

# *Pneumocystis* Dihydropteroate Synthase (DHPS) Gene Mutations and Mortality of HIV-Associated *Pneumocystis* Pneumonia (PCP)

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## BACKGROUND

The impact of *Pneumocystis* dihydropteroate synthase (DHPS) gene mutations on mortality in HIV-infected patients with *Pneumocystis* pneumonia (PCP) is unclear.<sup>1</sup> Prior studies offer conflicting results and report on PCP episodes before 2000.

## OBJECTIVES

To examine predictors of DHPS genotype and mortality among HIV-infected PCP patients according to DHPS genotype.

## METHODS

**Study Design:** Prospective study conducted at 3 geographically distinct medical centers.

**Subjects and Settings:** HIV-infected adult patients with PCP admitted to San Francisco General Hospital from May 1997 through December 2004, Medical Center of Louisiana at New Orleans from June 2003 through December 2004, and University College of London from May 1997 through November 2001.

**DHPS Genotyping:** DHPS genotyping of diagnostic specimens was performed at the Centers for Disease Control and Prevention (CDC). Wildtype DHPS genotype = Thr55 and Pro57; Mutant genotype = amino acid substitution at one or both positions.

**Clinical Data:** Clinical data including all cause mortality at 6 weeks was collected through standardized chart abstraction.

**Statistical Analyses:** Stata, version 8.0 (StataCorp).

## RESULTS

Overall, 421 PCP subjects were enrolled; 372 (88%) had their specimens successfully genotyped at the DHPS locus. 268 (72%) patient specimens contained a mutant DHPS genotype (including 82 with mixed DHPS genotype infection) and 104 specimens (28%) contained wild-type DHPS genotype.

San Francisco patients were significantly more likely to have a mutant DHPS genotype (79%) compared to patients from New Orleans (51%) or London (47%) ( $p < 0.0001$ ). Patients receiving trimethoprim-sulfamethoxazole (sulfa) or dapsone (sulfone) prophylaxis within the preceding 3 months were also more likely to have a mutant DHPS genotype (90%) compared to patients who received no prophylaxis (66%) ( $p < 0.001$ ).

San Francisco patients were also significantly more likely to have received sulfa/sulfone prophylaxis (31%) compared to their New Orleans (7.5%) and London (3.1%) counterparts ( $p < 0.001$ ).

In multivariable regression analysis, San Francisco residence and sulfa/sulfone prophylaxis use were both independent predictors of a mutant DHPS genotype (Table 1).

**Table 1. Predictors of Mutant DHPS Genotype**

Predictor	Odds Ratio	95% CI	P-value
Sulfa/Sulfone Prophylaxis	3.68	1.74-7.77	0.001
SF residence	3.18	1.48-6.82	0.003
NO residence	1.12	0.46-2.71	0.80

The findings were comparable if patient specimens that contained a mixed DHPS genotype infection were classified as "wild-type."

The majority of patients at all three sites were prescribed trimethoprim-sulfamethoxazole (TMP-SMX) for PCP treatment. Among patients with a mutant DHPS genotype, 84% received TMP-SMX treatment.

Thirty-six (10%) patients died within 6 weeks of PCP diagnosis. PCP was reported to be the primary cause of death in 29 of these patients and the only cause of death in 20 patients. Regardless of outcome, there was an insignificant trend for patients with mutant DHPS genotypes to have an increased mortality (Odds Ratio range = 1.28-1.74).

There was also an insignificant trend for patients with a mutant DHPS genotype who were treated with TMP-SMX to die and to die from PCP.

## CONCLUSIONS

In this prospective study from 3 geographically distinct medical centers, San Francisco residence and use of sulfa/sulfone prophylaxis were significant predictors of a mutant DHPS genotype.

Although patients with a mutant DHPS genotype tended to have worse outcomes, the majority of these patients responded to trimethoprim-sulfamethoxazole treatment and survived (6 weeks).

The presence of a mutant DHPS genotype may be potentially only one of multiple factors that impact mortality in HIV-associated PCP. Larger studies are needed to address these multiple factors.

### Reference

1. Huang. Dihydropteroate Synthase Gene Mutations in *Pneumocystis* and Sulfa Resistance. *Emerg Infect Dis* 2004;10:1721-1728.