Introduction of an antifungal stewardship programme targeting high-cost antifungals at a tertiary hospital in Cambridge, England

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Background: Antifungal stewardship aims to promote the optimal use of antifungals through the careful selection of agents based on patient profile, target organism, toxicity, costs and the likelihood of emergence and spread of resistance.

Methods: We report on an observational prospective 12 month study conducted by an antifungal stewardship team targeting the use of echinocandins (caspofungin and micafungin), voriconazole and liposomal amphotericin B in a tertiary referral hospital in the UK.

Results: One-hundred-and-seventy-three patients were reviewed on 294 occasions. Clinical advice was given and implemented during review of 45 (88.2%) of micafungin prescriptions, 70 (78.7%) of those receiving voriconazole, 78 (62.4%) of those receiving liposomal amphotericin B and 3 (27.3%) of those receiving caspofungin. Except for voriconazole, nearly half of all treatments reviewed were stopped or changed. This study found that a crude cost saving of £180000 in antifungal drugs was generated compared with the previous year.

Conclusions: Using a multidisciplinary team, antifungal stewardship can achieve significant improvements in patient management and it may reduce costs.

Keywords: voriconazole, liposomal amphotericin B, caspofungin, micafungin

Introduction

Antifungal stewardship refers to a systematic programme that promotes the optimal use of antifungals through the careful selection of agents based on patient profile, target organism, toxicity, costs and the likelihood of emergence and spread of resistance.

Antifungals have become an essential part of modern healthcare due to the increased incidence of invasive fungal infections linked to immunosuppression and the widespread use of invasive devices. A European point-prevalence survey involving 186 hospitals found that 30% of patients were receiving an antimicrobial agent; antifungals accounted for 4% of these.1 Despite the costs associated with these agents, the quality of antifungal prescribing remains poor, with one study reporting unnecessary usage in 16% of cases, the wrong choice of antifungal in about one-third of cases and suboptimal duration of treatment in almost half of patients.2

In this study, we describe the clinical value and possible impacts on costs of a recently introduced antifungal stewardship programme (ASP) targeting patients receiving high-cost antifungals (specifically liposomal amphotericin B, voriconazole, caspofungin and micafungin) at our centre.

Patients and methods

Setting

Cambridge University Hospitals NHS Foundation Trust is a large, single-site, tertiary teaching hospital in the East of England with ~1100 beds, 70000 inpatient admissions and 170000 total admissions per annum. The hospital offers a number of specialist services, including solid organ transplantation (multivisceral, liver and renal transplants), haematology/oncology (including stem cell transplantation) and neurosurgery.

Study design and patients

In July 2013, an ASP was launched for all adult inpatients receiving high-cost antifungals (liposomal amphotericin B, voriconazole, caspofungin and micafungin). An antifungal stewardship team comprising a consultant microbiologist and an antimicrobial pharmacist was formed for the purpose of delivering this programme.

Dispensing records for all patients aged ≥18 years on systemic antifungals were prospectively interrogated from the pharmacy system (Ascribe®) and transferred to a spreadsheet on a weekly basis. The antimicrobial pharmacist (C. M.) selected the patients receiving the target antifungals and together with a consultant microbiologist (D. A. E.) screened each of these patients’ pathology results, visited the patients on the
wards, reviewed the drug charts and medical notes and discussed the cases with the clinical teams. Patients who were on therapy but had been discharged prior to review were nevertheless reviewed when possible.

**Variables**

Data collected included patient demographics, indication for antifungal, primary diagnosis, antifungal, significant clinical results and types of interventions. Referrals by e-mails/calls were also accepted from ward pharmacists and doctors directly involved in patient management and all relevant interventions documented. Mortality was calculated at day 28 and 3 months after the initial visit.

**Definitions**

Indications for systemic antifungal prescription were categorized according to the EORTC/MSG criteria as prophylaxis, possible, probable and proven for haematology patients (and a modified version for solid organ transplant recipients). Candidaemia was defined as the isolation of *Candida* from blood cultures and invasive *Candida* disease as the isolation of *Candida* from a normally sterile site.

**Microbiology**

Identification and susceptibility testing of *Candida* spp. were performed by Vitek 2 (bioMérieux, Marcy-l’Etoile, France). Moulds were identified by morphology and susceptibility testing was performed at the PHE Mycology Reference Laboratory in Bristol, UK. Serum and bronchoalveolar lavage galactomannan bioassay (Bio-Rad, Hemel Hempstead, UK) was available for use throughout the study. It was available for routine use by the haematology team but could also be used by the transplant team after discussion with one of the microbiology consultants (D. A. E., S. H. A. and N. M. B.).

The Trust's antifungal prescribing policy was to use micafungin as the first-line echinocandin and this was used principally for invasive infections due to *Candida* spp. Voriconazole was the standard therapy for invasive aspergillosis. This policy did not change in the years reviewed.

**Interventions**

Interventions were classified as follows:

- **Clinical**: diagnostic and therapeutic advice was provided (e.g. stopping or changing antifungals, due to side effects, or to optimize treatment, advising on side effect/drug interaction management, the taking of and acting on results of voriconazole serum assays and de-escalation, if warranted) and advising further investigations (e.g. galactomannan assay, bronchoscopy and radiology).
- **Financial**: included switching patients to a cheaper agent or stopping therapy and returning unused stock when therapy was stopped or switched.

**Financial savings**

Total costs for the high-cost antifungals were compared for the year preceding implementation of the ASP (1 July 2012 – 30 June 2013) with the year of implementation.

**Results**

From 1 July 2013 to 30 June 2014, the ASP team undertook 294 visits to review 173 patients on high-cost antifungals. Patient demographics and specialty are shown in Table 1. The most common reason for the antifungal prescription was Aspergillus infection (n = 88, 50.8%). *Candida albicans* was the most common organism isolated (n = 23), followed by *Candida glabrata* (n = 16) and *Aspergillus fumigatus* (n = 6).

For patients started on liposomal amphotericin B alone and reviewed by the team, 40.8% (n = 51) prescriptions were changed to an alternative agent or stopped. Only 16 (18%) voriconazole prescriptions were changed or stopped. Caspofungin was changed or stopped on 8 occasions (72.7%) and 33 patients on micafungin (64.7%) were stopped or changed to another antifungal agent.

When examining the interventions for patients receiving monotherapy, clinical advice was provided for 45 (88.2%) micafungin prescriptions, 70 (78.7%) of those on voriconazole, 78 (62.4%) of those on liposomal amphotericin B and 3 (27.3%) of those on caspofungin (Table 2). Overall, five (45.5%) patients on caspofungin were switched to micafungin (for financial reasons). A greater proportion of patients receiving micafungin (n = 22, 43.1%) were changed to a drug with a narrower spectrum of activity (typically fluconazole) when compared with 2 (18.2%) of those on caspofungin. Only 25 (20%) patients on liposomal amphotericin B and 2 (2.3%) of those on voriconazole were switched to narrower-spectrum agents (fluconazole; when infection with *Candida* was suspected or confirmed). Antifungal reviews where advice on side effects or drug interactions was offered included 46 (51.7%) of those initiated on voriconazole, 11 (21.6%) of those on micafungin, 25 (20%) those on liposomal amphotericin B and 1 (9.1%) of those on caspofungin. Advice on therapeutic drug monitoring was given for 69 (77.5%) patients receiving voriconazole.

Ten patients received combination therapy with more than one antifungal agent. After review, only four patients continued on dual therapy.

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**Table 1. Patient demographics and clinical parameters (173 patients)**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 years</td>
<td>110</td>
<td>63.6</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
<td>63</td>
<td>36.4</td>
</tr>
<tr>
<td>Male</td>
<td>100</td>
<td>57.8</td>
</tr>
<tr>
<td>Specialty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology</td>
<td>87</td>
<td>50.3</td>
</tr>
</tbody>
</table>
| Multivisceral transpl.
| 21     | 12.1       |
| Medical specialties | 30     | 17.3       |
| Surgical specialties| 29     | 16.8       |
| Liver and renal transpl.
| 6      | 3.5        |
| Patients on intensive care | 87 | 50.3 |
| Reason for antifungal prescription | | |
| Aspergillus spp.   | 88     | 50.8       |
| Candida spp.       | 46     | 26.6       |
| Prophylaxis        | 33     | 19.1       |
| Fusarium solani    | 3      | 1.7        |
| Cryptococcus neoformans | 2 | 1.2 |
| Trychophyton rubrum| 1      | 0.6        |
| Histoplasma spp.   | 1      | 0.6        |
| Unknown            | 5      | 2.9        |

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The most common indication for antifungal prescription was invasive aspergillosis (n = 88, 50.8%). *Candida albicans* was the most common organism isolated (n = 23), followed by *Candida glabrata* (n = 16) and *Aspergillus fumigatus* (n = 6).

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Ten patients received combination therapy with more than one antifungal agent. After review, only four patients continued on dual therapy.
Table 2. Antifungal stewardship interventions per episode

<table>
<thead>
<tr>
<th>Antifungal/combo</th>
<th>Number (%) given clinical advice</th>
<th>Number (%) switched to a drug with a narrower spectrum</th>
<th>Number (%) advised regarding interactions/adverse events</th>
<th>Number (%) given advice to stop or switch therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal amphotericin</td>
<td>78 (62.4)</td>
<td>25 (20)</td>
<td>25 (20)</td>
<td>51 (40.8)</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>3 (27.3)</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Micafungin</td>
<td>45 (88.2)</td>
<td>22 (43.1)</td>
<td>11 (21.6)</td>
<td>33 (64.7)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>70 (78.7)</td>
<td>2 (2.3)</td>
<td>46 (51.7)</td>
<td>16 (18.0)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>10 (100)</td>
<td>4 (40)</td>
<td>8 (80)</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>

Twenty-three patients (13.3%) had died by day 28 and 35 (20.2%) died within 3 months of the initial visit.

The total costs for the four drugs amounted to £1.835 million for the year July 2012 to June 2013 and £1.656 million for the intervention year, giving a net saving of £178 708. Expenditure decreased for echinocandins by £188 426 and for liposomal amphotericin B by £51 900. Voriconazole expenditure increased by £61 168.

The time taken for the ASP was ~1–1.5 days per week for a consultant microbiologist and an antimicrobial pharmacist. In general, clinical teams accepted the clinical advice provided by the ASP, although this was not formally recorded.

Discussion

Our 12 month study presents descriptive data that illustrate the added value of an ASP on the quality of antifungal prescribing and a possible reduction in costs. We suggest a possible cost saving of £178 708 over the year. This represents a crude marker of cost savings and does not include factors such as the time taken for the ASP ward round, changes in laboratory costs (particularly the increased number of voriconazole assays requested by the ASP team) or earlier discharge from hospital when oral therapy was recommended. The costs of the drugs remained the same and there were no changes with regard to laboratory diagnostics (i.e. galactomannan availability) in 2012–13 and 2013–14. A limitation of the study is the lack of outcome data for the year preceding the intervention. Further limitations include lack of compliance data for the advice given, lack of DDDs/1000 patient days and potential changes in clinical case mix, volume of activity, type of clinical activity etc.

Standiford et al.6 (2012) describe the implementation of a 7 year antimicrobial stewardship programme utilizing an infectious diseases physician and an infectious diseases pharmacist in a large tertiary hospital. Before implementation, annual antifungal expenditure exceeded $3.7 million, declining to $1.3 million by the end of the programme. This study also looked at outcome measures such as hospital stay, readmissions and mortality and found significant changes, before, during and after programme termination. Similarly, Mondain et al.5 (2013) implemented a 6 year ASP with an antifungal stewardship team and found that advice was given for 54% of cases reviewed with a compliance rate of 88%. Cost and DDDs remained constant throughout the programme.

Apisarnthanarak et al.5 (2010) described a quasi-experimental, interventional study that launched an ASP in a tertiary care hospital.

Inpatient prescriptions for candidiasis were observed prospectively 18 months before and 18 months after the implementation of the programme. Inappropriate antifungal use fell from 71% to 24% and there was a decrease in antifungal use. There were also decreases in incidence of infection with C. glabrata and Candida krusei but there was an increase in C. albicans infections. There was also a cost saving of ≥$31 000 during the post-intervention period.

López-Medrano et al.7 (2013) launched a non-compulsory programme for the control of antifungals and for 12 months reviewed prescriptions of voriconazole, caspofungin and liposomal amphotericin B. This study recommended a change in treatment for 29% of cases (compared with 36% in our study). However, stopping therapy was advised in 8% of their cases (4.7% for our study). This may be because we had a high number of patients with probable or proven invasive fungal disease.

Valerio et al.2 (2014) proposed a scoring system for evaluating adequacy of the antifungal prescriptions for 100 patients over 2 months. Their study revealed that most of their prescriptions came from medical departments and 25% from haematology/oncology. A total of 16% of antifungal prescriptions were judged as unnecessary and in our study 36% of single antifungal agent episodes were inadequate, necessitating a change/cessation of therapy.

Our study shows that an ASP using a multidisciplinary team is achievable, possibly cost-effective and could be standard of care in hospitals with specialist units as well as a point of reference for non-infectious specialists.

Funding

This study was carried out as part of our routine work.

Transparency declarations

C.M. has received funding to attend conferences from Astellas and an educational grant from Pfizer. S. H. A. has served on UK Advisory Boards for liposomal amphotericin B (Gilead), caspofungin (MSD) and posaconazole (MSD) and has received sponsorship to attend international meetings from Schering-Plough, Gilead and Wyeth. N. M. B. has received funding to attend conferences and lecture honoraria from Astellas. D. A. E. has received funding to attend conferences from MSD, Gilead and Astellas. R. S. and D. R.: none to declare.
References


