Antifungal drug resistance: an update

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ABSTRACT

The number of antifungal classes is small, and resistance is becoming a much more frequent problem. Much greater emphasis needs to be placed on susceptibility testing and antifungal stewardship. Such efforts demonstrably improve survival and overall clinical outcomes. Positively diagnosing a fungal infection with laboratory markers often allows antibacterial therapy to be stopped (ie, anti-tuberculous therapy in chronic pulmonary aspergillosis or antibiotics other than cotrimoxazole in *Pneumocystis* pneumonia), contributing to antimicrobial resistance control generally. Non-culture based diagnostics for fungal disease are transformational in terms of sensitivity and speed, but only occasionally identify antifungal resistance.

Systemic antifungal therapy is crucial for survival and reduction in morbidity of a wide range of fungal infections — some invasive (ie, invasive aspergillosis and candidaemia), some chronic (ie, chronic pulmonary aspergillosis and mycetoma), some allergic (ie, fungal asthma) and a very large number that are superficial (ie, oral or vaginal candidiasis, tinea capitis or corporis (ringworm)). The current systemic antifungal drugs included on the WHO Essential Medicines List are shown in table 1.[1]

Antifungal resistance may be intrinsic or acquired.[2] Genus or species identification often reveals intrinsic resistance such as fluconazole resistance in *Candida krusei*, amphotericin B resistance in *Aspergillus terreus* or echinocandin resistance in *Cryptococcus* species. A tendency for higher rates of acquired resistance is also revealed by species identification, such as fluconazole resistance in *Candida glabrata* or azole resistance in *Aspergillus fumigatus*. So fungal identification is critical to good treatment decisions. A guideline on the therapy of rare mould infections has recently been published by the European Confederation of Medical Mycology which addressed therapy for intrinsically resistant mould fungi.[3]

However, the majority of antifungal resistance problems are acquired, meaning that the majority of strains from that species are susceptible, but some are not and have acquired resistance. The mechanisms of acquired resistance are many, and research continues to uncover more; many are combinations of changes leading to resistance. For azole resistance in *Candida*, the most common mechanisms are efflux (ie, increased export of drug from inside the fungal cell to the exterior), with less common causes related to chromosomal (or part chromosomal) duplication or target site mutation.[4] In *A. fumigatus*, the most common cause is target site mutation, often combined with increased copy number of the target gene (CYP51A).[5] Occasional strains of *A. fumigatus* have increased efflux of azoles, additional copies of a CYP51B protein and several other mechanisms conferring resistance. In *Cryptococcus neoformans*, chromosomal deletions (aneuploidy or disomy) account for most fluconazole resistance.[6 7] Different mechanisms account for amphotericin B, flucytosine, echinocandin and terbinafine resistance.

RESISTANCE IN DERMATOPHYTES

Tinea capitis, cruris, corporis and pedis are common infections across the world, affecting ~1 billion people. They are caused by a variety of filamentous fungi including *Trichophyton*, *Microsporum* and *Epidermophyton* species. Tinea capitis is especially common in children in Africa, affecting an estimated 138 million.[8] *Microsporum canis* infections are more difficult to treat and are refractory to terbinafine.[9]

In recent years, increasing resistance to terbinafine in *Trichophyton interdigitale* is increasingly recognised, especially in India. Multiple strains of *T. interdigitale* causing tinea corporis or tinea cruris are terbinafine resistant. For example, Khurana and colleagues analysed 64 strains from patients and 39 (61%) had elevated minimum inhibitory concentrations (MICs) to terbinafine (MIC >1 mg/L).[10] The European Committee on Antimicrobial Susceptibility Testing Antifungal Susceptibility Testing Subcommittee (EUCAST AFST) has determined an epidemiological MIC cut-off (ECOFF) of 0.125 mg/L for *T. interdigitale* and 0.03 mg/L for *Trichophyton rubrum*.[11] Common substitutions found in the target gene squalene epoxidase (ErgA) were usually associated with MICs of >32 mg/L, with others at 4 and 8 mg/L. All isolates were resistant to fluconazole *in vitro* but fortunately almost all are susceptible to itraconazole. Higher doses of itraconazole (ie, 400 mg daily) give response rates of ~65%. The recent emergence of resistance is notionally attributed to over the counter medication, incomplete courses of therapy and combined steroid, antifungal and antibacterial creams with incomplete coverage and low exposures.[12] The spread of resistance to other countries is documented. This resistant grouping of dermatophytes have been renamed as *Trichophyton indotineae*.[13]

Susceptibility testing of dermatophyte fungi is not usually done in Europe, but is now necessary in patients who are unresponsive to terbinafine. Multicentre validated methodology studies have been conducted by the EUCAST group.[14] National surveillance for dermatophyte resistance is required in countries with extensive links to the Indian subcontinent, probably using a sentinel site approach, preferably including clinical outcome data.

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Table 1 Essential antifungal agents as assessed by the WHO. Access and antifungal price by country is visible here: https://wwwgaffiorg/antifungal-drug-maps/.

Antifungal	Route(s)	Primary indications	Resistance concerns
Griseofulvin	Oral	Tinea corporis and capitis	Some clinical resistance described
Fluconazole	Oral, IV	Mucosal candidiasis, prophylaxis in leukaemia, HSCT and intensive care, treatment and maintenance therapy for cryptococosis	All moulds, including *Aspergillus* resistant. Lower response rates for endemic mycoses such as histoplasmosis. All *Candida auris* and *Candida krusei* strains resistant—some other species less susceptible or resistant
Amphotericin B	IV and topical	Invasive candidiasis and cryptococcal meningitis, endemic fungal infections. Empiric therapy in febrile neutropenia. Lower response rate for invasive aspergillosis than azoles	*Aspergillus terreus* and *nidulans* resistant. Some strains of *Candida auris* resistant. Several intrinsically resistant fungi
Flucytosine	Oral, IV*	Cryptococcal meningitis, neonatal candidiasis and *Candida* endocarditis and endophthalmitis, other rare fungal infections	Low levels of resistance in *Candida* and *Cryptococcus*. Aspergilli and most moulds and endemic fungi resistant
Itraconazole	Oral, IV*	All skin infections, all forms of aspergillosis, endemic fungal infections, mucosal candidiasis, prophylaxis in leukaemia	Rising problems with resistance in *Aspergillus fumigatus*, *flavus* and *niger*. Some cross resistance with fluconazole in *Candida*
Voriconazole	Oral, IV	Invasive and chronic aspergillosis, some rare moulds	Some azole cross resistance in *Aspergillus*. Mucorales intrinsically resistant
Natamycin 5%	Topical, eye	Fungal keratitis	Most effective agent, but some rarer fungi resistant, probably
Echinocandins (micafungin, caspofungin, anidulafungin)	IV	Candidaemia, invasive candiasis, invasive and chronic pulmonary aspergillosis, prophylaxis	Most effective agent for most *Candida* infections, notably the majority of *Candida auris* strains. Less effective than azoles for aspergillosis.

*Many countries only have oral
HSCT, haematopoetic stem cell transplant; ; IV, intravenous.

TRIAZOLE RESISTANCE IN *ASPERGILLUS FUMIGATUS*

A. fumigatus is the most common cause globally of invasive, chronic and allergic aspergillosis, collectively affecting ~10 million people. The only oral class of antifungal agents active against *Aspergillus* species is the triazole group—itraconazole and voriconazole (both WHO Essential Medicines) and posaconazole and isavuconazole. In 2007, alarming reports from Manchester and Nijmegen described increasing azole resistance in *A. fumigatus*.[15] Broadly, two circumstances led to the growing resistance problem. First, in the environment strains highly resistant to azole and triazoles emerged rapidly as a consequence of the widespread use of azole fungicides (about 1/3 of all fungicide use). Such strains are characterised by two principal genetic signatures (TR$_{34}$/L98H and TR$_{46}$/Y121F/T289A).[5 16] Second, in patients on long-term therapy, strains acquire a variety of resistance mechanisms including target site mutations, increased target copy number, efflux and other mechanisms still being described.[17 18] Most isolates that are resistant are resistant to at least two triazoles and most are pan-azole resistant. Resistance has been seen in every continent except Antarctica. Resistant rates in Europe vary from ~1–20%, with higher rates in northern Europe.[19] In Yunnan province in China, cultures from greenhouses found ~80% of *A. fumigatus* resistant to at least one medical triazole drug, with >30% showing cross-resistance to both itraconazole and voriconazole.[20] In southern Vietnam, azole resistance rates in *A. fumigatus* are about 90%.[21] Strains of *Aspergillus flavus* may also be azole resistant, with a recent report from Vietnam finding ~50% of environmental strains to be multi-azole resistant and 85% resistant to itraconazole.[22] These were linked to aquaculture, a new association.

Susceptibility testing of *Aspergillus* species is now well established and available in most developed countries. *Aspergillus niger* strains are always resistant to itraconazole and isavuconazole, and *Aspergillus terreus* and *nidulans* to amphotericin B. It is generally recommended to susceptibility test all strains grown in patients taking antifungal therapy (not including fluconazole), as resistance is suggested by a positive culture on therapy, and preferably all strains in whom therapy is planned, whether from invasive,

chronic or allergic aspergillosis.[23] While susceptibility testing can be slow, direct PCR detection of resistance is possible, particularly for the mutations found in the environment.[24–26] These data can all be part of antifungal stewardship which needs more emphasis in hospital practice. It would be helpful if the antifungal resistance programme run by the WHO Global Antimicrobial Resistance Surveillance System (GLASS) included surveillance for itraconazole and voriconazole resistance in *Aspergillus*.[27]

Patients with triazole resistance fail therapy.[17] A recent cohort study showed that the mortality in voriconazole-resistant invasive aspergillosis was 20–30% higher than in patients with voriconazole-susceptible disease,[16] indicating that the major advances in survival of patients through azole-based therapy are completely lost in resistant cases.

Alternative treatments for pan-azole resistance are all intravenous—amphotericin B and either micafungin or caspofungin (no data for anidulafungin). These agents are 15–20% less effective than azoles for invasive aspergillosis and are troublesome to administer long term. Some data are published on long term usage for chronic pulmonary aspergillosis.[28 29] There are several new agents in clinical development for aspergillosis that may address this problem, including rezafungin (once weekly IV),[30] ibrexafungerp (oral),[31] olorofim (IV and oral)[32] and fosmanogepix (IV and oral).[33]

To help retain the medically important azoles, reduction of usage of these triazole fungicides in the environment is required.[18] This could be a voluntary withdrawal from some or all fungicide market segments. New antifungal drugs with novel chemistries and modes of action in clinical development and/or commercially launched after regulatory approval should never be used as fungicides in agriculture. The authorisation procedure for new fungicides should include testing for activity against non-target fungi such as *A. fumigatus*, that are known to cause infections in humans.

MULTI-DRUG RESISTANT *CANDIDA GLABRATA* AND *CANDIDA AURIS*

The optimal therapy of invasive candidiasis and candidaemia relies on an intravenous echinocandin (caspofungin, micafungin

and andiulafungin) with the exception of a less susceptible or resistance species such as *Candida parapsilosis* complex, *Candida guilliermondii* (rare) and *Candida famata* (rare). In these cases amphotericin B or fluconazole are used, occasionally augmented with flucytosine combination therapy. Unfortunately *C. glabrata* is poorly responsive to fluconazole and is often associated with urinary tract infection (which is itself very common in hospitalised, catheterised patients). Echinocandin therapy is usually successful for systemic *C. glabrata* infection, but none of the echinocandin drugs are excreted into the urine. Some resistance to fluconazole is reported in *Candida albicans*, *Candida tropicalis* and *C. parapsilosis*, but this is not addressed here in detail.

What has emerged in the last 5 years has been multi-drug resistance in *C. glabrata* and global spread of *Candida auris*. In the 2015 Asia study of candidaemia, *C. glabrata* was the causative species in 14% of cases,[34] and in a later study of intensive care unit candidaemia in India (n=918 strains), *C. auris* caused 8.2% and *C. glabrata* 7.1%.[35] Multi-drug resistant (MDR) *Candida* species were found in 1.9%.

Increasing rates of MDR *C. glabrata* have been documented in candidaemia studies comparing rates over time. The number of cases is probably underestimated, as only initial blood isolates are included in surveillance studies. One study demonstrated echinocandin resistance in 21.6% of *C. glabrata* isolates from patients exposed to echinocandins for 7 days or longer.[36] MDR *C. glabrata* substantially increases mortality.

Resistant *C. glabrata* are also a significant issue for women with recurrent vulvovaginal candidiasis (rVVC) as intravenous therapy is inappropriate for these women and many become untreatable. At any one time, an estimated 138 million women suffer from rVVC,[37] and repetitive courses of local azoles (ie, clotrimazole) or oral fluconazole, almost certainly are directly linked to replacement of *C. albicans* with *C. glabrata*.

C. auris has caused outbreaks across the world and is now endemic in many countries including the USA (ie, New York),[38] South Africa, Colombia and India,[39 40] to name a few examples. One outbreak occurred in a neonatal unit in Colombia.[41]

The vast majority of clinical strains of *C. auris* are resistant to fluconazole, and the proportion that are also echinocandin or amphotericin B resistant varies by study. A common mechanism of fluconazole resistance is one of several mutations in zinc-cluster transcription factor-encoding gene TAC1B which increases drug efflux via increased CDR1 expression.[42] Almost all are susceptible to flucytosine but resistance emerges rapidly on therapy. A small proportion (3–10%) are pan-resistant and currently untreatable. Echinocandin prophylaxis is ineffective as it does not penetrate adequately to the skin surface where *C. auris* resides, and so breakthroughs of MDR *C. auris* are promoted by this practice.

Fluconazole resistant *C. parapsilosis* is also a problem and can cause outbreaks. One large study found widespread dissemination in South Africa,[43] especially in private hospitals, and other outbreaks have been described in Turkey and Mexico.[44 45]

All blood and other sterile site cultures of *Candida* should be identified to species level and susceptibility tested. Stewardship programmes should focus in part on stopping unnecessary antifungal therapy for suspected cases of candidiasis and for a positive culture which is not significant (notably respiratory samples). The use of rapid beta 1,3-D-glucan testing can be useful to allow the cessation of therapy as it has a high negative predictive value.[46]

ANTIFUNGAL STEWARDSHIP

Several studies have convincingly shown that antifungal stewardship reduces mortality in the hospitalised patient.[47–52] The basic elements of successful stewardship are: (1) comprehensive knowledge and continuous reference to the best clinical guidance on fungal disease management; (2) a primary focus on the best quality care, not on cost saving, as some expensive antifungals are the best choice (stopping unnecessary therapy is what saves money); (3) clinical experience to know when to infer likely results if not yet available or samples cannot or were not taken. One important tool to assist in top quality fungal disease stewardship is rapid diagnostic services, notably mycology results, but also imaging. Too often, turnaround time for the results takes days, and so empirical (and often wrong) choices need to be made. Another key tool is antifungal therapeutic drug monitoring (TDM), especially for voriconazole and itraconazole, but also flucytosine in neonates and patients with renal dysfunction.[53] A third key tool is immediate access to drug interaction data—one online tool which is curated weekly provides this, and can be downloaded onto Android phones.[54]

Outpatient antifungal stewardship relies on experienced clinicians seeing complex patients, and not assuming that 'any old clinic' will do. If long-term antifungal therapy is started, the follow-up requires those patients to see experienced clinicians for optimal care, including TDM if appropriate.

In many situations, if a fungal disease is diagnosed then antibacterial therapy can be stopped or drastically reduced.[55] Good examples are a diagnosis of chronic pulmonary aspergillosis so that tuberculosis can be ruled out, *Pneumocystis* pneumonia when only cotrimoxazole is needed, candidaemia, fungal asthma and *Aspergillus* bronchitis when treatment with antifungals drastically reduces exacerbations and antibacterial prescriptions.

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