

MYCOBACTERIUM AVIUM COMPLEX



Mycobacterium avium complex (my-koe-back-teer-ee-um ay-vee-um complecks) disease is among the most common bacterial infections in people living with HIV. In one study, MAC bacteria were found in the blood of 43% of people within two years of diagnosis with AIDS. MAC is most likely to occur in people with CD4+ cell counts below 50 and at least one other opportunistic infection (OI).

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Routine blood tests from people with low CD4+ cell counts can detect MAC at an early stage when it can be treated fairly easily. Drugs can also be used to prevent MAC disease in people with low CD4+ cell counts.

If you develop MAC disease, treatment can ease symptoms and improve your quality of life. And, if you

have had MAC disease, then you will need to continue taking drugs to stop the disease from returning. Drug resistance is a serious issue in treating MAC, but potent treatments can slow the development of drug-resistant MAC bacteria.

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cause

MAC is the term for two related bacteria: *Mycobacterium avium* and *Mycobacterium intracellulare* (MAI). These bacteria are found in water, dust, soil and bird droppings. They enter the body in food and water or sometimes through the lungs.

Most people usually have small numbers of these bacteria growing in their gut or lungs, but do not have any symptoms. This is because a weakened immune system allows the bacteria to attack the lining of the gut and multiply. From there, they can enter the blood and spread through the body, which is called *disseminated* infection.

diagnosis

MAC is diagnosed by culture from blood, tissue or bone marrow. If MAC bacteria are found in stool and sputum samples, this could mean the infection has spread. Doctors may have to use special methods to get cells or tissue for MAC diagnosis. These include taking bone marrow from the hip using a needle, or inserting a flexible tube into the stomach or bowels (*endoscopy*) or the lungs (*bronchoscopy*).

Some doctors choose to treat MAC infection while waiting for the test results, which can take several weeks. New tests are being developed to give a faster diagnosis. These include PCR and bDNA tests for MAC (the same methods used for HIV viral load tests). Severe anemia and liver problems can occur in MAC, so doctors may take blood samples to look for a low red blood cell count or raised alkaline phosphatase levels.

symptoms

The most common symptoms of MAC are persistent fevers plus night sweats, loss of appetite, weight loss, tiredness or worsening diarrhea. Symptoms of early disease often involve the gut: stomach cramps, nausea and vomiting. Disseminated disease can lead to bone, brain or skin infections, or cause painful joints.

Signs of MAC include swollen abdominal lymph nodes, usually on only one side of the body, and an enlarged liver and spleen. Coughing and wheezing are less common. Since many of these symptoms are similar to symptoms of other OIs, it's important to get a correct diagnosis before you start treatment. If you have symptoms like these, talk to your doctor.

A recent study showed that people who already have MAC when they start potent anti-HIV therapy sometimes have an unusual response. It has been called *MAC reversal syndrome* and results from improved immune function (increases in CD4+ cell counts). It involves fevers and the growth of lumps usually around the neck or spine. The drug prednisone can reduce these symptoms.



Over time, these people still benefit from anti-HIV therapy and their MAC infection stabilizes. So anti-HIV therapy does not always stop MAC in people with early MAC infection, but overall it seems to be beneficial whether or not MAC occurs. However, it may be useful to screen for MAC in people with symptoms like fevers before they start anti-HIV therapy.

treating *Mycobacterium avium* complex

Treatment reduces the symptoms of MAC disease and improves your quality of life. However, treating MAC is difficult for several reasons:

› **MAC can easily become drug-resistant.**

MAC strains found in people with HIV are naturally more drug-resistant than those found in most HIV-negative people. Treatment usually involves taking several drugs for a long time. Combining several drugs increases the chance of side effects and drug interactions and can be expensive. This may mean that people do not finish the full treatment, which can lead to drug resistance.

› **The needed dose of drug may cause serious side effects.**

Some drugs used to treat MAC are destroyed by stomach juices or cannot be dissolved in body fluids. It is particularly difficult for drugs to get into cells called macrophages, where MAC bacteria are found. In order to have high enough levels of the drug at the site of infection, higher doses may be needed. This may then lead to side effects.

› **The effect of a drug on MAC bacteria in a lab test is not a reliable guide to treating someone with MAC.**

Resistance patterns of MAC bacteria vary a lot. It may be difficult to work out the best MAC treatment for an individual.

Treating MAC infection requires several drugs because no one drug by itself is effective. MAC bacteria can quickly become resistant to a drug and to other drugs in the same family. Combination therapy is more effective and may slow the development of drug resistance.

The Public Health Service Task Force recommends that MAC treatment includes:

clarithromycin (Biaxin) 500mg twice a day, or
azithromycin (Zithromax) 500–600mg/day

PLUS

ethambutol (Myambutol) 15mg/kg/day

PLUS one or more of

rifabutin (Mycobutin), rifampin (Rifadin, Rimactane), ciprofloxacin (Cipro) or amikacin (Amikin)

Use of clofazimine (Lamprene) has been shown to increase the risk of death during MAC treatment in several studies, so it should not be used.

Azithromycin and clarithromycin are related antibiotics. They are approved for treating serious bacterial infections including MAC in combination with at least one other drug. Resistance to clarithromycin develops quickly when used alone. The higher the level of bacteria in the blood before starting therapy, the more rapid resistance develops.


Clarithromycin has been studied together with various anti-MAC therapies. Studies show that a combination of clarithromycin, ethambutol and rifabutin may prevent developing resistance to clarithromycin, which is common with two-drug combinations. One study also showed that people using the three drugs had fewer symptoms and lower levels of MAC bacteria in their blood. Survival was also longer on three-drug regimens.

This suggests that using clarithromycin or azithromycin together with ethambutol and rifabutin should now be the standard treatment for people with MAC disease. However, several studies have shown that people taking 1,000mg of clarithromycin twice a day had a higher death rate than those taking 500mg twice a day. The higher dose should not be used.

Doctors have had less experience with azithromycin for treating MAC compared to clarithromycin. Studies are underway to find the best treatment combination using azithromycin.

Several pharmaceutical companies have payment assistance programs for their anti-MAC drugs. Doctors should call the toll-free number:

- Azithromycin: Pfizer, Inc., 1-800-869-9979
- Clarithromycin: Abbott Laboratories, 1-800-688-9118
- Ethambutol: Dura Pharmaceuticals, 1-800-859-8586
- Rifabutin: Pharmacia, 1-800-242-7014



side effects

The most common side effects with azithromycin and clarithromycin are nausea, vomiting, diarrhea and abdominal pain. A rare side effect is hearing loss. Azithromycin may also cause swelling of the blood vessels and liver damage.

Ethambutol can cause nausea and vomiting. It may lead to impaired vision, so people taking this drug should have regular eye check-ups.

Common side effects of rifabutin include orange urine, stomach upsets and rashes. In some studies, up to a quarter of people taking rifabutin developed *uveitis*, a painful inflammation in the eye. This occurred more often among people who also took clarithromycin.

drug interactions

Interactions may occur between clarithromycin and rifabutin. Rifabutin can decrease clarithromycin levels in the blood by 50%, while clarithromycin can increase rifabutin levels by as much as 80%. Fluconazole, an antifungal drug, can also increase rifabutin levels by up to 80%. Increased levels of rifabutin could cause more severe side effects like uveitis. It's important to talk to your doctor about potential drug interactions.

Rifabutin and clarithromycin may interact with protease inhibitors (PIs). Azithromycin is not thought to interact with PIs so it may be the best choice for people taking a protease inhibitor.

In general, people taking PIs should avoid rifabutin. If a person has to take rifabutin, indinavir is the PI of choice, and the dose of rifabutin should be cut in half. Rifabutin may also interact with some non-nucleoside reverse transcriptase inhibitors.

Although PIs might also raise clarithromycin levels, there are not enough data on this to say whether the dose of either drug should be changed. Clarithromycin may also decrease blood levels of zidovudine. For more details about interactions of anti-MAC treatments with other drugs, read Project Inform's publication, *Drug Interactions*, available at 1-800-822-7422 or www.projectinform.org.

cytokines

Because MAC bacteria often live in cells called macrophages, new treatments for MAC may target these cells. Macrophages are scavenger cells that eat up and kill bacteria and viruses. They circulate in the blood or live in organs like the liver, spleen or lungs. In people with HIV, macrophages can eat but not kill MAC bacteria. The bacteria grow inside the macrophages and can be spread through the body.

Cells of the immune system release chemicals, called cytokines, that enable them to signal and work with each other to fight infections. In the future, cytokines may be given to enhance the effect of anti-MAC drugs by helping macrophages kill MAC bacteria. A study combining azithromycin with *granulocyte macrophage-colony stimulating factor* (GM-CSF) is looking at this. Interleukin-12 (IL-12) is in early studies as well.

preventing the infection

It is difficult to avoid contact with MAC bacteria, but there are some ways to reduce the risk.

- ▶ Boil drinking water. MAC bacteria are found in most water systems, hospital water supplies and bottled water.
- ▶ Do not eat raw foods, especially salads, root vegetables and unpasteurized milk and cheese.
- ▶ MAC bacteria are killed at 176°F, so they are destroyed during normal cooking.
- ▶ Rinse and peel fruit and vegetables thoroughly.
- ▶ Avoid contact with animals, especially birds and bird droppings. Pigeons—common in most cities—can also transmit cryptococcosis, an OI affecting people with HIV.
- ▶ **Avoid or reduce alcohol intake. Drinking alcohol regularly can help MAC infection to spread more quickly in people with HIV.**

Drugs can be used to prevent or delay the onset of MAC in people with HIV. Three drugs are approved by the FDA for MAC prevention: azithromycin, clarithromycin and rifabutin. The decision to start MAC prevention should take into account possible drug side effects and interactions with other drugs. In addition, MAC bacteria may become resistant to a drug when it is used alone for preventing the disease.

The Public Health Service recommends that people with CD4+ cell counts below 50 should take either clarithromycin (500mg twice a day) or azithromycin (1,200mg once a week) for preventing MAC disease. Rifabutin (300mg/day) should only be used if clarithromycin or azithromycin cannot be taken. There is a risk of developing resistance to clarithromycin, so azithromycin might be the best first choice.

Studies have shown that clarithromycin can reduce the chance of developing MAC by 70%. Another study showed that outbreaks of MAC disease were reduced by 65% in people who took azithromycin. Both drugs also protect against bacterial infections in the lungs and airways. Rifabutin can reduce the risk of developing MAC by 30–50%. Combinations of these drugs have been tested for MAC prevention, but in all cases increased side effects and cost outweigh any added protection from disease.



One worrying outcome of these studies was that some people develop resistant MAC. MAC bacteria were three times as likely to become resistant to clarithromycin taken alone than to azithromycin. Taking clarithromycin with rifabutin did not decrease the risk of resistance to clarithromycin.

As clarithromycin is often the drug of choice to treat MAC, some doctors choose not to use it for MAC prevention. That way, it is still an option for treating the disease later if necessary. However, the chance of having an outbreak of MAC disease is very low when on preventive therapy with clarithromycin or azithromycin, so resistant bacteria are quite rare.

No studies have yet compared clarithromycin and azithromycin for MAC prevention. The two drugs are very similar, so developing resistance to one is likely to result in some level of resistance to the other (cross-resistance). Rifabutin belongs to a different class of drugs, so there should be no cross-resistance between rifabutin and either azithromycin or clarithromycin.

It's important to make sure that you do not have disseminated MAC disease before you start preventive therapy, as this may lead to drug-resistant bacteria. It is also essential to have a chest x-ray and tuberculosis (TB) skin test. The bacteria that cause MAC and TB are related. Some drugs used to treat MAC are also used for TB. If you have active TB, using a single anti-MAC drug may lead to resistant TB. This is most important before starting MAC prevention with rifabutin. Rifabutin is closely related to rifampin, a drug used to treat TB, and cross-resistance can develop.

stopping preventive therapy

Many studies have shown that OIs and deaths have been reduced since protease inhibitors were first used. Now several studies show that it may be safe for people on potent anti-HIV therapy to stop OI prevention if there is evidence of immune reconstitution.

One study looked at 643 people whose CD4+ cell counts had risen from below 50 to over 100 following potent anti-HIV therapy. About 60% of people in the study had viral loads below 500 copies HIV RNA. They were given either azithromycin (1,200mg once a week) or placebo (sugar pill).

After one year there were only two cases of MAC, and both cases were in the placebo group. So, people who have had a CD4+ cell count over 100 and a low viral load for at least three to six months may be able to stop taking MAC prevention. You should think about restarting MAC prevention if your CD4+ cell count falls back below 50.

maintenance therapy

People who have been treated for MAC disease have to take anti-MAC drugs for life as symptoms will often return if therapy is stopped. This is called *maintenance therapy*. The best maintenance therapy should lower the risk of drug resistance and should have few side effects. The current recommendation is to use clarithromycin or azithromycin plus ethambutol with or without rifabutin.

Successful treatment with potent anti-HIV therapy for several months may reduce the risk of relapse for people on maintenance therapy for MAC. However, it is not recommended that people stop their maintenance therapy as this has not been studied in enough people.

when making a decision about OI prevention, consider these guidelines:

- › Potent anti-HIV therapy restores the immune response slowly over time. It may be wise to wait until you establish a good response to anti-HIV therapy (HIV levels decrease and CD4+ cell counts increase) for at least a few months before changing prevention strategies.
- › The risk of stopping prevention is likely to be lowest in people who have never had an OI before they started anti-HIV therapy.
- › People who have the strongest and longest lasting improvement in CD4+ cell count due to anti-HIV therapy probably stand the best chance of success when stopping OI prevention.
- › A person's tolerance for the risk of getting an OI must be weighed against their willingness to take extra drugs and risk side effects.



children

Children with advanced HIV have a high risk of developing disseminated MAC. It is recommended that preventive MAC therapy with azithromycin (20mg/kg once a week, max. 1,200mg/day) or clarithromycin (7.5mg/kg twice a day, max. 1,000mg/day) be started in children in the following categories:

- ▶ Older than six years, CD4+ cells below 50.
- ▶ Two to six years old, CD4+ cells below 75.
- ▶ One to two years old, CD4+ cells below 500.
- ▶ Less than twelve months old, CD4+ cells below 750.



Azithromycin and clarithromycin are both available as a liquid for children. A solution of rifabutin can be made by a pharmacist using the powder from capsules. There have not been any studies on the safety of stopping MAC prevention in children whose CD4+ cell counts have increased due to potent anti-HIV therapy.

The guidelines for treating children with MAC are the same as those for adults. To stop MAC returning in children, they should take the following maintenance therapy: clarithromycin (30mg/kg per day in two doses) plus at least one of ethambutol (15mg/kg once a day) and rifabutin (5mg/kg once a day).

pregnancy

Pregnant women should take the same MAC preventive therapy as other adults. Animal studies suggest that clarithromycin, ethambutol or rifabutin may cause some harm to the developing child during the first three months of pregnancy. Doctors may prefer to wait until the second trimester to begin or continue preventive therapy.

Azithromycin should be the drug of choice in pregnant women. Clarithromycin should only be used if no other therapy can be taken. For maintenance therapy, azithromycin plus ethambutol are the preferred drugs.

commentary

Researchers are developing and testing new drugs and drug combinations that are more effective and have fewer side effects. More novel treatment ideas and better methods of drug testing are needed.

A better understanding of how MAC bacteria function will help pave the way to finding more effective drugs to kill them. There are many questions that still need to be answered:

- What makes one strain of MAC bacteria more harmful than another?
- How does the immune response affect how the bacteria behave?
- What factors influence the bacteria becoming drug-resistant?
- What are the differences between HIV-infected and normal macrophages?
- How does HIV change the complex system of cytokines that cells of the immune system use to signal to each other?

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the bottom line on m.a.c.

Mycobacterium avium complex is a bacterial infection found in water, dust, soil and bird droppings.

Symptoms

Persistent fever, night sweats, fatigue, weight loss, anemia, abdominal pain, dizziness, diarrhea and weakness.

Diagnosis

Culture from a sterile site such as blood, bone marrow or cerebral spinal fluid.

Preventive therapy (prophylaxis)

People whose CD4+ cell counts stay consistently below 50 should start preventive therapy.

Preferred: Clarithromycin (500mg twice a day); or azithromycin (1,200mg once a week).

Alternative: Rifabutin (300mg once a day).

Stopping preventive therapy

People with sustained CD4+ cells above 100 for 3–6 months and sustained viral load suppression may consider stopping preventive therapy.

Treatment

Preferred: Azithromycin (500–600mg once a day); or clarithromycin (500mg twice a day) + ethambutol (15mg/kg/day) + rifabutin (300mg once a day).

Alternative: Azithromycin or clarithromycin + ethambutol + rifabutin +/- ciprofloxacin (500–750mg twice a day) +/- IV amikacin (10–15mg/kg/day). IV amikacin can be added for severe disease.

Higher doses of clarithromycin (1,000mg twice a day) may be linked with increased risk of death. Clofazimine may be associated with increased side effects and risk of death and it should not be used.

Maintenance therapy

Everyone who has had MAC should be on maintenance therapy with either clarithromycin (500mg twice a day) or azithromycin (500mg once a day) if it has been proven there is no resistance to either drug + ethambutol (15mg/kg once a day) +/- rifabutin (300mg once a day).

Stopping maintenance therapy

People with sustained CD4+ cells above 100 for 6–12 months as a result of potent anti-HIV therapy may consider stopping maintenance therapy.

1999 Public Health Service prevention guidelines on MAC

Prevention:

- Preventive MAC therapy is needed for adults with CD4+ cell counts below 50.
- First choice: clarithromycin or azithromycin; second choice: rifabutin.
- Before starting preventive therapy, rule out active MAC or TB infection.
- Check for potential drug interactions.

Maintenance:

- Clarithromycin or azithromycin plus ethambutol and with or without rifabutin.

Prevention in children:

- Clarithromycin or azithromycin are the drugs of choice for children:
- Over 6 years, CD4+ cells below 50;
- 2–6 years, CD4+ cells below 75;
- 1–2 years, CD4+ cells below 500;
- Less than 12 months, CD4+ cells below 750.

Prevention during pregnancy:

- MAC preventive therapy is needed for pregnant women with CD4+ cell counts below 50.
- Azithromycin is the drug of choice.