## Molecular Epidemiology Linking Multihospital Clusters of Opportunistic *Pneumocystis jirovecii* Pneumonia

To the Editor—*Pneumocystis jirovecii* is responsible for severe inflammatory pneumonia in transplant recipients [1–6]. We encountered a cluster of fulminant *P. jirovecii* pneumonia (PJP) in 14 transplant recipients occurring a mean of 6.3 years (SD, 5.3 years) after transplant, beyond our 6-month trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis period [4]. Additional clusters emerged in 7 other Sydney hospitals (n = 30 patients), 3 regional hospitals (n = 8), 4 large interjurisdictional transplant units (n = 24), and 7 other interstate hospitals (n = 13) over 2 years, eventually controlled by reintroduction of universal TMP-SMZ prophylaxis for 12 months. Eight further patients presented (2 hospitals) following discontinuation of long-term prophylaxis, which was restarted after sites were disease-free for 14 months. In total, 97 PJP infections occurred in kidney (n = 87), liver (n = 4), liver-kidney (n = 1), and kidney-pancreas (n = 3) transplant recipients and 1 lupus patient and 1 hematology patient in 23 hospitals; there were 14 deaths and 10 kidney allograft failures.

Four-loci multilocus sequence typing of known variable regions within the *P. jirovecii* genome was undertaken [4] to define the outbreak's molecular epidemiology. We evaluated the concatenated sequences of 4 genetic loci (*β-tub*, *DHPS*, *mtLSU*, and ITS1/2) [5] from 48 patients with PJP and 11 unrelated controls; phylogenetic relationships were established using PAUP* 4.0b10 software (Sinauer Associates, Sunderland, Massachusetts). Genetic analysis of DNA sequences revealed an initial outbreak genotype (sequence type 1 [ST1]), and 2 closely related genotypes differing only by a single-nucleotide polymorphism in either the *mtLSU* (ST2) or ITS1/2 region (ST9), whereas the *β-tub* and *DHPS* sequences were identical. The last identified genotype (ST10), which emerged 52 months after the index case, differed by 6 nucleotides. Meticulous contact tracing found colocalization of asymptomatic prodromal PJP patients within our clinic waiting areas, and interhospital transmission facilitated by travel of infected patients with local cross-infection in distant locations.

Patient-to-patient transmission mediated by airborne droplets best explains the epidemiology, supported by molecular tracing evidence and individual exposure histories. A common environmental source is unlikely given multiple distinct clusters within disparate geographical locations, which infers the evolution of strains with greater virulence or persistence. The epidemiology of early opportunistic PJP in modern organ transplantation was fundamentally altered by routine TMP-SMZ prophylaxis, with presentations now occurring increasingly later or within clusters

from healthcare facilities [1, 2, 4, 6, 7], whose recognition is often obscured by long incubation periods [4, 7, 8] and infrequent presentation of individual "sporadic" cases.

Opportunistic PJP in the modern era is best conceptualized as clinical disease occurring in 1 or several susceptible hosts, emerging from immunocompromised subpopulations that have become colonized by pathogenic strains via airborne transmission, forming local clonal outbreaks. Interestingly, even the "control" *P. jirovecii* strains, methodologically included to demonstrate dissimilarity with outbreak strains, were themselves interrelated. These samples came from human immunodeficiency virus (HIV)–infected, oncology, or immunosuppressed patients, where retrospective analysis found temporal colocalization by genotype identity, revealing unsuspected local clusters. An individual's vulnerability to respiratory colonization and subsequent infection is influenced by any pulmonary disease and his or her immune response to the pathogen (determined by transplant immunosuppression, prior cytomegalovirus infection, etc, or CD4 levels with HIV infection) [3]. Hence, contemporary PJP likely represents a public heath problem, rather than the traditional explanation of reactivation of latent colonization by reduced immunity. We suggest centralized genotyping of all isolates to identify related clusters with mandatory reporting, to allow appropriate preventative countermeasures.

## Notes

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