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The impact of pharmacist-led antifungal stewardship interventions in the hospital setting: a systematic review

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Title

The Impact of Pharmacist-led Antifungal Stewardship Interventions in the Hospital Setting – A Systematic Review

Short title

Pharmacist-led Antifungal Stewardship

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All listed authors comply with the journal's Authorship policy.

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Ethics approval was not required for this systematic review.

Conflict of Interest Statement

DKCM has served on advisory boards for Becton Dickinson Pty Ltd and Merck Sharp & Dohme (MSD), and received financial support from MSD and F2G, all unrelated to the current work. JAR has consulted for Pfizer, Sandoz, MSD, Cipla, Biomerieux and Discuva Ltd and has received grants to The University of Queensland from MSD, The Medicines Company, Biomerieux, QPEX and Pfizer. MAS has received grants to her institution from Gilead Sciences, MSD and F2G and consulted for Pfizer, F2G, Merck and Gilead Sciences
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The Impact of Pharmacist-led Antifungal Stewardship Interventions in the Hospital Setting – A Systematic Review

Abstract

Aim

To summarise the evidence on pharmacist-led antifungal stewardship (AFS) programs in the hospital setting and to evaluate their impact on the quality of antifungal prescribing and infection management, antifungal usage and clinical outcomes.

Data sources

A systematic review of English language studies identified in MEDLINE and EMBASE was performed on 27th November 2020 and conducted in accordance with PRISMA. Search terms included antifungal agent, invasive fungal infection, antimicrobial stewardship, patient care bundles and pharmacist.

Study selection

Eligible studies describing pharmacist-led quality improvement intervention(s) implemented in the hospital setting targeted at optimising systemic antifungal prescribing.

Results

646 studies were identified, seven met inclusion criteria. Five were dedicated to optimising candidaemia management, one at optimising intensive care unit prescribing of caspofungin and one on antifungal prescribing in haematology and oncology units. All studies measured varied metrics relating to quality of prescribing and infection management, reporting improvement in proportion of effective antifungal therapy (n=1/1), appropriate antifungal selection (n=1/1),

dosing (n=2/3), management of drug-drug interactions (n=1/1) and reduced time to antifungal initiation (n=4/4). Studies that implemented a candidaemia bundle of care reported improvements in composite bundle adherence (n=2/2), with greatest improvement in ophthalmological consultation (n=4/4), echocardiography (n=2/2) and infectious diseases consultation (n=3/3). There was reduction in antifungal expenditure (n=4/4) and consumption (n=2/4). Pharmacist-led AFS programs did not influence clinical outcomes.

Conclusion

Available evidence suggests that pharmacist-led AFS interventions can improve the quality and timeliness of antifungal prescribing and reduce antifungal usage. Further research is required to assess the impact on clinical and microbiological outcomes.

Keywords: Antifungal stewardship, Antimicrobial stewardship, Invasive fungal disease, Antifungal agents, Pharmacist, Bundle of care, Candidaemia

Introduction

Invasive fungal diseases (IFD) are serious infections associated with high morbidity and mortality, particularly affecting immunocompromised and critically ill patients. Mortality rates for IFDs are in excess of 30-50% (1-3). The use of antifungal agents as prophylaxis and for treatment of IFD are associated with a substantial economic burden (4), high rates of adverse drug reactions (5), significant drug-drug interactions (6) and rising resistance to existing antifungals (7, 8). Observational studies have described high rates of suboptimal antifungal prescribing in the hospital setting (9-14). Consequently, there is an increasing focus on the stewardship of antifungals to optimise the management and prevention of IFD. Over the previous 10 years there has been an increase in studies assessing the impact of antifungal stewardship (AFS) interventions, demonstrating improvements in the quality of antifungal prescribing (15-18), reduction in the consumption of high cost antifungals (19) and improvements in the application of fungal diagnostics (17) and therapeutic drug monitoring (TDM) of antifungals (20).

Pharmacists are key members of antimicrobial stewardship (AMS) teams globally and have shown that they can lead AMS programs (21). Despite recent focus on AFS (22), the role of the pharmacist in AFS has not been extensively explored. The aim of this systematic review is to summarise the available evidence on pharmacist-led AFS programs in the hospital setting and to evaluate the impact of pharmacist-led AFS programs on the quality of systemic antifungal prescribing and infection management, antifungal usage and clinical outcomes.

Methods

The review protocol including the complete search strategy has been registered at the PROSPERO international prospective register of systematic reviews (CRD42020201318).

Eligibility criteria

Studies were eligible for inclusion if they described pharmacist-led quality improvement intervention(s) implemented in the hospital inpatient and/or outpatient setting specifically targeted at optimising the prescribing of systemic antifungal agents. Examples of quality improvement interventions include, but are not limited to, post prescription review and

feedback, prescribing restrictions and pre-authorisation, implementation of an infection management bundle of care, education, guideline development, audit and feedback, multi-disciplinary meetings and electronic medical record alerts or prompts. Non-interventional studies, studies that did not evaluate an outcome or described a general AMS intervention not focused on systemic antifungal agents were excluded as well as review articles. Non-English language articles were excluded.

Information sources and search strategy

A comprehensive search for articles was carried out using MEDLINE and EMBASE online databases. A combination of key terms were utilised: "antifungal agent" or "invasive fungal infection" and "antimicrobial stewardship" or "patient care bundles" and "pharmacist". The search was limited to English language and excluded conference abstracts. No date limitation was applied. The last search was performed on 27 November 2020. Reference lists of relevant articles and pertinent reviews were also searched. See Appendix 1 for detailed search strategy.

Study selection

Two investigators (AK, KC) independently performed the literature search and reviewed study title and abstracts for their eligibility based on the established inclusion criteria. If abstracts were not sufficiently informative to assess eligibility, full text articles were reviewed. These investigators were blinded to each other's decisions. Disagreement regarding an article's inclusion was resolved by discussion between the two investigators, with one investigator (JR) acting as an arbitrator if agreement could not be reached. An online systematic review screening and data extraction tool (Covidence®) was used to store and categorise studies for inclusion or exclusion and to resolve conflicts between investigators.

Data extraction

Full text of articles which met the study's inclusion criteria were retrieved. Data relating to the study methods, setting, patient population, patient identification method, members of the AFS team, interventions, pharmacist role, performance and outcome measures (antifungal usage, quality of antifungal prescribing and clinical outcomes) were extracted independently by two

investigators (AK, KC) into an inhouse template. The authors of original studies were not contacted in cases of incomplete or missing data.

Synthesis of results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) check-list was utilised as methodological support for this systematic review. Due to variability in interventions, patient populations, and outcome measures, a narrative synthesis approach was utilised to summarise findings. Where equivalent metrics were measured in studies of similar interventions, these results were combined to obtain an aggregate result. Pearson's chi square test was used to assess statistical significance. Exact binomial 95% confidence intervals were calculated for all proportions estimates. No subgroup analyses were performed. Although a formal risk of bias assessment was not performed, the strengths and limitations of each paper were critically reviewed by the authors that extracted the data and discussed as relevant in the paper.

Results

Search results

A total of 646 studies were identified by the initial database search and one study (23) was identified by screening reference lists of relevant articles extracted from the database search. After excluding duplicates and non-relevant studies (i.e. conference abstracts, studies which did not report an AFS quality improvement intervention, studies which were not focussed on antifungal prescribing or studies that did not include a pre and post intervention group), 25 articles were eligible for full-text assessment of which seven met the criteria for inclusion in the systematic review (Fig. 1).

Study characteristics

Of the studies included, six were quasi experimental before-after intervention studies (23-28) and one matched control analysis (29); Table 1. All studies were from single centre academic hospitals, mostly (n=6) from the United States of America (USA). Five studies were specifically dedicated to optimising candidaemia management at a hospital-level (23-27), one

at optimising prescribing of caspofungin in an intensive care unit (ICU) (29) and the remaining study focusing on systemic antifungal prescribing in adult haematology and oncology units (28). All studies included adult patients only. The median duration of intervention was 15 months (Range: 6-48) and included a median of 42 patients (Range: 20 – 103).

Interventions

All interventions were led by a pharmacist or group of pharmacists, either specialising in infectious diseases / AMS or clinical pharmacists working independently or in collaboration with infectious diseases physicians. No interventions took place in the hospital outpatient setting.

During the intervention period for five studies, the pharmacist received real-time notification of all patients with a with a positive blood culture for a yeast organisms resembling Candida via an electronic alert or directly by the microbiology laboratory (23-27). One further study, targeting optimising caspofungin prescribing for candidaemia in the ICU, identified patients initiated on caspofungin via the electronic medical record and electronic alerts (29). The role of the pharmacist in these studies was to perform a comprehensive review of the patient's medical record and to make recommendations to the primary treating team. The pharmacist made recommendations related to a candidaemia bundle of care which varied between studies, but could include both prescribing and infection management elements (Table 1). Prescribing recommendations included initiation of appropriate antifungal therapy, dosage selection, advice regarding duration of therapy as well as suggestions for de-escalation to a narrower spectrum agent or switching from intravenous to oral therapy. Infection management recommendations included requirement for infectious diseases and/or ophthalmology consultation, echocardiography, removal of a central venous catheter and repeat blood cultures to ensure resolution of blood stream infection. Recommendations made by pharmacists were based on local guidelines and acceptance by the prescribing physicians was voluntary in all studies. Additional interventions in one study included guideline development and education for medical staff (26).

For the single study aimed at enhancing the quality of systemic antifungal prescribing in the haematology and oncology units (28), the pharmacist evaluated every systemic antifungal prescription to provide feedback to physicians regarding drug choice, dosage, initiation,

discontinuation and clinically relevant drug-drug interactions. Recommendations were voluntary. Additional interventions implemented included education of physicians and the preparation and distribution of pocket cards summarising local guidelines.

Quality outcomes

Quality of antifungal prescribing

All studies reported quality of antifungal prescribing, employing a variety of metrics and definitions of appropriate prescribing (Table 2). Where measured, most studies (3/4) found no change in the overall appropriateness of antifungal prescribing following the intervention, while Reed et al demonstrated an improvement in rate of effective antifungal therapy following implementation of pharmacist-led recommendations for patients with candidaemia (26). Appropriate duration of antifungal prescribing was reported in five studies, showing no change in the proportion of patients receiving greater than 14 days of antifungal therapy following candidaemia clearance (23, 25, 27) (Table 3) or duration of effective antifungal therapy (26). Lachenmayr et al, reported improvement in compliance with guideline duration of antifungal therapy (28).

The appropriateness of the dose of antifungal was assessed in two studies finding an improvement in optimal dosing following the intervention (27, 28) (Table 3). Lachenmayr et al also assessed the proportion of antifungal prescriptions that were unnecessary, the rate of inappropriate antifungal selection and the rate of clinically significant drug-drug interactions pre and post intervention, finding improvements in each measure (Table 2) (28).

Time to therapy

Metrics relating to the time to initiation of antifungal therapy following a positive blood culture varied across four studies and included median time to adequate, appropriate or targeted therapy a well as time to an antifungal order being placed and administered. Time to therapy was measured in business hours, after hours and/or for the total population. Four studies found a reduction in time to initiation of antifungal therapy (23-26).

Bundle of care adherence

The quality of infection management was reported in four studies, measured as adherence to a composite candidaemia bundle of care or individual bundle elements (Table 2). Aggregation

of relevant study data demonstrated that composite bundle adherence was significantly improved following the interventions (Table 3). Care bundle elements with the greatest improvement were ophthalmology consultation, echocardiography and the rate of infectious diseases consultation. There were small but non-statistically significant improvements in CVC removal and repetition of blood cultures to confirm clearance of Candida infection (Table 3).

AFS program process measures

AFS program process metrics included the number of interventions made by the pharmacist, type of recommendations made, intervention acceptance rates and evaluation of physician satisfaction with the program (24, 28) (Table 4). The acceptance rate for pharmacist recommendations ranged from 66.1% (28) to 90.5% (24). Lachenmayr et al found higher rates of recommendation acceptance for interventions relating to initiation of antifungal prophylaxis, dosage adjustment and modification due to potential drug-drug interactions, compared with lower acceptance of recommendations concerning indication (28).

Usage outcomes

Cost

Four studies reported variable cost-related metrics (Table 4). Heil et al (24) and Guarascio et al (29) reported a cost saving per patient, Samura et al (27) reported a significant reduction in mean monthly expenditure on antifungals and Reed et al (26) reported a non-statistically significant reduction in total hospital costs and hospital costs during candidaemia treatment.

Antifungal drug consumption

Four studies measured antifungal drug consumption with variable units employed (Table 4); defined daily dose (DDD) per 100 patient days, median total treatment duration and median days of therapy (DOT) for all antifungals and also individual agents. Due to the lack of common measurement, a direct quantitative comparison between studies was not possible. Guariscio et al (29) reported a halving of antifungal DOT following implementation of a pharmacist-led antifungal management bundle in the ICU and Samura et al (27) reported a reduction in antifungal consumption which was mostly attributed to a reduction in echinocandin prescribing. The remaining studies reported minor increases in antifungal consumption that were not statistically significant (24, 28).

Clinical outcomes

Mortality

Five studies reported mortality outcomes (Table 4), with analysis of aggregated data finding no change in mortality between pre and post implementation groups (Table 3). Studies which reported median hospital length of stay (LOS) and infection related LOS also found no change (31-34).

Infection and microbiology related outcomes

Four studies reported a variety of infection and microbiology related outcomes (Table 4). Time to culture clearance was reduced by one day following implementation of rapid fungal diagnostic and pharmacist review (24), possibly owing to faster organism identification and reduced time to targeted antifungal therapy. Reed et al found no difference in species isolation between the pre and post intervention groups but did find a possible reduction in C. albicans and C. glabrata resistance to fluconazole (26).

Discussion

To our knowledge, this is the first study to critically review published literature on the outcomes of pharmacist-led AFS interventions. We have demonstrated that pharmacist-led AFS interventions are able to support improvements in the quality and timeliness of antifungal prescribing, the quality of IFD management and may reduce antifungal usage.

Our work has shown that pharmacists have an important role in AFS whereby the extensive knowledge that pharmacist's possess of drug pharmacokinetics ensures that they are to be able to offer tailor-made advice relating to antifungal selection, dosing and management of drug-drug interactions (30). However, the studies suggest that, similar to AMS, successful AFS requires a multidisciplinary approach (22, 30). This was supported by Lachenmayr's observation of marginal acceptance of recommendations relating to drug indication provided by the pharmacist alone (28). In addition to pharmacists, recommended core members for AFS program include infectious diseases specialists, microbiologists and haematologists (30, 31) where every profession contributes their focus and expertise to AFS. Engagement with clinical specialists from high-prescribing specialties and identification of "champions" is recommended for building trust and strong communication (22, 30). While the focus of this

systematic review was on pharmacist-led interventions, similar to other AMS initiatives, there is scope for a well-trained nurse to participate or support AFS, this role may be critical in the setting where there is limited or no access to a pharmacist.

Interestingly, the pharmacist-led AFS programs reported to date have mostly focussed on optimising candidaemia management. Candidaemia is frequently associated with delayed or missed diagnosis, worsening outcomes in critically ill and immunocompromised patients (32, 33) and a high mortality rate of 36-60% (34, 35). Unlike mould infections, several factors make candidaemia an appealing target for AFS including an easily and routinely identifiable laboratory prompt for patient identification. The focus on candidaemia may have been facilitated by the broad experience with similar pharmacist-led and multi-disciplinary AMS interventions for optimisation of bacteraemia management demonstrating improvements in process measures, appropriate prescribing and clinical outcomes (36-38). Importantly, there are limited quality improvement studies that explore antifungal prophylaxis as well as empiric and directed antifungal prescribing in high risk haematology and oncology groups where mortality from invasive mould infections is high (1-3) and high rates of suboptimal antifungal prescribing have been observed (9-14).

We have found large variability in metrics and definitions of antifungal prescribing quality employed across all studies. As such it was difficult to aggregate and quantify the impact of interventions on the outcomes which then impacted our ability to accurately compare studies. This observation highlights a need to define the most meaningful and feasible metrics for AFS that can routinely be applied in studies and in clinical practice. An international Delphi study was recently conducted to achieve expert consensus on a core set of AFS metrics and to determine their feasibility for implementation (39). If the findings of the consensus document are consistently applied in practice, this may assist hospitals and AFS programs to interpret data effectively and to structure suitable quality improvement programs which will allow benchmarking locally, nationally and internationally.

In the current review, five studies had employed a bundle of care to guide optimal candidaemia management. Recommendations for ancillary management measures in candidaemia are included in the Australian (40), American (41) and European (42) guidelines and include requirement for early CVC removal, ophthalmological consultation, echocardiography, repeat blood cultures and a 14 day duration of therapy following clearance of blood cultures.

Strategies to improve adherence to candidaemia guideline recommendations, including timely initiation of appropriate antifungals and implementation of a bundle of care, have been shown to improve patient outcomes (18, 43-46) including a demonstrated mortality benefit (43, 44). Pettit et al (25) implemented the most extensive bundle of care incorporating all recommended management strategies in addition to the requirement for infectious diseases consultation. An almost two-fold improvement in composite bundle compliance was achieved when pharmacists provided advice to the treating team to guide implementation of bundle of care elements following real-time notification of a positive blood culture. Our review of the literature supports the utilisation of an evidence-based bundle of care as part of a multi-disciplinary and pharmacist-led candidaemia AFS intervention.

Metrics relating to antifungal usage are frequent performance measures for evaluating AFS programs (19, 47) and are commonly used as justification to hospital executives for resources to support AFS programs. In addition to quantifying antifungal usage, it is essential that AFS programs employ measures that assess the overall effectiveness of interventions (22). Assessing an intervention's impact on the quality of antifungal prescribing is usually not a focus of AFS publications (19, 47), thus it was encouraging that all the work presented in the current systematic review had assessed one or more quality outcomes. The high baseline rates of appropriate antifungal prescribing in the candidaemia studies discussed in this review limited the ability for these studies to demonstrate statistically significant improvements in prescribing quality. Importantly, Lachenmayr et al was able to show clinically and statistically significant improvements in a number of areas related to the quality of antifungal prescribing following an initial audit to identify key targets for quality improvement (28). Their work highlights the benefit of conducting quality audits to identify gaps in practice to guide targeted quality improvement interventions.

Five of the included studies evaluated one or more clinical outcomes but were unable to identify a reduction in mortality, hospital or infection related LOS. These may be challenging targets to influence with AFS interventions given the complexity with managing immunocompromised patients with comorbidities (22, 39). By employing rapid fungal diagnostic in conjunction with pharmacist notification and review, Heil et al showed an improvement in the time to 'fungal' clearance from the blood, a halving of hospital-LOS and a reduction in-hospital mortality (24). Though these outcomes did not reach statistical significance in this small single centre study, the results are indicative of the potential impacts

of such AFS intervention on the patient's clinical and microbiological outcomes. While it is not known whether a similar intervention led by a medical clinician would have achieved similar or varied outcomes, it does suggest an intervention led by a health professional can be effective.

The ability to translate and implement the pharmacist-led candidaemia management interventions presented in this review into the Australian setting may be limited due to local institutional practices. Five of the studies used direct microbiology laboratory notifications to the pharmacist to notify of patients with a blood culture that is associated with a positive blood culture for a yeast organisms resembling Candida. Where stated in the studies, the standard of care was the microbiology laboratory contacting a member of the treating team (medical or nursing) to notify of the positive blood culture. In Australia, the accepted best practice in several hospitals is for the microbiology laboratory to notify the infectious diseases unit when a yeast or a Staphylococcus aureus has been isolated in a blood culture. A model of microbiology referrals to a multidisciplinary AMS team has been successfully trialled in patients with positive blood cultures in an Australian hospital (36). We have noted that the pharmacist-led AFS interventions involved notification of a positive blood culture across various hours, including around the clock (23), business hours (26), and extended hours (24, 25). Implementing one of these models of care will depend on local institutional factors. Australian clinical pharmacy services mostly operate during regular business hours with an on-call system for overnight or after-hours (48). Comparatively, hospitals in the USA often deliver 24-hour pharmacy services, 7 days a week (49).

In the current systematic review, a risk of bias was introduced to all studies by the lack of randomisation and the non-blinded assessment of outcomes by the investigators. The before-after study design adopted by most of the studies in the current review may have introduced confounding as it is known that over time there is a shift in Candida species away from C. albicans which results in more difficult to treat infections (8, 35, 50). The retrospective nature of data collection in the studies included in our review presents difficulty due to a lack of consistent documentation of interventions which may impact data analysis. For those studies that implemented a candidaemia bundle of care, it is difficult to draw conclusions as to whether pharmacist intervention, an element of the bundle of care or a combination resulted in the observed outcomes. Additional limitations of our review include the low number of research

papers identified and the narrative synthesis approach employed due to the large variability in interventions and outcome metrics utilised. Incomplete retrieval is possible for papers outside of the MEDLINE and EMBASE databases.

Conclusion

There is currently a dearth of information regarding the impact of pharmacist-led AFS interventions on the quality and quantity of antifungal prescribing as well as patient's clinical outcomes. Available evidence suggests that pharmacist-led AFS interventions can improve the quality and timeliness of antifungal prescribing, the quality of IFD management and may reduce antifungal usage. Further research is required to determine the optimal interventions and to assess the impact on clinical and microbiological outcomes.

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Table 1. Description of studies included in systematic review

Reference	Design	Setting	Population & focus	Number of patients		Duration (months)		AFS team members	Patient identification	Pharmacist intervention and hours of operation	Bundle of care elements	Antifungals included
				Pre	Post	Pre	Post					
Heil et al 2012 (24) (USA)	Quasi-experimental before-after study	Not stated Single centre	Hospital inpatients (adult) Candidaemia	61	21	15	9	Clinical on-call pharmacist	PNA FISH assay performed on yeast positive blood culture followed by notification of pharmacist by microbiology lab	Contact clinical pharmacist or primary team to provide recommendations on: - Drug selection - Dose optimisation - Duration of therapy Education of prescribing physicians re optimal antifungal prescribing Hours of operation: 07:00 – 21:30 7 days / week	N/A	Not stated
Pettit et al 2019 (25) (USA)	Quasi-experimental before-after study	Academic medical centre Single centre	Hospital inpatients (adult) Candidaemia	42	42	12	12	AMS pharmacists ID/AMS pharmacy resident	Real time electronic medical record notification to pharmacist re yeast detection in blood culture	Communication with primary team (verbal or page) to provide recommendations and ongoing review of: - Drug selection - Duration of therapy - Candidaemia bundle elements	ID consultation Ophthalmology consultation CVC removal Echocardiogram Repeat blood culture Duration of therapy	Not stated

										Hours of operation: 08:00 – 17:00 Mon-Fri		
Rac et al 2018 (23) (USA)	Quasi-experimental before-after study	Tertiary academic medical centre Single centre	Hospital inpatients (adult) Candidaemia	50	67	24	24	AMS pharmacist	Real time electronic notification of pharmacist on yeast being identified in blood culture	Comprehensive review of the patient's chart at time of notification (once only) and contact with primary team to provide recommendations on: - Initiation of appropriate antifungal - Candidaemia bundle elements	ID consultation Ophthalmology consultation CVC removal Repeat blood cultures	Echinocandins (micafungin) Fluconazole
Reed et al 2014 (26) (USA)	Quasi-experimental before-after study	Academic medical centre Single centre	Hospital inpatients (adult) Candidaemia	85	88	12	12	Pharmacist	Pharmacist notification of Candida spp. isolated in blood culture by microbiology lab	Communication with primary team to provide recommendations and ongoing review of: - Initiation of antifungal - De-escalation - IV to oral switch - Candidaemia bundle elements Development and distribution of guidelines and pocket cards Education	ID consultation Ophthalmology consultation CVC removal	Not stated

										Hours of operation: 08:00 – 17:00 Mon - Fri		
Samura et al 2020 (27) (Japan)	Quasi-experimental before-after study	Middle scale hospital Single centre	Hospital inpatients (adult) Candidaemia	17	20	48	48	ID pharmacist Clinical pharmacist ID physician	Pharmacist notification of yeast detected on blood culture	Communication with primary team to provide recommendations and ongoing review of: - Drug selection - Dose optimisation - Discontinuation - Duration of therapy - Candidaemia bundle elements Hours of operation: Not stated	Ophthalmology consult CVC removal Repeat blood culture Duration of therapy	Fos-fluconazole Micafungin Liposomal amphotericin
Guarascio et al 2013 (29) (USA)	Matched control analysis	Academic medical centre Single centre	ICU inpatients (adult) Caspofungin prescriptions (Candidaemia)	72	36	24	6	ICU clinical pharmacists	Daily assessment of caspofungin prescriptions	Communication with primary team to provide recommendations on: - Dose optimisation - De-escalation - Discontinuation - CVC removal Hours of operation: Each morning during ICU ward round	Dose optimisation De-escalation Necessity of ongoing treatment CVC removal	Caspofungin
Lachenmayr et al 2019 (28)	Quasi-experimental	Tertiary academic	Haematology & oncology units (adult)	104 (171 Rx)	103 (145 Rx)	6	6	Clinical pharmacist	Post prescription review and feedback for all	Review of antifungal prescriptions and communication with primary	N/A	All systemic antifungals

(Germany)	before-after study	medical centre Single centre	Systemic antifungal agents					ID physicians	systemic antifungal prescriptions	team to provide recommendations on: - Drug selection - Dose optimisation - Discontinuation - Indication - Drug-drug interactions - Initiation of antifungal prophylaxis - Undertaking TDM in setting of triazole adverse effects Education of prescribing physicians re optimal antifungal prescribing Development and distribution of guideline pocket cards Hours of operation: Mon-Fri (time not stated)		

AMS = Antimicrobial stewardship, CVC = Central venous catheter, ICU – Intensive care unit, ID = Infectious disease, IV = Intravenous, PNA FISH = Peptic nucleic acid fluorescence in situ hybridization, Rx = Prescription, TDM = Therapeutic drug monitoring

Table 2. Quality outcome measures reported for antifungal stewardship interventions (pre-intervention vs. post-intervention)

Study	Antifungal prescribing quality				Time to antifungal therapy	Adherence to bundle element
	Overall appropriateness	Appropriate duration of therapy	Appropriate dose	Other		
Heil et al 2012 (24) **(USA)**	Not reported	Not reported	Not reported	↑ Rate of targeted therapy following 1-week: 93% vs. 100%, p = 0.09	↓ Mean time to targeted therapy (days): 2.3 vs. 0.6, p= 0.0016	- Not reported
Pettit et al 2019 (25) **(USA)**	Appropriate initial antifungal: 100% vs. 100%, p=1.0	↑ Correct duration of therapy: 94% vs. 100%, p=0.5	Not reported	Not reported	↓ Median time to antifungal initiation (hrs): 4.8 vs. 3.3, p=0.58 ↓ Median time to targeted antifungals (hrs) 3.1 vs. 3.6, p = 0.63	↑ Composite: 48% vs. 83%, p=0.001 ↑ ID consult: 86% vs. 98%, p=0.11 ↑ Ophthalmology consult: 69% vs. 88%, p=0.03 ↑ CVC removal: 89% vs. 94%, p = 0.67 ↑ Echocardiography: 65% vs. 86%, p=0.04 Repeat culture: 98% vs. 100%, p = 1.0
Rac et al 2018 (23) **(USA)**	Adequate antifungal therapy: 92% vs. 95.5%, p = 0.459	↑ Min 14 days of adequate therapy from culture clearance:	Not reported	↑ Switch to adequate oral antifungal: 18% vs. 38.8%, p = 0.015	↓ Median time to adequate therapy (total	↑ Composite: 18% vs. 25.4% p = 0.343

	↑Appropriate antifungal therapy: 84% vs. 93%, p = 0.146	44.7% vs. 54.5%, p = 0.301			population): 3h 30m vs. 2h 9min, p = 0.021 Median time to appropriate therapy: 11h 15m vs. 12h 1m, p = 0.944	↑ ID consult: 36% vs. 74.6%, p < 0.001 ↑ Ophthalmology consult: 36% vs. 68.7% p < 0.001 ↓ Median time to ID consult (days): 3 vs. 1, p=0.002
Reed et al 2014 (26) **(USA)**	↑ Effective antifungal therapy: 88% vs. 99%, p = 0.008	↑ Median in-hospital duration of effective therapy (days): 9 vs. 11, p=0.56	↓ Inadequate fluconazole dose: 8.2% vs. 2.3%, NS	Not reported	↓ Median time to effective antifungal administration (hrs) BH: 13.5 vs. 1.3, p=0.04 AH: 5.0 vs. 2.6, p = 0.51	ID consult: 59% vs. 61%, p=0.76 ↑ Ophthalmology consult: 38% vs. 53%, p=0.05 ↑ Echocardiography: 66% vs. 78%, p = 0.09
Samura et al 2020 (27) **(Japan)**	Not reported	↑ Min 14 days of adequate therapy from culture clearance: 80% vs. 100%, p = 0.477	↑ Optimal dose prescribing: 71.4% vs. 100%, p= 0.028	↑ Definitive therapy transition or step down: 23.5% vs. 35%, p = 0.495 ↑ Insufficient effect related switching rate: 14.3% vs. 83.3%, p= 0.029	Not reported	↑ Ophthalmology consult: 35.3% vs. 45.0%, p = 0.738 ↑ CVC removal: 76.5% vs. 81.2%, p = 1.0 ↑ Repeat culture: 47.1% vs. 65%, p =0.331
Guarascio et al 2013 (29) **(USA)**	Adherence to bundle criteria post intervention: - Medical ICU 79% - Surgical ICU 58%	Not reported	Not reported	Not reported	Not reported	Not reported

Lachenmayr et al 2019 (28) **(Germany)**	Not reported	Timing of prophylaxis initiation per guideline: 53.5% vs. 84.4%, NS	↓ Inappropriate antifungal dose: 23.4% vs. 4.1%, p < 0.05	↓ Antifungal not necessary: 25.7% vs. 14.5%, p < 0.05 ↓ Antifungal selection not appropriate: 22.8% vs. 6.9%, p < 0.05 ↓ Clinically relevant drug interaction: 18.7% vs. 4.8%, p < 0.05 ↓ Proportion of empirical therapy: 60.8% vs. 53.1%, NS ↓ Proportion switch from prophylaxis to treatment: 37.5% vs. 31.4%, NS	Not reported	Not reported

AH = After hours, BH = Business hours, ID = Infectious diseases, ICU = Intensive care unit, NS = Not specified

Table 3. Aggregated outcome measures

Metric	**Pre-intervention** % [95% CI] (n/N)	**Post-intervention** (%) [95% CI] (n/N)	**p**	**Included studies**
Quality of antifungal prescribing				
Patients receiving > 14 days of antifungal therapy following candidaemia clearance	66.7 [55.9, 76.3] (60/90)	71.2 [61.4, 79.6] (74/104)	0.6	(31, 33, 35)
Appropriate antifungal dose	73.6 [69.0, 77.8] (298/405)	97.9 [95.4, 99.2] (277/283)	< 0.01	(35, 36)
Quality of infection management				
Composite candidaemia bundle adherence	31.5 [22.2, 42.0] (29/92)	47.7 [38.1, 57.5] (52/109)	0.03	(31, 33)
Ophthalmology consultation	43.8 [36.7, 51.1] (85/194)	64.1 [57.3, 70.4] (139/217)	< 0.01	(31, 33-35)
Echocardiography	66.1 [57.2, 74.3] (84/127)	80.8 [72.9, 87.2] (105/130)	0.01	(33, 34)
Infectious diseases consultation	58.8 [51.1, 66.1] (104/177)	73.6 [66.7, 79.6] (145/197)	< 0.01	(31, 33, 34)
Early central venous catheter removal	85.5 [73.3, 93.5] (47/55)	90.0 [78.2, 96.7] (45/50)	0.68	(33, 35)
Repetition of blood cultures to confirm clearance of Candida infection	83.1 [71.0, 91.6] (49/59)	88.7 [78.1, 95.3] (55/62)	0.40	(33, 35)
Clinical outcomes				
In-hospital mortality	26.5 [20.5, 33.3] (52/196)	29.5 [22.9, 36.9] (52/176)	0.60	(31, 32, 34)
30-day mortality	22.0 [12.3, 34.7] (13/59)	37.1 [25.2, 50.3] (23/62)	0.11	(33, 35)

Table 4. Antifungal usage, patient's clinical and infection outcome measures reported as part of antifungal stewardship interventions (pre-intervention vs. post-intervention)

	Usage outcomes		Clinical outcomes		Infection and microbiology outcomes
	Cost (USD)	**Drug usage**	**Mortality**	**Length of stay (LOS) (days)**	
Heil et al 2012 (24) **(USA)**	Potential cost saving per patient: $415	↑ Median treatment duration (days): 14 vs. 17, p=0.71	↓ In-hospital mortality: 31% vs. 24%, p >0.99	↓ Median hospital LOS: 25 vs. 12, p=0.82	↓ Median time to species identification (days): 4 vs. 0.2, p < 0.001 ↓ Median time to culture clearance (days): 5 vs. 4, p = 0.01
Pettit et al 2019 (25) **(USA)**	Not reported	Not reported	↑ 30-day mortality: 19% vs. 26%, p = 0.81	↓ Median hospital LOS: 24 vs. 18, p = 0.28	↑ Average time to blood culture clearance (days): 3.7 vs. 4.1, p = 0.7
Rac et al 2018 (23)	Not reported	Not reported	↓ In-hospital mortality: 34% vs. 31.1%, p = 0.761	↑ Hospital LOS: 18 vs. 27, p = 0.070	↑ Proof of candidaemia clearance: 76% vs. 85.1%, p = 0.214

(USA)				Infection related LOS: 10 vs. 10, p = 0.797	
Reed et al 2014 (26) (USA)	↑ Median total hospital costs: $44,616 vs. $56,875, p=0.29 ↑ Median hospital costs during candidaemia: $25,697 vs. $31,457, p=0.25	Not reported	↑ In-hospital mortality: 19% vs. 30%, p = 0.11	↑ Hospital LOS: 15 vs. 19, p = 0.37 ↑ Infection related LOS 10 vs. 11, p = 0.68	↓ Candida albicans resistant to fluconazole: 20% vs. 0%, NS ↓ Candida glabrata fluconazole dose dependant resistance: 50% vs. 26%, NS
Samura et al 2020 (27) (Japan)	↓ Mean monthly antifungal expenditure: $9,390.5 vs. $5,930.8, p=0.002	↓ Median antifungal DOT: 6 vs. 3.4, p < 0.001	↑ 30-day mortality: 29.4% vs. 60% p = 0.099	Not reported	Not reported
Guarascio et al 2013 (29) **(USA)**	Potential cost saving per patient: $1013	↓ Median caspofungin DOT: 4 vs. 2, p=0.001	Not reported	Not reported	Not reported
Lachenmayr et al 2019	Not reported	↑ DDD / 100 PDs: 16 vs. 18, NS	Not reported	Not reported	Not reported

(28) (Germany)					

AFS = Antifungal stewardship, DDD = Defined daily dose, DOT = Days of therapy, NS = Not specified, PD = patient days

Figure 1. PRISMA 2009 Flow Diagram