Impact of an antifungal stewardship programme in a tertiary respiratory medicine setting: A prospective real-world study

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ABSTRACT

There has been an increase in fungal infections in patients with chronic lung disease over the past decades, which is associated with rapidly increasing costs to healthcare systems.

An antifungal stewardship team was introduced to a tertiary cardiopulmonary hospital, consisting of a medical mycologist and pharmacy support providing weekly stewardship ward rounds, twice monthly multidisciplinary team meetings and a dedicated weekly outpatient clinic. A database was set up to record the activity of the stewardship team.

During the first eighteen months of implementation the antifungal stewardship team had reviewed 178 patients, with 285 recommendations made to inpatients, and 287 outpatient visits. The commonest diagnoses treated were allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis. Cystic fibrosis was the largest patient group treated followed by asthma and interstitial lung disease. There was a significant, sustained reduction in monthly antifungal expenditure (p=0.005) by £130,000 per month. There was also a significant reduction in antifungal use measured as Defined Daily Dose/100 bed days (p=0.017). There were no significant changes in expenditure on diagnostic tests. There has been a trend toward more patients having therapeutic levels of voriconazole (p=0.086) and a significant increase in therapeutic levels of posaconazole (p<0.0001).

This study shows that an effective antifungal stewardship programme can significantly reduce expenditure in a specialist respiratory service.
INTRODUCTION
Antimicrobial resistance has emerged as a major threat to modern healthcare systems (1). Within this context, the major focus has been on antibacterial resistance, which has had a major adverse impact on respiratory health both within the context of chronic respiratory disease as well as acute respiratory infection (2).

There has been an incompletely understood emergence of chronic fungal infection across multiple chronic respiratory diseases, in particular due to *Aspergillus fumigatus*. This may be in part due to increased awareness and recognition, as well as the introduction of prolonged fungal-specific culture and serological tests to aid in diagnosis. Additionally patients with chronic respiratory disease are surviving longer with impaired local immunity in the lung, allowing more fungal respiratory infections.

In contrast to invasive pulmonary aspergillosis, chronic pulmonary forms of aspergillosis are poorly defined (though systematic approaches have begun to take shape (3, 4)), and suffer from a relative lack of well-designed randomised controlled trials to guide treatment. Risk factors include bronchiectasis, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), transplantation, prolonged steroid use and other immunosuppressive agents such as chemotherapy (5, 6). *Aspergillus* infections have increased in incidence over the past 40 years (7), with recent estimates suggesting there may be 240,000 patients with chronic pulmonary aspergillosis (CPA) (3), and over 1,000,000 patients with allergic bronchopulmonary aspergillosis (ABPA) in Europe (8). A number of recent studies have highlighted the emerging threat of triazole multi-drug resistance in *Aspergillus fumigatus* (9). We and others observe emergent triazole resistance dependent both on agricultural exposure to triazoles (10) and *de novo* emergence of resistance in individuals receiving chronic triazole therapy; currently the only orally available mould-active
antifungal drug class. There are data that increasing rates of triazole resistance have been noted in patients with chronic pulmonary aspergillosis (11); that this may develop during treatment, and may be associated with sub-therapeutic drug levels (12). Achieving therapeutic levels of triazole using therapeutic drug monitoring (TDM) are associated with treatment success in invasive fungal disease (13–15), though there are no published data in chronic respiratory disease.

In the USA, national data suggest that 4.9% of antimicrobial expenditure in 2015 was due to antifungals (approximately $2.4 billion), an 18.8% increase compared to 2014 (16). The principles of antifungal stewardship are to optimise antifungal prescription by assessing spectrum of activity, pharmacokinetics, duration and route of administration (17). This is particularly important in the context of antifungal toxicities and costs. There are relatively few data on the effect of antifungal stewardship programmes and largely these refer to invasive fungal disease in the context of haematological disorders and on intensive care units. A UK stewardship programme demonstrated crude savings of £180,000 on antifungal expenditure in a year (18), whereas Spanish studies have reported reduction in antifungal expenditure by 11.8% ($370,681) (19) and 13.9% ($529,163) (20). To our knowledge there has not been an assessment of the effect of antifungal stewardship in chronic respiratory disease patients.

Taken together, these observations are indicative of an urgent clinical need to limit inappropriate triazole antifungal usage through judicious antifungal stewardship. We report on the delivery and impact of an antifungal stewardship programme targeting the use of antifungals within the respiratory directorate at our centre.
RESULTS

178 patients were reviewed over an 18-month period. The largest patient group was
cystic fibrosis (69 patients), followed by asthma (32 patients), sarcoidosis (25
patients), other interstitial lung diseases (15 patients), bronchiectasis (15 patients),
other primary immune deficiency (8 patients), chronic obstructive pulmonary disease
(5 patients), and the remainder with other underlying diseases. Diagnoses after
review by the stewardship team include allergic bronchopulmonary aspergillosis (63
patients), chronic pulmonary aspergillosis (31 patients), mycetoma (20 patients),
Aspergillus bronchitis (13 patients), infections with other mould species (13 patients),
Aspergillus colonisation (10 patients), pleuroparenchymal fibroelastosis (5 patients),
and 6 other diagnoses. 16 patients had no confirmed fungal infection.

Of the CF population, 51% were male and mean age was 27.9 (SD 7.6). In the non-
CF population, 62% patients were female and mean age was 56.7 (SD 12.8).

Apart from Aspergillus species, other moulds that were thought to be contributing to
respiratory disease included: Scedosporium apiospermum, Scedosporium
prolificans, Exophiala dermatitidis, and Rasamsonia argillacea; all in CF patients.
Current rates of resistance amongst screened isolates of A. fumigatus at RBHT are
13.1%, though there is insufficient data to see if this changed after the initiation of
the stewardship programme.

285 antifungal stewardship recommendations were made to inpatients by the
stewardship team. The recommendations included arranging review in specific
outpatient clinic or at the fungal MDT, advise on specific investigations to
confirm/refute diagnosis, stepping down treatment to oral antifungals, ensuring
appropriate dosing to attain therapeutic levels and avoid toxicity, stopping treatment
in patients without confirmed fungal disease or likely to have colonisation only, and on occasion escalating or adding in treatment to address failure to achieve therapeutic goals. Additionally, 287 outpatients appointments were made over the study period allowing the Medical Mycologist to direct antifungal management in these patients. Overall expenditure on antifungals was reduced from £290,000 per month to £160,000 per month (Figure 1A), a 44.8% reduction, and equivalent to over a million pounds a year has been saved in terms of antifungal expenditure. There was a significant effect when analysed by interrupted time sequence analysis (ITSA) (p=0.005). This was largely driven by reduced use of intravenous voriconazole and caspofungin. This was also reflected in a reduction in defined daily dose (DDD)/100 bed days of all antifungal medication (ITSA, p=0.017) (Figure 1B), which indicates a reduction in antifungal use while stripping out variations in individual medication cost. There was a similar effect on both intravenous and oral antifungal use (Figure 1C).

During the study period 6 patients died. 5 died of progressive respiratory failure related to their underlying respiratory condition (bronchiectasis, cystic fibrosis, interstitial lung disease, relapsing polychondritis) not directly related to their fungal disease, and one of liver failure secondary to cirrhosis and hepatocellular carcinoma. None of the deaths could be directly attributed to the fungal lung disease or antifungal medications.

Individual drug costs varied throughout the study period dependent on Trust - pharmaceutical company negotiations. In addition voriconazole came off patent in July 2016, potentially contributing to reduction in drug costs, though no obvious effect can be seen on expenditure data.
Despite this, while expenditure on diagnostics has shown a gradual increase over several years, this was not directly associated with the commencement of the stewardship programme. Spend on TDM has not changed significantly (ITSA, p=0.28) (Figure 2), serological testing for *Aspergillus* IgG and *Aspergillus* IgE has decreased, but not significantly (p=0.074 for *Aspergillus* IgG, and p=0.381 for *Aspergillus* IgE) (Figure 3A and 3B). Although numbers are small there has been an increase in galactomannan and β-D-glucan expenditure since the stewardship programme started (Figure 3C), though probably due to the relatively low usage this was not statistically significant (galactomannan: p=0.38, β-D-glucan: p=0.32). TDM analysis has shown a significant increase in posaconazole levels into the therapeutic range over time (p<0.0001), a non-significant increase in voriconazole levels (p=0.086), but no effect on itraconazole levels (Figure 4) as measured by linear regression analysis. Our dataset’s current length of follow up is inadequate to formally assess therapeutic clinical responses such as radiological changes, lung function, exacerbation rate and quality of life measurements.

Overall spending in fungal microbiology has increased over this time period. However this largely stems from the introduction of extended 4-week fungal culture of sputum for CF patients in October 2014. Once the period prior to this was excluded, microbiology fungal diagnostic expenditure remained static (ITSA, p=0.85) (Figure 5). *Aspergillus* PCR was trialled during this time, but was not found to be clinically useful.
DISCUSSION

The use of antifungals in chronic respiratory disease has increased markedly over the past decades (21). With patients surviving longer, and in particular with prolonged immunosuppression (e.g. oral steroids), the burden of fungal disease has increased. This has been particularly evident at RBHT, given that it is a provider of specialist cardiorespiratory care. Data on treatment is sparse with only a few randomised controlled trials (22–24) and observational data (25, 26) guiding treatment and informing guidelines (3, 4, 27).

The introduction of an antifungal stewardship team, outpatient review clinic and detailed discussion of patients by multidisciplinary assessment has been effective in reducing antifungal expenditure without an increase in morbidity or mortality. This is likely due to closer adherence to international guidelines, which have been incorporated into local trust microbiology guidelines. Common contributions to care given by the stewardship team include the use of therapeutic drug monitoring to optimise antifungal dosage prior to avoid switching agents, and rationalising dual antifungal treatment approaches. The reduction in expenditure has largely derived from the reduction of intravenous treatment, which would have the additional benefit of reducing inpatient stays and attendant costs. Improved therapeutic drug monitoring may also have enabled a lesser requirement for second line therapies.

Interestingly, there has been an increase in the number of patients with therapeutic levels of antifungals despite no increase in diagnostic costs. This may suggest that prior to the set up of the stewardship team these tests were requested but little heed taken to the results, likely due to the lack of confidence of clinicians in the use of antifungals. This was not seen with itraconazole, the drug most used by non-experts.
within the trust, perhaps supporting this speculation. The Trust has derived
significant savings, while continuing to provide excellent care.

There are data that suggest increased serum concentrations of voriconazole (14, 28)
and posaconazole (15) in therapeutic range have been associated with better
outcome, but are observational studies with few patients in invasive fungal disease.
In general, few patients achieve sufficient levels of antifungal drugs in serum (29).
There has not been previous data examining the use of TDM for chronic fungal
diseases. The lack of longitudinal data means that our data set is underpowered to
inform or comment on clinical responses to azoles. Indeed, tissue levels of
antifungals may be more relevant than serum levels in chronic pulmonary fungal
disease; currently there is no recognised mechanism of determining pulmonary
tissue drug penetration.

The use of antifungals in patients with chronic respiratory disease has been
increasing over the past few years. This is likely to be a result of better recognition
of fungal disease and patients with conditions such as COPD and sarcoidosis
surviving longer. There is also a suspicion that fungal infection may drive some
respiratory pathology, e.g. ABPA and pleuroparenchymal fibroelastosis. There is a
clear need for further research into how these moulds contribute to pathogenesis,
and the development of less toxic antifungal agents.

As such, the future increase in the use of antifungals in patients with chronic
respiratory disease seems likely, and we have shown that antifungal stewardship is
effective and safe. We would advocate that this model could be disseminated to
other centres where antifungal expenditure is climbing to good effect.
MATERIALS AND METHODS

The Royal Brompton & Harefield NHS Foundation Trust is a tertiary centre caring for patients with cardiac and respiratory disease. Within the respiratory directorate, care is provided for large patient cohorts across the south of England for chronic respiratory conditions such as CF, difficult asthma, and interstitial lung diseases. Many patients are referred when their secondary care physicians have difficulty managing them so there are a high proportion of patients with advanced and intractable diseases. There is no emergency department so the majority of inpatients have been admitted electively, often for intravenous treatment or monitoring.

In January 2015, a consultant Infectious Diseases (ID) physician who is also a medical mycologist and a new microbiology lead were appointed, partly to address the use of antifungals within the trust. An antifungal stewardship team comprising of the ID physician and a specialist pharmacist was set up, with a view to reviewing inpatients on antifungals on a weekly basis. A weekly outpatient clinic was organised to review those with chronic fungal lung disease resulting in the care of these patients being taken over by the medical mycologist. Monthly multidisciplinary team meetings were also arranged as a forum for outpatients to be discussed; involving the physicians primarily caring for the patient, radiologists, and stewardship team. This allowed the diagnosis to be reviewed, appropriate investigations to be carried out, and specific advice regarding antifungal prescriptions to be discussed.

The patients were identified by the pharmacy team using dispensing records and electronic prescribing systems, and all patients reviewed were entered onto a...
Microsoft Access database. There was also extensive re-writing of the antimicrobial guideline including a large section on antifungal use.

Data for the first 18-months of fungal stewardship implementation was recorded. This included patient demographics, underlying diagnoses, fungal diagnosis, therapeutic drug levels, microbiology, serology, radiology, and advice given. Calcofluor white fluorescence was used in sputum and bronchoalveolar lavage samples. Laboratory culture was used to identify moulds by morphology, and in-house susceptibility testing was performed, with samples also being sent to the Public Health England Mycology Reference Laboratory in Bristol. *Aspergillus* IgE and IgG were performed in house in the biochemistry laboratory. Serum and bronchoalveolar lavage levels of galactomannan were performed weekly in-house in the microbiology laboratory, with β-D-glucan levels sent to Public Health England Mycology Reference Laboratory. TDM was also performed in-house for itraconazole, voriconazole, and posaconazole by liquid chromatography and tandem mass spectrometry.

Results were analysed on Graphpad Prism 7, and the effect of intervention analysed using ITSA calculated by Newey West regression, a semi-quantitative statistical test, on Stata/MP 12.0. This study was registered with the Quality & Safety Department of RBHT.
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TRANSPARENCY DECLARATION

None to declare.


**Figure Legends**

Figure 1. Expenditure on antifungal drugs.

A) Expenditure on systemic antifungals against time shown as segmental linear regression and ITSA analysis (p=0.005). B) Defined daily dose of antifungals per 100 bed days by quarter shown as segmental regression and ITSA analysis (p=0.017).

C) Defined daily dose of oral and intravenous antifungals per 100 bed days shown as segmental regression.

Figure 2. Expenditure on therapeutic drug monitoring.

Expenditure on therapeutic drug monitoring shown as segmental linear regression and ITSA analysis (p=0.28).

Figure 3. Expenditure on fungal serological and biochemical markers.

A) Expenditure on *Aspergillus* IgE against time with segmental linear regression and ITSA analysis p=0.381, B) expenditure on *Aspergillus* IgG against time with segmental linear regression and ITSA analysis (p=0.074), C) Expenditure on galactomannan (p=0.38) and B-D-glucan (p=0.32) shown as segmental linear regression and ITSA analysis.

Figure 4. Therapeutic drug levels over time.

A) Correlation between date and itraconazole level (dotted lines mark the therapeutic range) R=0.0006, p=0.535, B) Correlation between date and voriconazole level R=0.013, p=0.086, C) Correlation between date and posaconazole level R=0.057, p<0.0001.
Figure 5. Microbiology fungal diagnostics expenditure.

A) Fungal diagnostic expenditure against time. B) Fungal diagnostic expenditure after prolonged culture for CF samples was introduced with segmental linear regression, ITSA analysis (p=0.85).
Figure 1. Expenditure on antifungal drugs.

A

Expenditure (£ per month)

Month

B

C

Quarter

Quarter

IV Antifungals

Oral Antifungals

DDO/100 bed days

DDO/100 bed days
Figure 3. Expenditure on fungal serological and biochemical markers.
Figure 4: Therapeutic drug levels over time.
Figure 5. Microbiology fungal diagnostics expenditure

A

B

Fungal diagnostic expenditure (€ per month)

Fungal diagnostic expenditure (€ per month)