Pneumocystis jiroveci Pneumonia
By Jefferson Porter

Pneumocystis jiroveci was originally discovered by a Brazilian physician named Carlos Chagas while studying Trypanosoma cruzi in 1909.\textsuperscript{[10]} At the time, due to the organisms protozoan characteristics, he believed it to be part of the *T. cruzi* lifecycle. While it was designated as its own species, *Pneumocystis carinii*, in 1912,\textsuperscript{[3]} the belief that the organism was protozoan persisted until the late 1980s. This belief was supported by the following: morphological features typical of a protist; lack of expressed genetic features commonly found in fungi; failure of antifungal medication in treatment, while finding success in treatment with medication used in protozoan treatment.\textsuperscript{[10]} During the 1940s and 1950s, the disease was documented in premature and malnourished infants in Iran.\textsuperscript{[3,10]} However, it was during the 1980s and 1990s that pneumocystosis became a disease that made headlines. During this time it was the most common AIDS-defining infection in the United States, and also one of the leading causes of death in AIDS patients, with more than 100,000 cases officially reported.\textsuperscript{[3]} In 1988, the classification of protozoa was corrected to fungus through the use of DNA analysis techniques,\textsuperscript{[10]} and in 2001, after further review of data from a 1999 study, the International Workshop on Opportunistic Protists renamed the organism *Pneumocystis jiroveci* after the Czech parasitologist Otto Jirovec who determined the organisms specificity to humans.\textsuperscript{[10]}

*Pneumocystis jiroveci* is an opportunistic yeast-like fungus that is found in the pulmonary alveoli of humans.\textsuperscript{[3,6,10]} The organism is non-motile and exists in three forms: the small trophozoite form, approximately 1-5 μm, that exists in large quantities during infection and results from asexual mitosis; the second is the sporozoite (or precystic form) that forms from the fusion of two haploid cells; the third are cysts approximately 5-8 μm that are not quite as abundant, but are the result of sexual reproduction (meiosis) and are the source of the “cystic” in the genus name.\textsuperscript{[3,4]} *P. jiroveci* is rather fastidious and thus failed attempts at isolating a pure culture have hindered detailed analysis into the organism.\textsuperscript{[10]} It has been noted that *P. jiroveci* lacks ergosterol, a sterol found in the cell membranes of most fungi, which is a primary target for antifungal medication, explaining its resistance to antifungal treatment.\textsuperscript{[10]} The fungus is not endemic to any specific area, but found globally with more than two thirds of children showing serological evidence of exposure during infancy.\textsuperscript{[3,5]} It was originally thought that pneumocystosis occurred in immunocompromised patients as a reactivation of the aforementioned childhood exposure, but a retrospective study involving renal transplant patients and HIV-positive pneumocystosis patients found that the *Pneumocystis jiroveci* pneumonia (PJP) contracted by the renal
transplant patients was the same strain as carried by the HIV-infected patients, indicating airborne transmission.\textsuperscript{[3,6,9,11]}

*Pneumocystis jiroveci* infection evokes a powerful inflammatory response that results in pulmonary injury and critically debilitated gas exchange.\textsuperscript{[11]} A patient suffering from PJP generally presents three different ways: those without HIV have an acute presentation; those with HIV have subacute presentation; and between 25\% to 50\% of patients present with little to no symptoms.\textsuperscript{[3,5,6,7,8]} Possible symptoms include fever (low-grade with HIV, high fever without), fatigue and/or malaise, dyspnea, dry cough and pleuritic chest pain.\textsuperscript{[3,5,6,7,8]} The objective signs of PJP might include low oxygenation, rales upon auscultation, elevated Alveolar-arterial \((A-a)\) gradient, tachycardia and tachypnea.\textsuperscript{[3,5,6,7,8]} A chest x-ray will often yield diffuse bilateral infiltrates, pleural effusion, and/or pneumothorax; anytime a chest x-ray yields positive for pneumothorax in an HIV-infected patient, it is treated as PJP until ruled out.\textsuperscript{[3,5,6,7,8]}

Serological testing is not practical for confirmation due the previously mentioned childhood exposure affecting the majority of the populace. Running a serum lactic dehydrogenase (LDH) can indicate the level of lung injury in the affected patient, and up to 90\% of patients with PJP have shown an elevated LDH level.\textsuperscript{[3]} The LDH level, however, is not a confirmation of PJP diagnosis, just that there has been injury. Chest x-ray can help indicate fluid buildup in the lungs, but differentiation between PJP and other lung diseases, such as tuberculosis, is not possible from x-ray alone.\textsuperscript{[7]} The most effective way to diagnose is through histological testing, but the sensitivity of the test is dependent upon the method of collection: the least sensitive (and least invasive) option would be yielded from a sample collected through sputum induction via inhalation of hypertonic saline solution; a more sensitive option would come from a sample collected via bronchoalveolar lavage (BAL); a sample from a lung biopsy nears 100\% specificity and sensitivity, but is of the greatest risk to the patient.\textsuperscript{[3,5,6,7,8]} Following sample selection, several histologic tests might be completed for identification, including: a Diff-Quick stain that detects the trophozoite and cyst forms; a Silver Gram stain that selectively stains the cyst wall; or a Papanicolaou smear that, when positive, will show foamy-appearing eosinophil encased *Pneumocystis* organisms.\textsuperscript{[3]}

Treatment of pneumocystosis depends on the severity of the disease, with milder cases being treated with oral antibiotics and outpatient.\textsuperscript{[3]} Without question, the first choice to treat PJP, regardless of severity, is trimethoprim-sulfamethoxazole (TMP-SMX) or Bactrim.\textsuperscript{[3,5,6,7]} However, between 25\% and 50\% of patients show sensitivity to the sulfur in SMX, some with anaphylactic reactions.\textsuperscript{[7]} Due to this, other therapy must be used. In milder cases, aerosolized pentamidine (NebuPent) or atovaquone
oral suspension (Mepron) is used. In more severe cases, the followup selection is trimethoprim-dapsone or a combination of clindamycin and primaquine, but both dapsone and primaquine required that a serum level of glucose-6-phosphate dehydrogenase (G6PD) must be tested first. Treatment with dapsone can cause methemoglobinemia which requires treatment with methylene blue; the use of methylene blue in a patient who is G6PD deficient can cause severe side effects in the patient, most often renal and/or liver failure. Treatment with primaquine can cause the same severe side effects in patients with G6PD deficiency directly. If any of these treatments prove able to combat the organism, it will begin to degrade and might initiate an inflammatory response with the potential to send the patient into respiratory failure. This situation can be avoided with the treatment of corticosteroids like Prednisone. All patients with positive histologic findings for *P. jiroveci* should be isolated to prevent further spread to other immunocompromised patients, and severe cases should be moved to the intensive care unit (ICU) and placed on mechanical ventilation. Prognosis is directly related to the severity of hypoxemia and degree of response to treatment.

Fortunately, the incidence of PJP patients has declined over the last thirty years due to increased awareness and prophylaxis protocols. Prophylaxis options are similar to those used in treating patients with active *P. jiroveci* infections, including: TMP-SMX, Dapsone, Mepron, and NebuPent. Indirectly, HIV infected patients can dramatically reduce risk of *P. jiroveci* infections by taking and complying with highly active antiretroviral therapy or HAART. Prophylaxis should be initiated in the following circumstances: a CD4\(^+\) count of less than 350 cells per microliter; oral candidiasis or other AIDS defining illnesses; CD4\(^+\) concentration of less than 14%; children with a history of PJP; or stem cell transplant recipients. Prior to these options and protocol, 70% to 80% of AIDS patients contracted PJP with an associated 20% to 40% mortality rate. Recent incidence rates in the United states have been reported at less than one in one hundred person-years, or approximately 9% of hospitalized HIV patients. Globally estimates indicate that there are approximately 10 million people with advanced HIV/AIDS who are at risk for PJP; of those, the incidence rate ranges from 2% to 4%. Currently there is no vaccine approved for humans, but the p55-v3 DNA vaccine has shown promise in rats. In addition to this, MiniVax has reported they are entering the clinical trial stage for their potential DNA vaccine, MVX504, based on a fragment of kexin protein.
References


