

Cryptococcus gattii

Signs and Symptoms	<ul style="list-style-type: none"> Symptoms depend on affected body system; typically pneumonia (cough, shortness of breath, chest pain, fever) and/or meningitis (headache, fever, neck pain, nausea and vomiting, sensitivity to light, altered mental status). May be asymptomatic. Cryptococcomas in the lungs, skin, brain, or other organs.
Incubation	Not well-established; average 6-7 months (range 2-13 months), potentially years.
Case classification	<p>Clinical criteria: None required</p> <p>Confirmed: A case with any of the following from a clinical specimen: isolation of <i>C. gattii</i>; detection of <i>C. gattii</i>-specific nucleic acid; demonstration of <i>C. gattii</i> by immunohistochemistry; MALDI-TOF result specific for <i>C. gattii</i></p>
Differential diagnosis	Coccidioidomycosis, histoplasmosis, blastomycosis, other fungal infections, viral or bacterial causes of pneumonia or meningitis
Treatment	Appropriate antifungal, generally fluconazole for asymptomatic to moderate pulmonary infections or amphotericin B and flucytosine for severe lung infections or CNS infections. Case fatality rate in published literature ranges from 13-33%.
Duration	Can cause long-term infection; treatment needs to be continued for at least 6 months. Some people may require surgery to remove cryptococcomas.
Exposure	Inhalation of fungal spores from the environment in endemic regions. No person-to-person or animal-to-person transmission.
Laboratory testing	<p>Local Health Jurisdiction (LHJ) and Communicable Disease Epidemiology (CDE) arrange testing for individual cases and environmental testing for suspected outbreaks.</p> <p>Isolates should be submitted for speciation.</p> <ul style="list-style-type: none"> Washington State Public Health Laboratories can facilitate testing at CDC Best specimens: Fungal isolate. Testing can be arranged for serum or cerebrospinal fluid (CSF), although tests on these specimens do not differentiate <i>C. gattii</i> from other <i>Cryptococcus</i> species <p><i>Specimen shipping (Section 4):</i></p> <ul style="list-style-type: none"> Isolates must be submitted on a slant with a screw top. Petri dishes and paraffin blocks are not acceptable. Keep isolate (slants) at room temperature, clinical specimens cold, ship with Microbiology form https://www.medialab.com/dv/dl.aspx?d=1887088&dh=52b1a&u=69790&uh=0e2a1 Specimen Collection and Submission Instructions: https://www.cdc.gov/fungal/lab_submission.html
Public health actions	<p>Report cases to CDE.</p> <ul style="list-style-type: none"> Identify immunocompromising conditions (HIV infection, organ transplantation, malignancy, or other immune system alteration) that might affect treatment decisions Identify likely region of exposure, particularly if within Washington State Notify local environmental health program of locally acquired cases <p><i>Infection Control:</i> Standard precautions.</p>

Cryptococcus gattii

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To track the emergence of *Cryptococcus gattii* in Washington.
2. To improve the number of suspected cases that are laboratory confirmed.
3. To monitor trends in the epidemiology of cryptococcal disease due to *C. gattii*.

B. Legal Laboratory Reporting Requirements

1. **Health care providers and Health care facilities:** *C. gattii* infections notifiable to **local health jurisdiction** within 3 business days.
2. **Laboratories:** *Cryptococcus gattii* or undifferentiated *Cryptococcus* species (i.e., *Cryptococcus* not identified as *C. neoformans*) positive result by any method excluding cryptococcal antigen notifiable to **local health jurisdiction** within 2 business days; specimen submission required – isolate or if no isolate specimen (except serum) associated with positive result, within 2 business days; submission on request – serum within 2 business days.
3. **Veterinarians:** animal cases notifiable to Washington State Department of Agriculture <https://app.leg.wa.gov/WAC/default.aspx?cite=16-70>
4. **Local health jurisdictions:** notifiable to the Washington State Department of Health (DOH) Office of Communicable Disease Epidemiology (CDE) within 7 days of case investigation completion or summary information required within 21 days.

C. Local Health Jurisdiction Investigation Responsibilities

1. Identify potential travel-related or local exposures.
2. When possible, request medical records for completion of supplemental CDC case report form. (Note: CDE will assist in completing the supplemental form).
3. Facilitate transport of specimens to the Washington State Public Health Laboratories (PHL). Please call CDE prior to submitting specimens (206-418-5500 or 877-539-4344).
4. Report all *confirmed* cases to CDE (see definition below). Complete the cryptococcal report form <https://www.doh.wa.gov/Portals/1/Documents/5100/420-011-ReportForm-Cgattii.pdf> and enter the data into the Washington Disease Reporting System (WDRS).

2. THE DISEASE AND ITS EPIDEMIOLOGY

Background

Cryptococcus gattii is an environmental fungus previously known to occur in tropical or subtropical area associated with eucalyptus. *C. gattii* was recognized as a pathogen in the Pacific Northwest with animal and human cases during a 1999 outbreak on Vancouver Island (VI), British Columbia (BC), Canada. The fungus was found in environmental samples from VI, mainland BC, Washington, and Oregon. Disease occurs in humans and domestic and wild animals (dogs, cats, ferrets, horses, llamas, porpoises, pet birds).

A. Etiologic Agent

Cryptococcus species are saprophytic, encapsulated yeast. They are Gram positive and have a spheroid or ovoid shape. There are many species of *Cryptococcus*, but *C. neoformans* (varieties *neoformans* and *grubii*) and *C. gattii* are the primary human pathogens of this genus, causing nearly all cryptococcal infections. *C. neoformans* typically infects immunocompromised individuals; a study published by CDC indicates that, among persons with HIV/AIDS, the prevalence of cryptococcal antigen positivity was about 3%. *C. gattii* is less prevalent than *C. neoformans* and can cause infection in both immunocompromised and immunocompetent people, but disease may be more likely in people who are immunocompromised, have other lung conditions, are over 50, or smoke tobacco. **Surveillance in Washington State is only for *C. gattii*.**

B. Description of Illness

Infection with *C. gattii* usually begins the lungs and presents as pneumonia, but may also involve the brain, presenting as meningitis. Untreated cryptococcal meningitis is fatal within weeks to months. Reported symptoms depend upon the presentation, but may include severe, prolonged cough (lasting weeks to months), shortness of breath, fever, chills, night sweats, and loss of appetite. Lung, brain, or muscle cryptococcomas (large mass lesions or nodules) may develop. The skin may show aceniform lesions, ulcers or subcutaneous tumor-like masses. Infection of the kidneys, prostate, and bone may also occur. Occasionally, the causal agent may act as an endobronchial saprophyte in patients with other lung diseases. Asymptomatic infections can occur; typically, cryptococcomas have been identified during follow-up imaging studies for treatment of other diseases. Mortality rates among cases range from 13-33% and differ by geographic region, likely due to differences in patient and treatment characteristics.

C. *Cryptococcus gattii* in Washington State

During 2005, three cats living in Washington near the Canadian border were diagnosed with *C. gattii*, none of which had exposure in Canada. The first human case in Washington was identified in 2006. As of December, 2019, 58 human cases (including nine deaths) and over 50 animal cases have been identified in the state. Since the exposure period can be long, determining exposure location may be difficult. Environmental sampling has also identified the fungus in Washington.

D. Reservoirs

In the Pacific Northwest *C. gattii* was isolated from native trees, soil, air, and water and in Australia on certain eucalyptus species. *C. neoformans* can be isolated from in pigeon droppings.

E. Modes of Transmission

Presumably by inhalation. *Cryptococcus* is not transmissible from person to person or animal to person.

F. Incubation Period

Not well established. On average, 6-7 months (range 2-13 months; can be years). Pulmonary disease may precede brain infection by months or years.

G. Period of Communicability

Cryptococcal disease is not transmitted person-to-person or from animal-to-person.

H. Treatment

C. gattii infection can be treated with antifungal therapy. See specific treatment guidance published by the Infectious Disease Society of America (2010):

<https://academic.oup.com/cid/article/50/3/291/392360>

3. CASE DEFINITIONS

A. Clinical Criteria for Diagnosis

Infection with *Cryptococcus gattii* has variable symptoms. Collect information on clinical symptoms, whether the patient was hospitalized, date of onset of symptoms thought to be caused by cryptococcal infection, and any underlying diseases, especially immunocompromising conditions such as HIV infection or organ transplantation.

B. Laboratory Criteria for Diagnosis

1. Confirmatory:

- Isolation of *C. gattii* from a clinical specimen; or
- Detection of *C. gattii*-specific nucleic acid in a clinical specimen; or
- Demonstration of *C. gattii* in a clinical specimen by immunohistochemistry; or
- Result of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), performed on a clinical specimen, specific for *C. gattii*.

C. Criteria to Distinguish a New Case from an Existing Case

Cryptococcal infection is presumed to be chronic. A person may be a case only once. A new case is one that has not been previously reported.

D. Case classification (2015)

Confirmed: Confirmatory laboratory test for *C. gattii*.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

Diagnosis of cryptococcal meningitis is aided by the evidence of encapsulated budding forms on microscopic examination of cerebral spinal fluid (CSF) mixed with India ink. Cryptococcal antigen (CrAg) tests in serum and CSF are helpful in establishing a preliminary diagnosis. Confirmation is via histopathology or culture.

Standard methods of diagnosis in clinical laboratories do not differentiate *Cryptococcus gattii* from *C. neoformans*. An isolate is needed to conduct speciation. Cryptococcal isolates are plated on chromogenic medium called Canavanine-Glycine-Bromothymol blue (CGB) agar. The species can be determined based upon the growth and color reaction that is produced: *C. gattii* will trigger a blue color reaction as it grows on CGB agar, whereas *C. neoformans* will not grow on CGB agar and the medium remains yellow in color. Note that false positive or false negative results occur occasionally.

Genotyping of the organism provides useful information about the genetic changes and also helps to link cryptococcal cases to the Pacific Northwest or other geographic areas.

B. Testing Available at Washington State Public Health Laboratories (PHL)

PHL do not currently offer testing for *Cryptococcus*, but will facilitate transfer of specimens to the Centers for Disease Control and Prevention (CDC) for confirmation of species and for genotyping. Isolates should be sent on slants (room temperature). Petri dishes and paraffin blocks are not accepted.

Note that PHL require all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

Serology and histopathologic examination are not available through the public health laboratory system.

5. ROUTINE CASE INVESTIGATION

Interview the case and others who might provide pertinent information.

A. Evaluate the Diagnosis

Review the clinical presentation and use the case report form to itemize signs and symptoms. Get copies of laboratory reports that support the diagnosis. Since genotyping is always recommended, secure the isolate, if available.

B. Identify Source of Infection

Ask about travel and outdoor activity during the past two years, particularly in the Pacific Northwest including British Columbia.

C. Identify Potentially Exposed Persons

Because the incubation period is so long, it is difficult to pinpoint the source of infection, and therefore other potentially exposed persons. However, educate others sharing the exposure about symptoms for early diagnosis.

D. Environmental Evaluation

Notify the local environmental health program of locally acquired cases.

E. Infection Control Recommendations

1. Hospitalized patients should be cared for using standard precautions.
2. There is no need for patient isolation or work/day care restrictions.

6. MANAGING SPECIAL SITUATIONS

A. *Cryptococcus gattii* in an Animal

Confirmatory testing and genotyping of clinical isolates from animals is also available at the Centers for Disease Control and Prevention (CDC). Isolates must be submitted to Washington State Public Health Laboratories.

7. ROUTINE PREVENTION

A. Immunization Recommendations

A cryptococcal disease vaccine is not currently available.

B. Prevention Recommendations

There are no particular precautions that can be taken to avoid cryptococcal disease. You can, however, be alert for long lasting or severe symptoms and consult a health care provider for early diagnosis and treatment.

ACKNOWLEDGEMENTS

References:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5928a1.htm>

UPDATES

January 2011: First issued guideline for *C. gattii*. The Legal Reporting Requirements reflect the 2011 Notifiable Conditions Rule revision.

January 2014: Case definition updated for CSTE changes including adding PCR, immunohistochemistry or MALDI-TOF as confirmatory laboratory methods. Section 6 (Controlling Further Spread) was incorporated into Section 5.

January 2015: The 2015 CSTE change institutes standardized reporting of *C. gattii*; while there are still no clinical criteria for case classification, recommendations for reported clinical variables were updated in section 3A. The presumptive category of laboratory tests was deleted from section 3B.

December 2017: Added detail from 2015 CSTE definition describing criteria to distinguish a new case. Details added to disease and epidemiology. Links updated.

December 2019: Routine review.

December 2022: For 2023 WAC revision combined provider and facility reporting requirement (Section 1B2), updated laboratory submission (Section 1B3)

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