

## SUMMARY

## DECISION SUPPORT

## PATIENT EDUCATION/SELF MANAGEMENT

### GOALS

- ✓ Identify patients with signs and symptoms of coccidioidomycosis (“cocci”)
- ✓ Properly diagnose, treat, and monitor cocci patients
- ✓ Know exclusion policy for housing in the cocci hyperendemic area
- ✓ Recognize patients at risk for disseminated coccidioidomycosis

### ALERTS

- ◆ Suspect the disease– Determine exposure history, including moving through prisons in cocci endemic regions
- ◆ Consider TB infection
- ◆ Monitor for symptoms of disseminated disease
- ◆ Respond appropriately to rising cocci titers

- Coccidioidomycosis (Valley Fever or “cocci”) is caused by inhalation of the fungal spores of the genus coccidioides. It is most prevalent in the southwest US, including the southern and central valleys of California. In CDCR, cocci is considered hyperendemic at PVSP, ASP, COR, SATF, CCI, WSP, KVSP, and NKSP, with the highest rates of cocci at PVSP followed by ASP.
- Valley Fever or cocci usually causes a primary pulmonary infection which often resolves without therapy. In some cases a chronic pulmonary infection or, rarely, disseminated disease (extrapulmonary infection) may develop.
- Coccidioidomycosis is not transmitted from person to person so isolation of cases is not necessary.

### DIAGNOSTIC CRITERIA / EVALUATION (SEE PAGES 2, 3 AND 4)

	PRIMARY PULMONARY COCCI	CHRONIC COCCIDIOIDOMYCOSIS	
		Persistent Pulmonary Disease (with or without extrapulmonary findings)	Disseminated (Extrapulmonary) Disease
<b>General</b>	<ul style="list-style-type: none"> <li>◆ Symptoms may be very mild and self limited</li> <li>◆ Less than half of infected patients seek care</li> </ul>	Develops in about 5% of those infected with cocci: <ul style="list-style-type: none"> <li>• Residual pulmonary nodule(s)</li> <li>• Coccidioidal cavities</li> <li>• Pneumonia—fibrocavitary or reticulonodular</li> </ul>	Develops in < 1% of all who acquire cocci infection or in about 5% of those with recognized infections <ul style="list-style-type: none"> <li>✓ May occur at any site, most common:                             <ul style="list-style-type: none"> <li>• Skin or subcutaneous soft tissue</li> <li>• Skeleton (bones or joints)</li> <li>• Meninges, central nervous system</li> </ul> </li> <li>✓ May be rapidly fatal</li> <li>✓ May develop from symptomatic or asymptomatic pulmonary infections</li> <li>✓ May be initial presentation of cocci or manifest later</li> </ul>
<b>Symptoms</b>	Cough, dyspnea, fever, fatigue, night sweats, weight loss, arthralgias, myalgias, headache, chest pain	Patients may have increasing pulmonary involvement with persistent symptoms for months or years	Worsening headaches, bone pain, persistent progressive fatigue, fever, night sweats, new unexplained skin lesions Disease may be progressive in spite of therapy
<b>Exam</b>	Nonspecific. May have signs of pneumonia, fever, erythema nodosum or multiforme	Nonspecific, may have signs of chronic infiltrative pulmonary disease	Weight loss, progressive debility, skin lesions, bone mass or bone pain, neurologic abnormalities, joint pain or swelling, lymphadenopathy
<b>Lab Findings</b>	Possible eosinophilia or increased ESR, positive qualitative cocci serologies	Persistent low level (≤ 1:4) or rising quantitative cocci serology (clinical correlation required)	Elevated Erythrocyte Sedimentation Rate (ESR), rising quantitative serologies, ≥ 1:8 (See page 4)
<b>Diagnostic studies</b>	CXR—Negative or unilateral pneumonic infiltrate or ipsilateral hilar adenopathy	CXR -Progressive interstitial changes, fibrosis, volume loss, inflammation, possible cavitory lesions, including thin walled cavity, or stable nodule	Lumbar puncture—significant antibody titer. Bone scan—suspicious lesion(s) Abnormal CT / MRI Fungal elements identified on biopsy

### TREATMENT OPTIONS (SEE PAGES 6, 7)

**Primary pulmonary cocci:** May not need treatment. Determined on a case by case basis in discussion with the patient, based on risk factors (page 5), illness severity indicators, (page 5) and findings on follow-up of patient’s symptoms, exam, and serology every two to four weeks.

If treated: fluconazole 400 mg daily or itraconazole 200 mg twice daily until titer is stabilized at ≤ 1:4 and asymptomatic.

**Chronic pulmonary and disseminated cocci:** Often requires extended or lifelong antifungal therapy and occasionally surgical interventions. Best co-managed with infectious disease subspecialist familiar with cocci.

### MONITORING (SEE PAGE 6, 7)

In all cases, careful monitoring of the patient’s symptoms and overall condition is necessary as well as monitoring of cocci titers.

*Information contained in the guidelines is not a substitute for a health care professional's clinical judgment. Evaluation and treatment should be tailored to the individual patient and the clinical circumstances. Furthermore, using this information will not guarantee a specific outcome for each patient. Refer to “Disclaimer Regarding Care Guides” for further clarification.*

**COCCIDIOIDOMYCOSIS DIAGNOSIS**

**CLINICAL MANIFESTATIONS OF COCCIDIOIDOMYCOSIS**

**PRIMARY PULMONARY COCCI**

- ◆ Community acquired pneumonia with fever, cough, and fatigue occurring approximately 7 to 21 days after exposure is the most common presentation. Symptoms may persist for weeks to months.
- ◆ Presenting symptoms are usually nonspecific – must consider diagnosis in patients with symptoms of lower respiratory infection (identify risk based on location, time of year, wind/dust exposure, etc.).
- ◆ Illness is often subclinical, less than half of those infected seek medical attention (because they have no symptoms or symptoms are very mild).

<p><b>Common symptoms:</b></p> <ul style="list-style-type: none"> <li>▶ Fever</li> <li>▶ Cough</li> <li>▶ Fatigue</li> <li>▶ Weight loss</li> <li>▶ Night sweats</li> </ul>	<p><b>Other symptoms:</b></p> <ul style="list-style-type: none"> <li>▶ Chest pain</li> <li>▶ Shortness of breath</li> <li>▶ Chills</li> <li>▶ Arthralgias</li> <li>▶ Myalgias</li> </ul>	<ul style="list-style-type: none"> <li>▶ Sputum production</li> <li>▶ Headache (common even without meningitis)</li> <li>▶ Erythema nodosum</li> <li>▶ Erythema multiforme</li> </ul>
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**CHRONIC COCCIDIOIDOMYCOSIS**

- ◆ **PERSISTENT PULMONARY DISEASE** (With or without extrapulmonary findings)
  - Develops in < 5% of those infected with cocci (pulmonary nodule, cavity, chronic pneumonia).
  - Patients may have increasing pulmonary involvement with persistent symptoms or findings for months or years.
  - Chest X-Ray (CXR)—progressive interstitial changes, fibrosis, volume loss, inflammation, possibly cavitory lesions.
  - Prognosis may be worse in elderly and/or diabetics.

PRESENTATION	
<b>Residual pulmonary nodules</b>	<ul style="list-style-type: none"> <li>▶ Occur in about 4% of primary pulmonary cocci patients, usually asymptomatic.</li> <li>▶ May persist for months to years after symptom resolution.</li> <li>▶ May be several centimeters in diameter, often solitary and peripheral.</li> </ul>
<b>Cavitory lesions</b>	<ul style="list-style-type: none"> <li>▶ Occur in 2-8% of cocci pulmonary infections.</li> <li>▶ 50% resolve within two years.</li> <li>▶ Cavities may be thin-walled and stable. Usually asymptomatic, solitary, and peripherally located. Infrequently causes pleural discomfort or hemoptysis.</li> <li>▶ Cavity rupture: rare occurrence. Rupture often forms a bronchopleural fistula with symptoms of dyspnea and chest pain suggesting pneumothorax. On CXR there is commonly an effusion with an air fluid level.</li> <li>▶ Chronic fibrocavitory pneumonia. Usually a failure of resolution of primary pulmonary infection.                             <ul style="list-style-type: none"> <li>• Constitutional symptoms—night sweats, fatigue, weight loss.</li> </ul> </li> </ul>
<b>Diffuse reticulonodular pneumonia</b>	<ul style="list-style-type: none"> <li>▶ Usually arises from diffuse fungemia producing multiple septic emboli.</li> <li>▶ Usually occurs in those with cellular immune deficiency.</li> <li>▶ May occur with high inoculum exposure in immunocompetent patient</li> <li>▶ Symptoms include severe dyspnea and often fever and night sweats for days to weeks.</li> <li>▶ Bronchoalveolar washings positive for fungal organisms.</li> <li>▶ Serologic tests may be negative in up to 1/3 of patients.</li> </ul>

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION/SELF MANAGEMENT
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**COCCIDIOIDOMYCOSIS DIAGNOSIS**

**CLINICAL MANIFESTATIONS OF COCCIDIOIDOMYCOSIS (CONTINUED)**

**CHRONIC COCCIDIOIDOMYCOSIS (continued)**

- ◆ **DISSEMINATED COCCIDIOIDOMYCOSIS** (Spread from the initial pulmonary lesion to other parts of the body)
  - Approximately 1% of coccidioides infections disseminate (may develop from symptomatic or asymptomatic pulmonary infections).
  - The skin is the most common site of dissemination.
  - Other common sites are subcutaneous soft tissue, bones, joints, and meninges/central nervous system.
  - May be rapidly fatal.
  - Disseminated disease may be the initial presentation or manifest later (within weeks or more than two years after initial cocci diagnosis or with reactivation of previously treated cocci).

<b>DISSEMINATED COCCI SYMPTOMS</b>	
<b>Symptoms suggesting dissemination</b>	<ul style="list-style-type: none"> <li>• Fatigue, fever, weight loss, night sweats in a previously exposed or infected individual.</li> <li>• Persistent or worsening symptoms despite therapy.</li> </ul>
<b>Skin or soft tissue disease</b> <ul style="list-style-type: none"> <li>• Most common site of dissemination.</li> <li>• Many patients with dissemination to skin and soft tissue have other extrapulmonary sites of infection.</li> </ul>	<ul style="list-style-type: none"> <li>• New unexplained skin lesion, especially a verrucous granuloma at nasolabial fold or other granulomatous papule, nodule, plaque, especially on the head.</li> </ul>
<b>Bone or joint disease</b>	<ul style="list-style-type: none"> <li>• Bone pain or mass</li> <li>• Arthritis, usually monoarticular, knee most common site</li> <li>• Back pain with/without neurologic symptoms (vertebral disease, single or multiple sites)</li> <li>• Abnormal x-ray or bone scan</li> </ul>
<b>Meningeal or CNS disease</b> <ul style="list-style-type: none"> <li>• Cocci meningitis is usually chronic with insidious onset.</li> </ul>	<ul style="list-style-type: none"> <li>• Headaches:                             <ul style="list-style-type: none"> <li>* Worsening</li> <li>* Unusually severe</li> <li>* Change in pattern of existing headache disorder</li> </ul> </li> <li>• Fever</li> <li>• Blurred vision</li> <li>• Signs of meningeal irritation</li> <li>• Cognitive impairment or changes in mental status</li> <li>• Gait abnormalities</li> <li>• Focal neurologic deficits</li> <li>• Lumbosacral back pain (if lumbar meninges affected)</li> </ul>
<b>Other sites:</b> Endocrine glands, eye, liver, kidneys, genital organs, prostate, peritoneal cavity, others.	<ul style="list-style-type: none"> <li>• Symptoms in these tissues are not specific, often consistent with unspecified infection in these organs.</li> </ul>

SUMMARY		DECISION SUPPORT	PATIENT EDUCATION/SELF MANAGEMENT
<b>DIAGNOSTIC EVALUATION</b>			
<ul style="list-style-type: none"> <li>◆ Consider the diagnosis – essential first step in detecting most infections (based on exposure history and symptoms).</li> <li>◆ Skin Testing- useful to screen for prior disease, not useful to diagnose new infection (unless new conversion from negative to positive). Not routinely available yet.</li> <li>◆ Laboratory studies.</li> </ul>			
<b>LABORATORY STUDIES</b>		<b>RESULTS</b>	
Routine labs (CBC, CMP)		<ul style="list-style-type: none"> <li>• Usually normal</li> <li>• Eosinophilia &gt; 5% occurs in up to 25% of cases</li> </ul>	
Erythrocyte Sedimentation Rate (ESR)		<ul style="list-style-type: none"> <li>• Up to twice normal in most cases</li> </ul>	
Qualitative Serology (usually immunodiffusion) immunoglobulin M (IgM) or immunoglobulin (IgG)  [Enzyme immunoassay (EIA) may be used by some labs but may require confirmation by other test]		<ul style="list-style-type: none"> <li>• Reported as positive or negative</li> <li>• Recommended as initial test for presence of IgM and/or IgG to determine acuity (new vs. prior disease)</li> <li>• IgM usually detected one to three weeks after symptom onset (early or acute cocci), will persist three to four months. IgM detected with heat stable (TP) antigen. IgG detected with heat labile antigen, sometimes referred to as F antigen.</li> <li>• <b>IgG can persist for up to 2 years following clinical recovery or for many years in disseminated or chronic pulmonary disease.</b></li> <li>• If antibody initially undetectable but high index of suspicion, repeat test in one to two weeks</li> </ul>	
Quantitative Serology: complement fixation (CF) immunoglobulin (IgG) (Under some circumstances, quantitative immunodiffusion must be used to obtain a titer.)		<ul style="list-style-type: none"> <li>• Reported as a titer</li> <li>• Used to monitor treatment, the course of disease, and prognosis</li> <li>• May be low or undetectable in mild disease or in immunosuppressed patients</li> <li>• CF IgG usually positive within three months of infection</li> <li>• Remains detectable six to eight months or longer</li> <li>• Resolves as infection clears, desirable endpoint is usually titer 1:2, 1:4 or undetectable. (Titer may never revert to undetectable)</li> <li>• Persistence of titer &gt; 1:4 may indicate active infection including dissemination.</li> <li>• Titer of CF IgG antibodies should be performed at initial diagnosis, repeated at least once two to four weeks after the initial diagnosis, then at least every three months until titers drop to 1:4 or less</li> </ul>	
Histopathology		<ul style="list-style-type: none"> <li>• Stains for fungal elements from biopsies of suspicious lesions or sputum are helpful in diagnosis</li> </ul>	
Culture		<ul style="list-style-type: none"> <li>• Isolation of cocci in tissue, wound, or sputum</li> </ul>	
Polymerase Chain Reaction (PCR)		<ul style="list-style-type: none"> <li>• Very sensitive and specific, not routinely available yet</li> </ul>	
Lumbar puncture		<ul style="list-style-type: none"> <li>• Coccidioidal (IgM or IgG antibody detected in CSF is often associated with cocci meningitis but may be present when there is a juxtadural lesion (e.g. vertebral abscess) or when CF titer is high in the serum. IgM is infrequent in the CSF but it is associated with meningitis. Serologic results in lumbar CSF may differ from those in ventricular CSF</li> </ul>	
<b>DIAGNOSTIC IMAGING</b>			
Chest X-ray (CXR)	<ul style="list-style-type: none"> <li>▶ Recommended for patient diagnosed with or considered at high risk for cocci</li> <li>▶ PA and lateral views are normal in 50% of patients</li> <li>▶ May show a unilateral infiltrate or ipsilateral hilar adenopathy</li> <li>▶ Useful to document pulmonary lesions due to cocci. In 4-8% of cases the CXR has cavities or nodules</li> <li>▶ Useful to monitor course of disease</li> </ul>		
Bone scan	<ul style="list-style-type: none"> <li>▶ Useful to diagnose bone or joint involvement in those with skeletal pain or to screen for skeletal involvement in asymptomatic patients with persistent or rising cocci titers.</li> </ul>		
CT scan brain	<ul style="list-style-type: none"> <li>▶ Identify complications of CNS disease (hydrocephalus, abscess, focal lesion)</li> </ul>		
MRI with gadolinium	<ul style="list-style-type: none"> <li>▶ More sensitive than CT to assess meningeal or vasculitic complications</li> <li>▶ Baseline MRI desirable to determine extent of disease and for comparison during the course of illness</li> <li>▶ Also useful to identify and evaluate spinal arachnoiditis</li> </ul>		

## TREATMENT CONSIDERATIONS

**ILLNESS SEVERITY INDICATORS**

- ▶ Loss of > 10% body weight
- ▶ Night sweats > 3 weeks
- ▶ Infiltrates involving more than half of one lung or portions of both lungs
- ▶ Prominent or persistent hilar adenopathy
- ▶ Symptoms persisting > 2 months
- ▶ Complement fixing antibody concentrations  $\geq$  1:16
- ▶ Inability to work due to symptoms

**RISK FACTORS FOR DEVELOPMENT OF SEVERE OR DISSEMINATED DISEASE**

- ▶ Immunocompromised\*
- ▶ African-American or Filipino
- ▶ Diabetes
- ▶ Pregnancy

\*Immunocompromised includes:

- Patients with HIV infection
- Those on immunosuppressive agents such as anti-tumor necrosis factor (TNF) or glucocorticoids ( $\geq$  15 mg per day of prednisone or equivalent) for one month or more
- Lymphoma patients
- Solid organ transplant recipients

**References**

- Primary Coccidioidal Infections. UpToDate May 2012
- An Official American Thoracic Society Statement: Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients  
Andrew H. Limper, Kenneth S. Knox, George A. Sarosi, Neil M. Ampel, John E. Bennett, Antonio Catanzaro, Scott F. Davies, William E. Dismukes, Chadi A. Hage, Kieren A. Marr, Christopher H. Mody, John R. Perfect, and David A. Stevens, on behalf of the American Thoracic Society Fungal Working Group. *Am J Respir Crit Care Med* Vol 183. pp 96–128, 2011 DOI: 10.1164/rccm.2008-740ST Internet address: [www.atsjournals.org](http://www.atsjournals.org)
- New Perspectives on Coccidioidomycosis; Neil M. Ampel, *American Thoracic Society* Vol 7. pp181-185, 2010
- Coccidioidomycosis; John N. Galgiani, Neil M. Ampel, Janis E. Blair, Antonio Catanzaro, Royce H. Johnson, David A Stevens and Paul L. Williams, *Clinical Infectious Diseases* 2005; 41:1217-23

SUMMARY

DECISION SUPPORT

PATIENT EDUCATION/SELF MANAGEMENT

## MANAGEMENT OF COCCIDIOIDOMYCOSIS

### PRIMARY PULMONARY COCCI

- ▶ Community recommendations are that otherwise healthy patients without evidence of extensive coccidioidal infection or risk factors for more serious infection do not need antifungal therapy, including patients with pulmonary nodules or cavities that are asymptomatic and stable.
- ▶ In the CDCR, clinicians should consider management options including observation and monitoring without treatment and the risks and benefits of treatment vs. no treatment. Factors to review when considering therapy include: severity of illness, risk factors for severe disease, and risk factors for dissemination. (See page 5)
- ▶ Oral antifungal agents are the customary initial drug of choice within CCHCS when treatment is indicated. If treated, the first choice is the formulary agent fluconazole 400 mg once daily, the alternative formulary agent is itraconazole 200 mg orally twice daily.
- ▶ Duration of therapy for uncomplicated primary coccidioidal infection generally ranges from three to six months to one year or longer. There is no consensus regarding which factors should guide decisions about the duration of therapy and each case must be decided individually based on severity and extent of disease and response to therapy (when treatment is given). Useful indicators include a significant drop in CF titer and/or resolution of hilar adenopathy.
- ▶ Follow-up once or twice per month until the patient stabilizes and immunoglobulin titer is decreasing, then every one to three months for six months to one to two years or more, regardless of whether or not treatment is initiated.
- ▶ Treat with oral antifungal agent until symptoms resolve and titers fall and are persistently  $\leq 1:2$ .
- ▶ Progression of disease during treatment requires reevaluation of antifungal regimen and dose increase, change to another oral antifungal agent, or change to parenteral amphotericin B. If actual tissue destruction occurs, may need to reassess for consideration of surgical intervention. Consider testing for genetic mutation.

Monitor during treatment for:	Monitor after apparent symptom resolution (symptoms cleared and titer undetected or $\leq 1:4$ )
<ul style="list-style-type: none"> <li>▶ Improvement or progression of symptoms including night sweats, weight loss, cough, pain.</li> <li>▶ Signs of dissemination including persistence of symptoms, headache, bone pain, new skin lesions, increasing titers.</li> <li>▶ Fall in titer, increase in titer or titer failing to drop.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Pertinent symptom review and examination.</li> <li>▶ If titers do not normalize, but fall to 1:4 or less and remain stable with monthly reevaluation for at least three months, may increase monitoring interval. Consider discontinuing monitoring if asymptomatic and titers remain stable at 1:4 or less after at least three months off treatment.</li> <li>▶ Patients whose titers remain <math>\geq 1:8</math> require ongoing periodic monitoring of symptoms and titers.</li> </ul>

### CHRONIC COCCIDIOIDOMYCOSIS

#### PERSISTENT PULMONARY DISEASE

- ▶ Monitor for evidence of dissemination (worsening symptoms or new symptoms suggesting dissemination, increase in cocci titer)
- ▶ Monitor CXR when indicated

<b>Residual pulmonary nodules</b>	<ul style="list-style-type: none"> <li>▶ If nodule known to be result of cocci infection, usually asymptomatic and no treatment indicated</li> <li>▶ If found incidentally, may require invasive diagnostic test to rule out malignancy.</li> <li>▶ Radiologic abnormalities must be followed to establish resolution or stabilization of residua such as nodules or cavities. Pulmonary lesions which are documented to develop into stable residual nodules need not be investigated in the future.</li> </ul>
<b>Cavitary lesions</b>	<p><b>Thin-walled</b></p> <ul style="list-style-type: none"> <li>▶ Usually asymptomatic and no treatment indicated. May change appearance, monitoring CXR at six month to two year intervals is useful to assess increase or decrease in size.</li> <li>▶ When present, symptoms often improve with oral antifungals but may return if treatment is discontinued.</li> <li>▶ Very rarely surgical resection may be considered in a young patient with recurrent symptoms after long trial of oral antifungals.</li> </ul> <p><b>Ruptured Cavity</b></p> <ul style="list-style-type: none"> <li>▶ Surgery required</li> </ul> <p><b>Fibrocavitary pneumonia</b></p> <ul style="list-style-type: none"> <li>▶ Usually require treatment with oral antifungal agents for at least one year</li> </ul>
<b>Diffuse reticulonodular pneumonia</b>	<ul style="list-style-type: none"> <li>▶ Initial treatment usually IV amphotericin B. May require extended course of therapy with either oral or parenteral antifungal medication. Monitor CF IgG titer as well as response to therapy to determine medication used and dosage as well as duration of therapy.</li> <li>▶ After clinical improvement, may change to oral antifungal agent for at least one year</li> <li>▶ Indefinite treatment indicated for immunocompromised patients</li> </ul>

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION/SELF MANAGEMENT
<b>MANAGEMENT OF COCCIDIOIDOMYCOSIS</b>		
<b>CHRONIC COCCIDIOIDOMYCOSIS (continued)</b>		
<b>DISSEMINATED COCCIDIOIDOMYCOSIS</b>		
<b>General</b>	<ul style="list-style-type: none"> <li>• Consider consultation for disseminated cocci.</li> <li>• To determine medication used, dosage, and duration of therapy, monitor symptomatic response and CF IgG titer initially and at least monthly for:               <ul style="list-style-type: none"> <li>• improvement</li> <li>• failure to improve</li> <li>• worsening</li> </ul> </li> <li>• With improvement, monitoring interval can be lengthened.</li> <li>• Often requires extended course or lifetime therapy with either oral or parenteral antifungal medication (The current agents are fungistatic not fungicidal). Best co-managed with infectious disease consultant familiar with coccidioidomycosis.</li> </ul>	
<b>Skin or soft tissue</b>	<ul style="list-style-type: none"> <li>• Treat with oral antifungal agent:               <ul style="list-style-type: none"> <li>• Oral fluconazole 400 mg once daily or itraconazole 200 mg twice daily until resolution of skin lesions and disappearance or fall in cocci titer to persistently &lt; 1:4</li> <li>• Duration of treatment determined by resolution of lesions, a minimum of 1 year of therapy is recommended in most cases.</li> </ul> </li> <li>• Surgical intervention may be required.</li> <li>• Skin and soft tissue infection may be associated with disseminated disease elsewhere (especially bones and joints).</li> <li>• Evaluation for other foci of infection (which may be asymptomatic) is indicated if cocci titers rise or do not improve or if symptoms persist.</li> </ul>	
<b>Bone or joint (outside the spine)</b>	<ul style="list-style-type: none"> <li>• Duration and type of therapy of symptomatic bone disease outside the spine depends upon many factors. Consultation advised</li> <li>• Oral antifungal agent for at least one year or as indicated by response to therapy is recommended.</li> <li>• Lifelong therapy may be required.</li> <li>• May require surgical treatment.</li> </ul>	
<b>Vertebral Disease</b>	<ul style="list-style-type: none"> <li>• Vertebral cocci is a very complex condition which requires evaluation and management by infectious disease and neurosurgical consultants very familiar with this complication.</li> <li>• Treatment depends on extent of disease, stability of vertebral bodies, risk to spinal cord, and response to therapy.</li> <li>• Initial therapy is usually oral azole antifungal agent, fluconazole or itraconazole 400 mg/day or more. Amphotericin B is alternative therapy, especially for lesions that are progressive or in critical locations such as the vertebral column.</li> <li>• Without cord compression or vertebral instability, medical treatment alone may be indicated with close monitoring of neurologic examination and repeat MRI (within one to two months).</li> <li>• May continue medical management with stable or improved lesions.</li> <li>• For progressive lesions, surgical debridement or stabilization may be important and even critical adjunctive treatment. Evidence of spinal cord impingement usually requires immediate surgical decompression.</li> </ul>	
<b>Meninges / CNS</b>	<ul style="list-style-type: none"> <li>• <b>Consultation with a specialist is indicated for all cases of CNS cocci.</b></li> <li>• Generally requires lifelong therapy, oral agents are the preferred initial therapy. In some cases intrathecal amphotericin is initial therapy, in other cases it is reserved for those who do not respond to oral antifungal agents, when it may be given alone or concurrently with azole treatment.</li> <li>• Initially fluconazole 600-1000 mg/day, if response not adequate change to voriconazole 200 mg orally twice daily or 4 mg/kg IV every 12 hours or intrathecal amphotericin B.</li> <li>• Monitor clinical and CNS parameters at least monthly, increase space of visits with improvement, minimum of every three months for life.</li> <li>• Symptoms to monitor include headache, nausea and vomiting, personality changes, gait abnormalities, other focal neurologic findings.</li> <li>• Significant adherence problems are common with this lifelong treatment. Patients must understand that therapy will be lifelong because relapses upon discontinuation are common and potentially fatal.</li> <li>• There may be additional significant complications from shunt placement if amphotericin B must be used.</li> <li>• A decrease in titer usually reflects improvement, and an increase in titer suggests poorly controlled disease.</li> </ul>	
<b>Other</b>	<ul style="list-style-type: none"> <li>• Management of cocci in other sites is variable and consultation with a cocci specialist is recommended.</li> </ul>	

## SUMMARY

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## MEDICATIONS

## ORAL ANTIFUNGALS GENERAL COMMENTS

- ▶ Azole antifungals have many significant drug interactions. Consult prescribing information for complete list.
- ▶ Several of the azoles have black box warnings, consult product labeling or [www.fda.gov](http://www.fda.gov) for full text of these warnings.
- ▶ Serious/fatal hepatotoxicity has occurred with azoles.
- ▶ Preferred oral antifungals for coccidioidal infection are fluconazole and itraconazole. Preferred nonformulary agent is voriconazole.

MEDICATION	DOSING	SIDE EFFECTS*	COMMENTS
<b>Fluconazole (Diflucan®)</b>  Tablets: 50 mg, 100 mg, 150 mg, 200 mg Oral Suspension 10 mg/ml, 40 mg/ml IV: 100 mg, 200 mg, 400 mg strengths \$ <b>Covered Strength</b>	Uncomplicated primary pulmonary cocci: 400 mg orally once daily for three to six months or longer  Complicated or severe disease: 400 to 800 mg once daily orally or IV, some use 1000 mg/day initially for cocci meningitis  Take without regard to meals	Very high potential for drug interactions. Consult package information for full list.  Skin reactions, occasional dizziness or seizures, rare, serious or fatal hepatotoxicity  Contraindicated to coadminister with drugs that prolong QT interval (citalopram, methadone, quinidine, etc.)	Use with caution in liver disease  Dose adjustment may be needed in renal disease  Avoid use in pregnancy. Category D: positive evidence of risk, for all indications except single dose for vaginal candidiasis  Avoid with breastfeeding
<b>Itraconazole (Sporanox®)</b>  200 mg capsule  \$\$ <b>Covered Strength</b>	200 mg twice daily: for mild or uncomplicated disease  400-600 mg/day in two to three divided doses for more severe disease (fluconazole preferred for cocci meningitis)  Take capsule with food	Do not use with antacids  Use with caution with calcium channel blockers (increases negative inotropic effect of CCBs)  Transient or permanent hearing loss, neuropathy, rare cases of serious or fatal hepatotoxicity  <b>Black box warning:</b> Serious cardiovascular events including sudden death have occurred due to itraconazole induced increase in serum concentrations of cisapride, dofetilide, ergot alkaloids, felodipine, levomethadyl, lovastatin, methadone, midazolam, nisoldipine, pimozone, simvastatin, quinidine, triazolam. Concurrent use with these agents is contraindicated.  <b>Black box warning:</b> Contraindicated for onychomycosis in patients with ventricular dysfunction or history of heart failure.	May be more effective for skin, soft tissue, and bone disease than fluconazole  Monitor liver function in patients with preexisting liver disease and in those treated for > 1 month  Possibly monitor serum levels due to erratic bioavailability of capsules.  Use with caution in renal disease, limited information  Pregnancy: Category C, risk cannot be ruled out  Avoid with breastfeeding
<b>Voriconazole (Vfend®)</b>  50 mg, 200 mg tablets Oral suspension 40 mg/ml Injection 200 mg  \$\$\$\$ <b>Nonformulary</b>	Oral: 200 mg twice daily, max dose 600 mg/day  IV: 4-6 mg/kg twice daily  Give oral dose one hour before or one hour after a meal	CNS side effects including hallucinations, ocular effects (dose related) including photophobia, increased or decreased visual acuity, blurred vision  May increase creatinine  QT interval prolongation has occurred, arrhythmia, cardiac arrest, and sudden death have been reported  Severe exfoliative cutaneous reactions, including Stevens-Johnson have been reported. Patients should avoid strong direct sunlight exposure	Avoid use of IV dosage form in renal failure  Use with caution in severe hepatic disease, reduce maintenance dose 50% in Child-Pugh class A and B  Pregnancy: Category D, positive evidence of risk  Lactation: use not recommended
<b>Posaconazole (Noxafil®)</b>  Oral suspension 40 mg/ml  \$\$\$\$ <b>Nonformulary</b>	400 mg twice daily  Shake well before use  Give with food for best absorption	GI: diarrhea, nausea, vomiting, abdominal pain, constipation, headache, thrombocytopenia, anemia, neutropenia, hypokalemia, other electrolyte disturbances, cough, dyspnea, fever. Consult prescribing information for full list.  Many significant drug interactions. Posaconazole increases levels of some antipsychotics, benzodiazepines, CCBs, phenytoin, digoxin, etc.  Contraindicated to give with quinidine, cisapride, pimozone, others due to QT prolongation, possible torsades de pointes may occur Caution with cyclosporin and tacrolimus, do not give concurrently with sirolimus.  Do not administer with erythromycin, tamsulosin, ergots,	Monitor LFTs prior to and during therapy for evidence of severe hepatic injury  No adjustment for mild-moderate renal impairment  For Clcr < 20 ml/min, levels are highly variable  Pregnancy: Category C, risk cannot be ruled out  Use in lactation: probably excreted in breast milk

\*Side effect list is not all inclusive



## SUMMARY

## DECISION SUPPORT

## PATIENT EDUCATION/SELF MANAGEMENT

**AMPHOTERICIN B GENERAL REMARKS**

- ▶ Conventional amphotericin B may be given intravenously (IV) or intrathecally (IT). This agent is preferred due to cost.
- ▶ Lipid based products are better tolerated and cause less nephrotoxicity than conventional amphotericin B and they may be indicated when side effects of conventional amphotericin B are severe or dose limiting, there is significant risk of renal toxicity, patient is intolerant to conventional amphotericin, or the infection progresses despite adequate therapy with conventional amphotericin B.
- ▶ Lipid based formulations are much more expensive (approx \$400/day vs. \$10/day).
- ▶ Conventional and lipid based agents generally have equal efficacy.

MEDICATION	DOSING	SIDE EFFECTS *	COMMENTS
<b>amphotericin B (conventional)</b> <b>Fungizone®</b> <b>Amphocin®</b>  50 mg/vial  \$  Covered Strength	IV: 0.3-1.5 mg/kg/day over four to six hours every other day, not > 1.5mg/kg/day  Intrathecal (IT): For cocci meningitis: IT administration once daily. Low initial dose, gradual increase to maximum tolerated dose (up to 1.5 mg/day). With improvement, dose frequency gradually reduced. Usually given with concurrent oral azole therapy. If therapy is interrupted > 7 days, restart at lowest recommended dose and gradually increase.	Infusion reactions: chills, fever, hypotension, nausea, vomiting, anorexia, headache, tachypnea.  Nephrotoxicity—may be reduced with infusion of normal saline bolus before and after infusion. Risk of nephrotoxicity increases with doses > 1 mg/kg/day or large cumulative doses, especially > 5 gm. Risk also increased with concomitant nephrotoxic drugs or underlying renal disease.  Other side effects: edema, hypotension, rash, pruritus, hypokalemia, other electrolyte disturbances, LFT increases, dyspnea.  Risk of medication errors when conventional amphotericin doses confused with dosing of lipid based amphotericin formulations. Large overdoses have occurred when conventional amphotericin was inadvertently dispensed for lipid-based products. Single daily dose of conventional amphotericin B never exceeds 1.5 mg/kg.	Premedicate with NSAID +/- diphenhydramine, OR acetaminophen with diphenhydramine, or hydrocortisone 30-60 minutes prior to administration to patients who have chills, fever, hypotension, nausea, etc with infusions. May give meperidine if rigors occur during infusion.  Use with caution in renal impairment.  Monitor renal function, electrolytes, LFTs, coagulation parameters, CBC.  Pregnancy: Category B: No evidence of risk, recommended for treatment of serious fungal infections in pregnancy.  Lactation: Not recommended.  Do not use for noninvasive fungal infections.
<b>AmBisome® (liposomal amphotericin B [L-AmB])</b>  50 mg/vial  \$\$\$\$\$\$  Nonformulary	IV: usual dose for systemic fungal infection: 3-6 mg/kg/day given over about two hours	Nephrotoxicity (less than with conventional amphotericin B).  Other side effects: edema, hypotension, rash, pruritus, hypokalemia, other electrolyte disturbances, LFT increases, dyspnea.  Risk of medication errors when conventional amphotericin doses confused with dosing of lipid based amphotericin formulations. Large overdoses have occurred when conventional amphotericin was inadvertently dispensed for lipid-based products. Single daily dose of conventional amphotericin B never exceeds 1.5 mg/kg.	Premedicate with NSAID +/- diphenhydramine, OR acetaminophen with diphenhydramine, or hydrocortisone 30-60 minutes prior to administration to patients who have chills, fever, hypotension, nausea, etc with infusions. May give meperidine if rigors occur during infusion.  Monitor renal function, electrolytes, LFTs, coagulation parameters, CBC.  Pregnancy: Category B: No evidence of risk, recommended for treatment of serious fungal infections in pregnancy.  Lactation: Not recommended.
<b>Abelcet® (amphotericin B-lipid complex [ABLCL])</b>  5 mg/ml 20 ml vial  \$\$\$\$\$\$  Nonformulary	IV: Usual dose 5 mg/kg once daily rate of 2.5 mg/kg/hour.  Progressive disseminated cocci: 2-5 mg/kg/day  HIV positive with severe nonmeningeal infection: 4-6 mg/kg/day until clinical improvement then switch to oral fluconazole or itraconazole.	Nephrotoxicity, infusion reactions.  Other side effects: edema, pruritus, hypotension, rash, hypokalemia, other electrolyte disturbances, LFT increases, dyspnea.  Risk of medication errors when conventional amphotericin doses confused with dosing of lipid based amphotericin formulations. Large overdoses have occurred when conventional amphotericin was inadvertently dispensed for lipid-based products. Single daily dose of conventional amphotericin never exceeds 1.5 mg/kg.  [Lower cost than AmBisome®, higher incidence of nephrotoxicity and infusion related side effects.]	Premedicate with NSAID +/- diphenhydramine, OR acetaminophen with diphenhydramine, or hydrocortisone 30-60 minutes prior to administration to patients who have chills, fever, hypotension, nausea, etc with infusions. May give meperidine if rigors occur during infusion.  Monitor renal function, electrolytes, LFTs, coagulation parameters, CBC.  Pregnancy: Category B: No evidence of risk, recommended for treatment of serious fungal infections in pregnancy.  Lactation: Not recommended.

Amphotericin B (conventional): Drug information. Lexicomp, 2012, UpToDate  
 Liposomal Amphotericin B: Drug Information. Lexicomp, 2012, UpToDate  
 Amphotericin B lipid complex: Drug Information. Lexicomp, 2012, UpToDate

\*Side effect list is not all inclusive

## PATIENT EDUCATION



### COCCIDIOIDOMYCOSIS (VALLEY FEVER): WHAT YOU SHOULD KNOW

#### WHAT IS VALLEY FEVER?

- ◆ Valley Fever is a disease caused by a fungus found in the ground in parts of Mexico and the Southwest region of the United States, including parts of California's Central Valley.
- ◆ You get sick from breathing in the fungus spores from the dust in the air. You cannot get Valley Fever from another person.
- ◆ There are eight CDCR prisons where the fungus is more common:  
PVSP    ASP    KVSP    NKSP    WSP    SATF    COR    CCI

#### WHAT ARE THE SYMPTOMS OF VALLEY FEVER?

- ◆ Most people who have Valley Fever have very few symptoms and may not know they are sick.
- ◆ Common symptoms of Valley Fever are:
  - Fever
  - Cough
  - Tiredness
  - Headaches
  - Rash
  - Joint/muscle aches
  - Night sweats
  - Weight loss/lack of appetite
  - Pneumonia
- ◆ **You could have Valley Fever even if you have only a few of these symptoms.**
- ◆ Let your health care provider know if you have any of these symptoms. You may need lab tests or x-rays if your health care provider thinks you may have Valley Fever.
- ◆ If a person gets very sick, the fungus can spread to other parts of the body causing skin rashes, bone pain, and sometimes infections in the brain.



#### WHAT IS THE TREATMENT FOR VALLEY FEVER?

- ◆ If you are normally healthy, Valley Fever will usually go away without any treatment
- ◆ You may be treated with antifungal medication if you have symptoms that do not go away
- ◆ Patients with serious infections may need to be put in the hospital for treatment
- ◆ Sometimes treatment is needed for a very long time for some Valley Fever infections

#### WHO CAN GET VALLEY FEVER?

- ◆ Anyone who lives, visits, or travels in areas where the fungus grows can get Valley Fever. **Tell your health care provider if you have lived in an area or been in a prison where Valley Fever occurs.**
- ◆ People who have certain other diseases are more likely to have serious symptoms of Valley Fever. If you have any of the conditions listed below, you should talk to your health care provider to discuss your risk of getting very sick from Valley Fever.
  - HIV
  - Lymphoma
  - Organ transplant
  - Cancer or are on chemotherapy
  - Medications that make your body less able to fight disease, such as steroids
  - You require oxygen therapy

#### HOW DO I KEEP FROM GETTING VALLEY FEVER?

- ◆ If you are in an area where there is Valley Fever:
  - ◆ Minimize your exposure to dust in the air.
  - ◆ On windy days, stay indoors. If you must go outside, cover your nose and mouth with a mask.
  - ◆ Before digging in the ground, get the dirt wet and use a mask

