

PCP Treatment



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Pneumocystis Carinii Pneumonia (PCP), although its rates have declined due to preventive therapies, is still a significant opportunistic infection in HIV disease, often the first indication of immune disorder in those who have not determined their HIV status and initiated prophylaxis (prevention). Even among those taking prophylactic measures against PCP, the disease may occur in late-stage illness when antibiotics in general seem to lose some efficacy. Also, despite adherence to a prophylactic regimen, PCP sometimes “breaks through”, though these cases tend to be milder. Treatment of PCP has been refined over the years and more drugs are available, providing greater options when initial therapies fail or are not tolerated. Treatment is usually effective, especially when diagnosed early. However, deaths from PCP still occur, despite the best treatment.

Cause

Pneumocystis carinii is an organism usually classed as a protozoan, but recent research suggests that it is more closely related to fungi, though it lacks certain fungal characteristics, preventing current antifungal drugs from being effective. (A new class of experimental antifungal drugs does work against PCP - see the section “Therapies in Development”.) It infects the lungs of humans and many animals and is present worldwide. Most people are infected early in life (almost all children have evidence of PCP infection by age 4) with no symptoms or damage. Most cases of PCP in HIV disease are due to an activation of this existing infection, but there is controversy over whether this is always the case or whether person-to-person transmission of a new infection can occur. However, outbreaks have not been seen in hospices and HIV treatment centers, arguing against the case for such transmission.

In the initial phase of PCP, pneumocystis cysts become visible within lung cells. This is followed by a phase in which replication increases and immature forms of pneumocystis can be detected. In the final phase, congestion and inflammation appear within the alveoli (lung sacs) and alveolar walls. If untreated, the pneumonia will result in respiratory failure and is almost always fatal.

The greatest risk of developing PCP occurs when the CD4+ cell count is less than 200 or the CD4+ cell percentage of total lymphocytes falls below 14 percent. Most cases, especially cases where PCP “breaks through” preventative therapy, occur when the CD4+ cell count is below 100. However, even above a count of 200, individuals experiencing thrush or recurrent fevers are at increased risk for PCP, as are those who have had their spleen removed. Also, during pregnancy CD4+ cell counts drop, even in HIV-negative women, during the third trimester. So, HIV-positive pregnant women may be especially susceptible to PCP during this period.

Symptoms

The first symptoms of pneumocystis infection are usually non-specific. Fever and fatigue are almost always present. Weight loss and drenching night sweats may also occur. These symptoms may occur for weeks or months before any specific respiratory problems develop. A low-grade fever that does not resolve itself after a few days is usually an indication of some kind of infection. It is important to take these apparently minor symptoms to a physician as soon as possible - early diagnosis, whether or not it turns out to be PCP, means easier and more effective treatment. Someone who waits for things to get worse courts a stay in the hospital. In addition, advanced cases, even when successfully treated, may leave irreversible lung damage.

As an untreated infection advances, respiratory problems develop. Usually there is a cough (non-productive, or producing a white, frothy sputum), shortness of breath (especially with exertion), and wheezing. Smokers may have a productive cough. Some report a “catching” sensation in the chest when inhaling deeply.

Extrapulmonary (outside the lungs) pneumocystis infection has also been observed, though rarely, in people with HIV. In this form, the infection involves other organ systems (often many at once) and/or the skin. Skin eruptions, innocuous looking and often involving the external ear canal, have a nondescript appearance. The most common site of infection is the eye, usually involving the choroid or retina. Infection here can cause visual impairment because of multiple choroidal lesions or retinal cotton-wool spots. Gastrointestinal pneumocystis can cause nausea, vomiting, diarrhea and/or abdominal pain. Infection of the middle ear can

Table of Contents

Cause	1
Symptoms	1
Diagnosis	2
Treatments	2-5
Therapies in Development	5
Adjunctive Therapies	5
The Bottom Line	6





PCP Treatment

cause loss of sharpness in hearing. Infection of the liver, spleen, lymph nodes, adrenal glands, kidneys, thyroid, brain, pancreas, heart, pleura, diaphragm, bone marrow, pituitary gland, meninges, testes, and peripheral vasculature have also been described. Wherever the infection, fever and fatigue again are usually present and night sweats and weight loss are common. Extrapulmonary infection can occur with or without concurrent PCP, but in almost all cases where it occurs outside of the lungs, aerosolized pentamidine has been used for PCP prophylaxis. This results in a situation where the lungs are protected, but not the rest of the body and underlines the importance of switching to a systemic prophylaxis (TMP/SMX or Dapsone - see the Project Inform Fact Sheet *PCP Prophylaxis*) if at all possible. The therapies described below for PCP are also effective against extrapulmonary pneumocystis - the problem is that such an infection without concurrent PCP is rare and may not be diagnosed until well advanced.

Diagnosis

Although pneumonia in people with AIDS is often presumptively treated as PCP, it is important to confirm the diagnosis in order to change treatment if something else is the cause. It is also important to look for concurrent infections by other organisms - sometimes more than just PCP is involved. Lung complications involving tuberculosis, MAC, cryptococcus and other fungi, herpes simplex, varicella zoster, lymphoma, CMV, and bacterial pneumonias have all been observed along with PCP.

The first step in diagnosing PCP in a person with HIV showing respiratory disorders, or the non-specific symptoms which may precede them, is to evaluate a chest x-ray. There are some characteristic signs of PCP which trained evaluators of x-rays can detect, but PCP may still be present even in their absence or the x-ray may be atypical: 10% have normal chest x-rays, especially early in the disease, and the use of aerosolized pentamidine for prophylaxis often results in atypical x-rays. The x-ray may also suggest the presence of other pathogens besides or in addition to PCP. The general procedure is for those with the characteristic signs in the x-ray to give an induced sputum sample (see below) and to start presumptive anti-PCP therapy.

If the chest x-ray is normal or atypical, the next step is to have a pulmonary function test, specifically for the diffusing capacity for carbon monoxide. If this is abnormally reduced, then the individual should give an induced sputum sample and start presumptive anti-PCP therapy. If it is not abnormally reduced, then a gallium scan should be done. The combination of pulmonary testing and gallium scan is about 90% sensitive in detecting an infection, but it is not specific for PCP. If the uptake of gallium is markedly increased, the individual should give an induced sputum sample and start presumptive anti-PCP therapy. If the uptake of gallium is normal or only slightly increased, the individual should be observed carefully, tested for other pathogens, and, if necessary, be re-evaluated for PCP as needed.

To obtain an induced sputum sample, a saline mist is inhaled for several minutes, inducing a vigorous, deep cough. Staining techniques as well as fluorescent antibody techniques are used to detect PCP in the sample obtained. If this test is positive (the large majority of cases with actual PCP), the diagnosis is regarded as confirmed. Diagnostic procedures for other pathogens, however, should not be terminated simply because PCP has been detected.

If the induced sputum test is negative and no other pathogen has been found that could cause the symptoms, a bronchoscopy may be necessary. A bronchoscope is inserted into the lungs and tissue is irrigated to obtain fluid samples (bronchoalveolar lavage). Tests of these samples are 96% to 99% sensitive and specific for PCP. In rare cases these tests will also be negative while there is a strong clinical picture of PCP. In this case a second bronchoscopy to obtain a tissue sample (transbronchial biopsy) should be done. Biopsy is slightly more sensitive than lavage. Bronchoscopy is uncomfortable and distressing, has some potential (but rare) complications, and a high cost. This is why it is used as a last resort in diagnosis; but it is important to use this step, if necessary, to obtain a definitive diagnosis of the illness and assure correct therapy. A bronchoscopy may also be necessary if the individual does not respond, or does not respond fully to treatment. In this case another undetected pathogen may be co-involved with PCP and need to be diagnosed. It should be noted that if symptoms are light, some physicians may not empirically treat for PCP if prophylactic measures against it have been used. In this case the likelihood of another infection increases and the physician may, legitimately, want to wait for a definitive diagnosis. However, the physician should not contradict an expressed desire for presumptive treatment.

Extrapulmonary pneumocystis is usually diagnosed from biopsies or needle aspirations of the tissues affected. Also, pneumocystis infection has a characteristic radiographic and sonographic appearance; thus, a CAT scan may assist in a diagnosis.

On the experimental front, a PCR test (a procedure which can detect minute amounts of genetic material) is being developed for PCP. This may provide a fast and accurate diagnosis of PCP.

Treatments

The problems associated with PCP are due to the inflammation of the lungs. During the first week of therapy, many, even those with relatively mild disease, experience a worsening of this inflammatory response due to the sudden death of pneumocystis organisms. While the use of corticosteroids (see the section "Adjunctive Therapies" below) can reduce this inflammation, do not be too concerned if you need more oxygen after a day or two of therapy or find yourself even shorter of breath. It is a sign that the drugs are having some effect.

The general course of a successful therapy is 21 days. It is sometimes the case that adverse reactions or insufficient response to the

PCP Treatment



first drug used will lead to a second and maybe even a third drug being tried. This is especially true for those with a history of multiple opportunistic infections, cancers, or wasting syndrome, who frequently will not respond fully to antibiotic therapy.

Some of the therapies noted below are contraindicated if there is a G6PD deficiency (a liver function indicator, determined by a blood test). While these therapies may be started before the results of the test are available, daily blood counts and reticulocyte counts should be obtained because a G6PD deficiency may result in massive hemolysis (destruction of red blood cells).

For the therapies below only the most frequent side effects and most important drug interactions (chosen because the drugs may be commonly used in HIV disease) have been noted. For complete information, consult a Physician's Desk Reference or the package insert that comes with the drug (available at pharmacies). Project Inform also has a "Drug Interactions" fact sheet.

TMP/SMX

TMP/SMX (trimethoprim/sulfamethoxazole, Bactrim, Septra, also available in generic forms) is the treatment of choice for PCP. This inexpensive drug, administered either orally (in mild to moderate cases) or IV (in severe cases), is cheap and effective, but a significant percentage of people experience adverse reactions, often severe enough to require that the drug be discontinued and other therapies initiated. By far the most frequent side effect is a rash with accompanying fever. If this rash is not too severe (and other side effects are not severe) it is often possible to "treat through" the reaction by administering oral antihistamines to control the rash. Note that TMP/SMX very rarely induces a severe, extensive and potentially life-threatening skin eruption called Stevens-Johnson syndrome; in this case the drug must be discontinued immediately. TMP/SMX is also the most effective prophylaxis against PCP, but a high percentage of individuals who try the drug, experience an "allergic" reaction, and switch to other prophylaxis. There are regimens which can be used to desensitize individuals to TMP/SMX so that it can be used for prophylaxis (see the Project Inform fact sheet "Preventing PCP"). Doing so is important for treatment as well - if you have desensitized yourself and PCP does break through, TMP/SMX can more likely be used to treat it.

TRIALS. TMP/SMX has been studied extensively. Papers describing three major studies (Wharton, Sattler, and Klein) are noted in the bibliography at the end of this fact sheet. All three studies demonstrated that TMP/SMX and IV pentamidine are roughly equal in efficacy and that the occurrence of adverse reactions was high on either drug, but in Sattler's study all 36 patients on TMP/SMX completed 21 days of treatment, some with the liberal use of antihistamines (86 percent survived the episode of PCP). In addition, AIDS Clinical Trials Group (ACTG) Protocol number 108 is a double-blind, randomized comparison of oral TMP/SMX, dapsone

plus trimethoprim, and clindamycin plus primaquine in 256 patients with mild to moderate PCP. It was found that there was no significant differences between the three treatment regimens.

OTHER SIDE EFFECTS. Leukopenia (low white cell count), elevated transaminase (a liver enzyme) levels, thrombocytopenia (low platelet count), and neutropenia (low neutrophil count).

DRUG INTERACTIONS. Use with antineoplastics (anti-cancer drugs) may increase risk of anemia and neutropenia. Use with AZT may increase risk of anemia and neutropenia and may increase AZT levels and reduce AZT clearance. Use with diuretics may increase risk of thrombocytopenia.

Dapsone plus Trimethoprim

Dapsone plus Trimethoprim (Proloprim, Trimplex and generics) is a second-line oral treatment for those with mild to moderate PCP who fail or cannot tolerate TMP/SMX (though many are intolerant to this regimen as well). It is inexpensive and has far fewer adverse side effects than TMP/SMX. While it has not been studied as extensively as TMP/SMX, it appears effective if the illness is not too severe. The most common side effects are rash (which again, if not too severe, can be "treated through" with oral antihistamines), gastrointestinal upset and methemoglobinemia (a transformation of hemoglobin in the blood, usually not severe enough to require treatment or discontinuation). Dapsone should not be used if there is a G6PD deficiency. Trials: Two studies (Leoung and Medina) are listed in the bibliography. Both these studies, though small, established this combination as effective in mild to moderate PCP.

OTHER SIDE EFFECTS. Anemia, leukopenia, thrombocytopenia, and elevated transaminase levels.

DRUG INTERACTIONS. Use with AZT may increase risk of bone marrow toxicity. Use with clofazimine may decrease the effectiveness of clofazimine. Use with ddC may increase the risk of neuropathy. When used with rifampin, higher doses of dapsone may be needed because it is more rapidly excreted. Dapsone and ddI need to be taken two hours apart - otherwise dapsone has no activity.

Clindamycin + Primaquine or Chloroquine

Clindamycin (Cleolin, IV or oral, generics) plus Primaquine or Chloroquine (Aralen, oral and generics) - is an effective therapy for mild to moderate PCP for those who have failed or cannot tolerate TMP/SMX. Many physicians prefer this as a second-line treatment over dapsone plus trimethoprim. Clindamycin is used for many bacterial infections and primaquine was developed as an anti-malarial. It is a well tolerated therapy, the major adverse reaction being a rash (in half the participants in one study, three quarters in another, probably due to the clindamycin), but most are able to continue the drugs with the use of antihistamines or low-dose steroids (topical or systemic). Both drugs are given orally in mild PCP. IV clindamycin



PCP Treatment

may be used initially in moderate PCP, switching to the oral form after some clinical improvement. This combination should not be administered in the presence of a G6PD deficiency.

TRIALS. Three studies (Toma, Black, Noskin) are noted in the bibliography. In Toma's study, which compared this combination (27 patients) head-to-head with TMP/SMX (22 patients) in mild to moderate PCP, the two therapies appeared to be equally effective. In that study 6 patients failed to tolerate clindamycin plus primaquine and 4 failed to tolerate TMP/SMX - antihistamines were used to attempt to "treat through" and reduce rashes.

OTHER SIDE EFFECTS. Gastrointestinal upset, diarrhea, transaminase elevation, methemoglobinemia, and neutropenia. Methemoglobinemia is particularly prevalent, but usually without symptoms and not requiring intervention. The occurrence of diarrhea and gastrointestinal upset is the most common reason for discontinuing the drug.

DRUG INTERACTIONS. Antagonism has been seen in vitro between clindamycin and erythromycin. It is suggested these drugs not be used together.

Pentamidine

Pentamidine (brand name Pentam) - is administered intravenously and is highly effective against severe PCP. In comparisons with TMP/SMX, neither drug has proved more effective or better tolerated than the other, but because some side effects of pentamidine, such as pancreatitis, may be irreversible, it is reserved as a second-line therapy for use after TMP/SMX failure or intolerance. After the condition stabilizes, most people can be switched to one of the oral therapies. Aerosolized pentamidine has been tested as primary therapy with mild cases of PCP because of its lower toxicity when administered in this fashion. Results have been disappointing and it is not recommended.

TRIALS. See the studies listed under TMP/SMX.

OTHER SIDE EFFECTS. Nausea, low blood pressure, kidney insufficiency, rash, pancreatitis, bone marrow suppression, low calcium levels, and both low and high blood sugar.

DRUG INTERACTIONS. Use of ddI should be discontinued while using pentamidine because it can increase the risk of pancreatitis. Use with antineoplastics, alpha interferon or AZT may increase the risk of bone marrow toxicity. Use with foscarnet may increase the risk of severe low calcium levels and kidney toxicity.

Atovaquone

Atovaquone (brand name Mepron) - is an oral drug licensed by the Food and Drug Administration (FDA) in 1992 for mild to moderate PCP when the individual is intolerant to TMP/SMX or has had an inadequate response to it. Until there is more experience with this drug, however, clinicians are likely to use it as a fourth-line treatment

after TMP/SMX, dapsone-trimethoprim, and clindamycin-primaquine. Atovaquone is a broad-spectrum antiparasitic drug, originally synthesized as an antimalarial. It is not as effective as TMP/SMX, but is more easily tolerated. One problem is that this drug is not as readily absorbed in its current oral formulation, so its lower effectiveness may be due to undiagnosed absorption problems. In the presence of diagnosed malabsorption (or even in the presence of unexplained weight loss and/or persistent diarrhea), the use of this drug is inadvisable. It should be taken with fatty food to improve absorption. Because of the low incidence of adverse reactions and its low rating for toxicity, it is an attractive option for mild to moderate PCP in pregnant women. A suspension form of this drug is in development which has initially shown 30% better absorption. In addition, a pro-drug of atovaquone, code-named 17C91, is in development and has achieved two to three times higher serum levels in animals. Burroughs-Wellcome has a patient assistance program for Mepron. Physicians can call 1-800-722-9294 for information and to enroll patients.

TRIALS. Two studies (Dohn, Hughes) are listed in the bibliography. In the Hughes study nearly three times as many patients failed to respond to atovaquone as failed to respond to TMP/SMX, most likely because of poor absorption of the drug by many patients.

SIDE EFFECTS. Headache, nausea, diarrhea, rash, fever, and elevated transaminase levels, but these are usually mild and require that the drug be discontinued for less than 10% of those using it.

DRUG INTERACTIONS. Use with acetaminophen, acyclovir, benzodiazepines, cephalosporins, rifampin or laxatives may decrease atovaquone levels. Use with AZT, fluconazole or prednisone may increase atovaquone levels.

Trimetrexate

Trimetrexate (brand name NeuTrexin) - is an intravenously administered drug which inhibits an enzyme necessary both to PCP and to human cells, often causing severe bone marrow toxicity. Administering leucovorin with trimetrexate protects human cells (which it can enter) but not pneumocystis (which it can not enter). Leucovorin is also sometimes administered with TMP/SMX or dapsone, because these drugs also inhibit this enzyme as part of their actions (though not as powerfully as trimetrexate does). Trimetrexate, formerly available only as a salvage therapy under compassionate use rules, was fully approved in December 1993 as a PCP therapy, for use with moderate to severe illness where TMP/SMX therapy has failed or is contraindicated. TMP/SMX blocks two enzymes necessary for the pneumocystis life cycle and trimetrexate blocks only one and is not as effective. A trial to combine trimetrexate and dapsone, to block both enzymes, is scheduled to start in 1994. Trimetrexate is expensive. For information about reimbursement and patient-assistance programs, patients and physicians can call 1-800-8USBIO, an information line run by U.S. Bioscience, the makers of NeuTrexin.

PCP Treatment



TRIALS. Two trials (Allegra, Sattler) are noted in the bibliography. In Sattler's trial comparing trimetrexate head-to-head with TMP/SMX as a first-line therapy, trimetrexate was effective in 68% of the patients and had less toxicity than TMP/SMX. On the other hand, TMP/SMX had 80% effectiveness. Also, after 49 days from treatment start, 16% of the TMP/SMX patients had died, but 31% of the trimetrexate patients had died.

SIDE EFFECTS. Trimetrexate is better tolerated than TMP/SMX. The side effects are relatively mild, rarely require discontinuation of the drug, and include neutropenia, thrombocytopenia, elevated transaminase levels, gastrointestinal upset, fever and rash. Trimetrexate is not recommended for use with pregnant women - it may cause harm to the fetus.

DRUG INTERACTIONS. Cimetidine may reduce trimetrexate metabolism and acetaminophen may alter the relative concentration of trimetrexate metabolites. Clotrimazole, ketoconazole, and miconazole may inhibit trimetrexate metabolism. Erythromycin, rifampin, rifabutin and fluconazole may interact with trimetrexate because they interact with the enzyme system that metabolizes it. Patients using these drugs with trimetrexate should be carefully monitored.

Therapies in Development

As noted above, new formulations of atovaquone that are better absorbed are being developed. In addition, new dihydrofolate reductase (DFHR) inhibitors (the class of drugs including trimethoprim and trimetrexate) are being tested. Additionally, a very promising new class of anti-fungal drugs, called echinocandins, is being developed and shows powerful activity against *Pneumocystis*.

Adjunctive Therapies

Following a recommendation of the NIH in 1990, it has been the standard of care to use corticosteroids as adjunctive therapy in the treatment of moderate to severe PCP to reduce inflammation of the lungs. The decrease in PCP mortality and the need for intubation (in which a tube is inserted down the windpipe so that a machine can take over the effort of breathing and high levels of oxygen can be supplied) when corticosteroids are used is well documented, despite concerns related to their use.

The major concern is that corticosteroids may activate latent infections (such as TB) or exacerbate an active undiagnosed condition (especially fungal infections). In the case where there has been a presumptive diagnosis of PCP, all efforts should be made to confirm the diagnosis whether or not corticosteroids are used - other opportunistic infections may present in the same manner as PCP. Even if PCP is confirmed, other infections, particularly TB, disseminated fungal infections, and concomitant bacterial pneumonia should be ruled out, because treatment for them is especially important if cor-

ticosteroids are used. During the course of treatment with corticosteroids, it may be best to put an individual with a history of candidiasis on suppressive fluconazole therapy and those with a positive TB skin test on suppressive TB therapy. Corticosteroids are definitely contraindicated in the presence of diabetes which is out of control, when there is active gastrointestinal bleeding, in the presence of psychoses induced by steroid use, and in uncontrolled hypertension.

If the case of PCP is serious enough to require hospitalization, supplemental oxygen will probably be required. This usually involves the use of a tube which goes around the head, with two smaller outlets inside the nostrils (a nasal cannula), or various kinds of masks that fit over the nose and mouth. In more severe cases, a more elaborate machine may be necessary to provide positive pressure inside a mask, tightly fitted over the nose and mouth.

If PCP is very advanced, or if the condition degrades despite therapy, intubation and ventilatory support may be needed to avoid respiratory failure. Unfortunately, there are cases where, despite aggressive therapy with several of the drug regimens listed above, the individual has not responded fully and respiratory failure is a possibility without intubation. In this case, intubation should be done if the individual desires aggressive therapy, but a positive outcome is unlikely and it is reasonable for the individual to consider whether simply palliative care should be given. Intubation is most likely to have a positive outcome when (1) a confirmed diagnosis of PCP has not been made or the individual has not received an adequate length (i.e. less than 7 to 10 days) of appropriate anti-PCP therapy, (2) the individual has documented PCP and a treatable respiratory co-infection, or (3) the individual's condition has deteriorated acutely as a result of a diagnostic procedure.

The Bottom Line

- Use prophylactic measures to prevent PCP (see Project Inform's *PCP Prevention*).
- Know the early signs of possible PCP and seek early diagnosis.
- TMP/SMX is the first-line treatment for all cases of PCP (unless contraindicated by other factors).
- Dapsone plus trimethoprim, Clindamycin plus primaquine and Atovaquone are second-line treatments for moderate PCP.
- IV Pentamidine and Trimetrexate are second-line treatments for severe PCP.
- Corticosteroids can reduce the risk of mortality and the need for intubation in moderate to severe PCP.