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Sterol Composition of *Pneumocystis jirovecii* with Blocked 14α-Demethylase Activity

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ABSTRACT. Several drugs that interact with membrane sterols or inhibit their syntheses are effective in clearing a number of fungal infections. The AIDS-associated lung infection caused by *Pneumocystis jirovecii* is not cleared by many of these therapies. *Pneumocystis* normally synthesizes distinct C_{28} and C_{29} 24-alkylsterols, but ergosterol, the major fungal sterol, is not among them. Two distinct sterol compositional phenotypes were previously observed in *P. jirovecii*. One was characterized by Δ^7 C_{28} and C_{29} 24-alkylsterols with only low proportions of higher molecular mass components. In contrast, the other type was dominated by high C_{31} and C_{32} 24-alkylsterols, especially pneumocysterol. In the present study, 28 molecular species were elucidated by nuclear magnetic resonance analysis of a human lung specimen containing *P. jirovecii* representing the latter sterol profile phenotype. Fifteen of the 28 had the methyl group at C-14 of the sterol nucleus and these represented 96% of the total sterol mass in the specimen (excluding cholesterol). These results strongly suggest that sterol 14α-demethylase was blocked in these organisms. Twenty-four of the 28 were 24-alkylsterols, indicating that methylation of the C-24 position of the sterol side chain by *S*-adenosyl-L-methionine:sterol C-24 methyl transferase was fully functional.

Key Words. AIDS, human lung, opportunistic infection, pneumocysterol, *S*-adenosylmethionine:sterol C-24 methyltransferase.