

*Lyme Disease Diagnosis & Therapy Suggestions 2006 ACAM Meeting*

## DIAGNOSIS AND THERAPY OF CHRONIC SYSTEMIC CO-INFECTIONS IN LYME DISEASE AND OTHER TICK-BORNE INFECTIOUS DISEASES

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The diagnosis of Lyme Disease should be based on clinical and laboratory data as well as the likelihood of exposure to the Lyme spirochete. Most Lyme Disease patients have multiple co-infections. In addition to the Lyme spirochete (*Borrelia burgdorferi*), the majority of Lyme patients are also infected with tick-borne mycoplasma, rickettsia and/or protozoa. There are a number of considerations when undergoing therapy for multiple infections found in chronic illnesses, including whether to use traditional as well as integrative nutraceutical approaches. These are discussed in the following sections, including antibiotic/antiprotozoan therapies and dietary supplements.

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Lyme Disease is the most common tick-borne disease in North America and has been reported in 48 U.S. states and in Eastern Canada. Found in Old Lyme, CT in 1975, the infection is caused by a tick bite and the entry into the skin approximately 24 hours later of the spiral-shaped spirochete *Borrelia burgdorferi* [1] and other co-infections. *Borrelia* and its co-infections can be carried into new habitats by a variety of ticks, such as the deer tick, black-legged tick and bear tick, and their vectors, such as rodents, birds and other animals. After its incubation for a few days to a month, the *Borrelia* spirochete and also its co-infections migrate through the skin and into the lymph and blood where it can disseminate to near and distant sites in the host [2]. Transplacental transmission of *Borrelia* (and its co-infections) can occur in pregnant animals, including humans, and blood-borne transmission by blood transfusion is likely but unproven. The tick-borne co-infections can and usually do appear at the same time and may also be introduced by tick bites. These will be discussed in this brief review of Lyme Disease diagnosis and treatment.

### DIAGNOSIS OF TICK-BORNE CO-INFECTIONS: *BORRELIA*, *MYCOPLASMA*, *BABESIA* AND OTHERS

About one-third of Lyme Disease cases start with the appearance of a round, red, bulls-eye skin rash called erythema migrans at the site of the tick bite, usually within 3-30 days [2]. Within days to weeks after the entry of the *Borrelia* spirochete from the tick mild flu-like symptoms can occur that include shaking chills, intermittent fevers and local lymph node swelling (local disease). After this localized phase that lasts weeks to months, the infection can spread to other sites (disseminated disease), and patients then show malaise, fatigue, fever and chills, headaches, stiff neck, facial nerve palsies (Bell's palsy) and muscle and joint pain and other signs and symptoms. Later this disseminated disease can become persistent or chronic and involve the central and peripheral nervous systems as well as ophthalmic, cardiac, musculoskeletal and internal organ invasion. At this late persistent phase chronic arthritis, neurologic impairment with memory and cognitive loss, cardiac problems (myocarditis, endocarditis causing palpitations, pain, bradycardia, etc.) and severe fatigue are often apparent [2-4]. Unfortunately, the signs and symptoms in the late persistent phase of the disease usually overlap with other chronic conditions, such as Chronic Fatigue Syndrome, Fibromyalgia Syndrome, Rheumatoid Arthritis, among others [5], causing confusion in the diagnosis and treatment of the late persistent phase in Lyme Disease patients. Some contend that the late persistent phase is not even related to Lyme Disease, resulting in failure to successfully identify and treat the chronic condition. The involvement of co-infections, such as *Mycoplasma* species, among other co-infections, in causing chronic signs and symptoms in patients has not been investigated; however, such infections on their own have been shown to produce similar signs and symptoms [6].

As is the case for many chronic illnesses, diagnostic laboratory testing at various clinical stages is,

unfortunately, not full-proof, and experts often stress the need to diagnose Lyme Disease with a checklist of signs and symptoms and potential exposures, along with multiple laboratory tests [2,7]. The laboratory tests used for Lyme Disease diagnosis include: detection of *Borrelia* surface antigens by enzyme-linked immunosorbant assay (ELISA), immunofluorescent assay (IFA), and Western blot of *Borrelia* proteins. Alternatively, polymerase chain reaction (PCR) for *Borrelia* DNA has been used to detect the intact organism in blood. A true-positive test result usually consists of more than one positive test from the above list. The problem with these tests is that they are blood tests requiring the presence of antibodies or *Borrelia* proteins in the blood or are dependent on the spirochete and thus its DNA being present in the blood. Some of the tests, such as serology testing for antibodies against *Borrelia* antigens, can cross-react with other microorganisms and in some cases are only useful 4-6 weeks after onset of signs and symptoms; thus the quality of the test can vary. The most sensitive type of test (PCR) requires that the spirochete be released into the blood where its DNA can be detected. Other tests that are offered have been criticized. For example, diagnosis of Lyme Disease based on culture of *B. burgdorferi* is unreliable and is not recommended [7]. One laboratory offers a one-step Lyme antigen urine test (LUAT), but some researchers have criticized this test for its high rate of false-positive tests [8]. Most consider a patient positive if *Borrelia* antigens (more than one antigen by Western Blot analysis) are present in blood serum in more than one test, or the patient is PCR-positive for *Borrelia b.* in a blood test.

There are other co-infections that complicate the diagnosis and signs and symptoms of Lyme Disease. These infections can also occur by themselves or in various combinations. For example, another tick-borne infection is caused by the intracellular protozoan *Babesia*, first described in domestic animals in Romania [9]. There are over 100 species of the genus *Babesia*, but most infections in humans in the United States are caused by *Babesia microti* and in Europe by *Babesia divergens* and *Babesia bovis*. This type of infection can occur as a co-infection with *Borrelia* (about 20-30% of cases of Lyme Disease have *Borrelia* plus *Babesia* infections). When both infections are present, the number of signs and symptoms, their severity and duration of illness can be greater in the early stages of disease [9], including high fever, chills, generalized weakness, gastrointestinal symptoms (anorexia, nausea, abdominal pain, vomiting, diarrhea, among others), anemia, muscle and joint pain, respiratory problems and dark urine. This combination can be lethal in some patients (about 7% of patients can have disseminated intravascular coagulation, acute respiratory distress syndrome and heart failure), but the majority of patients with *Babesia* have the chronic persistent form of the infection. In *Babesia* infections patients can show mild to severe hemolytic anemia (probably correlating with the protozoan colonization of erythrocytes, which can be seen by experienced individuals in blood smears) and a normal to slightly depressed leukocyte count [9]. However, this is usually not seen in patients who have progressed to the chronic phase of the disease.

We have found that the most common co-infection with *Borrelia* are various species of Mycoplasmas. Approximately 60-70% of Lyme Disease patients also have mycoplasmal infections (*Mycoplasma fermentans* > *Mycoplasma hominis* > *Mycoplasma pneumoniae*, *M. genitalium*, *M. penetrans*, other species). In some cases multiple mycoplasmal infections can be present in Lyme Disease patients. The presence of mycoplasmal infections complicates the diagnosis and treatment of Lyme Disease, and some of the generalized signs and symptoms found in *Borrelia*-positive patients are also found in mycoplasma-positive patients [5,6]. Like the *Borrelia* spirochete, the mycoplasmas are found at intracellular locations in various tissues and are only rarely found free in the blood. This can make detection difficult, and in some patients the appearance of *Borrelia* and various mycoplasmas in their blood cells can be cyclic, and they are not present all of the time. We recommend that mycoplasmal infections be tested for in every case of Lyme Disease using the most sensitive PCR procedures to detect the mycoplasma DNA in white blood cells [5,6,10]. Mycoplasmal infections can independently cause many of the signs and symptoms found in Lyme Disease, and they generally exacerbate the clinical signs and symptoms and complicate treatment of the condition [10]. In addition to Lyme Disease, mycoplasmal infections have been found at high incidence (40-60%) in Fibromyalgia Syndrome, Chronic Fatigue Syndrome, Rheumatoid Arthritis and Gulf War Illness [5,6,10]. These are emerging infections, and the medical community is just beginning to respect the involvement of this type of co-infection in many clinical conditions.

Another co-infection found in some Lyme Disease patients is a rickettsial infection caused by *Ehrlichia* species [2,3]. These small, gram-negative, pleomorphic, obligate intracellular infections are similar to Mycoplasmas in their structures, intracellular locations and resulting patient signs and symptoms. Commonly found species are *E. chaffeensis* and *E. phagocytophila*, and these microorganisms can cause signs and symptoms within 1-3

weeks of exposure, resulting in fever, shaking chills, headache and muscle pain and tenderness and less commonly nausea, vomiting, abdominal pain, diarrhea, cough and confusion [3]. Laboratory features include mild to moderate transient hemolytic anemia, decreases in white blood cell count (leucopenia, thrombocytopenia) and elevated erythrocyte sedimentation rate, and sometimes increases in liver enzymes and less often increases in blood urea nitrogen and creatinine. Serology is usually only positive after 1-2 weeks with the limitations discussed above. Since culturing the microorganism is not practical, PCR has been used for confirmation of the infection [3].

Lyme Disease patients are at risk for a variety of other opportunistic infections, including other bacterial infections as well as viral and fungal infections. These can complicate diagnosis and treatment, but they may be principally a problem in the late, persistent phase of the disease. Late stage patients with neurological manifestations, meningitis, encephalitis, peripheral neuropathy and other signs and symptoms may have complicated co-infections that are not recognized or treated by their physicians.

### TREATMENT OF LYME DISEASE *BORRELIA* AND CO-INFECTIONS

If their physician recognizes the complex nature of their disease, patients with *Borrelia* infections or combinations of *Borrelia* and *Mycoplasma*, *Babesia*, *Bartonella* and/or *Ehrlichia* infections can do well on combinations of antibiotics plus nutritional modifications and nutraceutical support. Experts agree that Lyme Disease is much easier to treat in the earlier phases, but some of the co-infections can be difficult to treat, especially if the disease is in the late chronic persistent stage. The most common recommendations for the treatment of Lyme Disease *Borrelia* and co-infections involve antibiotics that can effectively suppress early localized or early disseminated Lyme disease *Borrelia* [2-4]. A variety of antibiotics in 2-week regimens show good activity against early-stage *Borrelia* infections, such as combinations of doxycycline plus amoxicillin, doxycycline plus penicillin V and amoxicillin or penicillin V plus cefuroxime axetil, in that order, in terms of effectiveness and expense [2,11], although some reports indicate that the latter antibiotics are just as effective as the doxycycline combinations [12,13]. Also, doxycycline also shows good activity against most species of *Mycoplasma* and *Ehrlichia*, and doxycycline shows good penetration into the central nervous system (CNS). Doxycycline should not be used in children under the age of 8 years, but some have suggested that short duration treatment (2 weeks) at pediatric doses are very useful [11]. Alternatives include the use of erythromycin, but most experts do not consider this a first line treatment for Lyme *Borrelia* [2,11].

A major problem in the treatment of Lyme Disease is finding effective treatments of the late stage persistent or chronic disease, especially when they involve CNS infections. The table below (Table 1) shows the antibiotics useful for treating Lyme Disease based on the clinical situation [11,12].

**Table 1. Treatment of Lyme Disease During the Different Stages of the Disease (refs. 11, 12)**

<i>Clinical Stage</i>	<i>Time</i>	<i>Primary Treatment</i>	<i>Alternative Treatment</i>	
<b>Early localized</b>	3-30 days	doxycycline	erythromycin,	
		amoxicillin	clarithromycin	
		cefuroxime axetil	azithromycin	
<b>Early disseminated</b>	1-12 wks	doxycycline	erythromycin	
		amoxicillin	clarithromycin	
		cefuroxime axetil	azithromycin	
		with CNS involvement	ceftriaxone (iv)	penicillin G (iv)
			doxycycline (iv or po)	
<b>Late disseminated</b>	>2 months	with arthritis	amoxicillin	penicillin G (iv)
			doxycycline	doxycycline (iv or po)
		with CNS involvement	ceftriaxone (iv)	penicillin G (iv)
				doxycycline (iv or po)
		with cardiac involvement	ceftriaxone (iv)	
		amoxicillin		

Since with time late stage *Borrelia* infections are intracellular with cystic or persistent forms, Plaquenil, Falgyl or Tinidazole should be added along with a macrolide (azithromycin, Biaxin or Dynabac) and/or fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, ofloxacin). With antibiotic treatment, Herxheimer reactions (or 'die-off' reactions involving chills, fever, night sweats, muscle aches, joint pain, short term memory loss and fatigue or a general worsening of symptoms) usually occur for days to weeks due to release of bacterial cell wall degradation products and stimulation of interleukins or chemical messengers that cause worsening of some signs and symptoms. Oral antibiotics must be taken with a full glass of water, crackers or bread to avoid esophageal irritation (do not lie down for at least 1 hr). With some antibiotics direct sunlight must be avoided. To overcome Herxheimer reactions or other adverse responses i.v. antibiotics have been used for a few weeks—then oral. Oral Benadryl (diphenhydramine, 50 mg) should be taken at least 30 min before antibiotics, and lemon/olive drink (1 blended whole lemon, 1 cup fruit juice, 1 tbs olive oil—strain and drink liquid) is often useful [15]. This period usually passes within a few weeks and differs from allergic reactions that can cause immediate rashes, itching, swelling, dizziness, trouble breathing and other problems—if these occur, seek immediate medical attention. Many antibiotics cannot be used during pregnancy or by infants. For Lyme Disease the dosing for pediatric use has been worked out [2].

#### **ANTIBIOTIC THERAPY FOR CO-INFECTIONS OF *BORRELIA*, *MYCOPLASMA*, *BABESIA* AND OTHERS,**

Patients with co-infections of *Borrelia plus Mycoplasma* species the therapy should be the same as in Table 1 (with doxycycline) but the duration of therapy must be increased. The reason for this is that the slow-growing mycoplasmal infections are not readily susceptible to antibiotics, and thus the therapy must be more gradual [6,14]. Some patients with mycoplasma co-infections may benefit from combinations of antibiotics other than those listed in the table, such as adding additionally azithromycin or a floxacin, especially if there are limited responses [14]. These can be worked into the regimen slowly over weeks, if necessary. The protocol for infections involving *Borrelia plus Mycoplasma* species should be continued for at least 6 months. If necessary, the antibiotics can be continued for 6-week on, 2-week off cycles, which in some cases can be supplemented with Augmentin (in between the 6-wk cycles) or concurrently, if needed, to help in suppressing other secondary bacterial infections.

When *Babesia* infections are present as co-infections with *Borrelia*, patients can be treated with quinine (Quinamm) and clindamycin (cleocin) [9]. For co-infections with *Mycoplasma* or *Ehrlichia* species doxycycline should be added to the antibiotic regimen [3]. Dr. Richard Horowitz has presented a scheme for treating co-infections in Lyme Disease [16], and I have added a section on *Mycoplasma/Ehrlichia* co-infections (Table 2). If in addition to Mycoplasmal infections *Chlamydia pneumoniae* is present, then two penetrating antibiotics active against these microorganisms should be considered, such as doxycycline plus a fluoroquinolone (levofloxacin, ofloxacin or gatifloxacin).

#### **GENERAL NUTRITIONAL CONSIDERATIONS WHEN UNDERGOING THERAPY**

Chronic illness patients are often immunosuppressed and susceptible to opportunistic infections, so proper nutrition is imperative [15]. You should not smoke or drink alcohol or caffeinated products. Drink as much fresh fluids as you can, lots of juices or pure water are best. Try to avoid high sugar and fat foods, such as military (MRE) or other fast foods and acid forming, allergen-prone and system stressing foods or high sugar/fat junk foods. Increase intake of fresh vegetables, fruits and grains, and decrease intake of fats and *simple or refined sugars that can suppress your immune system*. To build your immune system cruciferous vegetables, soluble fiber foods, such as prunes and bran, wheat germ, yogurt, fish and whole grains are useful. In some patients exclusive use of 'organic' foods has been beneficial. For heavy metal removal we find the use of Detoxamin suppositories useful ([www.detoxamin.com](http://www.detoxamin.com)). For help with bowel bacteria and bladder infections, many recommend D-mannose (Biotech). This natural sugar inhibits binding of bacteria to biological membranes.

Chronic illness patients are often depleted in vitamins (*especially* B complex, C, E, CoQ-10) and certain minerals. These illnesses often result in poor absorption. Therefore, high doses of some vitamins are useful; others, such as vitamin B complex, cannot be easily absorbed by the gut (oral dose). Sublingual (under the tongue) *natural* B-complex vitamins in capsules or liquids (also injectable) (Total B, Real Life Research or GNC or [www.vitaminshoppe.com](http://www.vitaminshoppe.com)) should be used instead of swallowed capsules. B complex vitamins are especially important in *Borrelia* and *Mycoplasma* infected patients. General vitamins plus extra C, E, CoQ-10, beta-

carotene, folic acid, bioflavoids and biotin are best. L-cysteine, L-tyrosine, L-glutamine, L-carnitine, malic acid and especially flaxseed or fish oils are reported to be useful. Certain minerals are depleted in chronic illness patients, such as zinc, magnesium, chromium and selenium. Some recommend up to 300 mcg/day sodium selenite, followed by lower doses. Extra vitamins and minerals are very important if patients are removing heavy metals with chelating agents. Vitamins and minerals should not be taken at the same time of day (3 hr difference) as antibiotics or antivirals (or oxygen therapy), because they can affect absorption. Some recommend that antioxidant vitamins be taken at least 2 hr before or after antibiotic therapy. The suggested doses of vitamins can vary dramatically among patients; consult with your physician or nutritionist for appropriate dosage. [Researched Nutritionals, 800-755-3402 [www.ResearchedNutritionals.com](http://www.ResearchedNutritionals.com) carries a 400mg CoQ 10]

**Table 2. Combination Treatments for Lyme *Borrelia* Plus Co-Infections (Horowitz, ref. 16)**

<i>Lyme Borrelia</i>	<i>Mycoplasma/Ehrlichia</i>	<i>Bartonella</i>	<i>Babesia</i>
Amox+Probenecid+ Macrolide+Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra	+Mepron +Malarone +Artemesia +Lariam
Bicillin+ Macrolide+ Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra	+Mepron +Malarone +Artemesia +Lariam
Cephalosporin (po/iv)+ Macrolide+Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra	+Mepron +Malarone +Artemesia +Lariam
Doxycycline+ Plaquenil ±Flagyl/Tinidazole	+Ciprofloxacin	+Septra +Rifampin	+Lariam +Malarone +Artemesia
Macrolide+Plaquenil ±Flagyl/Tinidazole	+Doxycycline	+Septra +Quinolone	+Mepron +Malarone +Artemesia +Lariam

#### OXIDATIVE THERAPY FOR CHRONIC LYME DISEASE CO-INFECTIONS

*Borrelia* and *Mycoplasma* species infections are intracellular infections and should be considered borderline anaerobic infections that grow and survive better in low oxygen environments. Oxidative therapy can be useful in suppressing a variety of anaerobic infections, but this approach should be considered experimental and should only be done in an approved clinical trial. We recommend several weeks to months of Hyperbaric Oxygen (1.5-2.0 ATM, 60 min) treatments, because these are well tolerated by most patients with chronic infections. Alternatively, American Biologics Dioxychlor, i.v. ozone or hydrogen peroxide might be useful. Some patients have used peroxide baths with 2 cups of Epsom salt in a hot bath or Jacuzzi. After 5 min, add 2-4 bottles 16 oz. of 3% hydrogen peroxide. Repeat 2-3X week; but no vitamins must be taken 4 hr before the bath. The hydrogen peroxide is added after your pores open. This appears to have some benefit to patients, especially those with skin/muscle problems. Hydrogen peroxide can also be directly applied to skin after a work-out or hot shower/tub. Leave hydrogen peroxide on for 5 min, and then wash off. For oral irrigation, mix 1 part 3% hydrogen peroxide with 2 parts water and use like a mouth wash 3X per day. Most chronic illness patients have periodontal problems, and oral infections and bone cavitation infections are common. These should not be ignored, because they can become systemic and spread to other sites.

## REPLACEMENT OF GUT FLORA

Patients undergoing treatment with antibiotics and other substances risk destruction of normal gut flora. Antibiotic use that depletes normal gut bacteria and can result in over-growth of less desirable bacteria. To supplement bacteria in the gastrointestinal system yogurt and especially live cultures of *Lactobacillus acidophilus* in capsules or powder are strongly recommended. Mixtures of *Lactobacillus acidophilus*, *L. bifidus*, *B. bifidum*, *L. bulgaricus* and FOS (fructooligosaccharides) to promote growth of these probiotics in the gut (example, DDS-1, NutraCeuticals, DDS-Plusor Multi-Flora ABF, UAS Labs, [www.uaslabs.com](http://www.uaslabs.com) Intestinal Care-DF. *L. acidophilus* mixtures (above 2.5-3 billion live organisms) should be taken 3X per day. For irritable bowel, the soil based probiotic, Prescript-Assist [distributed by Researched Nutritionals] has proven to be very effective in clinical trials. In addition, to improve digestion and especially absorption enzyme mixtures have proved useful. The best known of these is Wobenzym.

## NATURAL IMMUNE MODULATORS AND NATURAL REMEDIES

A number of natural remedies, such as ginseng root, herbal teas, lemon/olive drink, olive leaf extract with antioxidants are sometimes useful, especially during or after antibiotic therapy. More important examples are immune modulators, such as bioactive whey protein (ImuPlus, [www.imuplus.com](http://www.imuplus.com); Immunocal, [www.immunocal.com](http://www.immunocal.com)), Transfer Factor (Transfer Factor Multi-Immune, Researched Nutritionals, 800-755-3402 [www.ResearchedNutritionals.com](http://www.ResearchedNutritionals.com)). Some additional remedies are: olive leaf extract (many sources), NSC-100 (Nutritional Supply, Tahitian Noni (Morinda, 800-445-8596, [www.tahitiannoni.com](http://www.tahitiannoni.com)), Laktoferrin (Nutricology, 888-563-1506 or [www.iherb.com](http://www.iherb.com)), Echinacea-C (several sources). These products have been used to boost immune systems. Although they appear to help many patients, their clinical effectiveness in chronic illness patients has not been carefully evaluated. They appear to be useful during therapy to boost the immune system or after antibiotic therapy in a maintenance program to prevent relapse and opportunistic secondary infections.

## LIPID REPLACEMENT THERAPY FOR CHRONIC INFECTIONS AND RESTORING MITOCHONDRIAL FUNCTION

Lipid Replacement Therapy can be useful in providing membrane lipids in unoxidized form to repair nerve membranes and mitochondrial membranes that are damaged by heavy metals, chemicals and infections [16]. For Lyme Disease patients we recommend the oral supplement NT Factor Energy™ (Researched Nutritionals, 800-755-3402 [www.ResearchedNutritionals.com](http://www.ResearchedNutritionals.com)). This product comes as tablets that are taken twice per day. For children it should be ground up between two spoons into a coarse powder that can be added to several spoonfuls of applesauce. The NT Factor is not bitter, but it is slightly sour, and some children actually like the taste. The dose should be 4-6 tablets twice per day. For children 1/2-1 tablet for children up to 2 years-old, 2 tablets for 2-3 years old and 3-4 tablets for 4-5 years-old and 4-5 tablets 5 years-old and older. Research has demonstrated no adverse responses with NT Factor even many times these doses. Since this formulation is a completely natural membrane lipid mixture, there are no known toxicities and no known toxic dose limits.

## YEAST/FUNGAL OVERGROWTH WHILE ON ANTIBIOTICS

Yeast overgrowth can occur, especially in females (vaginal infections) [Please read the report by Dr. Teitelbaum on our website, [www.immed.org](http://www.immed.org)]. Gynecologists recommend Nizoral, Diflucan, Mycelex, or anti-yeast creams. Metronidazole [Flagyl, Prostat] has been used to prevent fungal or parasite overgrowth or other antifungals [Nystatin, Amphotericin B, Fluconazole, Diflucan or Pau d' arco, 7 capsules/2X/day] have been administered for fungal infections that can occur while on antibiotics. Some patients have as their principal problem systemic fungal infections that can be seen using dark field microscopy of blood smears. For superficial fungal infections, such as fungal nail, a topical mixture of Lamisil in 17% DMSO 2X/day is effective. As mentioned above, *L. acidophilus* mixtures are used to restore gut flora. Bacterial overgrowth can also occur, for example, in between cycles of antibiotics or after antibiotics have been stopped. Nutraceutical approaches to controlling yeast infections include: Pau d' arco, grapefruit extract, olive leaf, caprylic acid, garlic extract and oregano oil. Diet is especially important in controlling yeast overgrowth, and the dietary instructions above should be followed, such as the elimination of most simple sugars from the diet [15].

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