

TITLE: SUSCEPTIBILITY ANALYSIS OF *TRICHOSPORON* SPP. BIOFILMS AGAINST FLUCONAZOLE AND SIMVASTATIN

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ABSTRACT:

Trichosporon spp. are basidiomycetous yeasts widely found in nature and as part of the human microbiota. In recent years, they have been recognized as emergent agents of invasive infections, causing high mortality in immunocompromised patients, especially those neutropenic and under use of catheters. Infections linked to catheters can be associated with biofilms, which act as the source of persistent cells that possess resistant phenotypes against antifungals. *Trichosporon* spp. present limited susceptibility to amphotericin B and echinocandins, but triazoles, which inhibit the ergosterol pathway, have exhibited the best therapeutic results. In humans, simvastatin is used to decrease cholesterol biosynthesis and recently, it has been reported its antifungal activity against yeasts. However, the use of simvastatin against *Trichosporon* spp. biofilms has been little explored. Thus, this work aimed to analyze the susceptibility of planktonic and biofilm forming cells of *Trichosporon* spp. against simvastatin (SVT) compared to the fluconazole (FCZ) standard. We analyzed six reference strains of *Trichosporon* spp. from CBS (Centraalbureau voor Schimmelcultures), obtained from human infections. Biofilms of all strains were induced on 96-well polystyrene plates using RPMI-1640 medium, for 48 hours, and quantified by crystal violet staining method. Susceptibility tests for SVT and FCZ were performed with planktonic and biofilm forming cells according to the EUCAST (doc. 7.1) protocol and tetrazolium salt reduction (XTT), respectively. Minimum inhibitory concentrations (MIC) were determined at 48 hours readings. We found that *Trichosporon asahii* CBS2479, *T. asahii* CBS7631 and *T. asteroides* CBS2481 were low biofilm producers, whereas *T. faecale* CBS4828, *T. inkin* CBS5585 and *T. ovoides* CBS7556 were characterized as medium biofilm producers. The MIC of planktonic cells ranged from 2 to 8 µg/mL for FCZ and 16 to 128 µg/mL for SVT. In biofilms, the MIC ranged from 128 to 4,096 µg/mL for FCZ and 1,024 to >16,400 µg/mL for SVT. The biofilms inhibition was observed when used up to 2,000 times more FCZ and 1,000 times more SVT than the necessary to inhibit planktonic cells, independently of the amount of biofilm produced and the species analyzed. In conclusion, the high concentrations of SVT necessary to inhibit *Trichosporon* spp. *in vitro* limits its use as an alternative for isolated therapy of invasive and biofilm-related infections.

Keywords: *Trichosporon* spp., biofilms, simvastatin, fluconazole, susceptibility test.

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