Transmission of *Pneumocystis* Species among Renal Transplant Recipients

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*(See the article by de Boer et al. on pages 1143–9)*

Investigation of the transmission and epidemiology of *Pneumocystis* species in humans is hampered by several confounding variables imposed by both the organism and the host. The disease, a highly fatal pneumonitis, occurs almost exclusively in the severely immunocompromised host, who is also at high risk for other opportunistic infections of the lungs, with and without *Pneumocystis jiroveci* (also called *Pneumocystis carinii*) pneumonia (PCP). Furthermore, asymptomatic *Pneumocystis* infection occurs to the extent of seroconversion with detectable antibody in >75% of healthy individuals by 4 years of age, rendering serologic analysis useless as an epidemiological tool. The organism may reside as a latent form in the lungs for long periods of time. A conclusive diagnosis of PCP for research purposes requires the demonstration of pneumonitis by radiography, plus the identification of *Pneumocystis* species in pulmonary parenchyma by examination of bronchoalveolar lavage fluid or biopsy specimens. Microscopic examination of stained specimens is the standard method for identification of the organism. In recent years, the use of molecular techniques, such as PCR with DNA-based methods, have been utilized in epidemiological investigations. In human studies, the method used most often has been nested PCR that uses primers targeting the mitochondrial large subunit r RNA (mtLSU) of *Pneumocystis* species. A point to be made here—and one often not appreciated in some clinical studies—is that the histologic and molecular methods identify different entities: an infectious agent as a whole intact organism (cyst and trophozoite) with the former method and a molecular fraction of the organism with the latter method. Thus, PCR does not distinguish between intact *Pneumocystis* species and fragments of disrupted organisms.

Chemoprophylaxis for PCP in immunocompromised hosts is highly effective. As a standard of medical practice, prophylaxis has profoundly reduced the incidence and prevalence of PCP to the extent that an adequate number of subjects (even those with AIDS) is difficult to accrue for statistically sound studies. In addition, circumstances in which some of the subjects receive prophylaxis and some do not may not complicate the experimental design. Clearly, the incidence of PCP is directly related to the type and intensity of immunosuppressive therapy that affects cell-mediated immunity. It is noteworthy that the extent of immunosuppression may vary among patients under the same protocol for immunosuppressive treatment, as shown by pharmacogenetic and comparative studies.

The study by de Boer et al. [1] illustrates the difficulties investigators face with the aforementioned factors in clinical research. The 22 patients with PCP encountered over a 1-year period constituted a small, heterogeneous group: recipients of kidney-pancreas transplants or of kidney transplants alone. Ten patients (45%) received cyclosporine (a potent inhibitor of cell-mediated response) in addition to the protocol regimen; 5 patients (23%) were treated more intensively because of graft rejection. Another opportunistic infection (cytomegalovirus infection) occurred in 10 (53%) of 19 patients studied. Finally, organisms were identified by histologic methods in 16 patients (73%) and by molecular fractions (dihydropteroate synthase) in 6 patients (27%). One variable that did not affect this study was the use of chemoprophylaxis with trimethoprim-sulfamethoxazole for PCP.

Genotyping findings are difficult to interpret with regard to proof or disproof of person-to-person transmission. Although type Ne was detected in 12 patients (55%) and other types were detected in 4 patients (18%), genotyping failed in 6 cases (27%). Other studies show that a single sample may not necessarily reveal...
the genotype associated with PCP. For example, Helwig-Larsen et al. [2] studied 240 PCR clones obtained from multiple samples of each of the lungs from 3 patients with fatal PCP. A mixture of genotypes was found in each lung. Interestingly, not all genotypes present in the lungs at autopsy were detected in diagnostic respiratory specimens. In a study of 212 patients by Hauser et al. [3], 75% of the cases were found to have $\geq$2 genotypes in the bronchoalveolar lavage fluid specimens. The broad diversity of Pneumocystis genotypes in the human lung limits the usefulness of genotyping in transmission studies, especially for differentiation of recently acquired PCP from activation of a latent Pneumocystis infection. The long-standing concept that PCP occurs from latent infection provoked by immunosuppression has not been discounted and has been unequivocally demonstrated in animal experiments. It is likely that PCP may be due to either acutely acquired infection or activation of latent infection.

Of concern in the report by de Boer et al. [1] is the reluctance to use highly effective, safe, and inexpensive chemoprophylaxis for PCP. Published standards of practice in both Europe and America recommend trimethoprim-sulfamethoxazole or alternative drugs for prevention of PCP in high-risk renal transplant recipients. Surprisingly, some 19 patients with PCP and 1 death occurred over a period of 10 months before prophylaxis was introduced, which promptly terminated the “epidemic.” Similar situations have been reported by others within recent years, indicating the need for more attention to PCP prophylaxis in renal transplant patients. For example, at the University of Nijmegen, PCP occurred in only 13 (1.1%) of 1217 renal transplant recipients before 1991 [4]. However, in 1991 and thereafter, 28 (11.5%) of 243 recipients had PCP, with no explanation for the increase. No prophylaxis had been used, but when prophylaxis was introduced in 1993, no cases of PCP occurred among the subsequent 140 transplant recipients.

It is likely that human-to-human transmission of Pneumocystis species occurs by the airborne route. This has been satisfactorily demonstrated in animal models, which are highly representative of human disease, and has been suggested by the clustering of human cases described by de Boers et al. [1] and others. Without firm data to support the patient-to-patient contagion pattern, a policy for isolation of patients with suspected PCP at the time of entry to the hospital or clinic has not been firmly established. There is no need for individuals with normal immune responses to be isolated from those with active PCP, but it does seem prudent to isolate severely immunocompromised patients from such individuals. At most institutions, individuals at high risk of developing PCP are already receiving prophylaxis and can be exposed without discernible risk of acquiring the pneumonitis, so isolation is not necessary for these individuals.

Acknowledgments


References