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Epidemiology of *Pneumocystis* infection in Human☆

Épidémiologie de l'infection par Pneumocystis *chez l'homme*

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Summary *Pneumocystis jirovecii* (*P. jirovecii*) is an atypical fungus that causes pneumonia in immunosuppressed individuals and significant questions about its epidemiology and transmission remain unanswered. It is widely accepted that animal sources of *P. jirovecii* can be excluded because the *Pneumocystis* organisms that infect mammalian species are characterized by strong, close host species specificity. Similarly, an environmental reservoir of infection has not been found. Airborne transmission has been demonstrated in animal models and is assumed among humans. Highly sensitive PCR-technologies have allowed the detection of low numbers of *Pneumocystis* organisms in respiratory samples from colonized individuals who do not have *Pneumocystis* pneumonia. Studies have shown that individuals who have underlying Human immunodeficiency virus (HIV)-infection or other types of immunosuppression and those who are not immunosuppressed but have a chronic lung disease are often colonized by *P. jirovecii*. Further hypotheses claim that these groups may play a role in person-to-person transmission and that they may serve as reservoirs for future *Pneumocystis* infection in other susceptible individuals. On the other hand, *P. jirovecii* DNA was recently identified by molecular techniques in 35% of foetal lung and 5% of placenta samples from nonimmunodepressed women, who had a miscarriage, evidencing transplacental transmission in humans. Vertical transmission of *P. jirovecii* in humans could be an additional route of transmission of this stenoxenic microorganism that would ensure the persistence of *Pneumocystis* independent of environmental hazards. However, further studies are needed to confirm the role of this transmission route in the epidemiology of *Pneumocystis* infection in humans.

MOTS CLÉS
Pneumocystis ;
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Résumé *Pneumocystis jirovecii* (*P. jirovecii*) est un champignon atypique responsable de pneumonie chez les sujets immunodéprimés. Des questions significatives sur l'épidémiologie et la transmission demeurent sans réponse. On accepte en général que les animaux ne constituent pas une source d'infection pour l'homme car les *Pneumocystis* des divers mammifères présen-

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tent une très étroite spécificité d'hôte. Similairement, il n'y a pas d'évidence d'un réservoir environnemental. La transmission aérienne a été démontrée chez les modèles animaux et l'on suppose qu'elle existe aussi dans les populations humaines. Des techniques PCR hautement sensibles ont permis de détecter des faibles taux de *Pneumocystis* dans des échantillons pulmonaires de sujets colonisés par le champignon mais sans pneumonie. Des recherches ont montré que les patients VIH positifs ou immunodéprimés par d'autres causes ainsi que des sujets non immunodéprimés mais affectés de maladie chronique pulmonaire peuvent être colonisés par *P. jirovecii*. Il a été suggéré que ces groupes peuvent jouer un rôle dans la transmission interhumaine en faisant partie du réservoir et en pouvant transmettre l'infection par voie respiratoire aux sujets susceptibles. Par ailleurs, l'ADN de *P. jirovecii* a été identifié dans le poumon de 35 % des fœtus et dans 5 % des placentas de mères non immunocompromises développant des fausses couches, ce qui montre l'existence d'une transmission transplacentaire de *Pneumocystis* chez l'homme. Ainsi, la transmission verticale de *P. jirovecii* pourrait représenter une voie additionnelle de transmission pour ce microorganisme sténoxène ; elle assurerait sa persistance indépendamment des conditions environnementales. Des nouvelles recherches sont nécessaires pour confirmer cette voie de transmission et clarifier son rôle dans l'épidémiologie de l'infection humaine par *Pneumocystis*.

Introduction

Organisms that are known today as *Pneumocystis carinii* (*P. carinii*) were thought to be life cycle stages of American trypanosomes in 1909, but 3 years later were identified as a different genus and species altogether. During the next two decades, these organisms remained in the realm of medical curiosities until they were linked to epidemics of plasma-cellular interstitial pneumonia that plagued institutionalized premature and malnourished infants in Europe around World War II [8,10]. For many years, the entity named ''*P. carinii*'' was considered like a unique pulmonary pathogen able to cause pneumonia in immunosuppresed hosts. Only for the last years, marked genetic divergence was documented among the *Pneumocystis* strains of different mammals and now it is well-recognized that each form of *Pneumocystis* possesses unique genetic characteristics and strict host specificity [1]. The explanation for such strict host specificity has not been determined and is largely unprecedented in the fungi. More recently, the form that infects humans has been renamed *Pneumocystis jirovecii* (*P. jirovecii*) and *P. carinii* is now the name used to describe specifically the organism that infects rats [38,41].

The dramatic increase in the incidence of *Pneumocystis* Pneumonia (PcP) with the emergence of Human immunodeficiency virus (HIV) pandemia made *Pneumocytosis* a major medical and public health problem in the 1980s. During the 1990s, advances in the treatment of HIV reduced the frequency of PcP. Although at the beginning of the 21st century, the incidence of frank pneumonia caused by these organisms has decreased in developed countries, the prevalence of AIDS-related PcP in developing countries remains high and poorly controlled. Likewise, the number of patients who have an altered immune system or who are receiving chronic immunosuppressive medications and are thus at a risk for PcP is rapidly growing [16,27]. But at the beginning of the third millennium, the interest in *Pneumocystis* infection goes beyond PcP because a new spectrum of disease seems to emerge in immunocompetent hosts and mounting evidence points to new niches being exploited by these fungi. The presence of *P. jirovecii* in patients with underlying chronic diseases such as chronic obstructive pulmonary disease has been suggested to be a comorbidity factor [7,28].

The strategies used by these organisms to grow and survive in the context of an intact or debilitated host defenses are largely unknown and limited progress has been made in understanding its life cycle due in large part to the absence of a continuous in vitro culture system. Many questions about *P. jirovecii* epidemiology and transmission remain unanswered. Until now, human is the only known reservoir host for *P. jirovecii* and groups at risk for carriage probably represent a major species-specific reservoir of infection, which would allow *P. jirovecii* propagation [29].

Detection methods

As *P. jirovecii* cannot be grown in culture from clinical specimens, laboratory diagnosis of PcP has relied mainly upon microscopic visualization with conventional cytochemical or immunofluorescence staining of organisms in respiratory samples. These methods are useful when the organism burden is relatively high but they are insufficient for reliable detection when there is a small parasite load [18]. Although some investigators have detected *Pneumocystis* carriage by using traditional staining methods, these methods are generally not adequate for detection of *Pneumocystis* colonization, and researchers have turned to more sensitive molecular techniques [6,39].

Pneumocystis were first detected without the need to visualize the organisms through microscopic examination by the application of polymerase chain reaction (PCR) methods [51]. Nested PCR protocols soon supplanted standard single-cycle amplification owing to their increased sensitivity. More recently, real-time PCR has allowed levels of detection similar to the nested procedures, but is advantageous as it is performed in a one-step process [2,16]. Several straintyping methods of amplified PCR products have allowed insight into epidemiology and transmission of *P. jirovecii* [4]. These sensitive techniques have enable detection of very low levels of *P. jirovecii*, not detectable by conventional histochemical