Wild-Type MIC Distributions and Epidemiological Efficacy Values for Fluconazole, Posaconazole and Voriconazole versus Cryptococcus neoformans as Determined by 72 hour CLSI Broth Microdilution Method

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ABSTRACT

Background: When clinical susceptibility (breakpoints) (CBPs) are established, they are used to guide clinical decision-making and detect emerging resistance. We determined species-specific fluorescent-antimicrobial protein (FAP) breakpoints for Cryptococcus neoformans (CNEO) and Cryptococcus gattii (CGII) using an extensive epidemiological dataset. Results: A total of 3,208 CNEO and 46 CGII isolates collected from 64 centers worldwide between 2001-2008 were tested. The results were used to establish wild-type (WT) MIC distributions and breakpoints for fluconazole, itraconazole, posaconazole and voriconazole. Conclusion: We established the 72-h ECVs for fluconazole, itraconazole, posaconazole, and voriconazole, using an extensive epidemiological dataset. These breakpoints may be useful in detecting the emergence of potential resistance to fluconazole over a 13-year period.

INTRODUCTION

Cryptococcal meningitis is the most common cause of meningitis in patients with AIDS and other immunocompromising conditions. The Clinical and Laboratory Standards Institute (CLSI) Subcommittee for Antifungal susceptibility testing of yeasts (M38-A3) established methods for in vitro susceptibility testing of C. neoformans against fluconazole and other azoles through an iterative CLSI validation process. Testing has developed standard broth microdilution (MD) and disk diffusion (DD) methods for in vitro susceptibility testing of C. neoformans against fluconazole and other azoles. Although these tests were shown to be reproducible, the CLSI method was not optimal for testing C. neoformans, the CLSI M38-A3 DD method has been shown to be non-reproducible in wild-type (WT) strains.

MATERIALS AND METHODS

Organisms: A total of 2,875 C. neoformans isolates from wild-type strains were collected from 2001-2008 from centers in the Americas (103), Europe (63), Asia-Pacific (294), and Latin America (127). Isolates were obtained from adult patients with cryptococcal meningitis or cryptococcal disseminated disease. The MICs were determined using the CLSI M27-A3 broth microdilution method (72-h incubation). All isolates were tested against fluconazole, itraconazole, posaconazole, and voriconazole.

RESULTS

- The WT MIC distributions for fluconazole, itraconazole, posaconazole, and voriconazole were established using the CLSI M27-A3 broth microdilution method.
- The modality fluconazole MIC remained unchanged at 4 µg/mL.
- The modal MICs for itraconazole, posaconazole, and voriconazole were 0.12 µg/mL.

TABLE 1: Wild-Type MIC distributions and ECVs for floconazole, itraconazole, posaconazole and voriconazole for 2,875 Cryptococcus neoformans isolates using CLSI reference broth microdilution method.

CONCLUSIONS

We established the 72-h ECVs for fluconazole, itraconazole, posaconazole, and voriconazole using an extensive epidemiological dataset which served as the sources for the breakpoints for these agents C. neoformans. The ECVs is proposed here to help in detecting the emergence of potential resistance as these azoles are more often used. The very low frequency of strain with MICs to fluconazole suggestive that routine antifungal susceptibility testing of isolates may not be necessary. This is still important to periodically monitor for the emergence of resistance.

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REFERENCES