Editorial

The Threat of Multiresistant Nosocomial Fungi

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In 2014, the World Health Organization (WHO) raised concern about the worldwide threat of antimicrobial resistance to public health.[1] Many bacteria which cause common infections are now resistant to a broad range of antimicrobials. The WHO recently released a list of antibiotic-resistant "priority-pathogens" warranting urgency for research and control.[2] Featured in this list of 12 pathogens were carbapenem-resistant *Acinetobacter baumannii, Pseudomonas aeruginosa*, and third-generation cephalosporin-resistant *Enterobacteriaceae*. These pathogens are also common in local hospitals.[3] However, noticeably absent from the WHO list were fungal pathogens.

Candidaemia is the fourth most common cause of nosocomial bloodstream infection (BSI) worldwide.[4] *Candida* causing nosocomial outbreaks have been well described especially because of biofilm formation on devices and in intensive care units.[5,6] Amongst the *Candida* species causing nosocomial BSI are many non-albicans *Candida* with a higher frequency of resistance to azoles and echinocandins.[7,8] However, the threat of a pan-drug-resistant nosocomial *Candida* joining the ranks of multi-resistant bacteria was not apparent until the recent emergence of *Candida auris*.

Candida auris was first described in Japan in 2009[9] and since then, has been progressively reported worldwide, including the United States, Europe, Africa, North Asia, South Asia and nearby Malaysia.[10] Amongst the cases reported—invariably linked to healthcare institutions—have been reports of drug-resistant *C. auris* outbreaks[11,12] aided by environmental contamination by the yeast. In this issue of the Annals, Tan and her colleague report the first 3 cases of *C. auris* in Singapore.[13] The first case was in 2012, the second and third were in 2016. The temporal sequence of presentation (with the first case 4 years apart from the other 2) highlights a number of challenges; first with diagnosis. *Candida auris* can be misidentified with automated and conventional microbiological phenotypic and biochemical techniques employed in many microbiology laboratories including ours in Singapore, such as the Vitek 2 system and API 20C (both Biomerieux, Marcy-l'Étoile, France), BD Phoenix yeast identification system (BD, Franklin Lakes, NJ, USA) and MicroScan (Beckman Coulter, Brea, CA, USA) yielding instead the related but less resistant *C. haemulonii* or other rarer yeasts such as *Rhodotorula*. Tan and her colleague did not report if there had been difficulties with initial identification in their cases although their index of suspicion for *C. auris* was raised early prompting molecular confirmation and appropriate treatment modification. Microbiology facilities in Singapore and elsewhere who use automated systems may consider reviewing previous *C. haemulonii* cases as it has been reported that incidence of misidentification of *C. auris* as *C. haemulonii* might be as high as 88%.[14] This is not just academic but it has significant infection control implications.

The 3 cases illustrated here highlight many of the important characteristics of *C. auris* infection. There are significant differences between the 4 geographical clades of *C. auris* as elucidated by genetic analyses[15] and it may well be the *C. auris* is actually *C. auris* "species complex" similar to *C. glabrata*. Such variation is reflected in the antifungal resistance profile of the *C. auris* cases described here. Most previously reported strains have high fluconazole minimum inhibitory concentration (MIC), reduced susceptibility to other triazoles, amphotericin and variable MIC to echinocandins.[16] For the individual patient, treatment choice should be guided by in vitro MIC determination to determine the most effective antifungal agent, although at present, echinocandins appear to be the most effective with resistance rates of less than 10% compared with about 30% for amphotericin and 80% for azoles. However, consensus breakpoints for *C. auris* have yet to be established so it is not clear how well these in vitro results correlate with clinical success.

All 3 patients described here shared some notable traits. They were transferred from overseas hospitals to Singapore for continuing care and had received extensive

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prior treatment including broad-spectrum antimicrobials for their primary condition. It was probably not coincidental that all 3 patients were screened positive for drug-resistant carbapenemases of NDM-1 and OXA-232. All our hospitals now actively perform carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) screening for patients with identified epidemiological risks.[17] The epidemiological risks for *C. auris* carriage and infection are similar to that of the CREs. As Tan and her colleague point out, heightened and possibly targeted concurrent screening for *C. auris* in patients with CP-CRE may need to be conducted to avoid large scale outbreaks such as those that have happened in other countries. As with all active surveillance programmes, the cost-effectiveness of such measures will need to be clearly demonstrated. Thanks to the vigilance of Tan and her colleague leading to the prompt implementation of appropriate infection control measures related to CP-CRE, there were no local transmissions reported arising from the 3 cases. Nonetheless, this report, in tandem with the others already described worldwide, places *C. auris* on the world stage of multidrug-resistant organisms (MDROs) necessitating a comprehensive approach including microbiology, molecular and clinical epidemiology, pharmacology, infectious diseases and a strong public health commitment to appropriate action to prevent this emerging multiresistant fungal pathogen from taking root and causing serious morbidity and mortality in our vulnerable patients in intensive care units, haematology-oncology units, surgical and transplant wards.

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REFERENCES

1. World Health Organization. Antimicrobial Resistance. Global Report on Surveillance: Global Report on Surveillance 2014. Available at: http://www.who.int/drugresistance/documents/surveillancereport/en/. Accessed on 17 February 2018.
2. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. 2017. Available at: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/. Accessed on 17 February 2018.
3. Cai Y, Venkatachalam I, Tee NW, Tan TY, Kurup A, Wong SY, et al. Prevalence of healthcare-associated infections and antimicrobial use among adult inpatients in Singapore acute-care hospitals: results from the first National Point Prevalence Survey. Clin Infect Dis 2017;64:S61-7.
4. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309-17.
5. Tumbarello M, Posteraro B, Trecarichi EM, Fiori B, Rossi M, Porta R, et al. Biofilm production by Candida species and inadequate antifungal therapy as predictors of mortality for patients with candidemia. J Clin Microbiol 2007;45:1843-50.
6. Chai LY, Denning DW, Warn P. Candida tropicalis in human disease. Crit Rev Microbiol 2010;36:282-98.
7. Pfaller MA, Moet GJ, Messer SA, Jones RN, Castanheira M. Candida bloodstream infections: comparison of species distributions and antifungal resistance patterns in community-onset and nosocomial isolates in the SENTRY Antimicrobial Surveillance Program, 2008-2009. Antimicrob Agents Chemother 2011;55:561-6.
8. Farmakiotis D, Kontoyiannis DP. Epidemiology of antifungal resistance in human pathogenic yeasts: current viewpoint and practical recommendations for management. Int J Antimicrob Agents 2017;50:318-24.
9. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H. Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol 2009;53:41-4.
10. Chowdhary A, Sharma C, Meis JF. Candida auris: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathog 2017;13:e1006290.
11. Schelenz S, Hagen F, Rhodes JL, Abdolrasouli A, Chowdhary A, Hall A, et al. First hospital outbreak of the globally emerging Candida auris in a European hospital. Antimicrob Resist Infect Control 2016;5:35.
12. Biswal M, Rudramurthy SM, Jain N, Shamanth AS, Sharma D, Jain K, et al. Controlling a possible outbreak of Candida auris infection: lessons learnt from multiple interventions. J Hosp Infect 2017;97:363-70.
13. Tan YE, Tan AL. Arrival of Candida auris fungus in Singapore: report of the first 3 cases. Ann Acad Med Singapore 2018;47:260-2.
14. Kathuria S, Singh PK, Sharma C,Prakash A, Masih A, Kumar A, et al. Multidrug-resistant Candida auris misidentified as Candida haemulonii: characterization by matrix-assisted laser desorption ionization-time of flight mass spectrometry and DNA sequencing and its antifungal susceptibility profile variability by Vitek 2, CLSI broth microdilution, and etest method. J Clin Microbiol 2015;53:1823-30.
15. Chatterjee S, Alampalli SV, Nageshan RK, Chettiar ST, Joshi S, Tatu US. Draft genome of a commonly misdiagnosed multidrug resistant pathogen Candida auris. BMC Genomics 2015;16:686.
16. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender MP, et al. Simultaneous emergence of multidrug-resistant Candida auris on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis 2017;64:134-40.
17. Singapore MOH. Guidelines for control and prevention of multi-drug resistant organisms (MDROS) in healthcare facilities, 2013. Available at: https://www.moh.gov.sg/content/dam/moh_web/Publications/Guidelines/Infection%20Control%20guidelines/GUIDELINES%20FOR%20CONTROL%20AND%20PREVENTION%20OF%20MULTI-DRUG%20RESISTANT%20ORGANISMS%20%28MDROS%29%20IN%20HEALTHCARE%20FACILITIES%20-%20Nov%202013.pdf. Accessed on 17 February 2018.