

A retrospective chart review was performed in order to collect the following data: (i) patient characteristics: age, gender, medical history, underlying condition, immune status, use of corticosteroids or other immunosuppressive agents, presence of a central venous line, parenteral nutrition and biological parameters (i.e. kidney and liver function tests, and white blood cell and neutrophil counts); (ii) fungal disease characteristics: clinical and radiological signs, microbiological data, including microscopic and histopathological findings, culture and susceptibility test results, and serological test results (i.e. Aspergillus galactomannan, Candida mannan and antimanann antibodies, and Cryptococcus antigen); (iii) antifungal therapy: indication for antifungal prescription, start and stop dates, dosage, including loading and maintenance doses, frequency and route of administration, serum level monitoring and concomitant medication; and (iv) admission and discharge dates, response to antifungal therapy and survival status.

Therapeutic strategies

Antifungal prescriptions were classified as prophylactic, empirical, pre-emptive or targeted therapy following the classification proposed by Herbrecht and Bercerou.

In short, prophylactic treatment was defined as treatment initiated in patients at high risk of invasive fungal disease, but without any signs or symptoms of fungal disease and with negative mycological results based on a significant sample.

In neutropenic patients, empirical therapy was defined as treatment initiated in the case of persistent fever despite broad-spectrum antibacterial therapy, without any signs and symptoms of invasive fungal disease and in the absence of positive mycological results. In non-neutropenic patients, empirical therapy was defined as treatment initiated in febrile critically ill patients with risk factors for invasive candidiasis, in the absence of any other known cause of fever.

Pre-emptive therapy was defined as an early treatment based on proposals by Segal et al., Eggimann and Ostransky-Zeichner and Playford et al. Pre-emptive therapy aimed to treat a suspected early invasive fungal disease by using clinical or radiological data and/or laboratory markers to define the likelihood of the invasive fungal disease. The episodes were then classified as: (i) possible invasive fungal disease as defined by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria for cancer patients, allogeneic HSCT recipients and other severely immunosuppressed patients; and (ii) uncertain invasive fungal disease in cancer patients, allogeneic HSCT recipients and other severely immunosuppressed patients with signs and symptoms that were insufficient to identify a possible invasive fungal disease, but without any other known cause or in patients without host criteria as defined by EORTC/MSG and clinical or radiological signs suggestive of invasive fungal disease.

Targeted therapy was defined as treatment given for a probable invasive fungal disease in cancer patients, allogeneic HSCT recipients and other severely immunosuppressed patients as classified by EORTC/MSG for cancer patients and by the American Society of Transplantation for solid organ transplant recipients. In addition, targeted therapy included patients with proven invasive fungal disease according to EORTC/MSG criteria, irrespective of the underlying condition.

Recommendations and guidelines

The recommendations used to assess the adherence to antifungal prescribing were the labelling of each antifungal agent approved by the European Medicines Agency in addition to the international guidelines proposed by the ECIL and IDSA for Aspergillus, Candida and Cryptococcus infections. The guidelines available during the treatment period were the primary references. IDSA guidelines were used for non-haematological patients, and ECIL recommendations for haematological patients and HSCT recipients. Updated guidelines presented at major congresses or published in part on web sites prior to full paper publication were also accepted as potential references.

Antifungal therapy assessment criteria

Each antifungal treatment was jointly assessed by a physician who was not involved in the prescription and a pharmacist. Antifungal therapy indication was classified as appropriate if given in accordance with labelling or international guidelines. In all other cases, the prescription was assessed as debatable or inappropriate (Table 1). The appropriateness of antifungal therapy was assessed during the initial phase of treatment after identifying the fungal pathogen and receiving the results of susceptibility tests, and in cases of any new hepatic or renal failure. The assessment criteria used to define the appropriateness of antifungal prescriptions were the indication, dosage and presence of drug–drug interactions or contraindications.

Statistical analysis

Anonymized collected data were first entered into a relational database (Microsoft Excel 2000, Seattle, WA, USA). The outcome was assessed as the 12 week survival. Most patients were followed for 12 weeks.
Eighteen were lost to follow-up before 12 weeks and were censored for survival at the time of loss to follow-up. Survival was defined from the first day of antifungal therapy until death, loss to follow-up or a maximum of 12 weeks and analysed using GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). Analysis was performed according to the Kaplan–Meier method. Curves were compared using the log-rank test in order to estimate the difference between appropriate, debatable and inappropriate therapy. P values, 0.05 were considered to be statistically significant. Cause of death was assessed using the criteria defined by Nivoix et al.18

### Results

Between January and April 2007, 199 treatments were given for 179 different episodes in 133 patients. Patients were primarily hospitalized in the oncology and haematology department (n=82, 62%), followed by the medical intensive care unit (n=26, 20%) and surgical intensive care unit (n=25, 19%).

### Patient characteristics

The majority of patients were male (n=86, 65%), with a mean age of 60 years (range: 18–99 years) and mean weight of 76 kg (range: 37–120 kg). Mean creatinine clearance was 71 mL/min (range: 11–163 mL/min), calculated using the Cockcroft and Gault equation, with 28 (14%) cases presenting creatinine clearance <30 mL/min. All patients had haematological malignancy, HSCT or solid organ transplantation, or single or multiple organ failure. Underlying conditions and associated risk factors for fungal infection are summarized in Table 2.

### Indications for antifungal use

Overall, 16 episodes fulfilled the criteria for proven invasive fungal disease, with 13 cases of candidiasis, including 1 with concomitant probable pulmonary aspergillosis, 2 cases of aspergillosis and 1 case of fusariosis. In addition, 12 episodes fulfilled the criteria for probable infection, with 11 cases of aspergillosis and 1 case of mucormycosis. Six episodes were classified as possible pulmonary fungal diseases according to EORTC/MSG criteria.

In total, 38 cases of infections were classified as uncertain invasive fungal disease without fulfilling EORTC/MSG criteria for possible infection, but with pre-emptive antifungal therapy being initiated. All of these patients presented clinical or

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**Table 1. Assessment of antifungal therapy**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
<th>Drug–drug interactions</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate</td>
<td>in accordance with SPC and/or with guidelines and adapted to mycological data</td>
<td>appropriate dose$^a$ or under- or overdose by $\leq$10% and respect of loading dose when recommended</td>
<td>no concomitant drug with potential of clinically significant drug–drug interaction or concomitant drug with possibly mild to moderate consequences, but close clinical and biological monitoring and appropriate dose adjustment when required</td>
</tr>
<tr>
<td>Debatable choice of antifungal not recommended by SPC or guidelines, but based on published clinical data, evolving clinical experience or absence of appropriate alternative</td>
<td>under- or overdose$^b$ by $\leq$25% and/or absence of loading dose and/or no discontinuation or dose adjustment in the case of grade $\geq$2 clinically or biologically related adverse events</td>
<td>concomitant drug with possibly mild to moderate consequences, but no adequate clinical and biological monitoring or no dose adjustment when required</td>
<td></td>
</tr>
<tr>
<td>Inappropriate choice based on SPC, guidelines or mycological results with existence of an appropriate alternative</td>
<td>under- or overdose$^b$ by $&gt;25$% and/or no discontinuation or dose adjustment in the case of grade $&gt;2$ clinically or biologically related adverse events when an appropriate alternative is available and/or lack of therapeutic drug monitoring when required and when serum level management was locally available</td>
<td>concomitant drug with potential severe consequences, including failure of antifungal therapy and/or combination of two antifungals of the same class</td>
<td>contraindication according to SPC</td>
</tr>
</tbody>
</table>

$^a$According to SPC or guidelines, including dose adjustment according to renal and hepatic functions.
Antifungal treatment

Among the 199 antifungal agents prescribed, 193 (97%) were given as monotherapy and 6 as combination therapy. In addition, 157 (88%) episodes were treated with one line of therapy, 19 with two lines and 1 with three lines. Treatments were prescribed for targeted therapy (n=42), pre-emptive therapy (n=48), empirical therapy (n=17) and primary (n=81) or secondary (n=11) prophylaxis, with 100 antifungal therapies (50%) being administered orally. Median treatment duration was 16 days (range: 1 to >100 days).

Fluconazole accounted for 133 (67%) prescriptions, followed by voriconazole (n=37, 19%), caspofungin (n=19, 10%), posaconazole (n=4, 2%), liposomal amphotericin B (n=3, 2%), amphotericin B deoxycholate (n=1, <1%), itraconazole (n=1, <1%) and terbinafine (n=1, <1%). The combination therapies used were caspofungin and liposomal amphotericin B (one case), caspofungin and fluconazole (one case), and voriconazole and terbinafine (one case of disseminated fusariosis).

Assessment of appropriateness

Indication and antifungal choice

Antifungal choice was found to be appropriate in 130 (65%) cases (Table 3). In addition, 26 (13%) prescriptions of antifungal therapy were classified as debatable as follows: prophylactic treatment with fluconazole in high-risk patients (nine autologous HSCT and four gastrointestinal surgery patients), empirical therapy with fluconazole (six non-neutropenic and five neutropenic patients in the intensive care units) and pre-emptive treatment with voriconazole (two suspicious cases of invasive candidiatis in patients colonized by fluconazole-susceptible strains).

In total, 43 (22%) prescriptions were considered as inappropriate for the following reasons: (i) primary prophylaxis with fluconazole in 19 haematological malignancy patients with unexpectedly prolonged neutropenia after cytotoxic chemotherapy; (ii) secondary prophylaxis with fluconazole in 1 patient following prior fluconazole-resistant infection; (iii) empirical therapy with fluconazole in 2 neutropenic patients with haematological malignancy and with voriconazole in 1 intensive care patient; (iv) pre-emptive therapy in 11 patients, including 2 patients receiving caspofungin for primary treatment of a possible aspergillosis, 8 patients receiving fluconazole for an uncertain *Candida glabrata* infection and 1 patient receiving voriconazole for an uncertain *C. glabrata* urinary tract infection with resistance to fluconazole and voriconazole previously demonstrated in vitro; and (v) targeted therapy in 9 patients, including 5 patients treated with first-line caspofungin for probable or proven aspergillosis and 3 treated with fluconazole for a documented *C. glabrata* or *Candida krusei* infection.

Dosage

Overall, antifungal dose was considered appropriate in 124 (62%) of the 199 prescriptions (Table 3). However, 33 (17%) antifungal therapies were classified as debatable for the following reasons: disregard for the recommended loading dose in 28 prescriptions (fluconazole=13, voriconazole=6 and caspofungin=3), underdosage by 10%–25% in 7 cases (voriconazole=6 and caspofungin=1) and overdosage by 10%–25% in 4 cases (voriconazole=4).

Overall, 42 (21%) prescriptions were deemed inappropriate for the following reasons: (i) lack of dose adjustment for renal function (13 prescriptions of fluconazole) and hepatic function (1 prescription of caspofungin); and (ii) under- or overdosage by >25% of the recommended dose in 28 prescriptions (fluconazole as prophylaxis at <400 mg daily in 11 autologous HSCT patients; fluconazole for empirical or pre-emptive therapy at a low dose in 9 patients; voriconazole at a fixed dose unadjusted for body weight in 4 patients; posaconazole as prophylaxis at 800 mg daily instead of 600 mg daily in 2 patients; itraconazole at a very low dosage of 100 mg daily in 1 patient without therapeutic drug monitoring to assess adequate serum concentration; and terbinafine overdosage in 1 patient according to a previous clinical trial).
Among the 62 (31%) cases with renal dysfunction, only 46 (74%) received the appropriate dosage, with lack of dose adjustment to renal function mostly relating to fluconazole therapy.

**Drug–drug interactions and contraindications**

The prescription of concomitant medication possibly leading to severe drug–drug interactions was found in three (2%) cases: one combination of rifampicin and voriconazole, and two combinations of antifungal treatments of the same class involving voriconazole and fluconazole taken for 2 days by one patient and itraconazole and fluconazole taken for 13 days by another patient. Eight prescriptions classified as debatable involved concomitant administration of omeprazole and voriconazole, with no dose adjustment of omeprazole. No contraindications were recorded in the patient medical records.

**Overall appropriateness**

The overall incidence of appropriate use was 34% (Table 3). Inappropriate antifungal therapy mostly related to fluconazole therapy.

**Survival**

In total, 40 (30%) deaths were reported during hospitalization. Causes of death were concomitant disease in 31 cases, underlying conditions in 6 and fungal infection in 3. The overall survival rate at 12 weeks was highest in patients receiving appropriate therapy, being 81% versus 72% and 68% in the debatable and inappropriate therapy groups, respectively (Figure 1). The between-group differences were not statistically significant 

\( P=0.49 \). Survival curves were not significantly different 

\( P=0.26 \) when analysis was restricted to patients receiving targeted, empirical or pre-emptive therapy.

**Discussion**

To date, only a small number of studies have assessed the use of antifungal agents. In 1996, Gutiérrez et al. undertook an audit of systemic antifungal usage at a tertiary care university hospital in the UK. At the time of their study, the antifungal armamentarium was still limited, with the authors assessing the therapeutic appropriateness of amphotericin B deoxycholate, liposomal amphotericin B, flucytosine, fluconazole, itraconazole, ketoconazole and miconazole. Therapy was considered to be unconventional in 27% of courses and 41% of regimens, mainly due to the indication or duration of treatment not conforming to conventional practice. In their conclusion, the authors highlighted the need for consensus recommendations in order to aid physicians in improving their prescriptions.

At present, some of the agents included in the study of Gutiérrez et al. are no longer available or are used only rarely, while others have since been developed. New agents, such as voriconazole, posaconazole, caspofungin, micafungin and anidulafungin, are widely used because of their increased efficacy and tolerability. In addition, guidelines have been elaborated by national and international societies or expert committees. In 2007, Pavese et al. assessed the adequacy and conformity of 203 prescriptions of liposomal amphotericin B, caspofungin and voriconazole based on marketing authorization, national recommendations and scientific data. Treatment indications were found to be appropriate for 127 (63%) prescriptions.
In contrast to most published studies, we analysed the appropriateness of loading and maintenance doses, including assessment was extensive and took into account the indication, agents in a tertiary care university hospital. In addition, our assessment cases. In 2009, Raymonds et al. conducted an audit of 118 prescriptions of liposomal amphotericin B, voriconazole and caspofungin in order to assess guideline compliance. The overall rate of conformity was 54%, with antifungal drug being justified in 113 (96%) prescriptions. In 30% of the cases, a cheaper, more efficient or less toxic alternative could have been administered instead. The loading and maintenance doses were correct in 80% and 92% of the cases, respectively. In addition, the authors noted overprescription of caspofungin and, in five paediatric cases, insufficient dosage of voriconazole. Other assessments of antifungal therapy were limited to the treatment of a specific fungal infection, such as candidaemia, and targeted a single medical unit or a particular therapy, e.g. fluconazole. In our study, however, all systemic antifungal prescriptions were assessed in three departments (oncology and haematology, medical intensive care and surgical intensive care), covering 70% of all prescriptions of systemic antifungal agents in a tertiary care university hospital. In addition, our assessment was extensive and took into account the indication, appropriateness of loading and maintenance doses, including adjustment for renal and hepatic function, adaptation to mycological results and analysis of potentially harmful drug–drug interactions.

In our study, the rate of appropriate prescriptions (34%) was far less than the figures previously reported in the scientific literature, which may be accounted for by the very stringent assessment criteria used in our analysis. In this context, a variation of >25% above or below the recommended daily dose was considered to be a major deviation, whereas previous studies either did not assess dose appropriateness or accepted variations up to 50%. In contrast to most published studies, we analysed the prescription of concomitant drugs and investigated drug–drug interactions that were potentially harmful to the patient.

Therefore, several of the criteria we deemed debatable or inappropriate were not taken into account in other studies. Yet, we strongly believe that stringent criteria are required for antifungal therapies, especially regarding drug dosage and drug–drug interactions. Insufficient exposure to the newer azoles was associated with lower response rates or breakthrough infections, while high exposure was shown to increase toxicity. The recommended dose prescription, adjustment to renal and hepatic function, and respect for concomitant drug contraindications are all critical in terms of outcome; therefore, these parameters must be strictly integrated into prescription assessments. In our opinion, for some of the azoles, monitoring of serum levels should be part of future studies, although pertinent recommendations are still lacking (e.g. IDSA guidelines for aspergillosis).

As expected, fluconazole and voriconazole were the most frequently prescribed antifungals. Fluconazole was mainly used as prophylaxis in leukaemia patients and HSCT recipients, while voriconazole was the reference treatment for invasive aspergillosis, the latter being the most common invasive fungal disease in the oncoology and haematology department and medical intensive care unit of Hautepierre Hospital. In contrast, caspofungin was more frequently used in the surgical intensive care unit, where invasive Candida diseases were the predominant fungal infections.

In our study, only 34% of the fluconazole prescriptions and 32% of the voriconazole prescriptions were deemed appropriate. The main reasons for debatable or inappropriate use of fluconazole were non-approved indications for prophylactic treatment and lack of dose reduction according to renal function. Non-approved indications resulted in an overexposure to fluconazole, thereby increasing the risk of emerging fluconazole-resistant strains. The main reasons for debatable or inappropriate use of voriconazole included the lack of loading doses on the first day of therapy and insufficient maintenance dosages (fixed dose of 200 mg twice daily for the intravenous form of voriconazole instead of 4 mg/kg twice daily).

The appropriateness rate for caspofungin was estimated at 37%. The main reasons for the inappropriate use of caspofungin included the absence of dose adjustment in patients weighing >80 kg and the use of caspofungin as first-line therapy in patients with invasive aspergillosis in the absence of contraindications to voriconazole or liposomal amphotericin B. Three cases of debatable prescriptions were related to the omission of a loading dose.

As antifungal agents are typically prescribed in high-severity settings, an inappropriate prescription may dramatically affect patient outcome. In our study, patients receiving inappropriate or debatable prescriptions of antifungal agents presented a poorer 12 week survival (70%) compared with those receiving appropriate therapy (81%), with the between-group differences in survival not being statistically significant (P=0.24). Patel et al. reported a higher infection resolution rate in patients receiving a treatment that was in accordance with the IDSA recommendations, along with a lower rate of death in those attending infectious diseases consultations. In addition, as shown by Zilberberg et al., inappropriate antifungal therapy has an impact on patient outcome: patients with inappropriate empirical antifungal therapy for candidaemia (therapy initiation
delayed >24 h or inadequate dosage) presented a higher death rate.

Our study has several limitations. Its retrospective trial design did not allow us to collect ‘in real-time’ the reasons for antifungal prescription and analyse the data according to the information available to the clinicians at the given time. For the same reason, we were not able to estimate precisely either the delay in antifungal therapy initiation, which may significantly impact invasive fungal disease outcome, or the duration of therapy. As most recommendations did not define a minimum duration of therapy, except for invasive Candida infections, this parameter was not used as a criterion in our study. Finally, in our analysis, nearly half of the treatments were given as prophylactic therapy. However, as the analysis revealed that the rate of appropriate therapy was also low (40%) in the case of prophylactic therapy, a posteriori assessment of this antifungal therapy group was justified, resulting in a higher rate of appropriateness. In the prophylactic therapy group, the main deviation was inappropriate dosage, similarly to the targeted therapy group.

Conclusions

Our evaluation revealed a high proportion of inappropriate or debatable use of antifungal agents, while highlighting significant issues, such as inadequate dosage or indications, and identifying areas for improvement. The results were presented and discussed within Hautepierre Hospital, with a separate analysis for each unit involved in the evaluation being provided to the corresponding physicians. In addition, easy access to IDSA and ECIL guidelines was made available via our hospital’s intranet. Furthermore, we recommended that for all cases of invasive fungal infections, a mycologist, an infectious diseases physician or a physician with appropriate expertise in invasive fungal diseases be consulted. Lastly, regular case report discussions were implemented in Hautepierre Hospital, with the objective of highlighting potential difficulties in treating invasive fungal diseases.

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Recommendations for antifungal agent use


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