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Antifungal stewardship with an emphasis on candidaemia

Malini R. Capoor[a], Chinari P. Subudhi[b], Andrew Collier[c], Abhijit M. Bal[d,*]

[a] Department of Microbiology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 110029, India
[b] Department of Microbiology, Bolton NHS Foundation Trust, Minerva Road, Farnworth, Bolton BL4 0JR, UK
[c] Department of Medicine, University Hospital Ayr, Dalmellington Road, NHS Ayrshire & Arran, Ayr KA6 6DX, UK
[d] Department of Microbiology, University Hospital Crosshouse, Lister Street, NHS Ayrshire & Arran, Kilmarnock KA2 0BE, UK

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ABSTRACT

Antimicrobial resistance is a global threat. To counter the growing menace of antibiotic resistance, several stewardship initiatives have been incorporated as part of the overarching strategy of healthcare delivery. In contrast, antifungal stewardship (AFS) has attracted less attention for several reasons, such as limited antifungal resistance and the lesser burden of fungal infections compared with bacterial infections. However, the emergence of resistant fungi, such as multidrug-resistant *Candida auris*, has provided impetus to AFS programmes. This review summarises existing data on AFS programmes, particularly in relation to invasive candidiasis, both in the empirical setting and in the setting of proven infection.

Contents

1. Introduction

Antimicrobial resistance is acknowledged as one of the most serious challenges of modern health care [1]. Despite having been highlighted as a significant problem for several years, antimicrobial consumption continues to go unchecked [2]. Moreover, the antimicrobial pipeline is dry, leading to calls for new regulations in relation to patenting of antimicrobial agents with the hope that this would incentivise research in this field [3]. However, new antimicrobial agents add to the cost of health care. Prudent use of antimicrobial agents is therefore necessary. Healthcare delivery systems have invested in antimicrobial stewardship (AMS) in order to minimise the adverse impact of growing resistance [4].

For many years, antimicrobial resistance has focused mainly on antibiotics, but there is increasing recognition that antifungal stewardship (AFS) is a vital component of antimicrobial management. Whilst there are commonalities between antibiotic stewardship and AFS, there are also striking differences [5]. Unlike bacteria, plasmid-mediated resistance is not encountered in fungi of medical importance [6]. Therefore, antifungal resistance is not on the same explosive scale as antibiotic resistance, hence cost and clinical outcomes are the main drivers of AFS [7]. Clinical

* Corresponding author.
E-mail address: abhijit.bal@nhs.net (A.M. Bal).

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experience with fungal infections is also limited compared with bacterial infections. Detection of fungal pathogens and antifungal susceptibility testing are not routinely available in diagnostic laboratories. Finally, there is much less expertise in AFS with very few centres formally participating in AFS programmes, leading to a paucity of data and limited sharing of experience.

AFS programmes have been developed in a variety of settings, ranging from office settings to critical care units [8]. Candidaemia is still the most common invasive fungal infection (IFI) in hospitalised patients. Recently, outbreaks of multidrug-resistant *Candida auris* infections have been reported from several parts of the world, reigniting interest in the judicious use of antifungal agents [9–11]. This narrative review aims to summarise the literature on AFS with a focus on invasive candidiasis. A comprehensive strategy on how AFS can be implemented in practice in relation to invasive *Candida* infections is also provided.

2. The need for an antifungal stewardship programme in candidaemia

Treatment of candidaemia has evolved in the last few years, with echinocandins becoming the mainstay of therapy particularly in critically ill patients. Echinocandins are more reliable than fluconazole as empirical therapy [12]. Echinocandins are also fungicidal [13]. Despite being active against a wide range of *Candida* spp., echinocandins are narrow spectrum in relation to their overall antifungal activity against moulds, retaining meaningful activity only against *Aspergillus*, which reduces any selection pressure on other pathogenic fungi. Thus, they appear to be ideally suited for first-line therapy [14]. However, there are drawbacks to echinocandin therapy. Resistance to echinocandins is emerging [15] and acquisition of resistance during therapy has been reported [16]. Moreover, echinocandins are expensive and are available for parenteral use only. For this reason, switch to oral fluconazole is preferred in the course of candidaemia therapy, particularly in patients who are clinically stable and who have documented infection with fluconazole-susceptible *Candida* [17].

Guidelines of the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) have extensively addressed the issues in the management of candidaemia. The IDSA guidelines recommend treatment with an echinocandin in patients with increased risk of *Candida glabrata*, including patients with diabetes or malignancy, the elderly and patients who have recently been prescribed azole therapy. Echinocandins are also indicated in patients who might suffer from an adverse outcome as a result of suboptimal initial antifungal therapy, e.g. patients with haemodynamic instability. In patients without these risk factors, fluconazole can be used as an alternative to echinocandins. The ESCMID guidelines recommend commencing therapy with an echinocandin in all patients with candidaemia, without any clinical risk stratification. Both guidelines favour switching to an oral agent after a variable duration of intravenous (i.v.) therapy. Removal of a central venous catheter (CVC) where feasible, investigations such as echocardiogram, and routine fundoscopy to rule out endophthalmitis are some of the good practice recommendations in the management of candidaemia. The duration of treatment with an antifungal agent should be $\geq$14 days from the first negative culture [17,18].

AFS programmes can streamline the management of candidaemia by incorporating good practice recommendations into clinical practice. The AFS team is suitably placed to provide sustained input in the management of candidaemia, as individual clinicians are unlikely to encounter a significant number of cases owing to the fact that *Candida* bloodstream infections (BSIs) occur in a variety of clinical settings such as intensive care, haematology and oncology, neonatal units, and general surgical and medical wards. Indeed, a recent study found that senior doctors were less informed than junior residents in the management of *Staphylococcus aureus* bacteraemia and candidaemia, possibly resulting from attrition of knowledge [19]. Due to the modest sensitivity of diagnostic techniques, a large proportion of antifungal prescribing is empirical and of limited benefit. Data from Spanish hospitals reveal that >60% of antifungal prescribing is in the empirical and pre-emptive setting [20]. In French hospitals, usage of antifungal agents was appropriate in only 60% of cases and mortality was higher in patients with inappropriate prescribing [21]. Targeted therapy in patients with candidaemia also places emphasis on an appropriate duration of treatment and certain investigations necessitating clinical oversight by specialist teams. The AFS team can recommend therapy at initiation, provide advice on switching to oral treatment, and triangulate between the laboratory, the clinician and the pharmacist in order to optimise therapy in individual patients. A retrospective study of patients with candidaemia found that as many as 61% of patients receiving echinocandins were not switched to fluconazole despite the fact that the *Candida* isolates were susceptible to the latter agent [22]. Other studies have found a dismal rate of change of therapy (as low as 12%), perhaps due to lack of familiarity with antifungal susceptibility testing [23]. Even in critical care units that are familiar with the use of antifungal agents, the rate of de-escalation has been shown to be approximately 20% [24]. Early de-escalation (Day 5) was recorded in only 22% of patients as part of a post-hoc analysis of the AmarCAND2 study [25]. In contrast, prospective AFS interventions that have specifically targeted antifungal de-escalation have demonstrated better results [26]. AFS interventions have also been shown to reduce the time to commencement of therapy from 3 h 30 min to 2 h 9 min ($P = 0.021$) [27]. Delay in the initiation of antifungal therapy has been shown to be associated with increased mortality [28]. A recent systematic review of the impact of AFS programmes demonstrated favourable results. Analysis of the 14 studies selected by the authors for their review showed that interventions focused mainly in relation to change of antifungal therapy, with significant emphasis on measures of performance (antifungal consumption, antifungal costs, therapeutic advice and impact on mortality). The AFS programmes demonstrated value addition with adherence to therapeutic advice ranging from 40–88%, although there was no demonstrable impact on mortality [29].

Despite the benefits, data in relation to the uptake of AFS programmes are disappointing. Only 43% of hospitals in England have an AFS programme in place, with a lack of resources being the main reason for not having one [30]. The main driver of the AFS programme is cost. It is important for AFS teams to focus on quality improvement. Quality improvement requires a multidisciplinary approach and is discussed in detail in previous reviews on the subject [31]. One suggested design for quality improvement programmes is to implement a candidaemia care bundle, which has been shown to improve compliance in various elements of care [32]. Care bundles not only lead to enhanced awareness of quality improvement initiatives but facilitate the measuring of individual elements, exposing the areas that are in need of attention. Care bundles with investigation of each element have been studied [33]. In future, monitoring for emergence of resistant isolates, improving patient outcomes and reducing adverse events will be additional focus areas for AFS teams [34].

3. Barriers to the antifungal stewardship programme

There are a variety of challenges facing successful implementation of AFS programmes. Invasive candidiasis (IC) is typically oversuspected and underdiagnosed, which leads to both unnecessary therapy in many patients without invasive infection and lack

of adequate therapy in patients with infection. The diagnostic sensitivity of IC is modest and thus a significant number of patients with proven IC are not captured by AFS programmes. Various clinical scoring criteria have been proposed to compensate for the poor diagnostic sensitivity of laboratory tests for the detection of candidaemia and IC. The clinical criteria taken into account are systemic signs of sepsis (e.g. fever), underlying illness (e.g. surgery, cancer), length of hospital stay particularly in the intensive care unit, total parenteral nutrition, prior antibiotics that increase the risk of susceptibility by inducing selection pressure, and colonisation with *Candida* [35]. However, the signs and symptoms of IC are non-specific. Empirical antifungal therapy was not shown to be associated with improvement in relation to a composite outcome [36]. Thus, one of the objectives of an AFS programme is to reduce empirical prescribing in clinical settings where the benefits of this approach are uncertain. Testing for biomarkers such as (1,3)-β-D-glucan (BDG) and *Candida* mannan/anti-mannan antibodies have been evaluated and demonstrate a high negative predictive value in the diagnosis of candidaemia. Rautemaa-Richardson et al. investigated the utility of BDG testing on reducing unnecessary use of micafungin [37]. Of 68 patients in their audit, 22 had cessation of antifungal therapy following a negative BDG test [37]. Patients who have been empirically commenced on antifungal therapy should be followed-up to assess clinical progress, and consideration should be given to stopping antifungal treatment or de-escalating therapy to narrow-spectrum antifungal agents where feasible. Technological upgrades such as electronic prescribing may facilitate capturing of data in relation to empirical antifungal prescribing as well as minimising dosing errors [38].

AFS teams should champion improvements in diagnostic techniques. The choice of antifungal therapy guided by clinical risk factors for *C. glabrata* infection is recommended by the IDSA guidelines. However, none of the risk factors, e.g. diabetes, cancer and elderly age, are exclusively associated with *C. glabrata* [39]. A recent study demonstrated no difference in the distribution of these risk factors between patients with BSI caused by *C. glabrata* and those with *Candida* infections other than *C. glabrata* [40]. Rapid laboratory diagnosis in the context of species identification could guide therapy and replace clinical stratification based on risk factors. It is important to emphasise that species identification alone might not be the sole determinant of therapy. For example, in a randomised controlled trial (RCT), both microbiological and clinical response were significantly better in patients treated with anidulafungin compared with fluconazole in the subgroup of patients with IC caused by *Candida albicans*, a species that is susceptible to fluconazole [41]. The challenge for AFS teams is to balance the risks and benefits of therapy as dictated by microbiological results and proven effective therapy as evidenced by clinical trials. It would therefore seem prudent to use echinocandins as first-line therapy while using rapid species identification for promoting the use of fluconazole for *Candida parapsilosis*, as the efficacy of echinocandin against this species is less certain. Daily reviews of patients and the use of BDG to guide the duration of parenteral therapy in proven candidaemia was found to be associated with a reduced rate of clinical failure, improved survival and fewer adverse effects related to antifungal agents [42]. Rapid identification of *Candida* BSI with T_2-weighted magnetic resonance imaging (MRI) has the potential to shorten the time to initiation of therapy to 0.6 days compared with $\geq$2.5 days with fluorescence in situ hybridisation (FISH)- or matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF)-based identification [43].

Another major barrier to AFS programmes is funding. AFS teams should explore whether the programme could align with local quality management strategies with sufficient budgetary provisions. AFS programmes need to explore whether they could be self-reliant by seeking funding on a spend-to-save basis. For example, pharmacy departments might consider funding AFS programmes on the basis of expected cost reductions as a result of streamlining of antifungal prescribing. Similarly, local provision of galactomannan testing might reduce the need for empirical prescribing for invasive aspergillosis (IA) in haematological settings and so laboratories should seek funding opportunities where feasible.

AFS teams must seek co-operation from clinical teams. This can be challenging because the clinical priority for individualised care does not always align with the overall strategic objectives of the AFS programme. The AFS team should work towards harmonising their goal with that of clinicians by triangulating between clinical teams, diagnostic laboratories and pharmacy units. Agrawal et al. describe a leadership model using consensus to arrive at clinical decisions facilitated by peer-to-peer advice and communication [44]. Electronic prescribing to minimise dosage errors, feedback from regular audits and maintaining databases can provide the stimulus for continuing quality improvement with a high level of motivation.

Finally, enrolling new members in the team has been suggested as a way of reducing fatigue, as the latter might impact on the team's performance after initial success. It is also important to publish the achievements of the team in order to keep motivation levels high [31].

4. Data on antifungal stewardship with an emphasis on candidaemia

AFS in candidaemia should consider the local epidemiology, antifungal resistance, application of therapeutic guidelines, treatment strategies (empirical, pre-emptive, de-escalation and switch, and step-down strategies), CVC management, ophthalmological and cardiac evaluations, and the best available diagnostic tests for candidaemia. Data are available on AFS in the common IFIs such as candidaemia, but are scarce for other infections such as IA, mucormycosis and hyalohyphomycosis [45]. AFS requires collaboration between clinical and laboratory services as partners in patient care. A multidisciplinary team model has been proposed in order to facilitate communication among clinical teams, promote adherence to clinical pathways and optimise the use of resources [46]. Several healthcare facilities have successfully implemented AFS using post-prescription review and feedback, education, and the development of clinical guidelines [47–49].

4.1. Antifungal stewardship in the empirical setting

An AMS programme at the University of Maryland Medical Centre (Baltimore, MD, USA) demonstrated the effectiveness of the programme by way of cost reduction from US$44 181 per 1000 patient-days prior to full implementation of the programme to US $23 933 by the end of the programme over a period of 8 years. This translated into an overall reduction of approximately US$3 million in the first 3 years, attributed mainly to a decrease in the use of antifungal agents [50]. Another study that focused on the use of echinocandins assessed the utility of an antifungal bundle protocol in an intensive care setting [51]. The bundle consisted of a specific antifungal protocol that included the date of caspofungin treatment, indication for treatment and the planned duration along with additional follow-up questions in relation to dose optimisation, de-escalation, need for continuation of therapy and device removal. A total of 36 patients in the prospective intervention group who were prescribed caspofungin were matched to 72 patients from a retrospective control group. Of the 36 patients, 19 had their caspofungin discontinued within 3 days and 6 had antifungal therapy de-escalated. The investigators

demonstrated a reduction in the median days of caspofungin therapy when comparing the prospective group with the retrospective group (2 days vs. 4 days) without any adverse impact on clinical outcomes. The predominantly empirical nature of caspofungin prescribing might explain the high proportion of early discontinuation of therapy [51]. A Japanese team also investigated the use of an AFS bundle consisting of weekly lectures on infectious diseases, recommendations to draw multiple blood cultures before administration of any antifungals, and restricted use of antifungals for positive growth from non-sterile or non-invasive specimens [52]. The programme was incrementally enhanced by including ward rounds and active participation of infection control personnel. Comparing the first year of the study period with the last year, there was an overall reduction in the use of micafungin from 12.7 to 5.2 defined daily doses per 1000 patient-days (DDD/PD) and of voriconazole from 1.07 to 0 DDD/PD but with slowing of the trend as the programme matured. More importantly, there was a reduction in mortality in patients with fungal BSI from 55% to 31.4% following the introduction of the bundle ($P = 0.08$) [52]. More recently, a reduction in unnecessary empirical use of antifungal agents and switching to more appropriate therapy by a process of feedback and recommendation was shown to be associated with significant cost savings in a major teaching hospital in London (UK) [53].

5. Antifungal stewardship in relation to specific fungal infections

A team of French investigators focused on the diagnostic and therapeutic management of suspected IA and candidaemia from 2005–2010 as part of an AFS programme [47]. The antifungal management team, which comprised a clinical microbiologist, an infectious diseases specialist, an infection control professional, an antimicrobial pharmacist and a haematologist, focused on costly antifungal agents. The team carried out regular audits, offered feedback to clinicians, promoted adherence to guidelines, initiated on-site diagnostic tests for IA and therapeutic drug monitoring (TDM) for agents such as voriconazole, and specifically offered advice on the use of echinocandins or fluconazole for the treatment of candidaemia. The AFS team was able to demonstrate optimisation in the standard of care for the timing of antifungal therapy, recommended first-line therapy, duration of therapy and removal of CVC. Improvement was also noted in certain performance measures, including echocardiography and follow-up blood cultures, along with standardisation of galactomannan testing and voriconazole TDM in relation to IA [47].

Benefits of introducing candidaemia care bundles have been reported, but with varying levels of compliance. Incorporating key elements from the IDSA guidelines, namely on utilisation of appropriate antifungal agents with appropriate duration of use, removal of CVC, repeat blood cultures every 48 h, monitoring of time until clearance of candidaemia, and performance of fundoscopic examinations, Antworth et al. demonstrated significantly improved compliance in relation to the completion of all candidaemia care bundle elements in the intervention group compared with the control group (78% vs. 40.5%; $P = 0.0016$) along with improved rates of fundus examination (97.6% vs. 75.7%; $P = 0.0108$), appropriateness of antifungal agent (100% vs. 86.5%; $P = 0.0488$) and compliance with an appropriate duration of therapy (97.6% vs. 67.7%; $P = 0.0012$). There was a trend toward higher rates of persistent candidaemia in the control group [54]. Incorporating the good practice points from the IDSA and ESCMID guidelines, Murri et al. devised a care bundle comprising the five core elements including appropriate selection of initial therapy, follow-up blood culture (at least one blood culture during the first 14 days following diagnosis), performance of echocardiography, ophthalmological examination, and removal of a CVC where applicable [33]. A majority of the 213 patients in their study had three or four elements of the bundle fulfilled, but only 16.9% complied with all of its requirements [33]. Reed et al. evaluated the impact of a candidaemia-specific pharmacy-led AFS programme comparing a pre-intervention group ($n = 85$) from 2008 with the post-intervention group ($n = 88$) from 2010 [55]. The median time to effective therapy was significantly shorter in the post-intervention group (1.3 h vs. 13.5 h; $P = 0.04$). AFS interventions standardised and improved the quality of care of patients with candidaemia [55].

Of all the various elements of a care bundle, the key therapeutic area is appropriate antifungal treatment. The current IDSA guidelines for the management of candidaemia recommend de-escalating from an echinocandin or amphotericin to oral fluconazole (or voriconazole for *Candida krusei* infection) within 5–7 days provided that the patient is clinically stable, has infection with an azole-susceptible isolate and has negative repeat blood cultures on antifungal therapy [17,56]. De-escalation strategies have been applied as part of clinical trials on candidaemia [57]. AFS programmes that have placed emphasis on step-down therapy have achieved successful outcomes. Bal et al. devised an i.v.-to-oral step-down following antifungal susceptibility testing of *Candida* bloodstream isolates to guide antifungal de-escalation and found significant cost savings when 70.3% of patients with candidaemia during the study period were switched from an echinocandin to fluconazole with a median time to switch of 5 days [26]. A multicentre, non-comparative, phase IV non-randomised trial evaluated an early step-down option from anidulafungin to oral fluconazole or voriconazole in patients who met specified criteria, including the following: ability to tolerate oral therapy; absence of fever for >24 h; haemodynamic stability; absence of neutropenia; and documented clearance of *Candida* from the bloodstream [58]. A total of 60% of patients in the study underwent step-down, a majority of them by Day 7 of treatment, and the response rate in the early switch subgroup was similar to the modified intention-to-treat (MITT) population. The median duration of i.v. therapy was 6 days in the MITT population, 5 days in the early switch subgroup and 10 days in the late switch subgroup [58]. The safety of early step-down at Day 5 has also been established in critical care settings [59]. There is support for a favourable budgetary impact of the de-escalation strategy compared with the escalation model where treatment is commenced with fluconazole and escalated if necessary [60]. Moreover, with declining acquisition costs of echinocandins, these data are likely to become even more favourable, supporting commencement of therapy with an echinocandin followed by fluconazole. However, RCTs in support of early i.v.-to-oral switch are lacking.

As there is a predictable relationship between species identity and antifungal susceptibility, appropriate commencement of therapy can also be guided by early species identification. Using MALDI-TOF-based rapid species identification, a significantly higher proportion of patients received appropriate initial therapy in comparison with patients whose bloodstream *Candida* isolates were identified by conventional methods (90.9% vs. 62.2%; $P = 0.01$) [61]. However, this study assumed that echinocandins are appropriate therapy only for *C. glabrata* and *C. krusei* [61]. The relationship between in vitro testing and in vivo efficacy is less predictable in practice. A multicentre RCT demonstrated a significant trend towards a favourable outcome with anidulafungin compared with fluconazole (an effect most noted in the subgroup of patients with invasive *C. albicans* infection) [41]. The study was, however, hampered by 'centre effect'. Analysis of data after removing a particular enrolment site reduced the gap between the success rates of the two groups thereby making anidulafungin non-inferior rather than superior to fluconazole [41]. Rapid species

Table 1
European Confederation of Medical Mycology (ECMM) Quality (EQUAL) of Clinical Candidemia Management score [66].

Quality indicator	Points
Adequate volume of blood culture (40 mL)	3
Identification of species	3
Antifungal susceptibility testing	2
Echocardiography	1
Ophthalmoscopy	1
Echinocandin treatment	3
Step-down to fluconazole if susceptible	2
Treatment for 14 days after first negative culture	2
CVC removal ≤24 h or >24 h and ≤72 h	3 or 2
Daily follow-up blood cultures	2
Maximum score[a]	22 or 19

CVC, central venous catheter.
[a] Maximum achievable score of 22 in patients with CVC or 19 in patients without CVC.

identification can still guide management particularly if *C. parapsilosis* is identified. In patients with *C. parapsilosis* infection, the European Conference on Infections in Leukemia (ECIL) guidelines recommends the use of fluconazole in preference to an echinocandin [62]. The availability of T_2-weighted MRI is a step further in diagnostics as it provides same-day species-specific results without the need for conventional blood culture. It is estimated that in facilities with >5000 high-risk patients annually, a cost saving of more than US$5 million could be realised by using the T_2-weighted MRI panel instead of conventional blood culture systems largely due to a reduction in the diagnosis of candidaemia and the consequent therapy, while preventing 60.6% of candidaemia-related mortality at the same time [63].

The current variability in antifungal use, inappropriate dosing and delays in initiating appropriate therapy indicate a need for AFS to improve the prevention, diagnosis and management of candidaemia. Results from AFS programmes support the advantages, none the less the best strategies for implementation need to be explored. As the availability of rapid molecular identification methods and non-culture-based diagnostics for IFI become more widely available, the best ways to incorporate them into AFS programmes requires multidisciplinary discussions. Creating collaborative institutional networks would be helpful to prospectively study the utility of AFS programmes in detail [45,56]. Further exploration into the use of care bundles as part of their multifaceted approach to promoting appropriate antimicrobial utilisation and optimising the management of patients with candidaemia is crucial. Given the scarcity of supporting literature, AFS programmes should be implemented coupled with a strategy to demonstrate their performance.

6. New developments in the field

The two internationally acclaimed guidelines published by the IDSA and ESCMID have improved the management of candidaemia. Several studies have audited compliance with these published standards [64,65]. One theme that emerges from candidaemia audits and care bundle adherence is the lack of overall compliance with the guidelines despite acceptable compliance in relation to individual elements. Clearly not all recommendations made by the two guidelines have the same importance: starting appropriate and timely antifungal therapy and removal of CVC appear to be more relevant and have more weight of evidence behind them compared with fundoscopic examination or echocardiogram, evidenced by the fact that echocardiogram is recommended by ESCMID but not by IDSA. The European Confederation of Medical Mycology (ECMM) recently published a scoring criterion, the ECMM Quality (EQUAL) of Clinical Candidemia Management score, which provides a hierarchy of the good practice recommendations. Scores ranging from 1 to 3 are awarded for individual practice elements as shown in Table 1, with a maximum achievable score of 22 (in patients with CVC) or 19 (in patients without CVC) [66]. A recent audit carried out in German hospitals revealed that the mean score achieved was only 9.9 (range 8–14) [67]. Although disappointing, this may be due to the fact that the audit covered the period prior to the publication of the EQUAL score [66]. Table 2 shows the key to successful uptake of the quality indicators along with existing challenges.

7. The challenges of antifungal stewardship in developing countries

AMS is most required in low- and middle-income countries (LMIC) where the problem of misuse of antimicrobials is significant [68]. In some of these countries, life expectancy and quality of life have dramatically increased, but regulations continue to be weak. In India, for example, quality health care matching western standards is available in cities and large towns, but other aspects of health care such as epidemiological surveillance and regulatory programmes are yet to catch up. Moreover, many countries with poorly developed health infrastructure none the less face challenges typical of affluent countries: the alarming increase in the number of diabetes patients in India is a case in point [69]. Many such countries are not equipped to face the challenge of IFIs. Sporadic infections and outbreaks of multi-drug-resistant *C. auris* have been recorded in Colombia, India, Oman, Pakistan, Panama and South Africa [70–75]. Similarly, the burden of invasive non-*Candida* yeast infections was recognised by the Asia Fungal Working Group under the auspices of the

Table 2
European Confederation of Medical Mycology (ECMM) good practice recommendations in candidaemia—optimisation and challenges.

Recommendation	How to meet the standards	Challenges
Adequate blood culture	Educating clinical staff	Patients may have difficult i.v. access
Species identification	Laboratory protocols mandating species identification of *Candida* isolated from bloodstream	Reference laboratory facilities must exist for species that are difficult to identify
Antifungal susceptibility	Laboratory protocols mandating antifungal susceptibility testing of *Candida* isolated from bloodstream	Not all species have breakpoints; reference laboratory facilities may be required
Echocardiogram and fundoscopy	AFS team review of patients	Patients may not be fit for certain investigations, e.g. TOE
Echinocandin treatment	Access to guidelines	Cost of treatment
Step-down treatment	AFS team review of patients, triangulating between laboratory, clinicians and pharmacy teams	Timely authorisation of laboratory reports and easy access to laboratory data
Duration of therapy	Access to guidelines	Lack of awareness among clinicians
CVC removal	Educating clinical staff	May not be possible in some patients, e.g. those with low platelet count
Follow-up blood cultures	Educating clinical staff	Adds to the burden of health care

i.v. intravenous; AFS, antifungal stewardship; TOE, transoesophageal echocardiogram; CVC, central venous catheter.

International Society for Human and Animal Mycology [76]. Indian mycologists called for establishment of an AFS task force and provided a framework for the future delivery of AFS programmes in collaboration with the British Society for Antimicrobial Chemotherapy [77]. The requirements of AMS in LMIC have been extensively reviewed [78].

8. Conclusions

AFS is a specialised area of stewardship requiring multidisciplinary input. AFS requires prior knowledge of and experience with general stewardship programmes, and those participating in AFS programmes need to be sufficiently competent in the management of fungal infections. Generic competencies in stewardship have been elaborated by an ESCMID working group [79]. In future, incorporating epidemiological surveillance could add value to AFS programmes by providing data for benchmarking.

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None declared.

Ethical approval

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