Tackling the growing problem of antifungal resistance

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Until relatively recently, resistance to antifungal drugs has gone largely unreported in mainstream media, unlike the extensive coverage of resistance to antibiotics. However, we are now being warned that the consequences of antifungal resistance for human health, as well as our food supplies, could be serious unless action is taken. Here, we look at the extent of the problem and what is being done to combat it.

Antifungal resistance has not received the same level of attention in recent years that has been seen with resistance to antibiotics and yet the existence of resistant fungal species, particularly those affecting immunocompromised patients, has been discussed in the medical literature for more than two decades.¹

The risk of fungal infection has risen over recent years, in part as a result of increasingly complex medical procedures, particularly transplant surgery, which usually require patients to be immunosuppressed; the elderly and people with cancer or HIV are also at greater risk.

The issue of antifungal resistance and its potential implications was brought to the attention of the wider public in the UK in May 2018 via a BBC report² on a review published in Science,³ which proposed that the widespread use of azoles for animal healthcare and crop protection, for example, as well as for human healthcare may have contributed to the emergence of resistant fungal species.

The review, authored by an international group of researchers, led by Professor Matthew Fisher from the Medical Research Council Centre for Global Infectious Disease Analysis, in the School of Public Health at Imperial College, London, is less than optimistic about the prospects for a world where food supplies and health are threatened by multidrug-resistant pathogenic fungi and antibiotic-resistant bacteria. They say that “crop-destroying fungi account for
perennial yield losses of approximately 20% worldwide, with a further 10% loss post-harvest. Fungal effects on human health are currently spiralling, and the global mortality rate for fungal diseases now exceeds that for malaria or breast cancer and is comparable to those for tuberculosis and HIV. Worldwide it is estimated that at least 1.4 million people die as a result of infection by Candida, Aspergillus (see Figure 1), Pneumocystis and Cryptococcus species.

Use of antifungals for prophylactic treatment of at-risk patients over long periods is thought to be another of the factors that have contributed to the development of antifungal resistance.

**Pockets of resistance**

Until recently, monitoring of antifungal resistance has not been a priority. The focus of attention in the first English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report in 2014, for example, was firmly on antibiotics (although the report did acknowledge that antimicrobials included antifungals). The 2015 report acknowledged the need “to identify gaps within current antifungal surveillance and seek to explore and implement improvements to national surveillance programmes”.

In 2016, ESPAUR devoted a chapter of its report to antifungal resistance, prescribing and stewardship. It noted the rising number of reports of resistant species of pathogenic fungi and cross-resistance to clinical azoles and broad-spectrum antifungals.

The 2017 ESPAUR report records that Aspergillus fumigatus is by far the most common mould isolated from clinical samples. The percentage of samples with reduced susceptibility to itraconazole (as measured using the European Committee on Antimicrobial Susceptibility Testing [EUCAST] methodology in samples from the Mycology Reference Centre in Manchester [MRCM]) has fallen from 20.1% in 2012 to 16.6% in 2015, and reduced susceptibility to voriconazole has fallen from 20.9% to 13.4% in the same period. By contrast, reduced susceptibility to posaconazole has risen from 16.5% to 19.8% between 2012 and 2015.

**Figure 2.** The proportion of Candida albicans specimens showing reduced susceptibility to fluconazole and echinocandins has been rising over the past few years

Samples from Public Health England’s National Mycology Reference Laboratory (MRL; tested using Clinical and Laboratory Standards Institute [CLSI] methodology) showing reduced susceptibility to itraconazole rose from 1.4% in 2012 to 8.5% in 2016. In 2012, 1.7% of samples showed reduced susceptibility to voriconazole in 2012 rising to 4.7% in 2016. The number of samples showing reduced susceptibility to posaconazole fell from 10.6% in 2012 to 6.9% in 2016. The ESPAUR report comments that “the difference in resistance levels could be due to population bias, with samples referred to the MRCM provided by a cohort of patients with chronic pulmonary aspergillosis”.

Resistance to all azole antifungal drugs has been recorded in the UK but it is rare. However, 100% triazole resistance was recorded for Aspergillus terreomutatus in aggregated data for MRCM samples 2012–15.

Only a small number of Candida albicans samples (the most frequently isolated Candida species; see Figure 2) from superficial sites are routinely tested for antifungal susceptibility (around 3–7% annually). Nevertheless, the percentage of all MRCM specimen types showing reduced susceptibility to fluconazole and echinocandins has been rising during the period 2012 to 2016. In 2016, 6.7% (14/210) of samples showed reduced susceptibility to fluconazole and 2.2% (2/91) showed reduced susceptibility to echinocandins. Thus far, no sample has shown reduced susceptibility to amphotericin B. By contrast, 100% of MRCM Candida glabrata specimens have shown reduced susceptibility to fluconazole since 2012, although the proportion of MRL isolates with reduced susceptibility was 31.3% (119/380).

Reports for most of the rarer fungi relate to invasive infection. For example, 100% of Lomentospora prolificans and Purpureocillium lilacinum isolates showed reduced susceptibility to amphotericin B, 100% of Rasamsonia argillacea isolates had reduced susceptibility to voriconazole and 100% of Mucorомycotina and Lomentospora prolificans isolates showed reduced susceptibility to caspofungin. The ESPAUR reports notes that many Fusarium spp. tested were from cases of fungal keratitis in contact lens wearers – the organism is commonly isolated from blood cultures from patients with disseminated infection. Of the samples tested by MRL, 34.3%, 62.4% and 96.3% of isolates showed reduced susceptibility to amphotericin B, voriconazole and caspofungin, respectively over an eight-year period to 2016. Also isolates from sputum samples of cystic fibrosis patients containing Scedosporium apiospermum and...
Exophiala spp. showed reduced susceptibility to caspofungin (64.3% and 90.9% of samples, respectively).8

Candida auris is causing some concern as it is associated with fatality rates of between 30% and 70% in those infected and it has caused prolonged outbreaks of hospital-acquired infection in five continents. It is associated with invasive infections, such as candidaemia, pericarditis, urinary tract infections and pneumonia and exhibits reduced susceptibility to fluconazole, and variable susceptibility to other antifungal agents. The good news for England, according to the latest (2018) ESPAUR report, is that up to the end of September 2018 the number of cases of colonisation and infection with C. auris was lower than 2017. Since 2013, 225 cases have been reported in England, 61 of which were infections, including 31 candidaemias. So far, no deaths have been associated with the cases.9

Public Health England guidance on management, infection prevention and control of C. auris was updated in August 2017 and a patient information leaflet as well as guidelines for care in community settings were made available.10 First-line therapy is an echinocandin and specific susceptibility testing should be carried out as soon as possible. Resistance can evolve quite quickly. Dual therapy may be needed to treat urinary tract or central nervous system infection with C. auris.11

Drug resistance varies from organism to organism and from country to country. For example, in its global report on surveillance of antifungal resistance in 2014, the WHO showed that resistance to fluconazole among all species of Candida ranged from 33% in Denmark to 0.9% in the Republic of Korea.12

Resistance mechanisms

In their Science review, Fisher et al. note that there are just four main classes of antifungal drugs used to treat clinical disease: polyenes (eg amphotericin B); azoles; a pyrimidine analogue (5-fluorocytosine); and the newest class, the echinocandins (eg caspofungin). Resistance has been documented to all licensed systemic antifungals, albeit at differing rates. Resistance to a broad range of antifungals has been recorded for Aspergillus terreus, Scedosporium spp, Fusarium spp, and members of the Mucorales. C. auris and C. glabrata are emerging as multi-drug resistant. The most common mechanism of resistance are mutations that change the conformation of the drug target site. Another mechanism involves upregulation of efflux pumps that prevent drug accumulating inside cells, reducing their efficacy.3

How to fight back?

Fisher et al. comment that a range of strategies are need to combat the threat posed by antifungal resistance, including improved stewardship and the development of novel antifungals with new modes of action. Writing in The Lancet, Perlin et al. add that rapid fungal diagnostics and therapeutic drug monitoring may also be needed.13

It may take some time for antifungal stewardship to be established widely in the health system. A survey of English acute Trusts published in 2017 found that although 46 of the 47 that responded to the survey had an antimicrobial stewardship programme, only five had a dedicated antifungal stewardship programme and overall just 20 included antifungal stewardship as part of their antimicrobial stewardship programme. Of the Trusts that did not have an antifungal stewardship programme, 14 said it was because of a lack of resources or staff time. Availability of rapid diagnostics and clinical support would enable them to conduct antifungal stewardship activities, 12 Trusts said.14

The NHS Improving Value Antifungal Stewardship Project, established in February 2017, aims to develop guidance for NHS England commissioning teams focusing on the following key areas:

- Optimisation of the use of empirical antifungal treatment
- Improvements in antifungal diagnostic testing to inform treatment and antifungal stewardship activities
- Reduction of selective pressure and the impact of resistant fungal pathogens
- Increased use of antifungals with lower acquisition costs.

Combination therapy, particularly using drugs with different modes of action, or alternating treatment with different drugs may be effective in slowing the development of resistance. Another approach being investigated is vaccination, particularly to protect high-risk groups from invasive fungal infection.15

Conclusion

The fact that resistance to antifungal drugs has received relatively little attention until recently means that the true extent of the problem is probably not yet fully understood. Nevertheless, the implications of fungal infections, particularly systemic disease, that are resistant to one or more antifungal drugs are potentially serious, particularly for those patients whose immune systems are compromised. It seems prudent therefore for healthcare professionals to pay more attention to the potential threat posed by drug-resistant organisms and do all they can to use antifungal drugs wisely, much as they are being encouraged to do with antibiotics. At the same time, it must be hoped that researchers will be supported and encouraged to continue to look for new ways of treating fungal infections, and that they are successful.

References

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Declaration of interests
None to declare

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