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REVIEW

How can we optimize antifungal use and stewardship in the treatment of acute leukemia?

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ABSTRACT

Introduction: The global need for antifungal stewardship is driven by spreading antimicrobial and antifungal resistance. Triazoles are the only oral and relatively well-tolerated class of antifungal medications, and usage is associated with acquired resistance and species replacement with intrinsically resistant organisms. On a per-patient basis, hematology patients are the largest inpatient consumers of antifungal drugs, but are also the most vulnerable to invasive fungal disease.

Areas covered: In this review we discuss available and forthcoming antifungal drugs, antifungal prophylaxis and empiric antifungal therapy, and how a screening based and diagnostic-driven approach may be used to reduce antifungal consumption. Finally, we discuss components of an antifungal stewardship program, interventions that can be employed, and how impact can be measured. The search methodology consisted of searching PubMed for journal articles using the term antifungal stewardship plus program, intervention, performance measure or outcome before 1 January 2024.

Expert opinion: Initial focus should be on implementing effective antifungal stewardship programs by developing and implementing local guidelines and using interventions, such as post-prescription review and feedback, which are known to be effective. Technologies such as microbiome analysis and machine learning may allow the development of truly individualized risk-factor-based approaches to antifungal stewardship in the future.

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Acute leukemia; antimicrobial stewardship; antifungal prophylaxis; antifungal resistance; antifungal stewardship; invasive fungal disease

1. Introduction

1.1. The importance of antimicrobial stewardship

There are many benefits for both patients and healthcare systems for prudent antimicrobial usage; however, the main global driver for antimicrobial stewardship (AMS) is antimicrobial resistance driven by selective pressure from the indiscriminate prescription of these agents. The National Institute for Care and Health and Care Excellence (NICE) define AMS as "an organizational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness" [1]. In contrast, the Centers for Disease Control and Prevention's (CDC) definition of AMS is more patient-focused: 'the effort to measure and improve how antimicrobials are prescribed by clinicians and used by patients' [2]. In reality, successful AMS is an activity that requires both patient- and organization-level interventions.

The importance of AMS was highlighted as part of the World Health Organization's (WHO) Global Action Plan on Antimicrobial Resistance in 2015, which emphasized the use of evidence-based medicine to ensure the correct use of antimicrobials for the appropriate patient groups by implementation of AMS programs [3]. In 2015, NICE published guidance with a recommendation for the implementation of AMS across healthcare sectors, and advice as to how this should be structured [1]. Antimicrobial resistance became one of the four national indicators that reflected the priorities in the United Kingdom National Health Service (NHS) as part of the 2016/17 Commissioning for Quality and Innovation (CQUIN) scheme, which linked healthcare provider performance benchmarked against national quality indicators to financial incentives [4]. Antifungal stewardship (AFS), a subset of general AMS for which many of the same principles apply, became a CQUIN target in the 2019/20 scheme, albeit with a focus on cost-reduction rather than minimization of fungal resistance development [5]. This CQUIN scheme was abandoned due to the COVID-19 pandemic. Similarly, the Joint Commission, who accredit many thousands of healthcare organizations in the United States of America (U.S.A.), added a new AMS standard in 2017, with subsequent updates in 2020 and 2023, which mandated that healthcare organizations implement AMS programs as a priority [6].

1.2. The burden of fungal disease

While the predominant focus of research on AMR has been in relation to antibacterial resistance, antifungal resistance (AFR) is an emergent risk. The overall global burden of fungal disease is substantial, with over a billion people infected with

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Article highlights

- Triazoles are the only oral and generally well-tolerated class of antifungal drugs licensed for use in acute leukemia, though they have interactions with important medications, can require therapeutic drug monitoring, and usage is associated with the development of resistance.
- Posaconazole is first-line antifungal prophylaxis in remission-induction chemotherapy for acute myeloid leukemia; echinocandins and liposomal amphotericin B are first-line empiric treatment for suspected invasive fungal disease of unknown cause. Most patients started on empiric antifungal therapy do not have invasive fungal disease.
- Prospective screening, and preemptive diagnostic strategies can safely reduce antifungal usage, but require easy access to diagnostic tests.
- In acute leukemia, antifungal stewardship teams consisting of an infection specialist, antimicrobial pharmacist, and hematologist can improve patient outcomes by developing local guidelines and optimizing antifungal usage.
- The future of antifungal stewardship will move from general group-based approaches to individualization of patient management.

superficial dermatoses [7]. Invasive fungal disease (IFD) is considered less common, though the true global burden is not known because data on all relevant conditions is not collected systematically at a national level [8]. The available incidence data and statistical modeling was used to estimate the global incidence of IFDs as of 2019–21, excluding the effect of COVID-19. This study estimated the global incidence of immediately life-threatening fungal disease to be over 6.5 million, predominantly invasive aspergillosis (IA) at 2.1 million infections, chronic pulmonary aspergillosis in the context of pulmonary tuberculosis (1.8 million), invasive candidiasis and candidemia (1.6 million), pneumocystis pneumonia (505,000), mucormycosis (211,000), and cryptococcal meningitis (194,000) [9].

While patients with acute leukemia represent only a small proportion of the total cases of IFD, the individual risk is high. This risk is driven by the highly immunosuppressive nature of the intensive chemotherapy and stem cell transplantation protocols deployed in such patients. The SEIFEM-2004 study, a retrospective cohort study which covered eleven tertiary hematology centers, found that the most common IFDs in allogenic stem cell transplant (allo-SCT) patients were due to *Aspergillus* spp. (incidence 6.3%) and *Candida* spp. (1.1%) [10].

In acute leukemia, estimates of the rate of IA vary widely; a recent study by the European Society for Blood and Marrow Transplantation (EBMT) found that 6.0% of patients, from 36 centers in 17 countries treated with allo-SCT, developed proven or probable IA during their remission-induction treatment for acute leukemia. Furthermore, the 1-year survival of the patients who had developed IA pre-SCT was lower than those who did not (68.8% vs 79.0%; HR 1.7 [1.1–2.5]; $p = 0.01$); however, these data are likely to be affected by survivorship bias [11]. A systematic review determined the incidence of IA to be approximately 4% during remission-induction chemotherapy (RIC) for acute leukemia in the presence of antifungal prophylaxis (AFP), and 11% without [12]. The relevance of historic data, much of which is observational and more than a decade old to contemporary clinical practice in the era of more advanced diagnostics, is unknown. Death attributable specifically to IA, rather than the underlying leukemia, is difficult to measure. The SEIFEM-2008 study estimated IA-related mortality to be 27% [13], and in a more recent systemic review, the case fatality rate within 100 days was 29% [12].

Following the introduction of fluconazole prophylaxis there has been a decrease in incidence of invasive candidiasis in patients with acute leukemia [14]. However, with more people at risk as we expand treatment for conditions such as acute leukemia, the overall incidence is rising [15].

The incidence of breakthrough IFD has been increasing due to the use of AFP, predominantly with non-*fumigatus Aspergillus*, non-*albicans Candida*, and Mucorales species. In a prospective multicenter cohort study in Spain, across 94 episodes of proven or probable breakthrough IFD in patients with hematological malignancies, 7 of them were caused by mucormycosis, and the 100-day mortality across all patients was 47% [16].

With the advent of AFP and improving treatments in acute leukemia the epidemiology of IFD will continue to change. Any intervention to reduce antifungal usage needs to be targeted so that there is not a secondary increase in the risk of morbidity and mortality in individual patients who are at risk of developing IFD.

2. Antifungal drugs and antifungal resistance

AFR is of major concern because of the existing limited antifungal armamentarium, especially of well-tolerated oral agents. As fungi are eukaryotes, there are few cellular processes that can be targeted that will not also be associated with toxicity to human cells, as observed in many antifungals in clinical use, such as amphotericin, which have significant toxicities. Financial cost is another factor that should be considered with the new agents likely to be expensive with the current antimicrobial reimbursement models in most countries. New models of reimbursement that delink payments from the volume used, such as that being piloted in the UK currently, may be appropriate for some new antifungal agents [17].

The main classes of antifungals regularly used for the treatment of hematology patients are triazoles, polyenes, and echinocandins.

2.1. Azoles

Triazoles (fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole) disrupt ergosterol synthesis by inhibiting the cytochrome P450 enzyme lanosterol 14α-demethylase [18]. They are used systemically and can be used for both prevention and treatment of IFD [19].

Fluconazole is a triazole mainly used to prevent and treat candidiasis and cryptococcosis, but has little to no-activity against invasive molds such as *Aspergillus*. Different species of *Candida* have varying susceptibility to fluconazole, some of which have recently had their taxonomy re-defined. *C. albicans* is the most common species causing invasive disease and has been historically susceptible, while non-*albicans* species are much more likely to be resistant (*e.g. C. auris* and *C. glabrata*

[now known as *Nakaseomyces glabratus*]), or are intrinsically resistant (e.g. *C. krusei* [now known as *Pichia kudriavzevii*]) [20]. Voriconazole and itraconazole have additional activity against IA, while posaconazole and isavuconazole are active against IA and mucormycosis [20,21].

Species replacement, where selective pressure from antibiotics reduces infections from susceptible species but increases it from resistant ones, has become a significant problem with an increase in the frequency of candidiasis by more resistant non-*albicans* species. In the U.S.A., *C. glabrata* accounted for 24% of IC isolates in the latest SENTRY report [22,23]. Triazole resistance of *A. fumigatus* is increasing in the UK (from 0.43% to 2.2%), and is most often caused by mutations in the *cyp51A* gene that encodes lanosterol 14α-demethylase [24].

Emergence of AFR is associated with AFP, protracted usage, biofilm formation, and suboptimal drug penetration to sites of infection [25]. Patients exposed to triazoles for seven or more days had oral colonization by a higher proportion of species that were intrinsically less susceptible to azoles (36.6% vs 12.9%); 90% of these patients had genetically related colonizing and invasive isolates suggesting that patients are infected by the same isolates that are colonizing them [26]. Azole usage is not limited to clinical situations, however, and agricultural use is likely to contribute to environmental *A. fumigatus* triazole resistance [27].

Triazoles have significant drug-drug interactions with important antineoplastic and immunosuppressive medications used in the treatment of hematological malignancies, primarily due to the inhibition of P450 enzyme CYP3A4 [28]. In such circumstances, the use of triazoles with calcineurin inhibitors requires close monitoring of drug levels [29], and the interaction between triazoles and vincristine can be potentially life-threatening [30]. Many of the novel targeted therapies increasingly used in AML are also metabolized by CYP3A4, such as the FLT3 inhibitors (midostaurin and, to a lesser extent, gilteritinib), venetoclax, and isocitrate dehydrogenase inhibitors (ivosidenib and enasidenib), which may require dose adjustment and closer monitoring [31]. Hepatoxicity and cardiotoxicity are also relatively common adverse events with triazoles; however, such toxicities appear to be less common in the next-generation agents such as posaconazole [32].

2.2. Polyenes

Polyenes include the topical agent nystatin and the parenteral amphotericin B (AmB) formulations. For the prevention and treatment of IA, lipid-associated AmB formulations are preferred over conventional AmB, when available, due to the improved safety profile and patient tolerance [33,34]. AmB has activity against most yeasts and molds, with a mechanism of action that involves drug binding to sterols in the fungal membrane with resultant pore formation and intracellular ion loss.

Overall, resistance to AmB in *A. fumigatus* is rare, noted in only 0.19% of clinical isolates [35]. *De novo* AmB resistance can occur in response to therapy, particularly in *C. auris* even if the isolate is initially susceptible [36]. Intrinsic resistance is present in *Aspergillus terreus, Candida lusitaniae, Scedosporium* spp., and *Trichosporon* spp [34].

Clinical failure rates of nystatin being used to treat oral candidiasis is high, despite the rarity of *in vitro* polyene resistance [37]. In severely immunosuppressed patients, a Cochrane review recommended that nystatin should not be used for the prophylaxis or treatment of candidiasis as it is/was inferior to fluconazole at preventing IFD (RR 0.40; 95% CI 0.17–0.93), though there was no statistical difference in mortality [38]. Such recommendations do not preclude nystatin use in non-severe oral candidiasis in a patient already treated with triazole prophylaxis.

Nephrotoxicity and acute-infusion related reactions are the main adverse events associated with AmB [34]. In a randomized, double-blind trial, nephrotoxicity (defined as a doubling of baseline creatinine) was an adverse event in 19% of patients on liposomal AmB (L-AmB). Infusion-related reactions occurred in 28% [39].

2.3. Echinocandins

Echinocandins, such as caspofungin and anidulafungin, bind to 1,3-β-d-Glucan (BDG) synthase, inhibiting BDG synthesis and thereby increasing fungal cell wall permeability. Caspofungin was approved for use in the U.S.A. in 2001 [40].

Echinocandins are active against *Candida* spp., though against *C. parapsilosis*, a common cause of candidemia, have a naturally higher minimum inhibitory concentration (MIC) while remaining effective [41]. *C. auris* can be resistant to echinocandins, without known prior exposure to these drugs, due to mutations in the *FKS* genes that encode for BDG synthase [42]. Resistance to echinocandins in *Aspergillus* spp. is rare and can also occur either due to mutations in *FKS* or by *FKS*-independent mechanisms that modify BDG synthase [43]. *C. neoformans* cannot be treated with echinocandins as the cell wall of this organism is more reliant on 1,6-β-d-Glucan than 1,3-β-d-Glucan [44]. Due to intrinsic resistance, echinocandins are not used in the treatment of mucormycosis, even in combination therapy with polyenes, in patients with hematological malignancies [45].

Rezafungin is a new echinocandin with a prolonged half-life, administered once weekly, which was approved for use in the U.S.A. in 2023 for the treatment of candidemia and IC, and in the UK in 2024 for the treatment of IC [46,47]. It has comparable activity with other echinocandins, being effective against *Candida* spp. and *Aspergillus* spp [48]. The MIC for rezafungin is lower than other echinocandins for *C. auris in vitro*; however it remains to be seen if these observations translate into clinical benefit [49]. Rezafungin could potentially be employed in an outpatient environment for appropriately clinically stable patients requiring ongoing parenteral therapy, though the number of such patients is likely to be low.

Adverse events related to echinocandins are relatively mild compared to other antifungals, but include headache, fever, and rash. Drug interactions are few, but do include a slight increase in exposure to echinocandins when administered with ciclosporin, due to reduced hepatic uptake [50]. Cost is a consideration with echinocandins with an NHS indicative

price of £230 per 50 mg dose of caspofungin and £300 per 100 mg dose of anidulafungin at the time of writing [51].

2.4. Novel antifungal drugs

2.4.1. Ibrexafungerp

Ibrexafungerp, an oral triterpenoid, was the first antifungal from a new class of agents approved since the echinocandins [52]. As a 1,3-β-d-Glucan synthase inhibitor, ibrexafungerp has a similar spectrum of activity to, and can share cross-resistance with, the echinocandins [53]. However, it is only approved for the treatment of VVC, though the current FURI study is investigating this agent for treatment of IA and IC [54].

2.4.2. Fosmanogepix

Fosmanogepix is currently undergoing phase 3 evaluations for the treatment of IFDs and represents another potential new class of antifungal medications. The mechanism of action of this agent is novel and involves inhibition of the enzyme Gwt1. Gwt1 regulates glycosylphosphatidylinositol (GPI) synthesis which is required for localization of mannoproteins to the fungal cell wall. It has *in vitro* activity against most *Candida* species including *C. auris* (except *P. kudriavzevii*), *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp., and some causes of mucormycosis [55,56]. Reduced susceptibility can occur due to mutations in the Gwt1 enzyme, but there appears to be no cross-resistance with other classes of antifungals. The implications of these observations are that fosmanogepix may represent a potential treatment option for otherwise multi-class-resistant fungal infections [57].

2.4.3. Olorofim

Orotomides are another novel class of antifungal with a unique mechanism of action. They inhibit dihydroorotate dehydrogenase (DHODH) required for pyrimidine synthesis, and are active against *Aspergillus* spp., as well as some rarer molds such as *Scedosporium* spp. and *Lomentospora prolificans*. These drugs do not have activity against yeasts or mucormycosis [58]. Olorofim is being developed for human use but has not yet been approved by the U.S.A. Food and Drug Administration (FDA), which has requested further safety data. The agricultural version of olorofim, ipflufenoquin, has been approved, but this has raised concerns about the potential for environmental resistance to emerge in *A. fumigatus* before olorofim can enter clinical use [59].

While the development of new classes of antifungals is undoubtedly encouraging, the relatively limited overall armamentarium, even with the new agents, emphasizes the importance of protecting what we already have via optimal and, preferably, targeted use.

3. Antifungal use in acute leukemia

We have discussed how antifungal resistance is driven by many factors, but predominantly by consumption. On a per-patient basis, hematology and intensive care are by far the main users of antifungals in the UK at 13,123 defined daily doses (DDDs) and 10,354 DDDs per 1,000 admissions respectively, against standard NHS secondary care consumption of 182 DDDs per 1,000 admissions [60]. These are priority areas, therefore, for trying to optimize usage and targeting antifungal stewardship (AFS) programs.

The Infectious Diseases Society of America (IDSA) [33], the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [61], the German Society for Haematology and Medical Oncology (DGHO) [62–64], the European Conference on Infections in Leukemia (ECIL) [65,66], the European Hematology Association (EHA) [31], and the Australasian Antifungal Guidelines Steering Committee [67–71] have produced recommendations on the use of antifungals in a variety of conditions, though we will focus on adult acute leukemia for the purposes of this review.

3.1. Antifungal prophylaxis

The main study underpinning the recommendation for the use of posaconazole over other triazoles for AFP was a multicenter RCT, published in 2007, that compared posaconazole with fluconazole or itraconazole, in 602 patients undergoing RIC for AML/MDS. Patients on posaconazole had significantly fewer diagnoses of proven or probable IA than on fluconazole/itraconazole (1% vs. 7%, $p < 0.001$), and lower 100-day all-cause mortality (16% vs. 22%, $p = 0.048$) [72]. This historic study, however, did not compare AFP directly to a diagnostic screening-based approach, which has emerged as a potential clinical strategy subsequently.

There is a lack of consensus between published guidelines as to which acute leukemia patient groups require primary antifungal prophylaxis (AFP). There is a general recognition that prolonged (≥7–10 days) and profound neutropenia (≤0.5 $\times 10^6$/mL) are significant risk factors for IFD, and that RIC for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) should receive AFP [33,61,62,65]. Some guidelines employ 'risk thresholds' for what is considered high enough risk to warrant AFP such as 8% [65] or 10% [67]; though with rates of IFD being widely different between studies, in the context of an absence of local and national reporting systems, it can be difficult to determine the risk for any single individual patient at any one center. Pre-chemotherapy patient factors that increase the odds of IFD include performance status of 2 or more (OR 3.1; $p < 0.001$), house renovation in the preceding 6 months (OR 4.01; $p < 0.001$), a high exposure job such as farming (OR 3.43; $p = 0.003$), and COPD (OR 3.96; $p = 0.012$), whereas patients with a higher body weight had a lower risk (OR 0.34; $p = 0.012$) [73].

Newer targeted AML therapies are a milestone in the management of AML. There is a lack of evidence for whether specific targeted therapies warrant the use of AFP, though a systematic review by Stemler *et al*. addresses each of them individually [31]. FLT3 inhibitors, such as midostaurin, are used alongside RIC in AML with *FLT3* mutation and improve overall survival [74]. Even if FLT3 inhibitors do not affect the risk of IFD themselves, patients are often already at high risk due to their underlying disease and use of RIC. FLT3 inhibitors are metabolized by cytochrome P450 3A4 and will interact with triazole prophylaxis [75] increasing the risk of adverse events and the need for closer therapeutic drug monitoring. The advent of these targeted therapies gives further need to

determine if there are safe alternatives to AFP in high-risk patients.

Venetoclax represents a different issue with AFP; while the risk of IFD is lower than that of intensive chemotherapy when used as monotherapy, the drug-drug interaction with posaconazole can be leveraged to increase exposure to venetoclax, reducing the required dose by up to 8-fold, and thus its associated cost [76]. This is a situation whereby AFP is required on a financial basis regardless of whether it is required clinically, which is clearly less than optimal, and other enzyme inhibitors, such as cobicistat, should therefore be investigated for similar effects.

For patients with acute lymphoblastic leukemia (ALL), the situation in relation to AFP is less certain as the incidence of IFD in this condition is lower than that in AML [10]. Due to the interaction between vincristine and triazoles [77], the DGHO guidelines states there is little evidence to recommend the use of L-AmB in ALL. ESCMID recommends against the use of L-AmB in ALL, while ECIL recommends cautious use of fluconazole only, and the IDSA does not make any specific recommendation [33,61,62,65]. Prophylaxis to prevent *Pneumocystis jirovecii* pneumonia is a separate issue but is recommended for patients with ALL undergoing intensive chemotherapy [78].

If AFP is required then posaconazole, where it can be safely prescribed avoiding interactions, is recommended as first line with a preference toward modified release tablets over oral suspension due to improved bioavailability [33,61,62,65,67]. Voriconazole and micafungin are considered alternatives with weaker recommendations [33,61,65,67]. Itraconazole is well recognized to have problems with tolerability, and there is a recommendation against its use in the ESCMID guidelines [61], while others recommend its use with caution [62,65,67].

3.2. Empiric therapy

All the relevant guidelines (IDSA, ESCMID, DGHO) recommend empiric systemic antifungal therapy (AFT) in high-risk acute leukemia patients who have fever refractory to more than 96 hours of broad-spectrum anti-bacterial therapy, though the DGHO guidelines recommend such an approach only in the absence mold-active prophylaxis. Either L-AmB or an echinocandin can be employed as first line agents in the treatment of suspected IFD, though caspofungin is associated with a significantly higher rate of survival compared to L-AmB (7-day OS 92.6% versus 89.2%, $p = 0.05$) [79]. Voriconazole is also a recommended empiric treatment, particularly if IA is suspected, but use is cautioned if the patient is already on azole prophylaxis [33,61,80]. In both clinical practice and trials, however, approximately 30% of patients, regardless of whether they are taking AFP or not, will receive unnecessary empiric AFT, highlighting the need for interventional AFS programs, which have been shown to optimize use and costs without impacting mortality [72,81,82]. Therapeutic drug monitoring is also performed sub-optimally in the UK NHS.

3.3. Directed therapy

Specific treatment for each condition, such as IA, IC, PCP, and mucormycosis, is out of the scope of this review, but where possible histopathological and/or mycological confirmation of the diagnosis combined with antifungal susceptibility testing should be obtained, and disease-specific guidelines referred to when necessary.

3.4. Alternative approaches to antifungal usage

Figure 1 shows different approaches to antifungal usage in acute leukemia and how they interact with each other. Prospective screening relates to the use of biomarker tests to detect IFD before such infection becomes clinically apparent. Such screening can be combined with a preemptive and diagnostic-driven therapeutic approach whereby positive biomarkers lead to further investigation and the possible initiation of AFT. Fungal biomarkers can be combined with a targeted therapy approach, whereas for patients who are commenced on empiric AFT, but who do not subsequently meet the criteria for a diagnosis of probable or proven IFD, antifungal therapy can be stopped.

DGHO, ESCMID, and Australasian guidelines recommend that twice-weekly biomarker testing with either a combination of aspergillus galactomannan (GM) and aspergillus PCR, or GM and BDG, during periods of high risk, could be used instead of mold-active AFP as part of a broader biomarker-driven antifungal strategy, that also includes early clinical assessment and high-resolution CT imaging in the presence of positive biomarkers or clinical deterioration [61,62,70]. GM is not recommended in the presence of mold-active AFP due to poor sensitivity [84], but in the absence of AFP can be positive several days before the onset of symptoms allowing early treatment [85].

Safe implementation of such biomarker-based approaches would be contingent on having short enough turn-around-times of biomarker tests to be able to make timely clinical decisions. In the UK NHS, approximately 80% of centers performing such tests send them to regional or national mycology laboratories, with often associated sub-optimal turn-around times, which is usually associated with delays in the pre- and post-analysis periods [86]. A randomized controlled trial (RCT) comparing a prospective biomarker-based screening strategy with no AFP versus standard mold-active AFP in patients being treated for acute leukemia is currently recruiting in the NHS [87].

ECIL recommend that in lower risk centers (<8% incidence of invasive mold disease) an approach using fluconazole prophylaxis with screening for molds with biomarkers could be used [65]. There is no recommendation for higher-risk patients; however, a recent RCT in AML/MDS where fluconazole prophylaxis was employed compared a preemptive treatment strategy informed by twice-weekly GM testing to no screening and empirical AFT with caspofungin. In the preemptive arm less than half of the patients received AFT (27% vs 63%; $p < 0.001$) with no significant difference in overall survival or IFD [88]. This study represents an important stepping stone by increasing the evidence-based options for IFD prevention and individualization of patient care.

For patients at low risk of IA, but who remain at risk of invasive candidiasis, a diagnostic-driven approach has been employed to reduce the usage of empiric AFT. In a case series of 24 patients with acute leukemia undergoing intensive chemotherapy or allo-

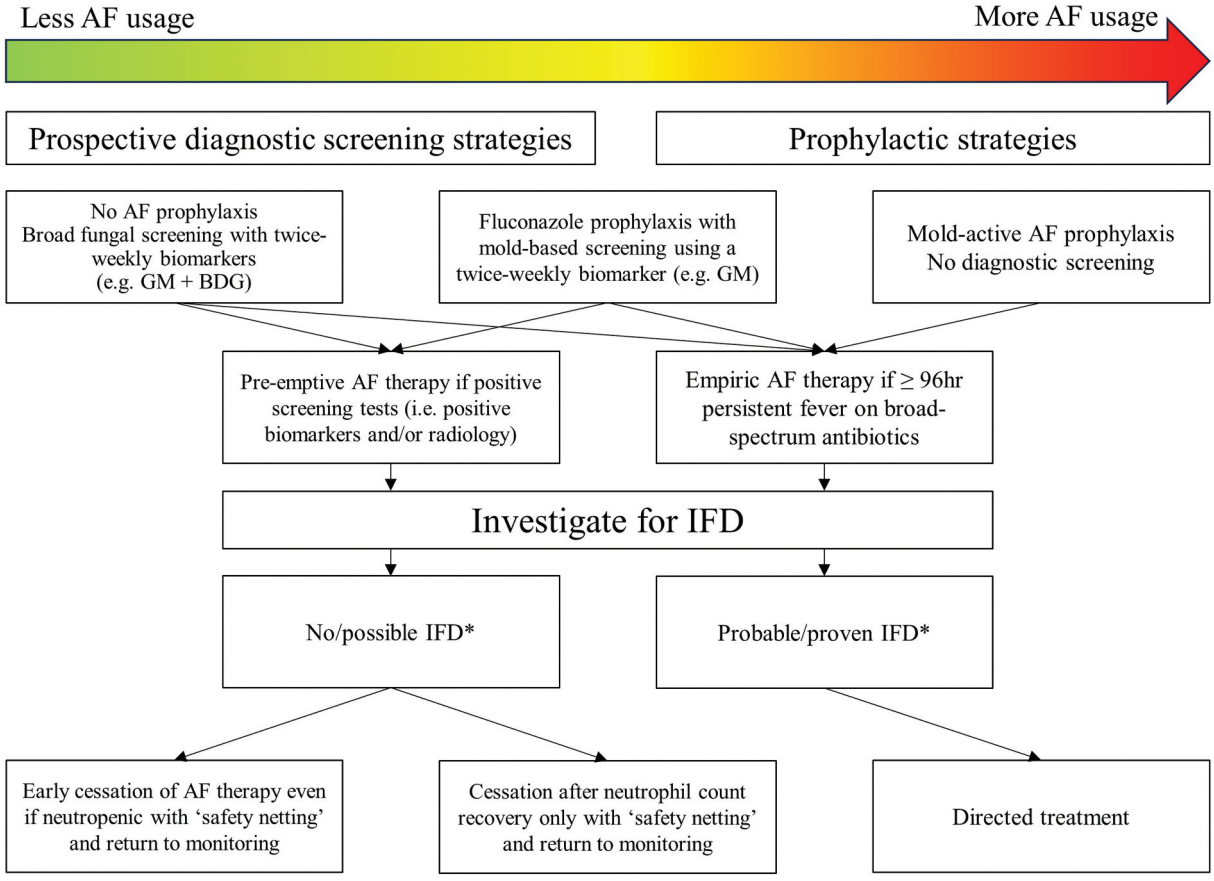

Figure 1. Antifungal management strategies – strategies to the right-hand-side use more antifungals. Patients at high risk of invasive fungal disease (IFD) can enter prospective screening or prophylactic AF strategies. Prospective screening can include twice-weekly mold and yeast screening such as with galactomannan (GM) and beta-D-glucan (BDG) and no prophylaxis; fluconazole prophylaxis with mold screening; or mold-active AF prophylaxis and no screening. Screening strategies can lead to preemptive investigation and therapy if biomarkers are positive, or empiric therapy if persistent fever, while mold-active AF prophylaxis can only lead to empiric therapy. Patients should be investigated for IFD and managed according to results. Stable patients unlikely to have IFD can have AF treatment stopped even if still neutropenic, or await for neutrophil count recovery with appropriate clinical 'safety netting.' Patients diagnosed with IFD should be managed definitively as per the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) consensus definitions [83].

SCT, patients received fluconazole prophylaxis and in the event of febrile neutropenia (FN) underwent blood BDG testing; if positive, they underwent CT imaging of the liver and spleen. Only in confirmed cases of candidiasis, or if a patient further deteriorated, did they receive AFT. While this did reduce empiric AFT by 77%, all 3 cases of chronic disseminated candidiasis were fluconazole-resistant *Candida*, and caution needs to be used with this approach in the context of rising fluconazole resistance [89].

Based on current evidence, we can safely reduce AF usage by:

(1) reducing the number of patients starting mold-acting AFP by using fluconazole and a preemptive therapy approach in patients being systematically screened for IFD with GM.
(2) stopping AFT early when started unnecessarily according to the clinical context and diagnostics performed and the established IFD diagnostic criteria.

These approaches are supported by an AFS study that found that more than 80% of patients who were commenced on AFT for IFD empirically had no evidence of IFD [82]. While there have been several studies on early de-escalation of antibacterial therapy in FN, there have been no trials on duration of empirical AFT. Only the Australasian guidelines refer to de-escalation of AFT with negative investigations, recommending that if patients are commenced on empiric AFT they should have investigations including cultures, aspergillus GM and PCR (if not on triazoles), CT or PET/CT, and biopsy of any radiologically abnormal sites. If these tests do not diagnose IFD, then AFT should be de-escalated to AFP if the patient was on it originally, or otherwise ceased [70].

4. Antifungal stewardship programs

The main aim of AFS programs should be to optimize antifungal usage while improving or maintaining patient outcomes, including health-related quality of life, which should also help patients in the future by reducing the development and spread of AFR.

An AFS multi-disciplinary team should ideally consist of an infectious diseases (ID) and/or microbiology clinician and a clinical/antimicrobial pharmacist as a minimum, but other specialists (such as hematologists) and supportive care health-care professionals (e.g. radiologists, infection prevention and control, epidemiologists, data managers) should also contribute

depending on the area targeted and the resources available [90]. To maximize the availability of limited resources and promote cross-program learning, AFS and AMS programs should be integrated whenever possible. In hospitals with a lower prevalence of IFD, antifungal consumption, or without tertiary hemato-oncology services, AFS could be delivered within an existing AMS program [71]. It is important that the AFS team has support from the hospital administration and resources to undertake its activities [91]. AFS teams will implement, ideally, evidence-based interventions and measure their impact using appropriate performance measures. At least a basic understanding of behavioral science, and the local facilitators and barriers to optimal prescribing, by the AFS/AMS team is important, but beyond the scope of this review.

4.1. Interventions

Potential AFS interventions are listed in Table 1, and there are several reviews and guidelines of these [71,91,92,97,105], including specific to diagnostic-driven approaches [101]. AFS interventions can be divided into persuasive and restrictive; persuasive interventions (e.g. education) are considered more difficult, time-intensive, and costly, and may be less sustainable, but have higher acceptance among clinicians. Restrictive interventions (e.g. prescription approval) are often more effective, but less accepted due to a perceived loss of autonomy. Structural interventions are those such as the availability of rapid diagnostics and TDM that help support AFS.

A key intervention is post-prescription review and feedback (PPFR) [92]. This is often done by the ID team and has been shown to reduce mortality [94], but in some centers this has been done by pharmacists [97,106,107]. It involves review of antifungal prescriptions by a member of the AFS team with specific treatment recommendations discussed with the responsible clinician. This should be done in conjunction with the development of local guidelines for the use of antifungals in prophylaxis and treatment as discussed in the antifungal use section.

4.2. Performance measures

Key to implementation of an AFS program is monitoring of performance measures and clinical outcomes. There are a range of different performance measures that can be considered, and there is no official standard. Table 2 lists some of the performance measures that can be used that are covered in the AFS guidelines [71,91,92,97,105].

5. Conclusion

AFS is a subset of AMS which brings its own challenges and requires its own skill-set. Use of broad-spectrum antibiotics increases the risk of fungal infections, necessitating the increased use of antifungals that in turn drive antifungal resistance, and highlighting the need for AMS and AFS programs to at least complement, if not integrate with, each other. Use of fluconazole is globally shifting the balance of *Candida* spp. infections to fluconazole-resistant non-*albicans* species, and use of fungicides in agriculture is driving environmental resistance to antifungals in molds. AFS is increasingly recognized internationally as an important activity for minimizing developing and spreading antifungal resistance in the clinical setting.

Table 1. Antifungal stewardship interventions divided into restrictive, persuasive, and structural or governance based. Antifungal stewardship (AFS); antimicrobial stewardship (AMS); multidisciplinary team (MDT); invasive fungal disease (IFD); intravenous (IV); computed tomography (CT); broncho-alveolar lavage (BAL); turnaround-time (TAT); United Kingdom (UK); commissioning for quality and innovation (CQUIN).

Intervention	Comments/examples	Reference
Restrictive		
Pre-prescription approval	Needs a robust and responsive approval system to ensure dispensing is not withheld due to the risk of harm in delay. Could allow for select indications or period of time prior to approval	[92–94]
Antifungal order forms	Approval for select indications; allows monitoring of usage	[95,96]
Selective release of susceptibilities	Has not been studied in AFS, though likely to be less impactful than in AMS	[71]
Persuasive		
Post-prescription review and feedback (PPRF)	Has been shown to be highly effective	[92]
Development of local guidelines	Formulated by MDT, based on local epidemiology of IFD, patient population, available diagnostics, and treatments	[90–92,95,97,98]
Therapeutic streamlining	Early IV to oral switch and de-escalation with results	[91,92]
Education	Has been shown to be effective for 12 months but requires regular reinforcement	[91,92,99,100]
Structural/Governance		
Regular AFS team meetings	Such as discussing all restricted antifungal usage on a weekly basis	[95]
In-reach	Dedicated in-reach person who is the first point-of-contact for clinicians, ideally the same person doing PPRF	[91,94,97]
Rapid diagnostic support	Such as availability of high-resolution CT scans, BAL, in-house fungal identification and susceptibility testing; biomarkers have been shown to substantially reduce antifungal consumption and cost	[92,101]
Therapeutic drug monitoring	For voriconazole and posaconazole to ensure adequate prophylactic/therapeutic dosing	[102,103]
Prescription support	Electronic prescribing, dose adjustment tools for weight or renal/hepatic function, accessible antimicrobial pharmacist	
Audit and Quality improvement	To monitor impact of interventions	[90,97]
Surveillance	To monitor antifungal use and fungal infections and susceptibilities at local/national level to inform AFS	[104]
National support/incentives	In the UK for example, AFS related CQUIN incentives Mandatory surveillance with feedback	

Table 2. Performance indicators and outcome measures that can be used to assess the performance of an antifungal stewardship program [71,91,92,97,105].

Basis of measure	Examples
Antifungal stewardship team activity	Number of prescriptions reviewed, patients reviewed, acceptance of guidance
Antifungal	Consumption (defined daily doses, days of therapy), correct choice, de-escalation and streamlining
Invasive fungal disease	Incidence, breakthrough infections, mortality, relapse
Diagnostic	Time to diagnosis, turn-around-times
Clinical outcomes	All-cause mortality, length of stay, readmission
Mycological	Causative organisms, antifungal resistance
Financial	Bed days saved, total cost
Prescriptions	Minimum standards of prescribing, adherence to guidelines, drug-drug interactions

Overall, there are very few classes of antifungals, and currently well-tolerated oral agents are only available within the triazole class, which have potentially life-threatening interactions and adverse effects, and have been linked to increasing AFR and reliance on other classes of antifungals that are intravenous and costly. There have been advances, however, with the emergence of the first-in-class ibrexafungerp, but this has not yet been fully evaluated for use outside of VVC.

Antifungal usage in acute leukemia is broadly divided into prophylactic, empirical, and directed therapy. Since the historic trials and studies that predominantly continue to inform clinical practice today, AFP diagnostics have improved, and screening and diagnostic-based preemptive antifungal strategies can reduce antifungal usage without impacting mortality.

Optimizing antifungal usage requires AFS programs to develop prescribing guidance accounting for local fungal epidemiology and available diagnostics and other resources. Such guidance must be implemented using evidence-based AFS interventions such as the education of prescribers and PPRF.

The immediate future of AFS should focus on developing such local strategies, doing the basics well and addressing 'low hanging fruit,' but this will require systems support. For the time being, in patients deemed to be at a risk level that justifies mold-acting AFP, the contemporary clinical evidence suggests that this can be safely dropped (for fluconazole when it can be used), providing a GM-based and diagnostics surveillance algorithm is employed to guide the need for systemic preemptive AFT. Ideally, this should be done within the framework of a well-resourced and active AFS program.

6. Expert opinion

The concept of AFS is relatively new, and in the next 5 years we should be working on getting the basics right rather than relying on the emergence of new technologies, although the latter are likely to contribute longer term. The known suboptimal IFD biomarker turn-around-time (TAT) for many centers in the UK is a good example of 'low hanging fruit' that the AFS community could target for rapid and relatively inexpensive improvement. The ideal AFS program focusing on optimizing the use of antifungals in acute leukemia is one where a multidisciplinary team of ID, microbiology, pharmacy, and hematology professionals work together to develop and implement local antifungal guidelines appropriate to the context within which they work and that optimize outcomes for patients and society. Which patients require screening or prophylaxis should be based on local epidemiological data on the rates of IFD in patient populations, the organisms implicated, and the associated antifungal susceptibilities.

Ideally, patients who require prophylaxis will have access to local TDM and prescribing tools to optimize dosing, and will be on prophylaxis for the shortest amount of time possible, ceasing it at soon as they are out of the risk-period. Those on a screening strategy will have rapid TAT biomarker results due to, preferably, in-house, and in the future point-of-care, testing. In the event of positive screening biomarkers, or ongoing neutropenic fever on broad-spectrum antimicrobials or other clinical contexts of concern for IFD, patients will have rapid confirmatory blood tests, imaging, and broncho-alveolar lavage (BAL) if appropriate, to determine if there is probable or proven IFD.

Patients commenced on AFT preemptively or empirically, according to the agreed local guidelines, will have a review by their local AFS team who will determine the most appropriate diagnostic tests for investigating IFD, and will discuss these with the responsible clinician. If IFD is unlikely, therapy will be discontinued promptly. When IFD is more likely, an individualized treatment plan will be made including what antifungals to use, when to de-escalate, monitoring/TDM, duration of therapy, and whether any surgical intervention is required. These patients will continue to be reviewed regularly by the AFS team to monitor for improvement or deterioration, but if there are concerns in between, the local team can contact their local in-reach AFS team member for advice or, when this is not possible, an experienced on-call infection doctor.

AFS team activities will be monitored with regular audit, and local antifungal and mycological surveillance will include species level and AFR monitoring. Short-to-medium-term financial challenges might make it difficult to deliver AFS. While some studies do show that AFS saves money by reducing unnecessary antifungal usage [98,103], sometimes the right antifungal is not the cheapest and AFS can potentially increase costs by using echinocandins over triazoles, for example in invasive candidiasis [94]. The cost of healthcare professionals' time must be considered, including any associated opportunity cost. As antifungals come off-patent they will become cheaper, and in our experience biomarker blood tests can be more expensive than prophylaxis for some hospitals in the UK, especially once transport costs are considered for those who do not test in house; so screening strategies that reduce antifungal usage compared to prophylaxis strategies may be more expensive. Clinical trial-based cost-effective analyses for the various approaches are required.

In the long term, successful AFS must reduce overall costs by reducing the number of multidrug-resistant infections,

which are inevitably more expensive to treat as ongoing medical intervention, including new and expensive antifungal agents, is required. In the UK, linking antifungal consumption and stewardship activities to financial CQUIN targets may help, as was originally planned prior to the COVID-19 pandemic, but are missing from the latest portfolio [108]. Bringing fungal diagnostics in-house may also help to reduce costs if there is sufficient throughput, though that would require initial investment and require robust quality assurance processes. If a regional model of reference laboratories for fungal diagnostics is employed, the reliable delivery of samples, and rapid access to results, which actually influence clinical decisions, through electronic laboratory-to-laboratory, or laboratory-to-clinician, communication must be ensured [109].

The current approaches to prevention and therapy of IFD in acute leukemias are predominantly 'broad-brush' in that they are based on group rather than personalized risk (i.e. the risk is considered the same for all patients with the same leukemia receiving the same chemotherapeutic regimen at the same institute). In real life, however, the risk of IFD is likely to differ considerably from individual to individual with some patients having a much higher risk than others because of factors such as their age, comorbidities, baseline microbiome, occupation, social situation, and days of neutropenia [73]. It may be possible using emerging technologies, such as genomics, 'big data' analysis, and artificial intelligence/machine learning, to quantify a patient's risk of IFD more accurately than currently with high-risk patients receiving AFP, and perhaps a lower threshold for empiric therapy, whereas in lower-risk patients diagnostic monitoring with preemptive therapy based on emerging results may be more appropriate [110,111]. Such approaches will, of course ,need to be tested for safety in high-quality randomized, controlled trials.

One potential example is using next generation sequencing (NGS), such as the Oxford Nanopore Technologies (ONT) Promethion that can currently multiplex up to 96 samples on a single flow cell [112]. Samples could be either of the microbiome, where all or most of the microbes in any given niche are determined, or of single organisms for whole genome sequencing. Clinical uses of this could include quantitatively determining if a patient is colonized at baseline or through chemotherapy by *Candida* spp. and therefore potentially at higher risk of invasive candidiasis [113,114], identifying the cause of an infection [115], or using strain-level identification and detection of resistance genes to determine an antifungal susceptibility profile similar to what we do currently in tuberculosis [116] and for other bacteria [117]. One study has recently shown how the bacterial diversity (based on 16S sequencing) in the lungs can predict outcomes in patients with IA, with patients having low diversity at onset (Shannon Diversity Index < 1.46) having worse 1-year survival than those with high diversity (>3.02), with a more than fourfold risk of death (HR 4.2, 1.34–13.1; $p = 0.014$) [118]. It would be interesting to see if NGS could improve this prediction further, or detect patients at risk of developing IA, by sequencing all microbes including bacteria and fungi, and using this in a preemptive machine learning model.

Machine learning has been used in AFS, using a natural language processing model to screen large volumes of pulmonary CT scan reports for language suggestive of IFD; 3014 reports were screened, of which 784 flagged positive and 90 of these had proven or probable IFD on clinical review. Approximately 1% of negative reports had possible IFD on review, but none had proven-probable [119]. Another study used machine learning to predict the risk of IFD in ICU patients using a database of 26,346 patients admitted to ICU at a single center over 12 years, of which 1.44% developed IFD; 70% were used in the training set and 30% in validation to develop 6 predictive models, of which the best one had an AUC of 0.88 (0.71–0.80) [120].

Developing a predictive model for patients with acute leukemia would probably require similarly large amounts of data. This is partly due to the difficulty in diagnosing IFD definitively [83], the low incidence of at-risk patients (in the UK there are only an estimated 1110 causes of AML per year in people aged < 70 [121]), and the lack of a national surveillance system or strategy [104].

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. National Institute for Health and Care Excellence. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15) [Internet]. 2019 [cited 2024 Jan 10]. Available from: www.nice.org.uk/guidance/ng15
2. Sanchez GV, Fleming-Dutra KE, Roberts RM, et al. Core elements of outpatient antibiotic stewardship. MMWR Recomm Rep. 2016;65 (6):1–12. doi: 10.15585/mmwr.rr6506a1
3. Global action plan on antimicrobial resistance [Internet]. Geneva Switzerland: World Health Organization; 2015 [cited 2024 Jan 10]. Available from: https://www.who.int/publications/i/item/9789241509763/
4. National CQUIN Guidance 2016/17 [Internet]. London (UK): Commissioning for Quality and Innovation; 2016 [cited 2024 Jan 10]. Available from: https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-16-17/
5. CQUIN guidance 2019/20 [Internet]. London (UK): Commissioning for Quality and Innovation; 2019 [cited 2024 Jan 10]. Available from: https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-19-20/
6. R3 report issue 35: new and revised requirements for antibiotic stewardship [Internet]. Oakbrook Terrace (IL): The Joint Commission;

2023 [cited 2024 Jan 10]. Available from: https://www.jointcommission.org/standards/r3-report/r3-report-issue-35-new-and-revised-requirements-for-antibiotic-stewardship/
7. Bongomin F, Gago S, Oladele RO, et al. Global and multi-national prevalence of fungal diseases–estimate precision. J Fungi (Basel). 2017;3(4):57. doi: 10.3390/jof3040057
8. Pegorie M, Denning DW, Welfare W. Estimating the burden of invasive and serious fungal disease in the United Kingdom. J Infect. 2017;74(1):60–71. doi: 10.1016/j.jinf.2016.10.005
9. Denning DW. Global incidence and mortality of severe fungal disease. Lancet Infect Dis. 2024;24(7):e428–e438. doi: 10.1016/S1473-3099(23)00692-8
10. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica. 2006;91(8):1068–1075.
11. Penack O, Tridello G, Salmenniemi U, et al. Influence of invasive aspergillosis during acute leukaemia treatment on survival after allogeneic stem cell transplantation: a prospective study of the EBMT infectious diseases working party. EClinicalMedicine. 2024;67:102393. doi: 10.1016/j.eclinm.2023.102393
12. van de Peppel RJ, Visser LG, Dekkers OM, et al. The burden of invasive aspergillosis in patients with haematological malignancy: a meta-analysis and systematic review. J Infect. 2018;76:550–562. doi: 10.1016/j.jinf.2018.02.012
• **Systematic review on the incidence and mortality rate of invasive aspergillosis in acute leukaemia, with and without antifungal prophylaxis.**
13. Pagano L, Caira M, Candoni A, et al. Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. Haematologica. 2010;95(4):644–650. doi: 10.3324/haematol.2009.012054
14. Abi-Said D, Anaissie E, Uzun O, et al. The epidemiology of hematogenous candidiasis caused by different candida species. Clin Infect Dis. 1997;24(6):1122–1128. doi: 10.1086/513663
15. Koehler P, Stecher M, Cornely OA, et al. Morbidity and mortality of candidaemia in Europe: an epidemiologic meta-analysis. Clin Microb Infect. 2019;25(10):1200–1212. doi: 10.1016/j.cmi.2019.04.024
16. Puerta-Alcalde P, Monzó-Gallo P, Aguilar-Guisado M, et al. Breakthrough invasive fungal infection among patients with haematologic malignancies: a national, prospective, and multicentre study. J Infect. 2023;87(1):46–53. doi: 10.1016/j.jinf.2023.05.005
17. National Institute for Health and Care Excellence. A new model for evaluating and purchasing antimicrobials in the UK [Internet]. 2024 [cited 2024 Jun 12]. Available from: https://www.nice.org.uk/about/what-we-do/life-sciences/nice-advice-service/models-for-the-evaluation-and-purchase-of-antimicrobials
18. Den Bossche H V, Willemsens G, Cools W, et al. Biochemical effects of miconazole on fungi. II. Inhibition of ergosterol biosynthesis in Candida albicans. Chem Biol Interact. 1978;21(1):59–78. doi: 10.1016/0009-2797(78)90068-6
19. Mellinghoff SC, Panse J, Alakel N, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the infectious diseases working party (AGIHO) of the German society for haematology and medical oncology (DGHO). Ann Hematol. 2018;97(2):197–207. doi: 10.1007/s00277-017-3196-2
20. Berkow EL, Lockhart SR. Fluconazole resistance in Candida species: a current perspective. Infect Drug Resist. 2017;10:237. doi: 10.2147/IDR.S118892
21. Thompson GR III. Antifungal drugs - azoles. In: Bennett J, Dolin R Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 9th ed. Philadelphia (PA): Elsevier; 2020. p. 501–508.
22. Pappas PG, Lionakis MS, Arendrup MC, et al. Invasive candidiasis. Nat Rev Dis Prim. 2018;4(1):1–20. doi: 10.1038/nrdp.2018.26
23. Pfaller MA, Diekema DJ, Turnidge JD, et al. Twenty years of the SENTRY antifungal surveillance program: results for candida species from 1997–2016. Open Forum Infect Dis. 2019;6(Supplement_1):S79–S94. doi: 10.1093/ofid/ofy358
24. Abdolrasouli A, Petrou MA, Park H, et al. Surveillance for azole-resistant aspergillus fumigatus in a centralized diagnostic mycology service, London, United Kingdom, 1998-2017. Front Microbiol. 2018;9:2234. doi: 10.3389/fmicb.2018.02234
25. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017;17(12):e383–e392. doi: 10.1016/S1473-3099(17)30316-X
26. Jensen RH, Johansen HK, Søes LM, et al. Posttreatment antifungal resistance among colonizing Candida isolates in candidemia patients: results from a systematic multicenter study. Antimicrob Agents Chemother. 2016;60(3):1500–1508. doi: 10.1128/AAC.01763-15
27. Zhang J, Debets AJM, Verweij PE, et al. Azole-resistance development; how the aspergillus fumigatus lifecycle defines the potential for adaptation. J Fungi. 2021;7(8):599. doi: 10.3390/jof7080599
28. Nivoix Y, Levêque D, Herbrecht R, et al. The enzymatic basis of drug-drug interactions with systemic triazole antifungals. Clin Pharmacokinet. 2008;47(12):779–792. doi: 10.2165/0003088-200847120-00003
29. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. Transpl Infect Dis. 2017;19(5):e12751. doi: 10.1111/tid.12751
30. van Schie RM, Brüggemann RJM, Hoogerbrugge PM, et al. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother. 2011;66(8):1853–1856. doi: 10.1093/jac/dkr223
31. Stemler J, de JN, Skoetz N, et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European hematology association. Lancet Haematol. 2022;9:e361–e373. doi: 10.1016/S2352-3026(22)00073-4
•• **First systematic review on the role of antifungal prophylaxis in patients being treated with novel targeted therapies.**
32. Chen L, Krekels EHJ, Verweij PE, et al. Pharmacokinetics and pharmacodynamics of posaconazole. Drugs. 2020;80(7):671–695. doi: 10.1007/s40265-020-01306-y
33. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016;63(4):e1–e60. doi: 10.1093/cid/ciw326
34. Cavassin FB, Baú-Carneiro JL, Vilas-Boas RR, et al. Sixty years of amphotericin B: an overview of the main antifungal agent used to treat invasive fungal infections. Infect Dis Ther. 2021;10(1):115. doi: 10.1007/s40121-020-00382-7
35. Fakhim H, Badali H, Dannaoui E, et al. Trends in the prevalence of amphotericin B-resistance (AmBR) among clinical isolates of aspergillus species. J Med Mycol. 2022;32(4):101310. doi: 10.1016/j.mycmed.2022.101310
36. Rybak JM, Barker KS, Muñoz JF, et al. In vivo emergence of high-level resistance during treatment reveals the first identified mechanism of amphotericin B resistance in Candida auris. Clin Microbiol Infect. 2022;28(6):838–843. doi: 10.1016/j.cmi.2021.11.024
37. Aljaffary M, Jang H, Alomeir N, et al. Effects of nystatin oral rinse on oral candida species and streptococcus mutans among healthy adults. Clin Oral Investig. 2023;27(7):3557. doi: 10.1007/s00784-023-04969-5
38. Gøtzsche PC, Johansen HK. Nystatin prophylaxis and treatment in severely immunodepressed patients. Cochrane Database Syst Rev. 2014;2014(3):CD002033. doi: 10.1002/14651858.CD002033.pub2
39. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. New Engl J Med. 1999;340(10):764–771. doi: 10.1056/NEJM199903113401004
40. Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. Ann Pharmacother. 2009;43:1647–1657. doi: 10.1345/aph.1M237

41. Pristov KE, Ghannoum MA. Resistance of Candida to azoles and echinocandins worldwide. Clin Microbiol Infect. 2019;25(7):792–798. doi: 10.1016/j.cmi.2019.03.028
42. Kordalewska M, Lee A, Park S, et al. Understanding echinocandin resistance in the emerging pathogen Candida auris. Antimicrob Agents Chemother. 2018;62(6):62. doi: 10.1128/AAC.00238-18
43. Satish S, Perlin DS. Echinocandin resistance in aspergillus fumigatus has broad implications for membrane lipid perturbations that influence drug-target interactions. Microbiol Insights. 2019;12:117863611989703. doi: 10.1177/1178636119897034
44. Kalem MC, Subbiah H, Leipheimer J, et al. Puf4 mediates post-transcriptional regulation of cell wall biosynthesis and caspofungin resistance in Cryptococcus neoformans. MBio. 2021;12(1):1–20. doi: 10.1128/mBio.03225-20
45. Kyvernitakis A, Torres HA, Jiang Y, et al. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clin Microbiol Infect. 2016;22(9):.e811.1–.e811.8. doi: 10.1016/j.cmi.2016.03.029
46. Syed YY. Rezafungin: first approval. Drugs. 2023;83:833–840. doi: 10.1007/s40265-023-01891-8
47. Medicines and Healthcare products Regulatory Agency. Rezzayo approved to treat adult patients with invasive candidiasis [Internet]. 2024 [cited 2024 Jan 29]. Available from: https://www.gov.uk/government/news/rezzayo-approved-to-treat-adult-patients-with-invasive-candidiasis
48. Arendrup MC, Meletiadis J, Zaragoza O, et al. Multicentre determination of rezafungin (CD101) susceptibility of candida species by the EUCAST method. Clin Microbiol Infect. 2018;24(11):1200–1204. doi: 10.1016/j.cmi.2018.02.021
49. Garcia-Effron G. Rezafungin—mechanisms of action, susceptibility and resistance: similarities and differences with the other echinocandins. J Fungi. 2020;6(4):1–23. doi: 10.3390/jof6040262
50. Denning DW. Echinocandin antifungal drugs. The Lancet. 2003;362(9390):1142–1151. doi: 10.1016/S0140-6736(03)14472-8
51. Trowell WJ. British national formulary [internet]. London (UK): BMJ and Pharmaceutical Press; [cited 2024 Jan 10]. Available from: https://bnf.nice.org.uk/drugs/
52. Lee A. Ibrexafungerp: first approval. Drugs. 2021;81:1445–1450. doi: 10.1007/s40265-021-01571-5
53. Jiménez-Ortigosa C, Perez WB, Angulo D, et al. De novo acquisition of resistance to SCY-078 in Candida glabrata involves FKS mutations that both overlap and are distinct from those conferring echinocandin resistance. Antimicrob Agents Chemother. 2017;61(9):61. doi: 10.1128/AAC.00833-17
54. Thompson GR, King T, Azie N, et al. 871. Oral ibrexafungerp outcomes by fungal disease in patients from an interim analysis of a phase 3 open-label study (FURI). Open Forum Infect Dis. 2022;9(Supplement_2). doi: 10.1093/ofid/ofac492.064
55. Shaw KJ, Ibrahim AS. Fosmanogepix: a review of the first-in-class broad spectrum agent for the treatment of invasive fungal infections. J Fungi. 2020;6(4):1–21. doi: 10.3390/jof6040239
56. Hodges MR, Ople E, Wedel P, et al. Safety and pharmacokinetics of intravenous and oral fosmanogepix, a first-in-class antifungal agent, in healthy volunteers. Antimicrob Agents Chemother. 2023;67(4):67. doi: 10.1128/aac.01623-22
57. Kapoor M, Moloney M, Soltow QA, et al. Evaluation of resistance development to the GWT1 inhibitor manogepix (APX001A) in Candida species. Antimicrob Agents Chemother. 2020;64(1):64. doi: 10.1128/AAC.01387-19
58. Wiederhold NP. Review of the novel investigational antifungal olorofim. J Fungi. 2020;6(3):1–11. doi: 10.3390/jof6030122
59. van Rhijn N, Storer ISR, Birch M, et al. Aspergillus fumigatus strains that evolve resistance to the agrochemical fungicide ipflufenoquin in vitro are also resistant to olorofim. Nat Microbiol. 2024;9(1):29–34. doi: 10.1038/s41564-023-01542-4
60. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2022 to 2023 [Internet]. London (UK): UK Health Security Agency; 2023 [cited 2024 Jan 10]. Available from: https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report
61. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24:e1–e38. doi: 10.1016/j.cmi.2018.01.002
62. Stemler J, Mellinghoff SC, Khodamoradi Y, et al. Primary prophylaxis of invasive fungal diseases in patients with haematological malignancies: 2022 update of the recommendations of the infectious diseases working party (AGIHO) of the German society for haematology and medical oncology (DGHO). J Antimicrob Chemother. 2023;78(8):1813–1826. doi: 10.1093/jac/dkad143
63. Heinz WJ, Buchheidt D, Christopeit M, et al. Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the infectious diseases working party (AGIHO) of the German society of hematology and medical oncology (DGHO). Ann Hematol. 2017;96(11):1775. doi: 10.1007/s00277-017-3098-3
64. Ruhnke M, Cornely OA, Schmidt-Hieber M, et al. Treatment of invasive fungal diseases in cancer patients—revised 2019 recommendations of the infectious diseases working party (AGIHO) of the German society of hematology and oncology (DGHO). Mycoses. 2020;63(7):653–682. doi: 10.1111/myc.13082
65. Maertens JA, Girmenia C, Brüggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European conference on infections in leukaemia. J Antimicrob Chemother. 2018;73:3221–3230. doi: 10.1093/jac/dky286
66. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433–444. doi: 10.3324/haematol.2016.152900
67. Teh BW, Yeoh DK, Haeusler GM, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021. Intern Med J. 2021;51(S7):67–88. doi: 10.1111/imj.15588
68. Keighley C, Cooley L, Morris AJ, et al. Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021. Intern Med J. 2021;51(S7):89–117. doi: 10.1111/imj.15589
69. Chang CC, Hall V, Cooper C, et al. Consensus guidelines for the diagnosis and management of cryptococcosis and rare yeast infections in the haematology/oncology setting, 2021. Intern Med J. 2021;51(S7):118–142. doi: 10.1111/imj.15590
70. Douglas AP, Smibert OC, Bajel A, et al. Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021. Intern Med J. 2021;51(S7):143–176. doi: 10.1111/imj.15591
71. Khanina A, Tio SY, Ananda-Rajah MR, et al. Consensus guidelines for antifungal stewardship, surveillance and infection prevention, 2021. Intern Med J. 2021;51(S7):18–36. doi: 10.1111/imj.15586
72. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. New Engl J Med. 2007;356(4):348–359. doi: 10.1056/NEJMoa061094
73. Caira M, Candoni A, Verga L, et al. Pre-chemotherapy risk factors for invasive fungal diseases: prospective analysis of 1,192 patients with newly diagnosed acute myeloid leukemia (SEIFEM 2010-a multicenter study). Haematologica. 2015;100(2):284. doi: 10.3324/haematol.2014.113399
74. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. New Engl J Med. 2017;377(5):454–464. doi: 10.1056/NEJMoa1614359
75. Dutreix C, Munarini F, Lorenzo S, et al. Investigation into CYP3A4-mediated drug–drug interactions on midostaurin in healthy volunteers. Cancer Chemother Pharmacol. 2013;72(6):1223. doi: 10.1007/s00280-013-2287-6
76. Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. Clin Ther. 2017;39(2):359–367. doi: 10.1016/j.clinthera.2017.01.003

77. Moriyama B, Henning SA, Leung J, et al. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses. 2012;55(4):290–297. doi: 10.1111/j.1439-0507.2011.02158.x
78. Busca A, Cattaneo C, De Carolis E, et al. Considerations on antimicrobial prophylaxis in patients with lymphoproliferative diseases: a SEIFEM group position paper. Crit Rev Oncol Hematol. 2021;158:103203. doi: 10.1016/j.critrevonc.2020.103203
79. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. New Engl J Med. 2004;351(14):1391–1402. doi: 10.1056/NEJMoa040446
80. Heinz WJ, Buchheidt D, Christopeit M, et al. Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the infectious diseases working party (AGIHO) of the German society of hematology and medical oncology (DGHO). Ann Hematol. 2017;96(11):1775–1792. doi: 10.1007/s00277-017-3098-3
81. Mansour Ceesay M, Sadique Z, Harris R, et al. Prospective evaluation of the cost of diagnosis and treatment of invasive fungal disease in a cohort of adult haematology patients in the UK. J Antimicrob Chemother. 2014;70(4):1175–1181. doi: 10.1093/jac/dku506
82. Whitney L, Al-Ghusein H, Glass S, et al. Effectiveness of an antifungal stewardship programme at a London teaching hospital 2010–16. J Antimicrob Chemother. 2019;74(1):234–241. doi: 10.1093/jac/dky389
83. Peter Donnelly J, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367–1376. doi: 10.1093/cid/ciz1008
84. Duarte RF, Sánchez-Ortega I, Cuesta I, et al. Serum galactomannan–based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. Clin Infect Dis. 2014;59(12):1696–1702. doi: 10.1093/cid/ciu673
85. Pazos C, Pontón J, Del Palacio A. Contribution of (1→3)-β-D-glucan chromogenic assay to diagnosis and therapeutic monitoring of invasive aspergillosis in neutropenic adult patients: a comparison with serial screening for circulating galactomannan. J Clin Microbiol. 2005;43(1):299–305. doi: 10.1128/JCM.43.1.299-305.2005
86. Borman AM, Fraser M, Patterson Z, et al. Fungal biomarker testing turn-around-times at the UK national mycology reference laboratory: setting the record straight. J Infect. 2021;83(6):e1–e3. doi: 10.1016/j.jinf.2021.10.010
87. Biomarker driven antifungal stewardship (BioDriveAFS) in acute leukaemia a multi-centre randomised controlled trial to assess clinical and cost effectiveness [Internet]. (UK): NIHR; 2022 [cited 2024 Jan 27]. Available from: https://www.fundingawards.nihr.ac.uk/award/NIHR132674
88. Maertens J, Lodewyck T, Donnelly JP, et al. Empiric vs preemptive antifungal strategy in high-risk neutropenic patients on fluconazole prophylaxis: a randomized trial of the European organization for research and treatment of cancer. Clin Infect Dis. 2023;76:674–682. doi: 10.1093/cid/ciac623
•• **Recent evidence on how a pre-emptive antifungal strategy without mold active prophylaxis can be delivered.**
89. Della Pepa R, Cerchione C, Pugliese N, et al. Diagnostic-driven antifungal approach in neutropenic patients at high risk for chronic disseminated candidiasis: preliminary observations on the role of 1,3-β-D-glucan antigenemia and multiphasic contrast-enhanced computed tomography. Support Care Cancer. 2018;26(6):1691–1694. doi: 10.1007/s00520-018-4138-9
90. Agrawal S, Barnes R, Brüggemann RJ, et al. The role of the multidisciplinary team in antifungal stewardship. J Antimicrob Chemother. 2016;71:ii37–ii42. doi: 10.1093/jac/dkw395
• **Details on how an antifungal stewardship team should be structured.**
91. Muñoz P, Bouza E, Alonso R, et al. The current treatment landscape: the need for antifungal stewardship programmes. J Antimicrob Chemother. 2016;71(suppl 2):ii5–ii12. doi: 10.1093/jac/dkw391
• **This article highlights the importance of having an antifungal stewardship team, how it can be set up, what goals and indicators can be used, and challenges that may be faced.**
92. Urbancic KF, Thursky K, Kong DCM, et al. Antifungal stewardship: developments in the field. Curr Opin Infect Dis. 2018;31:490–498. doi: 10.1097/QCO.0000000000000497
•• **Excellent review of antifungal stewardship interventions and performance measures.**
93. Ananda-Rajah MR, Slavin MA, Thursky KT. The case for antifungal stewardship. Curr Opin Infect Dis. 2012;25(1):107–115. doi: 10.1097/QCO.0b013e32834e0680
94. Menichetti F, Bertolino G, Sozio E, et al. Impact of infectious diseases consultation as a part of an antifungal stewardship programme on candidemia outcome in an Italian tertiary-care, university hospital. J Chemother. 2018;30(5):304–309. doi: 10.1080/1120009X.2018.1507086
95. Mondain V, Lieutier F, Hasseine L, et al. A 6-year antifungal stewardship programme in a teaching hospital. Infection. 2013;41(3):621–628. doi: 10.1007/s15010-013-0431-1
96. Apisarnthanarak A, Yatrasert A, Mundy LM. Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. Infect Control Hosp Epidemiol. 2010;31(7):722–727. doi: 10.1086/653616
97. Hart E, Nguyen M, Allen M, et al. A systematic review of the impact of antifungal stewardship interventions in the United States. Ann Clin Microbiol Antimicrob. 2019;18(1):24. doi: 10.1186/s12941-019-0323-z
98. Valerio M, Muñoz P, Rodríguez CG, et al. Antifungal stewardship in a tertiary-care institution: a bedside intervention. Clin Microbiol Infect. 2015;21(5):.e492.1–.e492.9. doi: 10.1016/j.cmi.2015.01.013
99. Santiago-García B, Rincón-López EM, Ponce Salas B, et al. Effect of an intervention to improve the prescription of antifungals in pediatric hematology-oncology. Pediatr Blood Cancer. 2020;67(4):67. doi: 10.1002/pbc.27963
100. Lachenmayr SJ, Strobach D, Berking S, et al. Improving quality of antifungal use through antifungal stewardship interventions. Infection. 2019;47(4):603–610. doi: 10.1007/s15010-019-01288-4
101. Chakrabarti A, Mohamed N, Capparella MR, et al. The role of diagnostics-driven antifungal stewardship in the management of invasive fungal infections: a systematic literature review. Open Forum Infect Dis. 2022;9(7):ofac234. doi: 10.1093/ofid/ofac234
102. Ashbee HR, Barnes RA, Johnson EM, et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British society for medical mycology. J Antimicrob Chemother. 2014;69(5):1162–1176. doi: 10.1093/jac/dkt508
103. Nwankwo L, Periselneris J, Cheong J, et al. A prospective real-world study of the impact of an antifungal stewardship program in a tertiary respiratory-medicine setting. Antimicrob Agents Chemother. 2018;62(10):62. doi: 10.1128/AAC.00402-18
104. Talento AF, Qualie M, Cottom L, et al. Lessons from an educational invasive fungal disease conference on hospital antifungal stewardship practices across the UK and Ireland. J Fungi. 2021;7(10):801. doi: 10.3390/jof7100801
105. Johnson MD, Lewis RE, Dodds Ashley ES, et al. Core recommendations for antifungal stewardship: a statement of the mycoses study group education and research consortium. J Infect Dis. 2020;222(Supplement_3):S175–188. doi: 10.1093/infdis/jiaa394
106. Samura M, Hirose N, Kurata T, et al. Support for fungal infection treatment mediated by pharmacist-led antifungal stewardship activities. J Infect Chemother. 2020;26(3):272–279. doi: 10.1016/j.jiac.2019.09.016
107. Kara E, Metan G, Bayraktar-Ekincioglu A, et al. Implementation of pharmacist-driven antifungal stewardship program in a tertiary care hospital. Antimicrob Agents Chemother. 2021;65(9):e0062921. doi: 10.1128/AAC.00629-21
108. National CQUIN guidance 2023/24 [Internet]. London (UK): Commissioning for Quality and Innovation; 2023 [cited 2024 Jan

10]. Available from: https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-23-24
109. Jones RG, Johnson OA, Batstone G. Informatics and the clinical laboratory. Clin Biochem Rev. 2014;35(3):177–192. doi: 10.1002/pds.3580
110. Al-Hussaini I, White B, Varmeziar A, et al. An interpretable machine learning framework for rare disease: a case study to stratify infection risk in pediatric leukemia. J Clin Med. 2024;13(6):1788. doi: 10.3390/jcm13061788
111. Brasier AR, Zhao Y, Spratt HM, et al. Improved detection of invasive pulmonary aspergillosis arising during leukemia treatment using a panel of host response proteins and fungal antigens. PLOS ONE [Internet]. 2015 [cited 2024 Jun 20];10(11):e0143165. Available from: https://pubmed.ncbi.nlm.nih.gov/26581097/
112. PromethION [Internet]. Oxford (UK): Oxford Nanopore Technologies; 2024 [cited 2024 Jan 29]. Available from: https://nanoporetech.com/products/sequence/promethion-24-48/
113. Pittet D, Monod M, Suter PM, et al. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg. 1994;220(6):751–758. doi: 10.1097/00000658-199412000-00008
114. Lau AF, Kabir M, Chen SCA, et al. Candida colonization as a risk marker for invasive candidiasis in mixed medical-surgical intensive care units: development and evaluation of a simple, standard protocol. J Clin Microbiol. 2015;53(4):1324–1330. doi: 10.1128/JCM.03239-14
115. D'Andreano S, Cuscó A, Francino O. Rapid and real-time identification of fungi up to species level with long amplicon nanopore sequencing from clinical samples. Biol Methods Protoc. 2021;6(1):6. doi: 10.1093/biomethods/bpaa026
116. Witney AA, Gould KA, Arnold A, et al. Clinical application of whole-genome sequencing to inform treatment for multidrug-resistant tuberculosis cases. J Clin Microbiol. 2015;53(5):1473–1483. doi: 10.1128/JCM.02993-14
117. Whittle E, Yonkus JA, Jeraldo P, et al. Optimizing nanopore sequencing for rapid detection of microbial species and antimicrobial resistance in patients at risk of surgical site infections. mSphere. 2022;7(1). doi: 10.1128/msphere.00964-21
118. Hérivaux A, Willis JR, Mercier T, et al. Lung microbiota predict invasive pulmonary aspergillosis and its outcome in immunocompromised patients. Thorax. 2022;77(3):283–291. doi: 10.1136/thoraxjnl-2020-216179
119. Baggio D, Peel T, Peleg AY, et al. Closing the gap in surveillance and audit of invasive mold diseases for antifungal stewardship using machine learning. J Clin Med. 2019;8(9):1390. doi: 10.3390/jcm8091390
120. Cao Y, Li Y, Wang M, et al. Interpretable machine learning for predicting risk of invasive fungal infection in critically ill patients in the intensive care unit: a retrospective cohort study based on MIMIC-IV database. Shock. 2024;61(6):817–827. doi: 10.1097/SHK.0000000000002312
121. Incidence [Internet]. York (UK): Haematological Malignancy Research Network; 2024 [cited 2024 Jan 30]. Available from: https://hmrn.org/statistics/incidence/