Editorial Commentary

Linking Pneumocystis Epidemiology, Transmission, and Virulence

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(See the Major Article by Sassi et al, on pages 1437–44.)

Since the beginning of the 1980s, outbreaks and clusters of Pneumocystis pneumonia (PCP) in immunocompromised populations have been reported with some regularity. Interhuman transmission of Pneumocystis jirovecii was already then suspected by the attending clinicians [1]. Long before this time, shortly after World War II, PCP was reported to occur clustered in institutionalized populations of malnourished or debilitated infants [2]. The advent of polymerase chain reaction enabled the development and application of genotyping methods for P. jirovecii in recent PCP outbreaks. A single or predominant P. jirovecii genotype was found in most of these epidemics, and the results were interpreted as being compatible with either interhuman transmission or a common environmental source [3]. Furthermore, postmortem studies as well as screening of respiratory samples showed that P. jirovecii can be detected in the lungs and airways of both healthy and immunocompromised individuals not having clinically manifest PCP [4, 5]. This phenomenon, characterized as colonization with P. jirovecii, is most likely a common condition. Distinct species of Pneumocystis are strictly linked to a specific mammalian host, and comparative sequencing studies revealed that co-evolution of Pneumocystis species and their hosts has taken place over the past millions of years [6]. Together these discoveries have led to the prevailing insight that the human population is the only reservoir for P. jirovecii. Notwithstanding the recent advances, the population dynamics of colonization as well as the extent of genetic and pathogenic diversity within the P. jirovecii species are still largely unknown.

Against this background, a study by Sassi et al, published in this issue of Clinical Infectious Diseases [7], explored the genetic similarity (or difference) between P. jirovecii isolates from 3 separately described PCP outbreaks among renal transplant recipients by using a new method based on restriction fragment length polymorphism genotyping. In particular, the study was designed to investigate whether a distinct strain with increased virulence might explain these sudden elevations in PCP incidence. From all 3 outbreaks, P. jirovecii DNA from a subset of involved cases was available and analyzed (Munchen, 13 of 16 cases; Zurich, 7 of 19; and Nagoya, 9 of 33). The confirmation that P. jirovecii isolates were genetically identical within outbreaks makes it unlikely that a longstanding prior P. jirovecii colonization simultaneously transitioned into clinically manifest pneumonia in multiple patients, induced by increased immune suppression. Exactly how then do PCP outbreaks originate and develop?

The occurrence of PCP outbreaks is a rare event even in immunocompromised populations at risk, that is, those not receiving prophylaxis. Thus, the presence of a set of specific conditions seems required to temporarily raise the reproduction number above 1. Despite the results reported by Sassi et al [7], there are still multiple possible explanations for the genesis of a PCP outbreak in a susceptible population.

A first hypothesis is that increased infectious pressure, with a subsequent PCP outbreak, originates from peak rates of colonization in the general population that includes the susceptible individuals. If colonization within this population is dominated by a single genotype, this would clarify the genotyping results of the current study and other PCP outbreak studies. In the study by Sassi et al [7], it would particularly explain how the 2 apparently separately evolving European outbreaks were caused by the same genotype. Although 300 km apart, the different locations could be part of the same geographic region with regard to colonization. Whether this hypothesis is
true can be confirmed or rejected only by study of *Pneumocystis* colonization (including genotyping) within the respective population, before or at the start of a PCP outbreak. For practical purposes, the outbreak isolates were instead compared with isolates from contemporary solitary cases of PCP. Solitary and outbreak isolates seemed genetically different, contradicting this first hypothesis. However, with regard to colonization, fluctuations in time and place of the genetic diversity of *P. jirovecii* is unknown. Hence, because of the relatively low number of solitary cases included and because only a subset of isolates from the large outbreaks in Zurich and Nagoya were genetically characterized, this possibility cannot be entirely excluded.

A second hypothesis follows a more classic model of an infectious disease epidemic: an index case giving rise to secondary cases from which the infectious agent is transmitted to another secondary cases from which the infectious agent is transmitted to another. The dynamics of *Pneumocystis* colonization in the general population are considered far less important here, apart perhaps from determining the likelihood of which genotype will initiate the epidemic. Many of the published PCP outbreak studies, as well as those reported by Sassi et al [7], elaborate on traceable contacts between observed patients. However, looking into the descriptive epidemiological data of the documented PCP outbreaks, these assumptions are often based on the information that patients visited the outpatient clinic on the same day or were hospitalized at the same time. This makes it presumable but uncertain that patients physically met each other before development of PCP. On the other hand, it is unknown how far exhaled *P. jirovecii* cysts can reach and for how long they remain infectious. Therefore, face-to-face contact might not be needed to establish transmission, although presence of an index case should precede secondary cases. In the study by Sassi et al [7], the missing link between the European outbreaks would then be undetected contacts, in a more broad sense, between patients from the 2 outbreaks. Nevertheless, if this is all it would take, why are outbreaks or smaller clusters of PCP not encountered more frequently?

Rethinking scenarios beyond epidemiological and genetic profiling alone, the rare emergence of PCP outbreaks may be explained by a deviant host-pathogen interaction pattern that interacts with one of the 2 described mechanisms. With regard to virulence, the concept that not all strains may be as pathogenic seems plausible in the context of our experience with other microorganisms. However, the species specificity of *P. jirovecii* as well as their dependence on their hosts strongly suggests that biologic properties that enable a commensal relationship with humans are preferred above those that translate into increased pathogenic capacity. After all, in the standard situation, *Pneumocystis* coexists with its immune intact hosts while doing little or no damage; unbalanced situations leading to the devastating clinical entity of PCP are the exception. From previous clinical studies, no clear evidence emerged that one, a few, or a particular group of *P. jirovecii* isolates exhibited increased pathogenicity [8]. In a study by Helweg-Larsen et al [9] that included 130 patients with PCP in Denmark, no association was found between the internal transcribed spacer genotype of *P. jirovecii* and clinical severity.

Moreover, when the genesis of the described PCP outbreaks is attributed to a *P. jirovecii* strain with increased virulence, the rates of transmission for this particular strain—either direct or indirect—would be expected to be relatively high, resulting in a higher incidence of colonization with this strain in the general population. This would subsequently tend to drive up the number of solitary cases of PCP caused by this strain, which has not been observed.

The above considerations make it clear that the roles of host factors and characteristics of the immunocompromised population as a whole deserve at least equal attention. During the past decades, the number of patients susceptible to development of PCP has been ever expanding. With regard to the host’s immune status, new immunosuppressive treatments have come into use and are more often successful in preventing graft rejection or ameliorating autoimmune disease. As a result, the level of immune deprivation may decrease significantly both among particular individuals within, for example, a renal transplant population and among this population as a whole. Because of the absence of reliable variables that indicate whether chemoprophylaxis to prevent PCP is needed in immunocompromised patients without human immunodeficiency virus infection, not all are adequately protected. Consequently, it has become more probable that a susceptible individual will encounter another individual who is exhaling higher loads of *P. jirovecii* or suffering from full-blown PCP. The likelihood of such transmission is modified further by the way care is delivered to these patients, for example, when they share busy waiting rooms or are hospitalized in the same ward or treated at dedicated clinics.

These intertwining developments may at times create the perfect setting for an outbreak to occur. One can only speculate whether outbreaks are driven by the frequency of contacts between the index case patient and other susceptible individuals (ie, “crowding”) or by unusually high burdens of PCP exhaled by one or a few severely immunocompromised individuals. A wide variation of transmission patterns may even exist.

In conclusion, it is clear from the PCP outbreak studies in which genotyping of *P. jirovecii* was performed that definite conclusions regarding the genesis of PCP outbreaks are still not possible. The challenges met by Sassi et al [7] in
interpreting the results of their study directly correspond to major unresolved questions with regard to the dynamics of P. jirovecii colonization, transmission of P. jirovecii, and diversity within the P. jirovecii species. So above all, the outbreaks repeatedly disclose the giant gaps in our knowledge about the nature and epidemiology of this sometimes opportunistic symbiont. Certainly, the complex symbiotic relation with the human species that developed over millions of years must be taken into account when attempting to unravel the genesis of PCP outbreaks. However, it is the characteristics of the immunocompromised population that have changed dramatically during the past decades, and these should thus be considered primarily causal in the chain of events.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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