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Effectiveness of an antifungal stewardship program at a London teaching hospital 2010-16

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Synopsis

Background

The need for antifungal stewardship is gaining recognition with increasing incidence of invasive fungal infection (IFI) and antifungal resistance alongside the high cost of antifungal drugs. Following an audit showing suboptimal practice we initiated an antifungal stewardship program and prospectively evaluated its impact on clinical and financial outcomes.

Patients and Methods

From October 2010 to September 2016, adult inpatients receiving amphotericin B, echinocandins, intravenous (IV) fluconazole, flucytosine or voriconazole were reviewed weekly by an Infectious Diseases Consultant and Antimicrobial Pharmacist. Demographics, diagnosis by EORTC criteria, drug, indication, advice, acceptance, and in-hospital mortality were recorded. Antifungal consumption and expenditure and candidaemia species and susceptibility data were extracted from pharmacy and microbiology databases.

Results

A total of 432 patients were reviewed, most commonly receiving AmBisome® (35%) or IV fluconazole (29%). Empiric treatment was often unnecessary, with 82% having no evidence of IFI. Advice was given in 64% of reviews (most commonly de-escalating or stopping treatment) and was followed in 84%. Annual antifungal expenditure initially reduced by 30% (£0.98 to £0.73million), then increased to 20% above baseline over a 5-year period; a significantly lower rise compared to national figures showing doubling of expenditure over the same period. Inpatient mortality, Candida species distribution and rates of resistance were not adversely affected by the intervention.

Conclusion

Provision of specialist input to optimise antifungal prescribing, resulted in significant cost savings without compromising on microbiologic or clinical outcomes. Our model is readily implementable by hospitals with high numbers of at risk patients and antifungal expenditure.

Background

Stewardship programs are effective in reducing inappropriate antimicrobial use, improving patient outcome and limiting emergence of resistance.[1,2] Due to the higher burden of bacterial infection, health policy has traditionally emphasised curtailing antibiotic resistance[3] and spread of hospital-acquired *Clostridium difficile* [4] and MRSA.[5] To date, implementation and evaluation of stewardship programs has therefore largely focused on antibacterials.[6,7]

The complexity of managing invasive fungal infection (IFI) poses a challenge to antifungal stewardship (AFS). The number of 'high risk' immunosuppressed hosts is growing which, coupled with poor local diagnostics and inadequate prescriber knowledge of IFI, results in high rates of inappropriate prescribing (25-75% of prescriptions).[8-11] This offers scope for specialist intervention. Stewardship may also help stem the emergence of antifungal resistance,[3,6,12] which poses an increasing threat to global food security and human health.[13]

An audit of antifungal prescribing at our hospital in 2009 identified suboptimal post-prescription review and performance of azole therapeutic drug monitoring (TDM). Following the appointment of a consultant infectious diseases physician with an interest in IFI we implemented weekly AFS rounds commencing October 2010. Our aims were to optimise care of patients with IFI; stop unnecessary empiric treatment; de-escalate antifungal therapy where possible; perform TDM appropriately; and reduce antifungal usage and expenditure, without compromising clinical outcomes or resistance rates.

To our knowledge, ours was the first dedicated AFS program introduced in England. Six years later, just 11% (5/47) of English acute NHS Trusts surveyed reported undertaking dedicated AFS.[7] Only a handful of reports on the effectiveness of AFS programs in the USA and Europe have been published

to date.[14-19] A single report from a tertiary UK centre demonstrated a crude saving of £188,000 in drug costs over a 1-year intervention period in 173 patients.[20] We present an evaluation of the effectiveness of our AFS programme (2010-16) based on comprehensive, prospectively collected clinical, microbiologic and financial outcome data.

Patients and Methods

Ethics

In keeping with St Georges Hospital Ethics Committee policy and guidance from the National Research Ethics Committee[21] no formal ethical approval was considered necessary as this was an audit of data collected during routine clinical activities.

Setting

St George's Hospital is a 1300-bed teaching hospital in Southwest London providing secondary care to 0.5 million people and tertiary care services to 3.4 million people in Southeast England. These include populations at risk of IFI: patients with acute leukaemia, autologous and allogenenic stem cell transplant (n=29/year in 2009, rising to 53 in 2016), renal dialysis and transplant, inpatients in an 18-bedded Infectious Diseases ward (admitting 100-120 HIV-infected patients p.a.) and 3 adult Intensive Care Units (General, Cardiothoracic and Neurosurgical: total bed expansion from 39 to 60 between 2010 and 2016). There is an Infectious Diseases consult service for all inpatients with suspected or proven infection and those on ICU. On site IFI diagnostics include Candida speciation and fluconazole susceptibility testing, Pneumocystis immunofluorescence (latterly PCR), twice weekly azole TDM, same day HRCT Chest, and histopathology with fungal-specific stains (Grocott/ PAS). Biomarkers (galactomannan, beta-D-glucan), fungal serology and PCR, mould identification and susceptibility are sent away to the National reference laboratory in Bristol.

AFS strategies in place prior to initiation of stewardship rounds were Antifungal Guidelines (since 2005, updated annually) and formulary restriction (Microbiology /Infectious Diseases authorisation for off-guideline use of amphotericin, echinocandins, posaconazole and voriconazole since 2008).

Patient identification

All adult patients receiving antifungal therapy amphotericin B (liposomal and conventional), echinocandins, intravenous (IV) fluconazole, flucytosine or voriconazole) were identified through interrogation of pharmacy computer systems. Paediatric patients, those on standard oral prophylaxis (posaconazole and itraconazole) and outpatients (haematology day care unit attendees excepted) were excluded. All patients identified were seen on a weekly stewardship ward round by an ID consultant and Antimicrobial Pharmacist, which incorporated reviewing medical notes, drug charts, laboratory tests and imaging. Cases are discussed with the clinical team whenever possible and recommendations for patient care documented in medical notes.

Data collection and classification

We prospectively recorded patient demographics; antifungal drug; indication for therapy (prophylaxis, empiric or targeted); site of infection; causative organism if identified; length of stay and in-hospital mortality into a Microsoft Excel (v2003) database. Recommendations made were also recorded and the antimicrobial pharmacist followed-up patients to assess implementation.

Targeted therapy was defined as the administration of an antifungal drug by the treating clinicians to treat IFI suspected on the basis of typical symptoms, signs or results of laboratory tests or imaging. In neutropenic patients, empiric therapy was defined as antifungal drugs administered to febrile patients not responsive to broad-spectrum antibacterial therapy, without focal signs, symptoms or microbiological results suggestive of IFI. Pre-emptive therapy was not included as a category due to the lack of routine biomarker screening in at-risk patients. In non-neutropenic patients, empiric

therapy was defined as treatment initiated in critically ill patients with risk factors for invasive candidiasis in the absence of other known causes.

Based on all results, the final diagnosis of IFI was classified by the stewardship team as 'none', 'proven', 'probable', or 'possible' IFI based on EORTC criteria.[22]

Antifungal consumption and expenditure data

Antifungal consumption data was extracted from Pharmacy records (JAC medicines management system v4.47) and reported as DDDs[23] from 1st April 2009 to 30th September 2016. As the DDD for liposomal amphotericin (AmBisome®) has not been described, the average prescribed daily dose of 200mg was used. Expenditure data is reported as cost of antifungals (in-patient and out-patient for all patient groups) issued from pharmacy per month, based on the price paid by St George's hospital. To contextualise expenditure data, occupied bed days (OBD) data was obtained for the Trust as a whole and within the three Adult ICUs, as well as the numbers of chemotherapy cycles and bone marrow transplants performed in adults over the period 2009-16.

Microbiologic Data

Candidaemia speciation and susceptibility results from 2008-16 were extracted from the microbiology database. Speciation was by MALDI-TOF from 2012 and using the germ tube test and API Candida (Biomerieux) prior to 2012. Candida fluconazole MIC testing was performed using Etest (Biomerieux) locally and by the reference laboratory for all antifungals for significant isolates. Persistent candidaemia (same Candida species cultured from a blood sample taken ≤30 days of first in a given patient) was analysed as a single episode, whilst episodes >30 days apart were defined as a recurrence and counted as two episodes.

Statistical Analysis

Data were analysed using Microscoft Excel v2003. Continuous variables were compared using the t-test and categoric variables using the Chi square test in Prism v7 (GraphPad software, CA, USA).

Results

Between 6th October 2010 and 30th September 2016 there were 512 antifungal prescriptions which triggered a review by the stewardship team in 428 patients (an additional 4 patients were reviewed at the request of the clinical teams). 432 patients were reviewed 769 times on 246 AFS rounds (median 3 per round, range 1-10). Median patient age was 56 years (range 16-93); 58% were male. Top specialties prescribing antifungals were haemato-oncology (n=209, 40%), intensive care (n=49, 11%: non-haemato-oncology patients only), general surgery (n=44, 9%), and infectious diseases (n=39, 8%). Two thirds of patients (n=285, 66%) were seen once; 16% (n=69) required 3 or more reviews (mainly those on targeted therapy). Seven patients died prior to review.

Indication for and appropriateness of antifungal prescribing (table1 & figure 1)

Of 516 antifungal prescribing episodes reviewed, the most common drug initiated was AmBisome® (181, 35%), followed by IV fluconazole (149,29%) and the echinocandins (120, 23%). Of 212 patients receiving targeted therapy, 60% (n=127) had proven IFI on EORTC criteria and 75% (n=158) had either proven, probable (n=16) or possible (n=15) IFI. In 24 cases, therapy was targeted at a positive culture from a non-sterile site. These were classified as either non-invasive fungal infection (n=33) or fungal colonisation, usually respiratory (n=7). In 14 cases, patients with clinically significant infections failed to meet EORTC criteria.

In the case of empiric prescribing, 82% (150/183) of patients were subsequently found to have no evidence of IFI on clinical, microbiologic and radiologic criteria. Only 21 patients (11%) subsequently met criteria for proven, probable or possible IFI. Of 121 patients receiving non-standard prophylaxis,

the majority (105, 87%) were haemato-oncology patients on primary prophylaxis (AmBisome® n=79; caspofungin n=25, micafungin n=1): 49 (47%) were deemed appropriate. Nine patients had antifungal prophylaxis switched or stopped prior to the AFS round. Switches in drug class (primarily to azoles) were recommended in 44 cases (AmBisome 28/79 and echinocandins 16/26) and stopping prophylaxis was recommended in 3 cases (2 caspofungin, 1 AmBisome). The most common indication for AmBisome was concomitant vincristine chemotherapy for ALL; for echinocandins it was adverse drug reactions.

Stewardship advice and acceptance (Table 2)

Advice was offered in two thirds of reviews (494/767, 64%), with 136 reviews resulting in multiple suggested interventions. Advice was followed in 84% of evaluable recommendations (471/558). The most common advice, switching to an alternative drug (n=122, 21%), had the lowest acceptance rate (85/118, 71%). Advice to stop antifungals (n=85), define treatment duration (n=71) or perform TDM (n=68) was also common with high acceptance rates (89%, 86%, and 83% respectively, table 2).

The remaining 265 reviews required no intervention: 126 were on appropriate treatment, 57 were on prophylaxis as per Trust policy (where azoles were contraindicated), and 82 patients had already had their antifungal therapy modified prior to the round (stopped in 55, switched in 27).

62% (86/138) of patients prescribed empiric antifungal therapy who had no IFI had their prescriptions stopped within one week, compared to 44 % (8/18) in our pre-implementation 2009 audit (p=0.15). De-escalation was performed where appropriate in 87% (26/30) compared to 50% (2/4) of patients pre-implementation (p=0.004). TDM was performed where indicated by Trust guidelines in 74% (51/69) versus 43% (10/23) of patients (p=0.008) and results outside the therapeutic range acted upon in 74% (14/19) of cases (0/2 pre-intervention).

Microbiologic and clinical outcomes (Table 3)

There were 131 proven IFIs. Microbiologically proven IFIs were diagnosed from blood (n=63) and other sterile sites (n=58). Nine IFIs were diagnosed on histology only, and one by cryptococcal antigen in CSF. *Candida albicans* was the most commonly isolated pathogen, both from blood and other sterile sites (n=58, 44%), followed by non-albicans *Candida sp.* (n=44, 33%). The abdomen was the most common site of infection (40/102). Proven mould infection was rare (n=13): 2 cases of invasive aspergillosis proven on culture only (prosthetic joint infection and discitis), 4 cases of aspergillosis and 1 of mucormycosis proven microbiologically and histologically; 4 cases of invasive aspergillosis and 2 cases of mucormycosis diagnosed on histology alone.

Figure 2 illustrates the number of candidaemia episodes and causative species distribution in adults and children during the pre- and post-AFS intervention period. Overall candidaemia numbers remained below the pre-intervention baseline of 30 per year. The proportion of Candidaemias due to non-albicans species was similar pre- and post-intervention: 27% and 45% in the 2 years preceding the intervention, and averaged 49% from 2010-2016 (range 33-70%). In terms of susceptibility of *C glabrata* to echinocandins, mode MIC for 34 isolates tested at the reference laboratory between 2009 and 2016 was 0.125 (susceptible) for each 2-year period except for 2015-16 when it was 0.25 (intermediate), with no instances of echinocandin resistance to date. There were no reported candidaemia episodes due to *C. krusei.*

Over 2010-16, 756 galactomannan (GM) tests were requested and sent away to the Reference laboratory, with a median(IQR) turnaround time (TAT) to result authorisation of 13 (11-17) days. As a result of the intervention, the number of GM tests increased from a baseline of 45 (2010) to 182 in 2016, increasing spend from £2025 to £8190 (total cost 2010-16, £34,020). Beta-D-glucan was less frequently requested with 37 tests sent away over 6 years (cost £2183) with a similarly long TAT (median 12, IQR 9-14). For TDM tests, we were able to obtain data on the number and costs of tests

done in 2015-17: 192, 301 and 112 tests respectively, costing £26,600 total, mean annual spend £8867. Extrapolating the latter figure to the period 2010-16, the estimated mean annual laboratory spend was £14,900.

Inpatient mortality (excluding patients on prophylaxis) was 27% (101/383), compared to 38% (19/50, p=0.1) in the pre-intervention period. In the prospective cohort, mortality was similar in patients with proven/ probable IFI compared to those without (42/150, 28% versus 61/231, 26%, p=0.7). Length of stay (LOS, median 34d, range 1-315d) did not alter significantly over the course of the intervention (28d years 1 and year 6, peak 37d in year 3). LOS was significantly higher for those with proven or probable IFI (47d versus 30d, p<0.0001).

Antifungal spend and consumption (Figure 3a & 3b)

Following implementation of our AFS program, total antifungal expenditure (adult and paediatric, inpatient and outpatient) initially showed a downward trend reducing by 26% in the first 3 years (from £0.98 million to £0.73 million). Expenditure then rose to between £1.17-1.4 million p.a.: a 20% increase compared to pre-intervention (2009/10). By comparison, NHS England data (P. Howard, NHS Improvement, personal communication) shows that national antifungal expenditure more than doubled from £37.8 million to £79.9 million during the 5 year period 2011-16.

Independent of the AFS program, changes in drug pricing impacted expenditure; anidulafungin was added to formulary in April 2011 as the echinocandin of choice in non-haemato-oncology patients (28% reduction in price compared to caspofungin), posaconazole tablets were introduced in October 2014 (cost neutral compared to liquid) and micafungin became the echinocandin of choice for all patients in October 2015 (cost neutral compared to anidulafungin, 28% reduction in price compared to caspofungin) with a further 38% price reduction in October 2016.

Parallel to the changes in expenditure, antifungal consumption initially decreased from 30,000 DDDs in 2009/10 to 22,103 in 2011/12 (a 26% reduction) before steadily increasing to 33,610 DDDs in 2016/17. All antifungal drugs followed a similar trend. Posaconazole consumption showed the largest increase from from 499 DDDs in 2010/11 (2.1% of total antifungal consumption) to 4907 DDDs (14.6% of total) following the introduction of posaconazole tablets to the formulary in October 2015. In 2016/17, liposomal amphotericin, itraconazole, flucytosine, and the echinocandins remained at lower usage compared to 2009/10, with voriconazole and fluconazole at a higher consumption compared to pre-intervention. The proportion of DDDs administered intravenously has reduced from 14% pre-intervention to 10% post-intervention as patients are switched from broad-spectrum intravenous antifungals to oral azole therapy.

Whilst occupied bed days (OBDs) remained constant within the Trust during the study period, numbers of patients at risk of IFI rose: admission to the adult ITUs increased substantially (33% increase from 3639 admissions in 2009 to 4828 in 2016) as did ITU-OBDs (41% increase in OBDs from 12113 to 17079 over the same period). A similar increase was seen in the number of adult stem cell transplants with 29 transplants undertaken in 2009, rising to 53 in 2016. Figures for patients receiving courses of chemotherapy for haematological malignancy (data available from 2012/13) show a 20% increase from 233 in 2012/13 to 280 in 2013/14, remaining stable since.

Discussion

To the best of our knowledge, this is the most comprehensive evaluation of an antifungal stewardship programme to date, providing 6 years' data on stewardship activities alongside clinical and financial outcomes. Our findings demonstrate that an antifungal stewardship programme has the potential to contain antifungal use and expenditure without adversely affecting patient outcomes, despite increasing numbers of "at risk" patients.

Our evaluation was based on reviews of over 400 adult patients, including 131 cases of proven IFI. Over half (51%) of patients belonged to the 'high risk' specialities of Haematology and Intensive Care, representative of a tertiary referral hospital population. Clinical management advice aside, the scope for intervention to stop or limit inappropriate prescribing was high, particularly in those on empiric therapy (82% with no IFI). For Haematology patients on prophylaxis, a class switch from high cost intravenous antifungals to azoles was recommended in 44/105 (42%) of reviews. Compared to the small pre-intervention audit, significant improvements were demonstrated with respect to de-escalation and stopping in those without IFI, and performance of TDM.

In its first three years, the St George's AFS program substantially reduced annual antifungal spend (>£300K, a 30% decrease from baseline). Since 2014, spend has increased, with expenditure reaching £1.2 million in 2016/17 (20% higher than 2009/10). Inflation notwithstanding, this rise is modest compared to UK-wide expenditure which more than doubled over the same timeframe. Moreover, this occurred in the context of increasing numbers of patients at risk of IFI in the organisation during this period, with a 40% expansion of OBDs in Intensive Care, an 85% increase in stem cell transplants and a 20% increase in chemotherapy courses administered over this period. These figures demonstrate the importance of incorporating denominator data as a surrogate for numbers of 'at risk' patients in comparisons of antifungal spend either longitudinally or between hospitals. Unsurprisingly, stewardship resulted in more laboratory tests and increased expenditure on this, however the mean annual expenditure of £14,900 is outweighed by the savings made on antifungal drugs.

In the published literature, we found relatively few articles describing the implementation and impact of AFS programs, often limited to specific settings (Haematology[17] or Intensive care[24]) or infection types (invasive candidiasis)[14,16] rather than encompassing a hospital-wide approach. Only

three papers from France, Spain and the UK describe comprehensive programs similar to ours, directed at treatment of all IFIs and selected prophylaxis,[15,18,20] of which just two employ the "gold standard" multidisciplinary approach with stewardship rounds as their core component.[15,20] Our program is unique amongst the published literature in reporting on all 6 suggested performance measures: antifungal expenditure and usage, adherence to therapeutic advice, mortality, incidence of IFI and quality of care (length of stay).[25]

The Spanish program achieved a comparable reduction in overall antifungal consumption over 3 years (20% versus 26%) and a cost saving of a similar order of magnitude to ours (US$370,682 over 12-months[18] versus £330,000 (US$450,000) over 3 years in our program. The other hospital-wide program reported from a tertiary hospital in Cambridge, UK[20] achieved a comparable percentage reduction in antifungal expenditure over the first year (9.8% versus 11%), on a background of a higher baseline expenditure (£1,835,000 versus £928,000). Our intervention rate was higher overall than the French program (68% versus 54%), but similar to that in the Cambridge program (72%) and was sustained across the 6-year program with consistently high acceptance rates (>80% each year).

Our study has several limitations. This was a single-centre study and the results may not be generalizable to hospitals with a different case mix. Adverse effects of antifungals and re-admission rates were not assessed. The only costs analysed were drug costs – we did not account for costs of laboratory diagnostics or hospital stay- although the median length of stay did not change over time. Whilst mortality in patients reviewed remained stable and appeared lower than in the pre-intervention audit, the observational nature of our study precludes an assessment of the impact of our AFS program on mortality attributable to IFI. We did not formally assess the costs of the stewardship program; however it typically took 3 hours of antimicrobial pharmacist time and 2 hours of ID consultant time per week.

Key challenges for any stewardship program are delays in reviewing patients due to frequency of ward rounds, currently only weekly, and access to timely diagnostic results. Despite being a large teaching hospital with a sizeable at risk population, to date the fungal biomarkers galactomannan and beta-D-glucan, fungal PCR and candida susceptibility testing (excluding fluconazole) are sent away to the National Reference laboratory, with a median TAT of just under two weeks for GM and BDG. Whilst we have access to same-day radiological investigations (high resolution CT chest), bronchoscopy and BAL for high-risk patients is only available weekly for non-ITU patients. All of these factors limit our opportunity to impact on prescribing decisions in real time, particularly stopping unnecessary empiric therapy. There is clear scope to improve on the proportion of our patients with no evidence of IFI who had their antifungals stopped within a week (62%). We are currently piloting the impact on antifungal prescribing of introducing beta-D-glucan testing in patients at risk of Invasive candidiasis on Intensive Care; in particular its impact on curtailing empiric echinocandin therapy in those without IFI. Of note, non-availability of rapid diagnostics and lack of resources (staff time) were two of the most frequent factors highlighted as a barrier to AFS in the recent English survey.[7]

The need for antifungal stewardship is more pressing than ever as antifungal resistance emerges as a significant threat[13] with outbreaks of *Candida auris*, and increasing reports of multi-drug resistant *C. glabrata* and azole-resistant *Aspergillus spp*.[12] The recently updated IDSA guidelines on antibiotic stewardship for the first time suggest implementation of interventions to improve the appropriate prescribing of antifungal treatment, advising that antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for programs to be successful.[26] AFS also represents a significant opportunity to reduce unnecessary expenditure on high cost medicines in austerity measures within the UK National Health Service. In England the majority of antifungal costs are not included within in-patient tariffs, so are paid for by NHS England, with currently few incentives to encourage individual hospitals to prioritise this issue. This was confirmed by a recent survey of

English Acute Hospital Trusts (n=47 responses), revealing that whilst 98% of Trusts had antimicrobial stewardship programs, only 5 (11%) had a dedicated AFS program,[7] illustrating an important gap that the NHS England Improving Value Project[27] seeks to address by introduction of financial incentives for implementation of AFS.

In summary, we demonstrate that an antifungal stewardship program is readily implementable and sustainable over 6 years, offering high scope for targeted intervention to prevent unnecessary prescribing, with good clinician acceptance and no compromise to clinical outcomes. Containment of expenditure compared to the national picture and in the face of rising 'at risk' populations was possible using only 2-3 hours of Consultant and Senior Pharmacist time each week. Future challenges for antifungal stewardship programs such as ours include lack of access to rapid turnaround, accurate 'rule out' diagnostics. Globally, antifungal stewardship remains a poor relation of antibiotic stewardship programs. To contain rising costs and the emergence of antifungal resistance, national initiatives are urgently needed to harmonise laboratory diagnostics in mycology and to encourage implementation of AFS by a greater proportion of English NHS hospitals.

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References:

1) Schuts EC, Hulscher ME, Mouton JW, *et al*. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; **16**: 847-856.

2) Davey P, Marwick CA, Scott CL, *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews* 2017; **2**.

3) Public Health England. *English Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR) Report*. London; 2017 https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

4) Duerden B, Contribution of a government target to controlling *Clostridium difficile* in the NHS in England. *Anaerobe* 2011; **17**: 175-179.

5) Duerden B, Fry C, Johnson AP, *et al*. The Control of Methicillin-Resistant *Staphylococcus aureus* Blood Stream Infections in England. *Open Forum Infectious Diseases* 2015; **2**: ofv035.

6) Ananda-Rajah MR, Slavin MA, Thursky KT. The case for antifungal stewardship. *Curr Opin Infect Dis.*2012; **25**: 107-15

7) Micallef C, Ashiru-Oredope D, Hansraj S, *et al*. An investigation of antifungal stewardship programmes in England. *Med. Microbiol*. 2017; **66**: 1581-1589

8) Gutierrez F, Wall PG, Cohen J. An audit of the use of antifungal agents. *J Antimicrob Chemother.* 1996; **37**: 175-85

9) Nivoix Y, Launoy A, Lutun P, *et al*. Adherence to recommendations for the use of antifungal agents in a tertiary care hospital. *J Antimicrob Chemother.* 2012; **67**: 2506-13

10) Sutepvarnon A, Apisarnthanarak A, Camins B, *et al*. Inappropriate use of antifungal medications in a tertiary care center in thailand: A prospective study. *Infect control Hosp Epidemiol.* 2008; **29**: 370-3

11) Valerio M, Rodriguez-Gonzalez CG, Munoz P, *et al*. Evaluation of antifungal use in a tertiary care institution: Antifungal stewardship urgently needed. . *J Antimicrob Chemother.* 2014; **69**: 1993-9.

435 12) Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal
436 resistance: prevalence, mechanisms, and management. *Lancet Infect Dis*. 2017;**17**:e383-e392.
437 13) Fisher MC, Hawkins NJ, Sanglard D, *et al*. Worldwide emergence of resistance to antifungal
438 drugs challenges human health and food security. *Science* 2018;**360**:739-742.
439 14) Reed EE, West JE, Keating EA, *et al*. Improving the management of candidemia through
440 antimicrobial stewardship interventions. *Diagn Microbiol Infect Dis.* 2014;**78**:157-61.
441 15) Mondain V, Lieutier F, Hasseine L, *et al*. A 6-year antifungal stewardship programme in a
442 teaching hospital. . *Infection.* 2013;**42**:621-8.
443 16) Apisarnthanarak A, Yatrasert A, Mundy L. Impact of education and an antifungal stewardship
444 program for candidiasis at a Thai tertiary care center. *Infect Control Hosp Epidemiol.* 2010;**31**:722-7.
445 17) Alfandari S, Berthon C, Coiteux V. Antifungal stewardship: Implementation in a french teaching
446 hospital. *Med Mal Infect.* 2014;**44**:154-8.
447 18) López-Medrano F, San Juan R, Lizasoain M, *et al*. A non-compulsory stewardship programme for
448 the management of antifungals in a university-affiliated hospital. *Clin Microbiol Infect.* 2013;**19**:56-
449 61.
450 19) Shah DN, Yau R, Weston J, *et al.* Evaluation of antifungal therapy in patients with candidaemia
451 based on susceptibility testing results: implications for antimicrobial stewardship programmes. *J*
452 *Antimicrob Chemother* 2011;**66**:2146–51
453 20) C. Micallef, S. H. Aliyu, R. Santos, *et al*. Introduction of an antifungal stewardship programme
454 targetting high-cost antifungals at a tertiary hospital in Cambridge, England. *J Antimicrob Chemother.*
455 2015;**70**:1908-11
456 21) NRES. Defining Research: NRES guidance to help you decide if your project requires review by a
457 Research Ethics Committee. *Ref 0987.* http://www.nres.nhs.uk/applications/is-your-project-research
458 22) De Pauw B, Walsh TJ, Donnelly JP, *et al*. Revised definitions of invasive fungal disease from the
459 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). *Clin Infect Dis.* 2008; **46**: 1813-21

23) World Health Organisation. ATC/DDD index [online] https://www.whocc.no/atc_ddd_index/

24) Guarascio AJ, Slain D, McKnight R, *et al*. A matched-control evaluation of an antifungal bundle in the intensive care unit at a university teaching hospital. *Int J Clin Pharm. 2*013; **35**: 145-8.

25) Bienvenu AL, Argaud L, Aubrun F, *et al*. A systematic review of interventions and performance measures for antifungal stewardship programmes, *J of Antimicrob Chemother*, 2018; **73**: 297–305

26) Barlam TF, Cosgrove SE, Abbo LM, *et al*. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, *Clin Infect Dis*, 2016; **62**: e51–e77

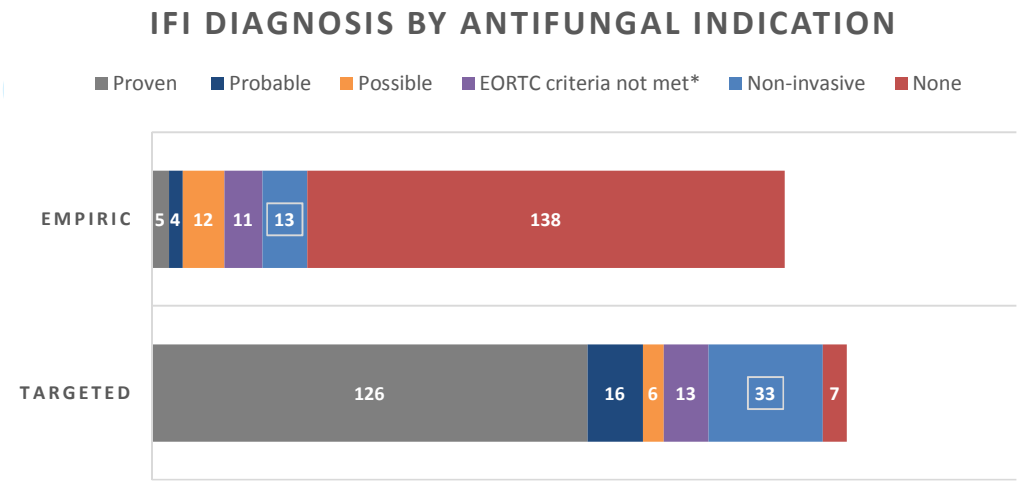
27) NHS England. Principles for sharing benefits associated with more efficient use of medicines not reimbursed through national prices. London; 2014. www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2014/01/princ-shar-benefits.pdf

Table 1. Antifungal drug, indication and final IFI classification

Antifungal drug prescribed	
AmBisome	181
Fluconazole	149
Caspofungin	61
Anidulafungin	56
Voriconazole	43
Micafungin	3
Itraconazole [a]	2
Not on treatment [a]	2
Combination therapy	19 (l-AMB + 5FC 7, l-AMB + MFG 1, l-AMB + VRC 2, FLC + 5FC 1, AFG + VRC 4, cAMB + 5FC 4)

Figure 1: Final IFI diagnosis by indication for antifungal prescribing

Total *n*=183 Empiric; 211 Targeted; 121 Prophylaxis



*Non-invasive fungal infection not meeting EORTC criteria: 4 candida endopthalmitis diagnosed by ophthalmology, 2 mediastinitis post oesophageal perforation, 8 candiduria with prosthetic material in situ, 2 mastoid osteomyelitis with Aspergillus from ear swab, 4 high risk patients empirically treated for IFI too unwell to undergo diagnostics (CT scan), 2 semi-invasive pulmonary aspergillosis, 2 penetrating wounds from tree branches

Table 2: AFS Advice and acceptance

Advice Given	Total	Accepted n (%)[a]
Switch to alternative drug	122	85/118 (72%)
Stop	85	74/83 (89%)
Duration recommended	71	53/63 (84%)
TDM	68	53/64 (83%)
Diagnostics	58	41/49 (84%)
IV to PO switch (same drug)	36	31/35 (86%)
Adjust dose	30	29/30 (97%)
Other[b]	121	105/116 (91%)
Total	591	471/558 (84%)

a acceptance of advice is not reported in all cases, for example if TDM was advised but the drug treatment ceased before TDM was required, or if advice was given on management of potential ADRs that didn't occur

b Includes advice on concurrent antibacterial/antiviral therapy (n=33), managing adverse drug reactions (22) or interactions (3), monitoring response to therapy (17), adjunctive treatment advice (28), escalation/treatment plans (11), prophylaxis post treatment (5) and follow up post discharge (4)

498 Table 3. Organism, sample and source of infection in proven IFI

Organism (n)	Samples (n)	Source/ focus of Infection (n)
C. albicans (59)	Blood culture (25)	Infective endocarditis (5), line (6), abdominal (2), urinary source (5), unknown (7),
	Pus/fluid (20)	Abdominal (17), Endovascular graft infection (1), Pleural effusion post CABG (1), Renal abscess (1)
	CSF (1)	Device-associated ventriculitis (1)
	Tissue (13)	Abdominal (3), prosthetic joint (3), endovascular graft infection (3), mediastinitis (1), sternal wound infection (1), urinary tract (1), alveolar proteinosis, with underlying fungal infection (1)
C. dublinensis (3)	Blood culture (2)	Abdominal (1), line (1)
	Pus/fluid (1)	Abdominal (1)
C. glabrata (25)	Blood culture (21)	Infective endocarditis (2), line (3), abdominal (6), urinary source (2), unknown (8)
	Pus/fluid (2)	Abdominal (2)
	Tissue (2)	Abdominal (1), mediastinitis (1)
C. guilliermondii (1)	Fluid (1)	Abdominal
C. krusei (2)	Fluid (2)	Abdominal (1), unknown (1)
C. lusitaniae (2)	Blood culture (2)	Abdominal (2)
C. parapsilosis (4)	Blood culture (3)	abdominal (1), urinary source (1), unknown (1)
	Tissue (1)	Endovascular infection
C. tropicalis (7)	Blood culture (5)	abdominal (1), line (1), unknown 2, urinary (1)
	Pus/fluid (2)	CNS (1), Abdominal (1)
Candida sp. (1)	Pus	Neurosurgical site infection (metal plate in situ)
A. flavus (1)	Tissue	Rhino-orbital/CNS
A. fumigatus (5)	Pus (1)	CNS
	Tissue (4)	prosthetic joint infection (1), CNS/rhino-orbital (2), discitis (1)
Aspergillus sp (4)	Tissue – histological diagnosis only (4)	Lung (2), brain (1), lung + brain (1)
Cryptococcus sp (10)	Blood culture + CSF (2)	
	Blood culture (2)	
	CSF (4)	
	Tissue (1)	
	CRAG + (1)	CNS
Histoplasma capsulatum (1)	Tissue	Disseminated
Lichtheimia corymbifera (1)	Tissue	Rhino-orbital
Saccharomyces cerevisiae (1)	Tissue	Mediastinitis post oesophageal perforation
Trichosporon mucoides (1)	Blood culture	Line
Mucormycosis (2)	Tissue	Abdominal (histological diagnosis)
Unspeciated (fungal spores with inflammation on biopsy) (1)	Tissue	Skin

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Figure 2. Numbers and species distribution of Candidaemia episodes at St George's Hospital 2008-2017. Non-sp (n=1) was not speciated.

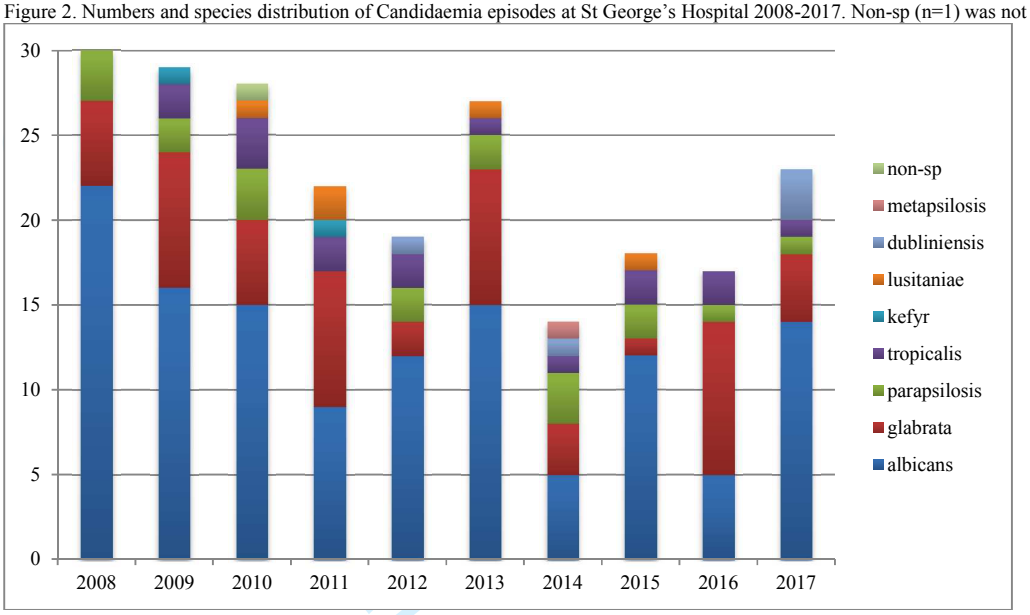

Figure 3. Total annual antifungal use (in- and outpatient, Adult and Paediatric) pre and post-implementation of antifungal stewardship program at St George's NHS Trust by financial year, 2009-17.a) Total annual antifungal expenditure: solid bars show St George's NHS spend (left Y axis) and solid line indicates spend in acute English NHS Trusts (right Y axis, source: NHS England; pre-2011 data not available) b) consumption of antifungal drugs (DDDs/1000 OBDs), by drug and total