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Impact of a diagnostics-driven antifungal stewardship programme in a UK tertiary referral teaching hospital

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Objectives: A concise invasive candidosis guideline (based on the ESCMID candidaemia guideline) utilizing an informative biomarker [serum β-1–3-D-glucan (BDG)] was developed in 2013 by an antifungal stewardship (AFS) team and implemented with the help of an AFS champion in 2014. The main aims of the AFS programme were to reduce inappropriate use of antifungals and improve patient outcomes. The aim of this project was to evaluate the compliance of the ICU teams with the invasive candidosis guideline and the impact of the AFS programme on mortality and antifungal consumption on the ICUs (total of 71 beds).

Methods: All patients who were prescribed micafungin for suspected or proven invasive candidosis during 4 month audit periods in 2014 and 2016 were included. Prescriptions and patient records were reviewed against the guideline. Antifungal consumption and mortality data were analysed.

Results: The number of patients treated for invasive candidosis decreased from 39 in 2014 to 29 in 2016. This was mainly due to the reduction in patients initiated on antifungal therapy inappropriately: 18 in 2014 and 2 in 2016. Antifungal therapy was stopped following negative biomarker results in 12 patients in 2014 and 10 patients in 2016. Crude mortality due to proven or probable invasive candidosis decreased to 19% from 45% over the period 2003–07. Antifungal consumption reduced by 49% from 2014 to 2016.

Conclusions: The AFS programme was successful in reducing the number of inappropriate initiations of antifungals by 90%. Concurrently, mortality due to invasive candidosis was reduced by 58%. BDG testing can guide safe cessation of antifungals in ICU patients at risk of invasive candidosis.

Introduction

Antimicrobial stewardship (AMS) aims to preserve the future effectiveness of antimicrobial agents and to reduce unintended adverse patient outcomes related to overuse.[1,2] Promoting selection of the optimal antimicrobial regimen, duration and route of administration are key in this endeavour. There are two fundamental tools in AMS: guidelines for empirical therapy; and reliable diagnostic tests that can guide initiation and discontinuation of antimicrobial therapy. Antifungal stewardship (AFS) shares the aims and approaches of AMS but has its own specific features and challenges, which include limited availability of diagnostic testing, long laboratory turn-around times, the lack of AFS expertise outside specialist centres and a paucity of evidence identifying effective AFS interventions outside specific patient cohorts.[3,4] Due to these challenges, there is a need for different leadership and

communication models if AFS is to be effectively practised. The focus of most AFS programmes has been on the management of invasive candidosis, the most common severe nosocomial fungal infection.[5] However, to date, most attention has been paid to reducing the use of expensive antifungal agents rather than the impact of AFS on patient outcomes or antifungal resistance.[6–10]

Candida species are an increasingly prevalent cause of bloodstream infections (BSIs) in the ICU.[11–14] Although candidaemia has a high attributable mortality, there is significant variation between centres and patient groups.[12,14–17] Early and appropriate initiation of antifungal therapy has been reported to improve outcomes.[18,19] Blood cultures remain the mainstay of diagnosis but their sensitivity is poor due to the low intensity of fungaemia.[20,21] This is a major challenge also for molecular methods. Biomarker tests such as serum β-1–3-D-glucan (BDG) are available but their specificity is low. Therefore, clinicians often rely on their clinical experience and judgement. This has led to overuse of empirical and prophylactic antifungal therapy, in particular echinocandins, in many ICUs.[12,22,23]

The AFS programme at Wythenshawe Hospital has been developed over the past 8 years. The key targets of the programme are to improve patient outcomes by: (i) updating and clarifying antifungal guidelines; (ii) involving and educating champions; (iii) improving access to timely diagnostic testing; and (iv) reducing unnecessary use of antifungal therapy. A local guideline for suspected or proven invasive candidosis (Figure 1) was developed based upon the ESCMID guideline for diagnosis and management of invasive candidosis in non-neutropenic adult patients.[24] Due to its very high negative predictive value in a low-prevalence setting such as ours, serum BDG testing was introduced as a rule-out test to guide the discontinuation of therapy in the absence of other microbiological evidence of invasive candidosis.[25,26] The launch of the guideline in January 2014 was followed up by an online clinical educational quiz for prescribers, circulation of guideline posters, and the active presence of the Infectious Diseases (ID) team in the ICUs. An intensive-care physician was recruited by the AFS team as an AFS champion.

The aim of this project was to evaluate the compliance of the ICUs with the current local guideline. Additionally, we aimed to evaluate the impact of the AFS programme on the use of antifungal therapy, and on mortality due to invasive candidosis.

Methods

There are two separate ICUs in Wythenshawe Hospital staffed by separate intensive-care teams: (i) a cardiothoracic and heart-lung transplant ICU; and (ii) a mixed medical and surgical (including burns) ICU; these two ICUs have a total of 71 beds. The compliance of the intensive-care teams with the current local invasive candidosis guideline was audited over a 4 month audit period (April–July) in 2014 and reaudited over the same period in 2016. All patients who were prescribed micafungin during the audit periods were identified from pharmacy databases. Patients treated for indications other than suspected or proven invasive candidosis, or those not admitted to an ICU, were excluded from analysis. All prescriptions were reviewed by the audit team against the local guideline (Figure 1). During the 2014 audit period the AFS team actively followed up patients who were prescribed micafungin, and guided the use and interpretation of diagnostic testing. In 2016, there was no additional involvement beyond routine clinical practice.

As per the local guideline (Figure 1), patients with *Candida* spp. isolated from blood cultures were classified as 'proven invasive candidosis'. Patients with persistent clinical symptoms, host risk factors for candidosis and with other diagnostic evidence of invasive candidosis (e.g. positive serum BDG or *Candida* spp. isolated from line tip cultures) were classified as 'probable invasive candidosis'. The use of antifungal therapy was defined as appropriate in all patients with proven or probable invasive candidosis. Patients with persistent clinical symptoms and host risk factors for candidosis but with negative blood cultures were classified as 'suspected invasive candidosis'. Initiation of antifungal therapy was deemed appropriate in patients with persistent clinical symptoms and host risk factors for candidosis but no diagnostic evidence of invasive candidosis (e.g. negative blood culture for *Candida* or negative BDG). In contrast, antifungal therapy was deemed inappropriate in patients with 'suspected invasive candidosis' but with no clinical symptoms and/or host risk factors for candidosis.

Hospital micafungin consumption data were analysed for a 3 year period (April 2014–March 2017). The data were obtained from the AFS team database. Appropriateness of antifungal treatment, compliance with the guideline, all-cause mortality during the 4 month audit periods and micafungin consumption were used as outcome measures. The incidence of invasive candidosis at Wythenshawe Hospital was audited for a 12 year period (2005–16). Cases of *Candida* spp. BSIs were identified from laboratory databases and the incidence calculated per 100000 bed-days.

Statistical analysis

Comparison of the proportions of patients with 'proven or probable invasive candidosis', 'appropriately suspected but candidosis excluded' or 'inappropriately suspected' in 2014 and 2016 was made using a Pearson χ^2 test and two-proportion *Z*-tests in SPSS version 22 (IBM Corp., Armonk, NY, USA). Analysis of changes in the incidence of invasive candidosis was made by linear regression. Statistical significance was set at $P < 0.05$.

Ethics

This study was a retrospective service evaluation and ethical approval was not required, as per UK Health Research Authority guidelines.

Results

2014 audit period

During the 4 month period in 2014, 39 patients admitted to ICU were treated for suspected or proven invasive candidosis (Figure 2a). Of these, 6 (15%) had *Candida* spp. isolated from blood cultures, with 3 patients receiving extracorporeal membrane oxygenation (ECMO). All patients with proven invasive candidosis were treated according to the local guideline.

When assessed by the AFS team, the initiation of micafungin treatment was deemed appropriate in 15/33 (45%) of the suspected invasive candidosis cases; in 3/15 (20%) patients micafungin was continued for at least 2 weeks (Figure 2a). For the remaining 12/15 (80%) patients treatment was discontinued within 1 week following advice from the AFS team, based upon negative blood culture or BDG result. Overall for those patients where treatment was deemed appropriate, 14/15 (93%) had blood cultures taken and 6/13 (46%) had BDG tests performed. One patient was prescribed a higher dose (150 mg) of micafungin in the absence of clinical suspicion of aspergillosis or oesophageal candidosis. In 18/33 (55%) cases of suspected invasive candidosis the initiation of treatment was deemed inappropriate. In 15/18 (83%) the indication recorded for the initiation of micafungin therapy was *Candida* spp. isolated from a single non-sterile site sample such as sputum or urine in the absence of clear risk factors for invasive candidosis. In 3/18 cases there was no clear indication of

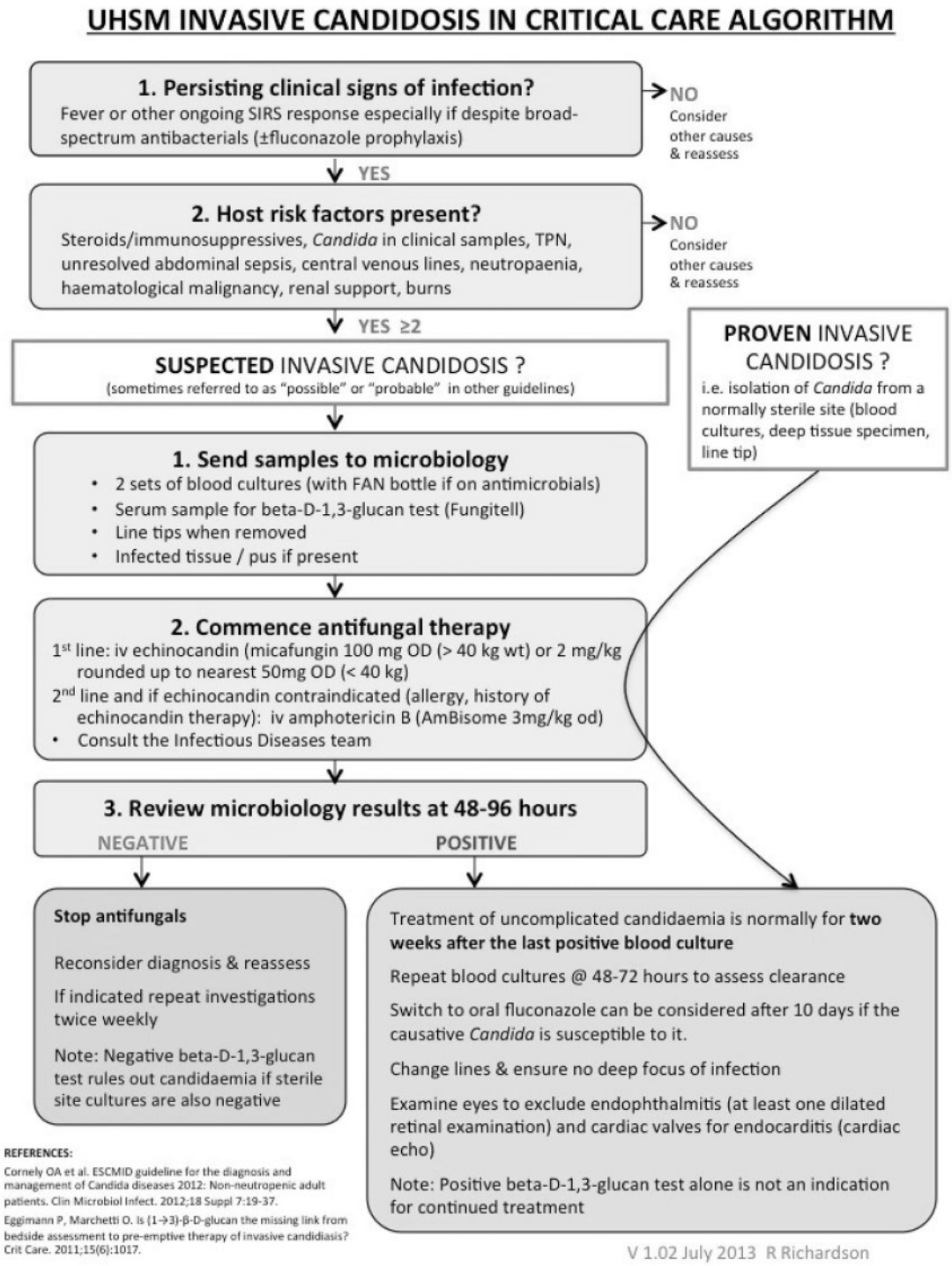

Figure 1. University Hospital of South Manchester, UK, invasive candidosis algorithm for ICUs launched in January 2014.

fungal infection. Micafungin treatment was discontinued within 1 week on the advice of the AFS in 13/18 (72%) cases where it was deemed inappropriate.

Overall, only 10/33 (30%) patients with suspected invasive candidosis had serum BDG requested and only one was taken at the time of initiation of micafungin therapy. Of all samples, 9/10 (90%) were negative. The correctly timed sample was negative but was not used to guide the stopping of therapy as the patient died soon after treatment was initiated.

None of the patients with proven invasive candidosis died within 30 days of micafungin initiation. Eight patients with suspected invasive candidosis died within 30 days of the initiation of treatment. These patients suffered from: multi-organ failure whilst on ECMO ($n = 1$), pulmonary haemorrhage ($n = 1$), post-surgical

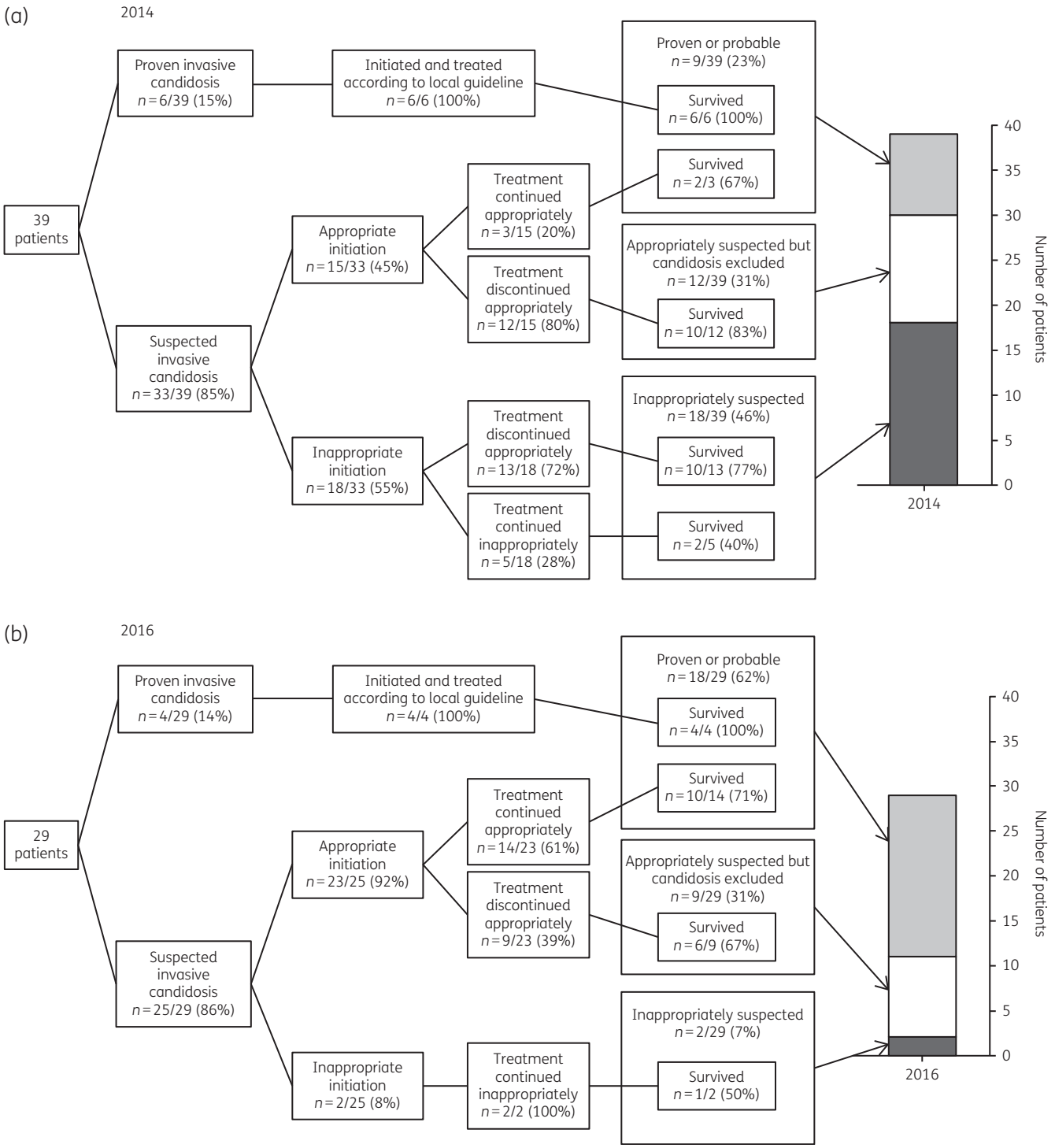

Figure 2. Summary of guideline compliance, diagnoses and patient outcomes in 2014 (a) and 2016 (b).

complications ($n = 2$), pneumonia ($n = 3$) and interstitial lung disease ($n = 1$). None of these patients had BDG testing performed on initiation of micafungin therapy. One patient who was on ECMO had *Candida albicans* DNA detected by PCR in blood, and died 8 days after initiation of micafungin; however, this patient was also bacteraemic with *Klebsiella* and *Escherichia* species.

2016 audit period

Twenty-nine patients admitted to ICU were treated for suspected or proven invasive candidosis (Figure 2b). Of these, 4/29 (14%) had *Candida* spp. isolated from blood cultures. All patients ($n = 4$) with proven invasive candidosis were treated according to the local guideline and all had positive serum BDG test results.

When assessed by the AFS team, the initiation of micafungin treatment was deemed appropriate in 23/25 (92%) patients with suspected invasive candidosis (Figure 2b). The treatment was discontinued within a week for 9/23 (39%) patients following advice from the AFS team, based on negative blood culture and/or BDG results. For 14/23 (61%) patients the treatment was continued for ≥2 weeks based on positive BDG or other clinical factors. Overall, of those patients for whom the initiation of treatment was deemed appropriate, 21/23 (91%) had blood cultures done, and 21/23 (91%) had BDG done; 8/21 (38%) BDG results were negative, and in 5 cases the negative result was used to guide discontinuation of therapy. One patient was prescribed a higher dose (150 mg) of micafungin in the absence of clinical suspicion of aspergillosis or oesophageal candidosis.

In 2/25 (8%) cases of suspected invasive candidosis the treatment was deemed inappropriate by the AFS team. In one case the indication recorded for the initiation of micafungin therapy was *Candida* spp. isolated from sputum in the absence of clear risk factors for invasive candidosis. In the other case there was no clear indication of fungal infection. Treatment was inappropriately continued for both patients. One patient had a blood culture performed but no BDG testing, and the other had neither blood culture nor BDG testing.

No patient with proven invasive candidosis died within 30 days of micafungin commencement. Eight patients with suspected invasive candidosis died within 30 days of micafungin initiation. These patients suffered from: multi-organ failure whilst on ECMO ($n = 2$) or left ventricular assist device (LVAD) ($n = 1$), post-surgical complications ($n = 3$), pneumonia ($n = 1$) and bacterial sepsis ($n = 1$).

Comparison of 2014 and 2016

Between 2014 and 2016, there were significant changes in the numbers of patients categorized as 'proven or probable invasive candidosis', 'appropriately suspected but candidosis excluded' and 'inappropriately suspected' ($P = 0.01$). The number of patients with 'proven or probable invasive candidosis' significantly increased from 9/39 (23%) in 2014 to 18/29 (62%) in 2016. Over the same period the number of patients 'inappropriately suspected' significantly reduced from 18/39 (46%) to 2/29 (7%).

Micafungin and laboratory expenditure

The monthly micafungin expenditure at the Wythenshawe Hospital decreased from £81000 (€90000) per month to £40000 (€45000) (−49%) during the 24 month follow-up (Figure 3). There was no change in the vial price of micafungin or in the consumption of other antifungal agents over the same period.

The BDG measurements were provided by the Mycology Reference Laboratory (MRCM) located at the Wythenshawe Hospital site. The mean monthly consumable costs for BDG tests (Fungitell, Associates of Cape Cod, MA, USA) in 2016 were £3739, which allows up to 21 tests done twice weekly. The cost of laboratory technician time (6 h per week) to do the tests was some £390 per month. Therefore, the total cost of BDG testing at Wythenshawe Hospital was £4129 per month.

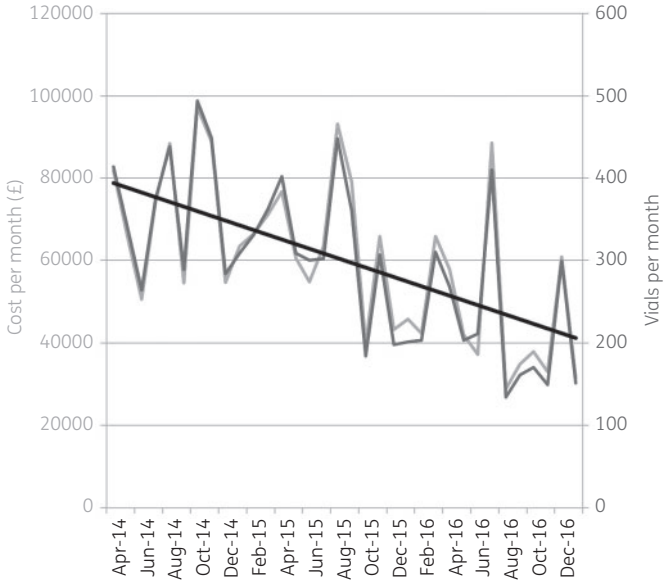

Figure 3. Total use of micafungin at Wythenshawe Hospital from April 2014 to December 2016. The black line is the linear regression trend line for cost per month (£).

Invasive candidosis incidence

The total number of patients reported with *Candida* spp. in blood cultures and the incidence of *Candida* BSIs per 100000 bed-days at Wythenshawe Hospital between 2005 and 2016 are summarized in Figure 4. The incidence of culture-positive invasive candidosis at Wythenshawe Hospital decreased significantly from 7.7/100000 bed-days in 2007 to 5.7/100000 bed-days in 2016 ($R^2 = 0.44$, $P = 0.037$; Figure 4a). The number of cases with *Candida* spp. isolated from the bloodstream on ICUs has remained stable (Figure 4b). In most years, *C. albicans* was the most common finding, followed by *Candida glabrata* and *Candida parapsilosis*. There has been no marked change in the species distribution over the years.

Discussion

Successful AFS programmes build on implementation of guidelines for prompt administration of empirical antifungal therapy coupled with diagnostic tests that can guide safe discontinuation of therapy. The aim of our programme was not to restrict the initiation of antifungal therapy in patients at risk of invasive *Candida* infection, as timely administration of empirical antifungal agents to patients with invasive candidosis is associated with reduced mortality.[18,19] During the data collection periods in 2014 and 2016, the overall crude mortality in patients with proven or probable invasive candidosis was 19% (5/27). This compares favourably with the overall crude mortality due to invasive candidosis of 45% (a reduction of 58%), reported by our centre for the period of 2003–07,[27] and >35% by others.[16,28]

The knowledge that early initiation of antifungal therapy improves outcomes, and the introduction of less toxic antifungal agents, such as the echinocandins, puts pressure on clinical teams to treat patients with early empirical therapy. Full diagnostic work-

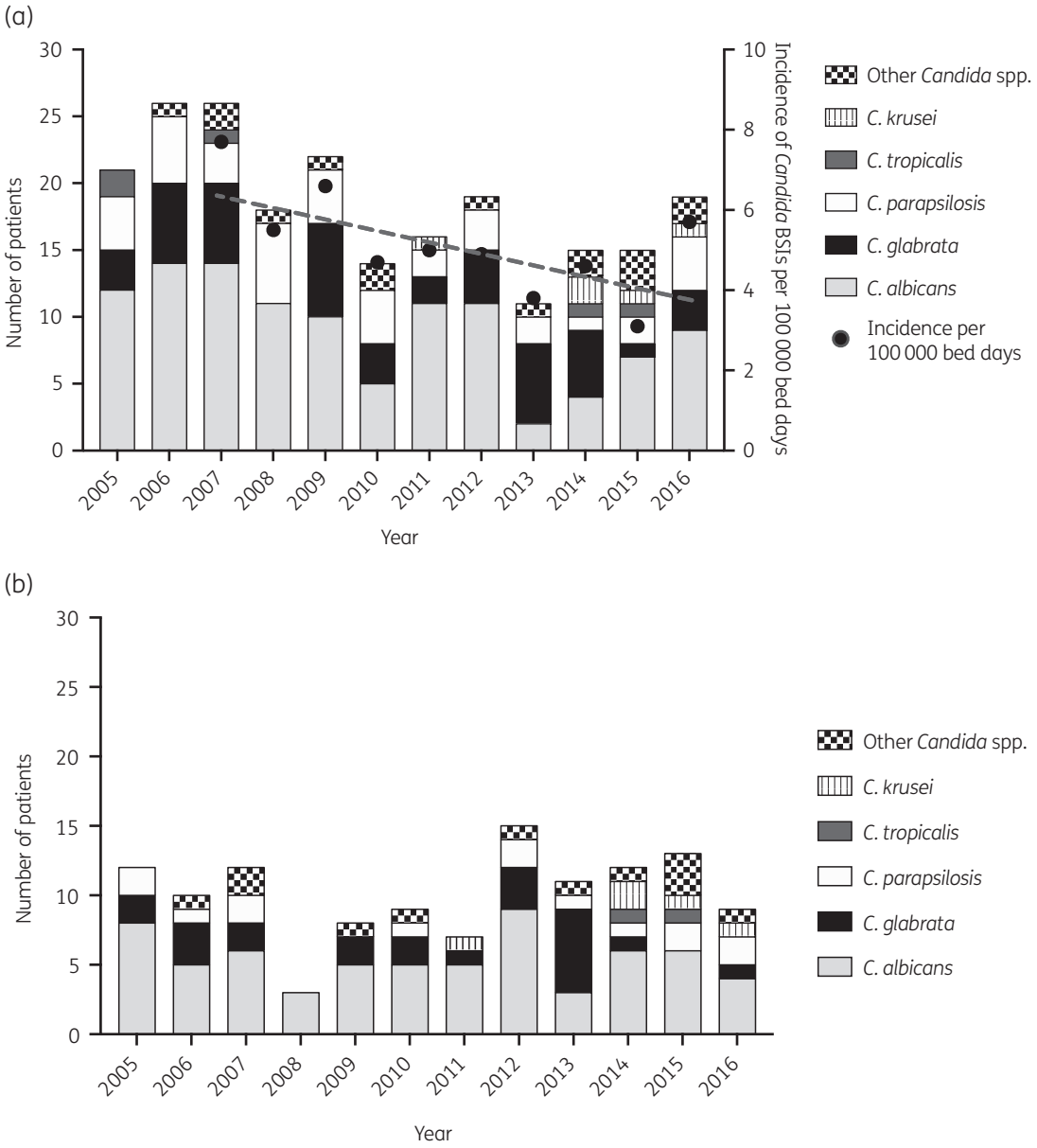

Figure 4. Number of *Candida* isolates reported and incidence of *Candida* BSIs per 100000 bed-days at (a) Wythenshawe Hospital and (b) Wythenshawe ICUs in 2005–15. The broken line is the linear regression trend line for incidence of invasive candidosis per 100000 bed-days ($R^2 = 0.44$, $P = 0.037$).

up including investigations for alternative causative organisms and use of fungal biomarkers such as serum BDG to guide discontinuation of antifungal therapy is fundamental for avoiding overuse of antifungal drugs. Our AFS strategy led to a 90% reduction in inappropriately initiated courses between 2014 and 2016. Reassuringly, the number of patients in whom invasive candidosis was appropriately suspected but excluded did not increase between 2014 and 2016. This demonstrates that the guideline recommending early initiation of antifungal therapy was not driving an increase in unnecessary empirical antifungal use. In contrast, the overall antifungal consumption approximately halved during the 2 year study period (Figure 3). This is in keeping with the reduction in the number of inappropriately initiated empirical antifungal courses during the same time period. A marked temporal variability is demonstrated in the use of antifungal agents.

The number of patients with proven or probable invasive candidosis doubled from 9 in 2014 to 18 in 2016. This increase is largely due to an increase in the number of patients with probable invasive candidosis as a result of increased use of the BDG test. However, the number of patients with *Candida* species isolated from blood culture in all of 2016 increased compared with 2015 and 2014 (Figure 4a). Figure 4 also demonstrates the marked natural fluctuation in the number of cases each year, which is likely to contribute to the spike in 2016. This does not, however, detract from the general trend towards a reduction in cases with *Candida* reported from blood culture.

Intravenous antifungal agents are commonly prescribed empirically for patients at risk of invasive fungal infections. These high-risk patients are typically cared for by clinical specialties familiar with invasive fungal infections such as intensive-care medicine, haematology and transplantation. However, there is a growing body of evidence that the involvement of infection specialists will improve outcomes in patients within these cohorts diagnosed with complex infection.[29] Implementing an AFS programme is challenging and requires credibility and good interpersonal skills to influence clinical practice. Our approach of recruiting an intensive-care champion facilitated an excellent working relationship between the ID and intensive-care teams, to which we attribute our success in influencing practice. The close working relationship between the AFS champion and ID team, fostered confidence in the clinical assessment of patients with suspected invasive candidosis, and increased the use of diagnostic tests, thus improving compliance with the local guideline. This ultimately led to a reduction in the input required from the AFS team and the resources needed for stewardship rounds.

Antifungal agents remain expensive, and decreasing inappropriate use will affect the healthcare costs of ICU patients. The monthly expenditure on BDG testing is equivalent to ∼20 doses of micafungin. Any additional doses that were not administered contributed to the increased savings. In this, minimizing laboratory turnaround times is key to success. By involving AFS champions, this can be achieved with minimal additional clinical staff costs. Due to the design of the BDG test kit the cost per test is lower the more tests are done at a time, which highlights the benefits of laboratory centralization. It is important to acknowledge that the incidence of candidaemia affects the negative predictive value of the BDG test, which is high only in low-incidence settings.

There are some limitations to this study. Firstly, the sample size is limited due to the low incidence of invasive candidosis. As the focus of this study was to audit the adaptation of the new ICU candidaemia guideline, only patients in ICUs were included. However, the majority of candidaemias occur in the ICU, and during the audit periods there were no patients with invasive candidosis on non-ICU wards. Secondly, this was a retrospective study and the data collection depended on documentation in patient records. However, the key variables analysed were available for all patients. During the audit periods there were no significant changes in the provision of clinical services at the University Hospital of South Manchester or overall mortality on ICUs. Thus it is likely that the reduction in mortality due to invasive candidosis was due to the implementation of the AFS programme. The impact of seasonal variation in candidaemia was minimized by including the same months in both audit periods. To further analyse the effectiveness of AFS, a prospective multicentre study using a stepped-wedge, cluster-randomized trial design would be ideal.

In conclusion, our real-world experience demonstrates that a clear and concise clinical guideline utilizing an informative biomarker and implemented with the help an AFS champion can be safe and effective at reducing inappropriate initiation of antifungal agents as well as improving patient outcomes. The cost of instituting the AFS programme was more than covered by the savings associated with reduced antifungal consumption.

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Transparency declarations

None to declare.

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