

HIV-Associated *Pneumocystis* Pneumonia (PCP) with Mixed Dihydropteroate Synthase (DHPS) Genotype Infection: Predictors and Outcomes.

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BACKGROUND

Prior studies assessing predictors of DHPS genotype and outcomes of PCP according to DHPS genotype have grouped mixed DHPS genotype infection with single mutant DHPS genotype infection. No prior studies have analyzed predictors and outcomes of patients with mixed DHPS genotype infection versus patients with single mutant DHPS genotype or wild-type infection.

OBJECTIVE

To determine predictors of DHPS genotype and outcomes of PCP according to DHPS genotype infection.

METHODS

Study Design and Setting: Prospective study at San Francisco General Hospital between May 1997 and September 2004.

Subjects and Clinical Data: HIV-infected adults diagnosed with PCP by sputum induction (SI) or bronchoalveolar lavage (BAL). Risk factors for DHPS mutation (PCP prophylaxis) and PCP outcomes (death) collected through standardized chart abstraction.

Specimens, DHPS Genotyping, and Definitions of Wild-type and Mutant: SI and BAL specimens. DHPS genotyping performed at CDC [Beard. Emerg Infect Dis 2000;6:265-72]. DHPS genotype categorized as follows: Wild-type = single genotype, Thr55 and Pro57; Single mutant = single genotype, amino acid substitution at Thr55 and/or Pro57; Mixed = >one genotype.

Statistical Analysis: Stata, version 8.0 (StataCorp). Associations between predictors and DHPS polymorphisms and DHPS genotype and outcomes examined using chi² or Fisher's exact tests. A P-value of < 0.05 was considered significant.

RESULTS

DHPS Genotypes: 324 HIV-infected patients diagnosed with PCP were enrolled; 279 (86%) patients had the *Pneumocystis* DHPS locus successfully sequenced. Overall, 60 (21.5%) patients had wild-type DHPS genotype, 159 (57%) had single mutant DHPS genotype, and 60 (21.5%) had mixed infection.

Predictors of DHPS Genotype: Demographic and clinical characteristics including age, gender, race, alveolar-arterial gradient, serum albumin and LDH were similar among patients infected with wild-type, single mutant, or mixed DHPS genotype infection. However, patients with a known HIV diagnosis, history of prior PCP, or sulfa or sulfone prophylaxis use within the preceding 3 months were significantly more likely to present with single mutant DHPS genotype (Table 1).

Table 1. Predictors of DHPS Genotype

Predictor	Wild-type (n=60) n (%)	Single Mutant (n=159) n (%)	Mixed (n=60) n (%)	P-value
Known HIV	37 (62%)	132 (83%)	42 (70%)	0.002
Prior PCP	9 (15%)	53 (34%)	5 (8.5%)	0.0001
Sulfa/Sulfone Prophylaxis	9 (15%)	70 (44%)	7 (12%)	0.0001

Patients with mixed DHPS genotype infection were similar to patients with wild-type infection in terms of the proportion with newly diagnosed HIV infection, no prior PCP and no prior PCP prophylaxis.

PCP Outcomes According to DHPS Genotype: There was a trend for PCP patients with mixed DHPS genotype infection and single mutant infection to have an increased all-cause mortality that was consistent at various time points (30-, 60-, 90-, and 120-days) (Table 2).

Table 2. PCP Outcomes According to DHPS Genotype

Outcome	Wild-type (n=60) n (%)	Single Mutant (n=159) n (%)	Mixed (n=60) n (%)	P-value
Death All-cause (90 days)	4 (6.7%)	20 (12.6%)	10 (16.7%)	0.25
PCP Death:				
PCP alone	1 (1.7%)	11 (6.9%)	5 (8.3%)	0.21
PCP + other	3 (5.0%)	6 (3.8%)	0 (0%)	
TMP-SMX Failure	3 (5.7%)	16 (13%)	7 (13%)	0.38

In addition, patients with mixed DHPS genotype infection and single mutant infection tended to be more likely to die of PCP alone. In contrast, patients with wild-type infection appeared to be more likely to die from PCP plus an additional illness (Table 2). Although not statistically significant, patients with mixed and single mutant DHPS genotype infection were more likely to fail trimethoprim-sulfamethoxazole (TMP-SMX) therapy.

CONCLUSION

Patients with mixed DHPS genotype infection had clinical predictors similar to wild-type infection but outcomes appeared to be more similar to patients with single mutant infection.

Predictors for patients with mixed DHPS genotype infection and wild-type infection are associated with an absence of potential sulfa/sulfone exposure. This suggests prior exposure may select for a single mutant DHPS genotype.

In contrast, outcomes for patients with mixed DHPS genotype infection tend to be associated with a higher risk of TMP-SMX failure, death at 30, 60, 90 and 120 days and death due to PCP alone.

