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Promoting antifungal stewardship through an antifungal multidisciplinary team in a paediatric and adult tertiary centre in the UK

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Background: Invasive fungal infections (IFIs) present significant challenges, especially among immunocompromised patients, with associated high morbidity, mortality and significant economic impact. Diagnostic difficulties and the emergence of antifungal resistance necessitates enhanced antifungal stewardship (AFS) efforts.

Methods: We report outcomes from a review of our multidisciplinary approach to AFS, based in a 1300-bed teaching hospital in the South-West of England. Retrospectively reviewing all adult and paediatric cases over 12 months in 2022, we investigated demographics, diagnosis, antifungal therapy and adherence to AFS advice, including clinical, mycological, financial and teamwork metrics. Data were extracted from our AFS database, supported by pharmacy records.

Results: The AFS multidisciplinary team (MDT) reviewed 111 patients, with 30 day and 1 year mortality of 22.7% and 35.4%, respectively. IFIs classified as proven accounted for 26%, with fungal pathogens identified in 36.3% of cases. Antifungal consumption (by 25.1%) and expenditure (by 59.9%) decreased from 2018 to 2022. The AFS MDT issued 324 recommendations, with a 93% acceptance rate.

Conclusions: Our approach to AFS, centred around a weekly MDT, demonstrated improvements in IFI management, antifungal consumption and cost-efficiency. This single-centre study highlights the value of a comprehensive, collaborative approach to AFS involving experts in mycology, infection, radiology, antifungal therapies and clinical teams. The programme's success in paediatric and adult populations and the near-universal acceptance of its recommendations show its potential as a model for replication. It represents a model for enhancing patient care and AFS practices, with future directions aimed at expanding service reach and the integration of further rapid diagnostic modalities.

Introduction

Invasive fungal infections (IFIs) represent an increasing public health concern, particularly impacting immunocompromised populations such as patients in haematology/oncology settings, those with solid organ or bone marrow transplants, and patients in critical care.[1–4] IFIs are associated with significant morbidity, mortality and economic burden.[4–6] Alongside the limited classes of antifungal agents available to treat IFIs,[7,8] other emerging risks relate to increasing numbers of patients in at-risk groups, changes in fungal disease epidemiology related to the recent COVID-19 pandemic, emerging pathogens such as *Candida auris*,

and escalating antifungal resistance.[1,7,9,10] Diagnosis is challenging, with limited access to timely diagnostics and prolonged turnaround times (TATs) outside of reference laboratory settings,[11,12] leading to a tendency to commence antifungal therapy in many patients often without clear evidence of IFI.[13,14]

Antifungal therapies are crucial to managing IFIs, yet rely heavily on only four classes of drugs.[4,6,7] These agents are costly, with potential for toxicities such as hepatotoxicity and QTc interval prolongation with triazoles or myelotoxicity with amphotericin or flucytosine.[15] Many have multiple drug–drug and non-drug interactions and in addition to variable uptake and metabolism therefore require appropriate therapeutic drug monitoring (TDM).[4,15,16] Given the rise in use of antifungal agents, antifungal resistance is increased and concerning.[4,9,17] Although resistance to echinocandins, often used in IFIs, remains rare in the UK, antifungal resistance worldwide is rising, with outbreaks of MDR fungi having huge impacts financially, on patient care and clinical services, leading to poor patient outcomes.[16,17]

Thus, there is a critical need to optimize fungal diagnostic pathways alongside promoting appropriate use of antifungal therapy.[18,19] Despite antimicrobial stewardship programmes being promoted worldwide, championing the optimal use of antimicrobials at healthcare system and organizational levels,[20] there has tended to be less focus on antifungal stewardship (AFS).[21,22] Although AFS has similar goals to all antimicrobial stewardship programmes, it has additional challenges and complexities. These include the appropriate use and interpretation of laboratory diagnostic tests, including biomarkers, and imaging, consensus on appropriate management and the underlying complexity of each patient in whom IFI is being considered, rendering clinical teams' involvement crucial to discussions.[4] Given the aim of AFS is to ensure the optimal use (and cessation where appropriate) of antifungal therapy, a multidisciplinary approach is therefore crucial and indeed has been demonstrated to reduce mortality in hospitalized patients.[23–27] This collaborative approach also promotes the education and training of both specialist and clinical teams.[10,26,27]

Here, we describe and present clinical, microbiological, financial and team-based outcomes of a specialist AFS programme over 1 year (2022) in an NHS trust in the South-West of England.

Methods

Context

The setting comprised a 1300-bed teaching hospital in South-West England, including adults and paediatrics, alongside a specialist haemato-oncological centre including management of acute leukaemia, stem cell transplantation, dental and ophthalmological centres and four ICUs—general, cardiac, neonatal and paediatric. The hospitals are closely linked to the Mycology Reference Laboratory (MRL) (UKHSA, Bristol) geographically, with some shared laboratory services, as well as MRL specialists' involvement in the AFS multidisciplinary team (MDT).

The AFS MDT comprises multiple professionals, summarized in Figure 1, as advised by Johnson *et al.*[4] These each have distinct, important knowledge of the clinical management of fungal infections, antifungal therapy and patients' predisposing clinical conditions. The MDT formally meets once per week to review cases, collaborating with clinical teams who are at the forefront of patient care. This collaborative approach enhances multidisciplinary working outside of MDT meetings, with clinical teams more likely to accept management recommendations from experts they engage with regularly.[27]

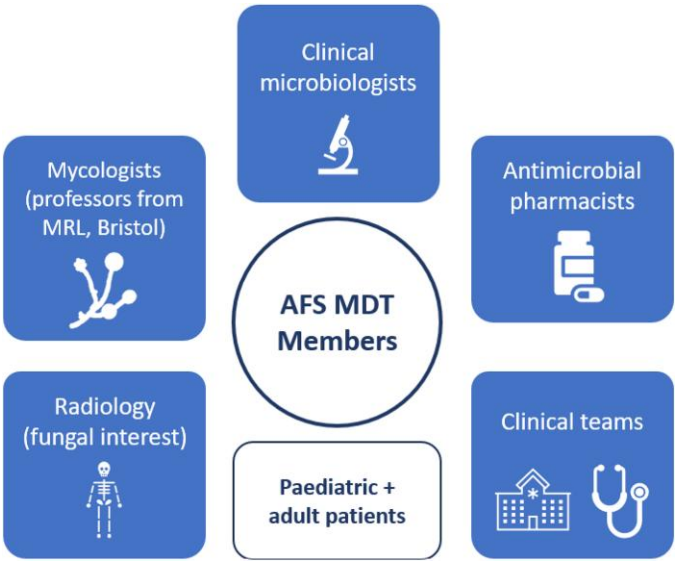

Figure 1. Members of the antifungal stewardship multidisciplinary team.

With electronic prescribing so far only used in intensive care settings in the Trust, patients receiving treatment dose antifungals are identified through four routes: clinical teams, clinical infection specialists, antimicrobial pharmacists' screening of electronic prescriptions on intensive care, and a weekly search of all β-D-glucan and galactomannan results performed Trust-wide. The AFS MDT meetings started during 2019 and are now well established with regular attendance from all members listed in Figure 1. We reviewed all cases from the AFS MDT over a 12 month period from 1 January to 31 December 2022, alongside antifungal drug consumption and costs over a 5 year period from 2018 to 2022.

Data collection

An AFS database, using Microsoft Excel®, is maintained weekly. This database includes patient demographics, referral criteria, site of infection, diagnosis, fungal diagnostics, organism(s) identified, indication for therapy (including whether on preceding prophylaxis), length of treatment, 30 day and 1 year mortality, and implementation of advice offered (i.e. whether advice offered has been adhered to by clinical teams). From the data, all diagnoses of fungal infections were classified according to an adaptation of 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) criteria,[28,29] as 'none', 'non-invasive', 'possible', 'probable' or 'proven'.

Microbiological data were reviewed and extracted from the electronic laboratory information management system. Fungal diagnostic methods are listed in Table 1.

Antifungal usage and expenditure

Data were extracted from the Refine 2024 (RxInfo®) system and accounts on all systemic antifungal agents used, other than griseofulvin and terbinafine. Patient admission data used by this system are taken from Hospital Episode Statistics (HES) data. In April 2020, two hospitals merged to form the current NHS trust, increasing the bed-base and therefore the denominator (consumption per 1000 admissions). The Refine system amalgamates all prescribing and patient admission data from prior to the merger, thus allowing comparison of use prior to the

Table 1. Fungal diagnostic tests and methods used[30]

Diagnostic test	Method
Fungal culture: *Candida* spp. + yeasts	Identification: MALDI-TOF Biotyper® (Bruker) Susceptibility testing: CLSI broth microdilution (followed by gradient strip tests as required)
Fungal culture: moulds	Identification: phenotypic/morphological, confirmed by MALDI-TOF Biotyper® (Bruker) Susceptibility: CLSI broth microdilution (followed by gradient strip tests as required)
β-D-Glucan	Fungitell (Associates of Cape Cod)
Aspergillus serology:	
Antigen (galactomannan)	Platelia EIA galactomannan test (Biorad)
Antibody	*Aspergillus* precipitins
Aspergillus-specific PCR	AsperGenius real time PCR, PathoNostics
Candida serology:	
Antigen (mannan)	Platelia *Candida* Ab Plus (Biorad)
Antibody	*Candida* precipitins
Cryptococcal antigen	First line: CrAg lateral flow assay (IMMY) Confirmatory positive + titres: CrAg latex agglutination (IMMY)
Pneumocystis jirovecii (PJP) PCR	PneumoGenius real time PCR kit, PathoNostics

implementation of the AFS MDT. With the AFS MDT weekly meetings having commenced in 2019, total consumption data from 2018 onwards were chosen to provide insight into the MDT's impact on prescribing and stewardship.

Ethics

No formal ethics approval was considered necessary as this was an audit of data collected during weekly AFS MDT meetings.

Results

Demographics

There was discussion of 111 patients on 174 occasions, with individuals often discussed on multiple occasions due to the long course of IFIs and complexity of patients' underlying conditions. Demographic and clinical characteristics are detailed in Table 2. Thirty-day (22.7%) and 1 year mortality (35.4%) were significant due to the significant underlying conditions of this cohort.

Diagnosis of IFI

Using the EORTC/MSG criteria,[28,29] 26% of patients were classified as having proven, 7% probable and 41% possible IFI (see Figure 2).

Fungal diagnostic testing

During the study period, 133 (1,3)-β-D-glucan (BDG) tests were performed, of which 24.1% ($n=32$) were positive. Sixty-one galactomannan antigen tests were also performed, with a 3.3% positivity rate ($n=2$). BDG tests had a mean lead TAT (time from sampling to authorization) of under 2 days, and galactomannans a mean lead TAT of under 4 days. TATs of other fungal biomarkers are outlined in Table S1 (available as Supplementary data at *JAC-AMR* Online). Alongside fungal biomarkers, sampling of specific sites for fungal culture and species-specific or panfungal PCR were undertaken where possible.

In 41 cases (36.9%) pathogen identification was possible. Of these, 18 (43.9%) were cultured from sterile sites—blood, pericardial fluid or joint fluid—and 15 (36.6%) from non-sterile sites—intra-abdominal drain fluid, respiratory tract and urinary tract samples. The remaining eight pathogens were identified by blood markers: PJP PCR, panfungal PCR and *Aspergillus* biomarkers. Identified organisms are outlined in Table 2.

Antifungal usage and expenditure

During the study period, 121 courses of antifungal agents were prescribed for 111 patients. Forty-five (40.5%) patients were prescribed empirical antifungal drugs, with 32 (28.8%) receiving targeted antifungals. The remaining 34 (30.6%) patients were prescribed empirical antifungals and then changed to targeted antifungals. Twenty-two patients (19.8%), all of whom had underlying haematological diagnoses, had received prior antifungal prophylaxis, largely with posaconazole ($n=14$) or voriconazole ($n=5$).

From a treatment perspective, the most prescribed antifungal agents were caspofungin, fluconazole and voriconazole, as illustrated in Figure S1.

Consumption

Total annual consumption of antifungal agents, measured as DDDs per 1000 admissions, decreased by 25.1% (96.9 DDDs) from 2018 to 2022: from 384 to 287 DDDs/1000 admissions. The COVID pandemic in 2020 resulted in a marked decrease in hospital admissions and stands out as an anomaly in the data.

Regarding specific agents, from 2018 to 2022 itraconazole consumption demonstrated the greatest reduction, from 84.4 to 19.5 DDDs/1000 admissions (76.9% reduction). Its use, recommended as prophylaxis for several haematological conditions, has declined in favour of oral posaconazole, which has better tolerability and an improved pharmacokinetic profile. The proportional use of posaconazole increased from 20% to 32% of total use in 2022. The use of liposomal amphotericin (AmBisome®) remained stable throughout the 5 year period, accounting for 8%–15% of total antifungal use. Of note, isavuconazole consumption has not increased markedly, with

Table 2. Patient demographics and diagnosis of IFIs

Characteristic	
Age, median (IQR), y	56 (38.5–66)
Paediatric (age <18) cases, *n* (%)	12 (10.8)
Adult cases, *n* (%)	99 (89.2)
Male, *n* (%)	65 (59)
Referring specialty, *n* (%)	
Medical	15 (13.5)
ICUs	28 (25.2)
Haematology/oncology	41 (36.9)
Surgery	15 (13.5)
Paediatrics	12 (10.8)
IFI risk factors, *n* (%)	
Haematological malignancy	39 (35.1)
ITU stay	14 (12.6)
Bone marrow transplant	12 (10.8)
Surgery in the last 3 mo	11 (9.9)
Solid organ malignancy	5 (4.5)
Steroid use	5 (4.5)
Diabetes mellitus	4 (3.6)
Indwelling lines (CVC, TPN, urinary catheter)	4 (3.6)
Chronic lung disease	3 (2.7)
HIV or other immunodeficiency	3 (2.7)
Other	9 (8.1)
Includes: alcohol excess, chronic granulomatous disease, necrotizing pancreatitis, other immunosuppressive medication, PWID, prematurity	
No apparent immunosuppression	2 (1.8)
Diagnosis of IFI	
Sites of IFI, *n* (%)	
Respiratory	61 (55.0)
Intra-abdominal	20 (18.0)
Bloodstream	11 (9.9)
Line	6 (5.4)
Urinary tract	5 (4.5)
Rhino-sinusoidal	4 (3.6)
Fungal pathogen identified ($n=41$), *n* (%)	
Candida albicans	19 (46.5)
Aspergillus species	8 (19.5)
Nakaseomyces glabratus (*Candida glabrata*)	6 (14.6)
Other *Candida* species and related yeast	5 (12)
Mucoraceous moulds	1 (2.4)
Pneumocystis jirovecii	1 (2.4)
Sarocladium kiliense	1 (2.4)

CVC, central venous catheter; ITU, intensive therapy unit; PWID, person who injects drugs; TPN, total parenteral nutrition.

consumption remaining below 10% of total use per annum. Antifungal consumption is detailed in Figure 3.

Expenditure

Total antifungal expenditure decreased over the 5 year period, by 59.9% comparing expenditure in 2018 with 2022 (£1 586 765 versus £636 297). Expenditure data for systemic antifungals (excluding griseofulvin and terbinafine) are illustrated in Figure 4.

Antifungal expenditure decreased year on year, by £288 170 (18.5%) from 2019 to 2020, by £281 565 (22.2%) from 2020 to 2021, and by £348 748 (35.4%) from 2021 to 2022.

Outcomes

Advice was offered on several aspects of the management of fungal infection: antifungal therapy and duration, investigations and radiology. For the 111 patients discussed, 324 recommendations were made. A summary of advice offered is in Table 3. Most frequently addressed was the continuation of antifungal therapy, and planning for its duration. Rationalisation of antifungal therapy (alternative agent or stopping antifungal therapy) was discussed in 19.4% of cases, with advice on TDM and biomarker usage each discussed in 10% of advice. Advice resulted in antifungals being stopped on 38 occasions. Overall, the acceptance rate of the advice given by the AFS MDT was 93%. Dosing advice (67% acceptance rate) and advice on TDM (88% acceptance rate) were the only two domains with acceptance rates of less than 90%.

Discussion

This review outlines our AFS MDT service, which has improved the management of cases of IFI in adult and paediatric populations, reducing antifungal use and expenditure, and aligning mycological and clinical expertise in the care of high-risk individuals. Despite being an emerging priority in combatting antimicrobial resistance, with the WHO's priority list of pathogens recently broadened to include fungal organisms,[1] AFS still lags significantly behind broader antimicrobial stewardship initiatives, with specific AFS programmes rare in England.[31] Although UK-based AFS programmes have been described,[13,14,22,26] more recent consensus and guidance state clear goals for AFS programmes,[4,27] several of which we describe here.

Our weekly MDT-based approach involves additional experts in the management of patients with IFIs compared with programmes described previously.[14,22] These include a radiologist with interest in IFI, patients' clinical teams, which are key to contextualizing cases, and the input of experts in clinical mycology (see Figure 1). Alongside clinical infection specialists and antimicrobial pharmacists, the breadth of our MDT offers comprehensive advice, addressing several key aspects for patient care, fungal epidemiology, diagnostics and therapeutics (including advice on drug pharmacokinetics, susceptibility, TDM and management of drug side effects) on a weekly basis, as recommended by Johnson *et al.*[4] As such, we believe our programme demonstrates the most complete approach to AFS described to date.

The demographics of our cohort are similar to previously described cohorts.[13,14,22,32] However, previous studies have excluded paediatric patients, whereas we have not, given the importance of excellent AFS in these cases as well. Overall, the burden of IFIs and AFS initiatives in paediatric populations is minimally described.[33–35] Only two UK-based studies have explored antifungal prescription in children: one in those aged <90 days,[36] the other in those aged 90 days to 18 years.[37] Both explore prescribing patterns rather than involvement of paediatric teams and patients in formal AFS initiatives. With our study including adult *and* paediatric cases across all specialties, we offer

insight into this gap in current knowledge. Although the number ($n=12$) of paediatric cases in our cohort is low, it is critical to include these, to recognize key components of a successful AFS initiative for those looking to develop similar programmes.

The 30 day mortality in our cohort (22.7%) was similar to the 26% in-hospital mortality of Whitney *et al.*,[14] although higher than that of Micallef *et al.* (13.3%).[22] The difference may be attributable to differing recruitment, as Micallef included patients on high-cost antifungal agents as prophylaxis. Their mortality rate also seems remarkably low given the proportion of patients (>50%) on antifungals to treat *Aspergillus* species, in which invasive aspergillosis would often carry at least 20% mortality.[38] However, they neither discuss diagnostics, nor certainty of IFI diagnosis, so their cohort may reflect presumed, rather than proven IFI.

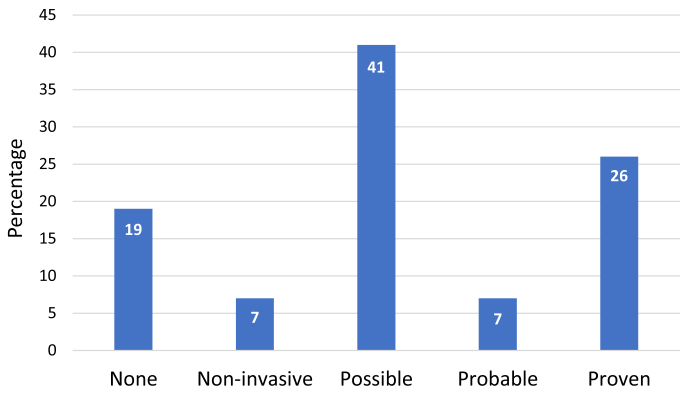

Figure 2. EORTC/MSG classification of IFIs in our cohort.

Only 26% of our cases had proven IFI, likely reflecting the challenge in diagnosing IFIs.[39] Although direct comparison with other studies is challenging due to varying definitions of proven IFI, this figure echoes other studies[14,17] in finding that whereas 25%–35% of patients had proven IFI, a far greater proportion (41%) had possible IFI, reflecting ongoing diagnostic uncertainty. In keeping with similar studies, pulmonary infection represented the greatest proportion of IFIs, with similar organisms found in those where an identifiable organism was found.[39]

This study also outlines the value of rapid diagnostics, a major barrier to AFS.[11,12,14,19,22,26] Johnson *et al.*[4] advocate for timely fungal diagnostics to ensure early AFS decisions can be facilitated. Due to our setting's proximity to the MRL in Bristol, the TATs of all fungal diagnostic samples were fast when compared with other UK sites,[14,31,40] with mean lead TAT for BDG of less than 2 days, and for galactomannan just over 3 days. Hamilton *et al.*[41] found that timely BDG TATs could result in significant cost-savings (£1643 per patient), with similar cost-savings in other settings.[42] Such rapid TATs available in our setting offered diagnostic information earlier than would have been available in other settings, impacting advice provided to clinical teams. It should be noted that the wider use of national networks could be beneficial as laboratories book in their own samples and then barcode them; these are then transported to the referral centre where they are uploaded and tested. Validated results are then immediately available on the requestor's laboratory information management systems. This not only eliminates the time required for postage of results but reduces the opportunity for typographical errors and negates the need for

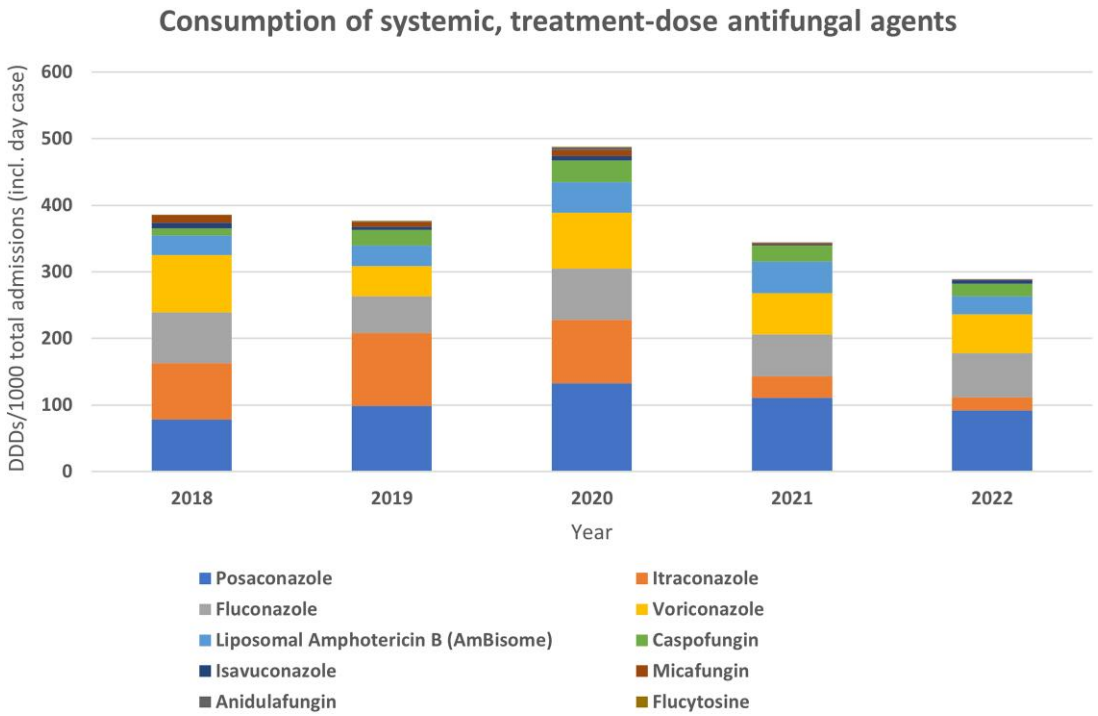

Figure 3. Consumption of systemic antifungals by calendar year.

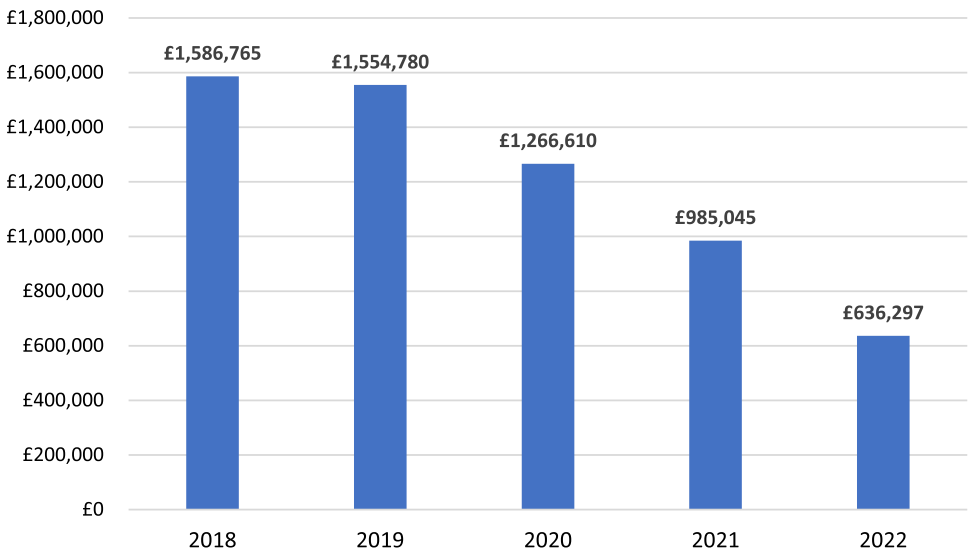

Figure 4. Total expenditure, systemic antifungals (calendar year).

Table 3. Antifungal stewardship advice

Advice given	Total ($N=324$), *n* (%)	Accepted ($N=300$), *n* (%)
Continue treatment course of antifungals	64 (19.8)	61 (95)
Continue antifungal prophylaxis	18 (5.6)	18 (100)
Dosing advice	15 (4.6)	10 (67)
Duration specified	61 (18.8)	59 (97)
IV-to-oral switch (same agent)	8 (2.4)	8 (100)
Biomarker advice	33 (10.1)	33 (100)
Start antifungal	9 (2.7)	9 (100)
Stop antifungal	38 (11.7)	36 (95)
Switch to alternative drug	25 (7.7)	25 (100)
Therapeutic drug monitoring (TDM)	32 (9.9)	28 (88)
Other[a]	21 (6.5)	13 (62)

[a]Includes obtaining further diagnostic specimens (e.g. bronchoalveolar lavage), need for further imaging, need for source control, clinical review by clinical infection team required.

duplication of effort in entering patient details at the referral centre and entering and validating results at the requesting centre, thus saving time.[40]

The AFS MDT has markedly reduced antifungal consumption and costs. Triazoles, specifically fluconazole then itraconazole, were the most used antifungals, in keeping with other cohorts,[13,14] although Logan *et al.*[17] found far greater use of empirical echinocandins in critical care settings. Generic caspofungin became available in the UK in 2017, affecting echinocandin choice, and reflected in updated guidelines from March 2019 recommending caspofungin over micafungin. Although this change inevitably led to a fall in drug costs, expenditure continued to decrease yearly after 2019, the point at which this change came into effect, suggesting additional factors also impacted the ongoing decrease. Isavuconazole remains unavailable as a generic equivalent and thus is only recommended by the MDT where its improved pharmacokinetic profile is beneficial, particularly its tendency to shorten, rather than prolong the QT interval, or when its enhanced spectrum, which includes some species of mucoraceous mould, make it a useful addition or follow-on oral option in some scenarios. However, it remains an expensive treatment option. We describe a 25% reduction in DDDs, similar to Whitney *et al*,[14] and comparable to a recent Spanish study focusing specifically on invasive candidiasis.[43]

Cost savings amount to £950 468 (59.9%) from 2018 to 2022, with the majority (£918 483) of this since the introduction of the AFS MDT in 2019. Other cohorts have described savings of between 9.7% and 30% in yearly antifungal costs,[14,21,44,45] whereas others suggest that savings of up to €250 000 per annum may be theoretically possible.[13] Nwankwo *et al*.,[46] investigating antifungal use for non-invasive FIs and IFIs, found they could save >£1 million yearly having introduced an AFS team. Although it can be difficult to compare figures between sites due to specialty mix at each site and differences in cost calculations, AFS interventions can substantially decrease antifungal consumption and costs, while offering enhanced patient care. After 4 years of AFS MDT in our setting, costs had reduced by over 50% and nearly £1 million.

Acceptance of advice in our cohort was remarkable, with over 90% acceptance by clinical teams. Previous cohorts[14,44] have demonstrated good acceptability but not with acceptance rates >90%. Even in aspects where acceptance of advice was below 90%, such as TDM, this echoes previous findings,[14] which may reflect challenges in antifungal TDM such as its time-consuming nature and uncertainty within clinical teams enacting TDM guidelines.[15,47] Although further qualitative work may be needed to clarify exactly why this is the case, the broad expertise available in our MDT, as well as the relationships fostered with clinical teams who regularly attend meetings to discuss their cases, likely contribute to this success.

Our study has several limitations. Although including adult and paediatric patients, this study remains a single-centre study, and therefore will have aspects that are challenging to generalize to other settings. Ultimately a multicentre study exploring the

diagnosis, management and outcomes of IFIs would be optimal to provide a comprehensive national dataset. Given our centre's access to mycologists, and proximity to the MRL for fungal diagnostics, the TATs that we report may not be generalizable to other UK sites, although this is clearly beneficial for our patient cohort. Methods for recruitment of cases for the AFS MDT rely on antimicrobial pharmacists and clinical teams presenting cases for discussion. Although this is robust enough to capture critical and complex cases there may be individual cases missed. With the planned introduction of electronic prescribing in our setting within 12 months, this will support identification of relevant cases for discussion. Fourth, cost analysis focuses on drug costs, without including staff costs and laboratory and radiological diagnostics costs, which could further strengthen this work. Finally, future data will include adverse effects of antifungal agents and the utility of the MDT on consequent advice, which have not been analysed in this cohort.

In summary, we demonstrate a comprehensive approach to an AFS programme, centred on a weekly MDT involving a broad range of specialists in IFI alongside clinical teams, particularly clinical mycologists. The complex nature of patients and cases warrants the MDT approach as suggested previously.[4,27] Offering AFS advice to an unselected patient cohort, in comparison with previous work that often focuses on specific groups, such as those in haemato-oncological or critical care settings or discounting paediatric patients, we demonstrate that our approach can support accurate IFI diagnosis, alongside reduction in antifungal consumption and expenditure. In addition to this, our approach has resulted in near exemplary acceptance of advice by clinical teams. Access to rapid fungal diagnostics clearly adds value to these tests in our cohort and must promote pathways to ensure sites further from such laboratory services can access testing as readily as possible, as this remains a significant barrier for locations without the geographical benefits of a local fungal diagnostic service. Future work is exploring expansion of the service to other local hospitals, and ultimately aiming for a regional AFS MDT to support the South-West region. This weekly MDT-based approach should represent a model that other AFS initiatives nationwide can look to replicate given its success in promoting AFS in a sustainable manner.

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Transparency declarations

All authors have nothing to declare.

Supplementary data

Table S1 and Figure S1 are available as Supplementary data at *JAC-AMR* Online.

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