

CRYPTOCOCCAL MENINGITIS



learn about the symptoms, diagnosing
and treating this disease

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Cryptococcal meningitis (crip-toe-CAWK-kull men-in-JYE-tis) is an inflammation and swelling of the brain and spinal cord tissues, caused by a fungus called *Cryptococcus neoformans*. This inflammation is dangerous and leads to death in nearly all people who are not treated. Treatments do exist, however, and are quite effective.

Cryptococcal meningitis is not very common. It is rare in people with CD4+ cell counts above 100. When it does occur, it typically strikes in people with compromised immune systems, usually when CD4+ cell counts falls below 50. It does also occur, though rarely, in people who are otherwise healthy and not living with HIV.

The fungus that causes cryptococcal meningitis is common in dirt and dust, especially in dirt containing bird droppings. People are normally infected when they breathe in dirt that contains the organism *Cryptococcus*. In healthy individuals, this infection is usually contained in the lungs and never causes disease. Scientists believe that most cases of cryptococcal disease are caused by a reactivation of previous infection rather than a new infection. However, it is wise for people living with HIV to avoid bird roosts and other places where they may come into contact with large amounts of bird droppings.

Cryptococcus can cause other conditions, such as lung infections, which can lead to pneumonia. Outside of the lungs and the central nervous system (CNS), *Cryptococcus* can infect the kidneys, bone marrow, urinary tract, lymph nodes and the skin. When the infection spreads beyond the lungs and CNS, it is called disseminated (throughout the body) infection. When a person experiences disseminated infection, the most common appearance is skin lesions. These lesions may look quite different from one person to another, and can even look a lot like other common skin conditions such as molluscum or herpes. The lesions occur in about 10% of all people who are later diagnosed with cryptococcal meningitis and are sometimes the first sign that a person may have *Cryptococcus*-related disease.

common symptoms of meningitis

fever
fatigue
stiff neck
headache
confusion/
disorientation
vision problems
nausea
vomiting
skin lesions



How can I tell if I have cryptococcal meningitis?

Many of the symptoms of meningitis are the same as other common infections including the flu. Sometimes, however, cryptococcal meningitis may present as nothing more than the worst headache of a person's life. Also, because these symptoms may appear slowly and gradually, it can be difficult for a person living with HIV to know for certain if they are ill with cryptococcal meningitis or something else. If you are experiencing confusion, disorientation, severe headache or seizures, you should contact a healthcare provider immediately and/or consider going to an emergency room. However, it may also be advisable to contact your healthcare provider if you experience any of the following symptoms for three or more days in a row:

- Moderate to high fever (over 100°)
- Nausea
- Vomiting
- Severe body aches, especially of the neck
- Irritation to the eyes from bright light

Normally your healthcare provider will confirm a diagnosis of cryptococcal meningitis through either a simple blood test, or a procedure called a spinal tap (also called a *lumbar puncture*). During a spinal tap, a needle is inserted in the middle of your back just above your hips. The needle removes a sample of your spinal fluid for testing. Although a lumbar puncture may sound frightening to some people, it is a very common procedure, and permanent bodily harm is extremely rare. To reduce discomfort, your doctor will inject an anesthetic (a numbing medicine) into the area before inserting the needle. A common side effect of a lumbar puncture is a headache that may last for several days. Some people are able to avoid or decrease the severity of the headaches by lying down for one or two hours immediately following the procedure.

The blood or spinal fluid is then tested. One of the most accurate and sensitive tests involves looking for *Cryptococcus* in the blood or spinal fluid. This test, called a CRAG test, is able to detect about 95% of people who are ill with cryptococcal meningitis. Meningitis can also be caused by different kinds of bacterial infection. If your healthcare provider thinks that you may have *bacterial* meningitis, you will normally be treated with antibiotics immediately while other tests, such as the CRAG test, are performed. This is because bacterial meningitis is deadly and progresses very rapidly without antibiotic treatment.

How to treat it?

If tests of your spinal fluid indicate that *Cryptococcus* is present, your healthcare provider will prescribe treatment based on the severity of your illness and based on previous therapies that you have used.

DOSING

AmB at 0.7 mg/kg/day + flucytosine at 100mg/kg/day (in divided doses) for two weeks,

THEN ...

Fluconazole at 400mg/day for eight weeks,

THEN ...

Fluconazole at 200mg/day for life.

Mild cryptococcal meningitis

For very mild cases of cryptococcal meningitis (people who have *Cryptococcus* present, but no mental status problems and normal cerebral spinal fluid [CSF] pressure), the doctor will normally prescribe a drug called fluconazole (Diflucan). A dose of 400–800mg a day in pill form is generally prescribed for 10–12 weeks. For people with low CD4+ cell counts (less than 50), a doctor may recommend that you continue to take fluconazole, beyond the first 10–12 weeks, at a lower maintenance dose (200mg a day) to reduce the chance of a reoccurrence of the disease.

Moderate to severe meningitis

For more severe cases of cryptococcal meningitis, the current treatment of choice is a combination of the intravenous (IV) drug amphotericin B (AmB, Fungizone) and flucytosine (Ancobon) in pill form. This combination is given daily until the CSF is sterile (contains no *Cryptococcus*), usually for two to four weeks. Most people are then switched to fluconazole for eight weeks. Following a moderate to severe case of meningitis, the chance of relapse after treatment is extremely high. Therefore, most physicians recommend that people continue to take fluconazole daily for the rest of their lives, even after completing a successful course of treatment.

Effective treatment for cryptococcal meningitis is still possible, however, for those who have become resistant to fluconazole. If an individual is known or suspected to have *Cryptococcus* that is resistant to fluconazole, it may be possible to substitute itraconazole (Sporanox). As with the course of treatment mentioned above, mild meningitis may be treated with itraconazole at a dose of 200mg three times a day for three days. On the fourth day, the dose is lowered to 200mg twice a day for six to 10 weeks. For more severe meningitis, amphotericin B should be used in combination with flucytosine until the CSF is sterile or for at least two weeks. Itraconazole is then recommended at a dose of 200mg twice a day for life.

Other treatments

Because people who take amphotericin B often experience severe side effects, other formulations of this medication are approved for use



in cryptococcal meningitis and are increasingly being used. The newer medications are a special formulation of amphotericin, which is liposomally encapsulated. Liposomal drugs are those that have an active drug like amphotericin B inserted into a liposome (a fat bubble). The liposome slows down the process by which the body breaks down and eliminates the active drug, allowing lower doses to be used. This can result in fewer side effects. For cryptococcal meningitis, those liposomal drugs include Amphotec, Ambisome and Abelcet.

Upon reviewing data from the studies of Ambisome in particular, many believe that, because Ambisome causes fewer side effects, it may be superior to standard amphotericin B as first line therapy for cryptococcal meningitis. Ambisome is recommended for patients with kidney problems or who can not tolerate amphotericin B.

However, a recent survey of experts on the treatment of cryptococcal meningitis indicates otherwise. Based on their interpretation of study results, combined with their extensive clinical experience treating cryptococcal meningitis, they do not find evidence to suggest that any of the liposomal drugs are significantly more effective or less toxic than standard amphotericin B. Their recommendation for first line therapy remains consistent with the current federal guidelines stated above. They do, however, believe the liposomal drug Ambisome to be superior to Abelcet or Amphotec, and they do recommend its use when patients have kidney problems or cannot tolerate amphotericin B.

fluconazole resistance

Some healthcare providers now discourage the use of fluconazole to prevent cryptococcal meningitis, candida (thrush), and other fungal diseases (read “Can meningitis be prevented” to the right). This is because each of these disease-causing fungi can become resistant to fluconazole. Should you become resistant to fluconazole while taking it to prevent an infection, you would then be unable to use it as treatment for that infection. Because fluconazole is considered the most effective treatment for each of these diseases, you may be better off in the long run if you save this drug for primary treatment. Moreover, fluconazole-resistant cryptococcus is likely also to have some degree of resistance (called cross-resistance) to itraconazole.

Other complications

One of the most dangerous complications in severe cases of cryptococcal meningitis is extreme swelling in the skull and the pressure this places on the brain. Therefore, it is recommended that your physician closely monitor the pressure on your brain (called intracranial pressure) beginning with the first lumbar puncture used to diagnose cryptococcal infection. Some physicians recommend draining CSF through lumbar punctures if intracranial pressure is exceptionally high (greater than 25 cm H₂O), though this procedure has not been studied well enough to prove a better treatment outcome.

Stopping maintenance therapy

The introduction of very potent combinations of anti-HIV drugs (like protease inhibitors) has reduced the overall number of people who get sick with opportunistic infections. People who respond the best to these combinations generally see their CD4+ cell counts rise and a reduction in the level of virus in their bloodstream to undetectable levels. When these changes are sustained for six months or longer, people tend to have fewer opportunistic infections such as cryptococcal meningitis.

Whether or not to continue with life-long fluconazole maintenance therapy is a challenging question faced by most people who have had success with a new combination of potent anti-HIV drugs. Unfortunately, there has been little recorded experience so far to help guide that decision. *The Federal Guidelines for the Prevention and Treatment of Opportunistic Infections* recommends that people continue to take fluconazole maintenance therapy even in the presence of successful anti-HIV combination therapy.

Can meningitis be prevented?

The antifungal drug fluconazole may be quite useful in preventing cryptococcal meningitis in people whose CD4+ counts are below 50. There is strong concern, however, that people may not benefit much in the long term from using this preventive treatment. This is partly due to the small number of people living with AIDS who become ill with cryptococcal meningitis.

Before the introduction of more powerful anti-HIV therapy, only 5–8% of all people living with HIV ever became ill with cryptococcal meningitis, and those numbers have decreased since 1996. More importantly, research shows that many people who used fluconazole to prevent cryptococcal meningitis did not respond well to fluconazole as maintenance therapy if they became ill with the disease. The other available antifungal drugs are less effective and may be more toxic. These therapies (itraconazole and ketoconazole) can be used effectively, however, in people who have used fluconazole extensively to prevent cryptococcus or other fungal infections.



For more treatment information, call Project Inform's toll-free National HIV/AIDS Treatment Information Hotline at 1-800-822-7422.

is treatment or prevention different for different populations?

Is it different for women?

At this time, there are no known differences in the way that women respond to therapy or in significant side effects to treatment. For pregnant women, however, treatment with any of the *azole* drugs including fluconazole, itraconazole, and ketoconazole (Nizoral) may cause severe birth defects. Amphotericin B alone until clearance of *Cryptococcus* is seen in the spinal fluid (2–4 weeks) is recommended as primary therapy for women who become ill with cryptococcal meningitis while pregnant.

Because of the high rate of relapse mentioned above, pregnant women who are successfully treated for *Cryptococcus* should be monitored closely for a reoccurrence of the infection. Also, because of the success of anti-HIV treatment in controlling other types of opportunistic infections, pregnant women who become ill with cryptococcal meningitis may want to strongly consider anti-HIV therapy. Lastly, if you were treated for cryptococcal meningitis during pregnancy, you should discuss the option of beginning maintenance therapy with fluconazole after giving birth to your child.

Is it different for children or infants?

Cryptococcal meningitis is much less common in children and infants than it is in adults and adolescents, occurring in less than 1% of all children living with HIV. Fever was the most common symptom experienced by those children who have become ill with cryptococcal meningitis. The only treatments available are generally not recommended for children or infants. Federal guidelines suggest using fluconazole as primary treatment for cryptococcal meningitis only in extreme situations. If treatment is absolutely necessary, however, fluconazole is the first choice for treatment at a recommended dosing of 3–6mg/kg by oral suspension daily. An alternative treatment is itraconazole at 2–5mg/kg by oral suspension every 12–24 hours.



Drug access information

Fungizone, Ancobon and Diflucan are all currently available through prescription from pharmacies around the country. Also, most states now cover these drugs through their AIDS Drug Assistance Programs (ADAP). The liposomal formulas of amphotericin B, although approved, may be more difficult to access. If either your private health insurance or your public benefits do not cover the treatments listed in this publication, you may contact Project Inform's hotline at 1-800-822-7422 for more information on how to obtain drug assistance. As contact information for drug assistance programs changes regularly, we are unable to list them here.

Commentary

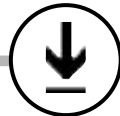
While a diagnosis of cryptococcal meningitis can be a serious and life-changing event, it is both treatable and survivable. You may find a number of Project Inform's other publications to be very helpful at this time. You may access them on our website at www.projectinform.org or by calling our toll-free hotline Monday–Saturday at 1-800-822-7422. We encourage you to call the hotline often for information and support. Some of the publications that may be helpful include *Building a Doctor Patient Relationship* and *Dealing with Drug Side Effects*.

do the drugs cause any serious side effects?

Nearly all prescribed medicines can cause at least some minor side effects in some people. Some side effects can be eliminated or treated. The chart below describes the most common ones associated with the drugs used to treat cryptococcal meningitis.

DRUG NAME	SIDE EFFECTS	NOTES
Amphotericin B (Fungizone) or Liposomal AmB (Amphotec, Ambisome, Abelcet)	Mild-to-Moderate: fever, chills, nausea, vomiting, diarrhea, headache and muscle pains Severe: immediate and severe allergic reaction, kidney toxicity, anemia	Acetaminophen* (Tylenol) and diphenhydramine (IV Benadryl) administered one half hour before taking amphotericin B can reduce minor side effects. Amphotericin B should be given only with extreme caution to people with kidney problems.
Flucytosine (Ancobon)	Mild-to-Moderate: nausea, headache, skin rash, vomiting, abdominal pain, diarrhea, increased triglycerides	Dosage reduction necessary in people with kidney problems. May cause birth defects if used in pregnant women.
Fluconazole (Diflucan)	Mild-to-Moderate: nausea, headache, skin rash, vomiting, abdominal pain, diarrhea, increased triglycerides	Pregnant women are advised not to use fluconazole or any of the azole drugs during pregnancy, as they may lead to severe birth defects.

* Acetaminophen (Tylenol) can be toxic to the liver and other alternatives are available like ibuprofen (Advil) and naproxen (Aleve).



the bottom line

If you think you have cryptococcal meningitis:

- Report symptoms to your healthcare provider immediately! Untreated meningitis is usually fatal.
- Simple lab tests should be performed to give a firm diagnosis of cryptococcal meningitis.
- If your healthcare providers suspects you have bacterial meningitis, you should be prescribed antibiotics while you wait for lab results.

If you have been diagnosed with cryptococcal meningitis:

- For moderate CM, simple treatment with fluconazole is highly effective and generally well tolerated among people who have previously not been on long-term fluconazole therapy.
- For people with long-term previous use of fluconazole or with severe CM, amphotericin-based therapies are the drug of choice.
- Newer liposomally encapsulated formulations of amphotericin B are effective and available for people who cannot tolerate standard amphotericin B.
- Once treated for CM, fluconazole maintenance therapy may be necessary for life.
- Flucytosine and fluconazole should not be used by pregnant women due to potential harm to her unborn child.

If you want to prevent cryptococcal meningitis:

- Primary prevention of CM is generally discouraged, as the overall incidence is low and preventive drugs may become ineffective as treatment later.