Cryptococcosis

Torulosis,
European Blastomycosis,
Busse-Buschke's Disease

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Importance

Cryptococcosis is an illness that affects a wide variety of mammals, including humans, with occasional cases also reported in birds, reptiles and amphibians. Two species, *Cryptococcus neoformans* and *C. gattii*, are responsible for most clinical cases. *C. neoformans* is an opportunistic human pathogen, and primarily affects people who are immunosuppressed; however, this does not seem to be the case for *C. gattii* in humans, or for either organism in animals. While *C. neoformans* and *C. gattii* are very common in some environments, most people and animals do not become ill after exposure. In a minority of cases, however, fungal infections become symptomatic in the respiratory tract, central nervous system (CNS) or other organs. Some infections are contained but not eliminated by the immune system, and can recur later in life. Cryptococcosis is sometimes fatal despite treatment.

Etiology

Cryptococcus spp. are fungi in the Division Basidiomycota. Although there are more than 30 species of *Cryptococcus*, only two organisms – *C. neoformans* and *C. gattii* (previously *C. neoformans* var. *gattii*) - commonly affect humans and animals. Other species including *C. laurentii, C. albidus, C. uzbekistanensis, C. adeliensis, C. curvatus, C. magnus, C. humicolus, C. luteolus, C. macerans, C. flavescens* and *C. uniguttulatus* have been found in clinical cases; however, this is rare. Of the latter group of organisms, *C. laurentii* and *C. albidus* have been described most often in people.

Cryptococcus spp. are dimorphic fungi, but they mainly occur in the yeast form in both the host and the environment, and usually reproduce by budding. Mating produces the perfect (mycelial) stage of the fungus. While there is evidence that both *C. neoformans* and *C. gattii* can mate in the natural environment (but not inside animal hosts), this has not yet been observed outside the laboratory. The perfect stage that results from mating between *C. neoformans* organisms is called *Filobasidiella neoformans*. *Filobasidiella bacillisporus* results from mating between *C. gattii*. It is useful to know both names for these organisms: although the vast majority of clinical reports refer to the pathogenic species as *Cryptococcus*, the name *Filobasidiella* can occasionally be encountered. Some strains of *C. neoformans* can also mate with *C. gattii*.

C. neoformans and *C. gattii* have been divided into serotypes, and also into "molecular" (genetic) types. There are four serotypes, A through D, based on the capsular antigens. *C. neoformans* currently contains serotypes A, D and AD, and is divided into two varieties: *C. neoformans* var. *grubii* (serotype A) and *C. neoformans* var. *neoformans* (serotype D). *S*erotype AD consists of hybrids between these two varieties. Serotypes B and C belong to *C. gattii*. Hybrids between *C. neoformans* and *C. gattii* also exist.

Molecular types are mainly used in epidemiological studies of outbreaks. *C. neoformans* var. *grubii* contains types VNI and VNII, and *C. neoformans* var. *neoformans* is equivalent to type VNIV, while hybrids between *C. neoformans* var. *grubii* and *C. neoformans* var. *neoformans* are type VNIII. *C. gattii* contains the molecular types VGI, VGII, VGIII and VGIV. Molecular types are of special interest in connection with an ongoing *C. gattii* outbreak in northwestern North America. Researchers are working to determine whether these organisms, which are subtypes of VGII and have affected an unusual number of people and animals, differ from *C. gattii* in other parts of North America and in other countries.

Species Affected

Mammals and marsupials

Cryptococcosis has been described in a many species of mammals and marsupials. This disease is relatively common in cats, and it has been described in other felids, especially cheetahs (*Acinonyx jubatus*). Clinical cases have also been reported in most other species of domesticated animals including dogs, ferrets, guinea pigs, horses, donkeys, cattle, sheep, goats, water buffalo, pigs and South American camelids (llamas, alpacas and vicunas). Among captive wild animals, cryptococcosis

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has been documented in red foxes (*Vulpes vulpes*), mink, a civet, gazelles, tapirs (*Tapirus* spp.), collared peccaries (*Tayassu tajacu*), mouflon sheep (*Ovis musimon*), tree shrews (*Tupaia tana* and *Tupaia minor*), elephant shrews (*Macroscelides proboscides*), a striped grass mouse (*Lemniscomys barbarus*), potoroos (*Potorous* spp.), koalas (*Phascolarctos cinereus*), wallabies, non-human primates and wild marine mammals. The diversity of affected species suggests that most mammals and marsupials might be susceptible.

Asymptomatic colonization of the nares has been reported in cats, dogs and koalas. Organisms have also been detected in the nares of horses and wild squirrels, but whether this was caused by colonization or environmental exposure is still unknown.

Information about the host ranges of *C. neoformans* and *C. gattii* is still incomplete, but both organisms are known to affect cats, dogs, ferrets and cheetahs. Many cases of cryptococcosis in horses seem to be caused by *C. gattii*. This organism also infects koalas in Australia, with consequences ranging from asymptomatic colonization to severe illness. In addition, *C. gattii* has been found in clinical cases from goats, llamas, alpacas, tapirs and marine mammals. Other species of *Cryptococcus* that may occasionally cause illness in mammals include *C. albidus* (horses and a dog), *C. magnus* (cats), *C. albidus* (cats and a California sea lion, *Zalophus californianus*), *C. laurentii* (dog, equine fetuses) and *C. flavescens* (dog).

Birds

C. neoformans can temporarily colonize the intestinal tract of some avian species. It can also be found in the guano of asymptomatic birds, either because it was shed from the bird or because the droppings provided the nutrients for environmental organisms to proliferate. This organism is especially prevalent in droppings from columbiform birds (e.g., pigeons), but it has also been detected occasionally in fecal matter or cloacal swabs from some psittacine and passerine species, chickens, swans (*Cygnus* spp.), rheas (*Rhea* spp.) and raptors. *C. gattii* has also been isolated occasionally from bird droppings or cloacal swabs.

Clinical cases are uncommon in birds, although psittacines are occasionally affected by *C. neoformans* var. *grubii* or *C. gattii*. Several cases of cryptococcosis, all caused by *C. gattii*, were described in captive North Island brown kiwis (*Apteryx australis mantelli*). Cryptococcosis seems to be very rare in poultry and pigeons, despite the exposure of pigeons to massive quantities of *C. neoformans*.

Reptiles and amphibians

A few cases of cryptococcosis have been described in reptiles, including lizards and snakes. Amphibians also seem to be susceptible: pulmonary cryptococcosis was reported in a wild toad that had been killed by a car.

Zoonotic potential

Humans can be affected by both *C. neoformans* and *C. gattii*. These organisms are thought to be acquired from the environment rather than from infected hosts, except under unusual circumstances such as accidental inoculation with infectious tissues. Human *C. neoformans* infections are occasionally associated with exposure to guano, especially that of pigeons. Cases have only rarely been linked to contact with droppings from pet birds. In one case, a person apparently acquired cryptococcosis from the feces of an asymptomatic pet magpie. Pet psittacines were implicated in rare cases in immunosuppressed persons. Many people with *C. neoformans* cryptococcosis have no history of direct contact with birds.

Geographic Distribution

C. neoformans occurs worldwide. *C. neoformans* var. *grubii* is much more common than *C. neoformans* var. *neoformans* in the environment, and it also accounts for most of the clinical cases. *C. neoformans* var. *neoformans* is reported to be most common in Europe.

C. gattii was originally thought to be limited to tropical and sub-tropical areas of Australia, New Zealand, the Americas, Asia and Africa. However, this organism is now recognized to occur in temperate regions as well. An important North American focus is on Vancouver Island, British Columbia, where an unusual number of cases have been reported since 1999. Related organisms have been described, less frequently, in nearby areas of Canada and the U.S., and it is possible that the Vancouver Island strains are spreading. Sporadic clinical cases have also been reported from other temperate regions in North and South America and Asia. In Europe, *C. gattii* is most common in the Mediterranean region, but a few clinical cases have been described in colder areas.

Transmission and Life Cycle

Cryptococcus spp. are almost always acquired from environmental sources, mainly by inhalation. In people, these organisms usually replicate initially in the lungs; however, primary colonization might also occur in the nasal cavity and sinuses of some animals. Cryptococcal organisms occasionally enter the body through breaks in the skin, where they typically cause localized disease. In cattle with cryptococcal mastitis, they enter the mammary gland through the teat. Other routes (e.g., ascending infections via the urinary tract) have also been proposed. Latent infections have been reported in both humans and animals: small numbers of viable organisms, encapsulated in granulomas in the lungs or lymph nodes by the immune response, may later serve as foci of infection if the host becomes immunosuppressed. Organisms can also persist in the prostate gland of men.

Direct transmission between people or animals seems to occur only in unusual circumstances (although infections can be acquired from bird droppings). One person

developed localized cryptococcosis after accidental self-inoculation of blood. Person-to-person transmission has also been reported during solid organ transplantation. A recent case of possible nosocomial transmission occurred in an intensive care unit in Taiwan. A mechanically ventilated, long term patient with pulmonary carcinoma apparently became infected from the patient in the adjacent bed, who had disseminated cryptococcosis. The isolates from both patients were identical, but the route of transmission was unknown. There are no reports of person-to-person transmission by casual contact.

Rare cases of possible or probable perinatal transmission have been documented in HIV-positive women, but not immunocompetent, HIV-negative women. Transplacental transmission was also reported in a harbor porpoise infected with *C. gattii*.

Environmental niches and life cycles

The life cycles and environmental niches of *C. neoformans* and *C. gattii* are still incompletely understood. Both of these organisms grow as yeasts inside the body, and reproduce by budding. In this setting, they form a large polysaccharide capsule, which is important in resisting phagocytosis by immune cells. In the environment, they usually proliferate as saprophytic yeasts, typically without a capsule. However, they can also transition from yeasts to a filamentous form, usually by mating. Filamentous forms are important because they can generate basidiospores, which are small enough to penetrate deeply into the lungs during inhalation. These spores, as well as desiccated yeasts (which can remain viable) are thought to be the infectious forms for people and animals. The relative importance of the two forms is still debated; however, the involvement of basidiospores suggests that the locations where cryptococci mate might influence the risk of becoming infected. Non-desiccated yeasts are not thought to be important in establishing pulmonary infections, as they are too large to enter the alveoli.

C. neoformans and *C. gattii* appear to occupy different environmental niches. *C. neoformans* is strongly associated with bird droppings. This organism can be found in fecal or cloacal samples from a wide variety of avian species, but pigeon guano is thought to be a major niche. Pigeon guano allows *C. neoformans* to proliferate extensively in the yeast form, especially when large accumulations of droppings are protected from sunlight in lofts or roosts. It also appears to support the mating of both *C. neoformans* var. *grubii* and *C. neoformans* var. *neoformans*. *C. neoformans* can remain viable for 2 years or more in fresh or desiccated pigeon feces. Droppings from some other birds, including parrots and canaries, can support the growth of *Cryptococcus* yeasts, but whether they can support mating is still uncertain.

Some authors speculate that trees might also be an important niche for *C. neoformans*. This organism can mate on autoclaved tree bark in the laboratory, and *C. neoformans* var. *neoformans* has been detected in decaying wood in the hollows of trees, and in the soil around some trees. Nevertheless, it is possible that these organisms originate from bird droppings, and they are not maintained long-term on trees.

Trees are thought to be the main reservoir for *C. gattii*. This organism occurs in decaying wood in the hollows of trees, and in the soil around some trees. At one time, *C. gattii* was linked mainly with eucalyptus trees; however, it has now been detected in more than 50 diverse tree species, including both angiosperms and gymnosperms. Some trees and soil appear to be permanently colonized, but colonization at other sites seems to be transient. Cutting of tree limbs, logging and soil disturbances can increase the concentration of infectious organisms in the air. Increased concentrations of *C. gattii* have also been detected in the air around eucalyptus trees when they bloom. *C. gattii* is also isolated occasionally from avian guano or cloacal samples, but unlike *C. neoformans*, it does not seem to be able to mate on pigeon guano alone.

C. neoformans and *C. gattii* can also be found in other environments, where they may survive for prolonged periods. *C. neoformans* has been recovered from a wide variety of contaminated objects. For example, the first isolation of this organism was from peach juice. *C. gattii* has been detected in freshwater and saltwater samples, which may become contaminated from soil runoff. This organism was reported to survive in distilled water or ocean water at room temperature for more than a year. No viable cells were found after 3 months in distilled water at 4°C, 10% NaCl at 4°C, or 15-20% NaCl at room temperature. Both *C. neoformans* and *C. gattii* have been associated occasionally with insects (e.g., a wasp nest and insect frass). Fomites, and environmental contamination from infected animals or people, might be responsible for disseminating infections from endemic foci (e.g., the area affected by *C. gattii* in the Pacific Northwest).

Cryptococcus spp. that are rare pathogens, such as *C. albidus* or *C. laurentii*, can be found in various environments including soil, plants, food and avian guano. *C. albidus* is a widespread saprophyte in the soil.

Disinfection

C. neoformans is susceptible to 70% ethanol, 0.5% chlorhexidine, 1.2% sodium hypochlorite, iodophors (e.g., betadine), phenolic disinfectants, glutaraldehyde and formaldehyde. Hydrogen peroxide (3%) or a preparation containing 0.05% chlorhexidine were not effective in one study. In biofilms, only 0.5% chlorhexidine and extremely high concentrations of sodium hypochlorite were reported to be fungicidal. *C. neoformans* can also be killed by moist heat of 121°C for a minimum of 20 minutes or dry heat of 165-170°C for 2 hours. Although ultraviolet light reduced the number of viable organisms in one experiment, it was not considered to be fungicidal, as there was less than a hundred-fold decrease in the fungal load.

Infections in Animals

Incubation Period

The average incubation period in animals is still uncertain, but some clinical cases can become apparent months or years after exposure. Few studies have investigated the onset of cryptococcosis in experimentally infected animals after inhalation. The median time to death in mice inoculated intranasally with an environmental *C. neoformans* (yeast) isolate was 34 days. Isolates from human clinical cases caused death sooner.

Clinical Signs

Cats

In cats, cryptococcosis can be either focal or disseminated, affecting a single organ system or many. The clinical signs can begin insidiously, and may gradually become more severe over weeks or months. Fever may be absent, and if present, is often mild. Other nonspecific signs can include lethargy, anorexia and weight loss. Cats with localized infections, including those in the nasal cavity, do not necessarily have constitutional signs.

Localized upper respiratory disease (unilateral or bilateral chronic rhinitis or sinusitis) is the most common form of cryptococcosis in cats. Frequently seen clinical signs include sneezing, snoring or snorting, dyspnea, nasal deformities and/ or a mucopurulent, serous or serosanguineous nasal discharge. Polyp-like masses sometimes protrude from one or both nostrils. Some cats also have concurrent cutaneous or subcutaneous swellings and nodules on the face, particularly the bridge of the nose, side of the face, upper lip or nostril. Some of these lesions may ulcerate. In addition, the submandibular lymph nodes are often enlarged. With time, infections involving the nasal cavity can spread to adjacent structures. Ulcerative or proliferative lesions may develop on the tongue, gingiva or palate. Extension to the ear can result in otitis media and vestibular signs. Dissemination to the retrobulbar tissues can result in exophthalmos and third eyelid prolapse. Extension to the brain is also possible.

Lower respiratory disease can also occur in cats, although it is less common than upper respiratory lesions. Syndromes may include pneumonia, pleuritis and mediastinal masses.

CNS involvement is common in cats, and both focal mass lesions (cryptococcomas) and cryptococcoal meningitis may be seen. The neurological signs can be mild to severe, with various presentations such as a change in temperament or behavior, depression, disorientation, vestibular signs (e.g., head tilt, circling, nystagmus), head pressing, ataxia, paresis or paralysis, tremors, seizures, abnormal pupillary responses and blindness. Meningitis may appear as pain over the thoracolumbar spine or pelvic limbs, but hyperesthesia and nuchal rigidity are uncommon. Deficits of cranial nerves 5 to 12 are often found. The CNS is sometimes involved even if there are few or no obvious neurological signs. In one case, the only sign was unusual sleepiness.

Ocular lesions such as chorioretinitis, optic neuritis, panophthalmitis, retinal hemorrhages and iridocyclitis have been reported. There may also be small transparent focal retinal detachments with a minimal inflammatory response. Ocular lesions often accompany other syndromes, especially CNS disease. Some cats can become blind.

Other organs including the bone (osteomyelitis), mediastinum, heart, thyroid gland, spleen, liver and urinary tract can also be affected. Cutaneous involvement usually appears as fluctuant or firm papules and nodules. Some skin lesions may ulcerate, but there is little or no pruritus. Generalized skin disease suggests disseminated cryptococcosis.

Direct inoculation of organisms into the skin can occasionally cause solitary lesions.

Dogs

Frequently affected sites in the dog include both the respiratory tract and CNS. Signs primarily of upper respiratory tract involvement have been documented in some dogs, especially those infected with *C. gattii*; however, concurrent involvement of the lower respiratory tract or CNS is common in this species. Other organs that may be affected include the eye (e.g., granulomatous chorioretinitis, optic neuritis); lymph nodes; various internal organs such the kidneys, spleen and liver; and muscle, bone or other tissues. Subcutaneous masses have been reported, and one dog had an intussusception caused by an extraluminal cryptococcoma. Disseminated cryptococcosis is reported to be more common in dogs than cats.

Ferrets

Various presentations, similar to those in other species, have been seen in ferrets. Some affected ferrets had disseminated disease, but localized masses (e.g., on the nose, spine or digit) were reported in others. Lymphadenopathy and respiratory signs are reported to be common in this species. Neurological signs, meningitis and ocular signs (chorioretinitis, blindness) have also been documented. Gastrointestinal signs were prominent in one ferret with disseminated disease; the presenting signs included lethargy, weight loss, diarrhea and retching, as well as dyspnea.

Ruminants

Pulmonary infections, CNS involvement and cryptococcal mastitis have been reported in cattle. In outbreaks of mastitis, the clinical signs may include anorexia, decreased milk production and enlargement of the supramammary lymph nodes. The affected quarters are usually swollen and firm. The milk may be viscid, mucoid and grayish-white, or it may be watery with flakes. Neurological signs were the presenting complaint in a bull with cryptococcal meningoencephalitis and a cow with isolated cryptococcomas. The clinical signs

included gait abnormalities and visual impairment in both animals, as well as various other signs such as depression, circling, head pressing, anorexia and abnormal reflexes. In the bull, the brain was the only affected organ at necropsy.

Pulmonary disease, mastitis and meningoencephalitis have been described in goats. One goat with cryptococcosis had an alopecic, exudative skin lesion on the head. Cases of mastitis, lung involvement and rhinitis have been reported in sheep, and mastitis has been documented in water buffalo.

Camelids

Syndromes that have been reported in camelids include lower respiratory disease, CNS disease and disseminated infections.

Horses

Published clinical cases in horses have described meningoencephalitis/ meningitis, lower respiratory disease or pneumonia, upper respiratory disease affecting the sinuses and/or nasal cavity, osteomyelitis, mass lesion in the intestinal tract, endometritis and abortions with mycotic placentitis, and disseminated disease. Obstructive growths in the nasal cavities and sinuses are a common presentation in some geographic areas. Lower respiratory disease was reported to be more frequent in Western Australia, where *C. gattii* is common. Cutaneous lesions were documented in a donkey.

Birds

Some psittacine birds with cryptococcosis have signs of an upper respiratory tract obstruction. These birds often have proliferative lesions, which may resemble neoplasia, around the beak or nares. The infection can progress to involve structures close to the nasal cavity, such as the rhamphotheca, nasopharynx, palate and sinuses. No internal organs, including the lower respiratory tract and CNS, were affected in most of these cases. However, severe invasive or disseminated disease affecting the lung, air sacs, CNS or other internal organs has been reported in a few psittacines.

Cryptococcosis seems to be very rare in pigeons. One racing pigeon developed a localized subcutaneous swelling below the eye. Localized disease was also reported in another pigeon, while a third bird had widely disseminated lesions.

Fatal *C. gattii* infections have been reported in captive kiwis. Extensive granulomatous pneumonia was found in two of these birds at necropsy, while the third had disseminated disease involving the heart, kidneys and proventriculus.

Other species of Cryptococcus

Species other than *C. neoformans* and *C. gattii* have rarely been reported to affect animals. *C. albidus* was found in a genital infection in one horse, and in cases of fatal disseminated cryptococcosis in a dog and a cat. Both *C. albidus* and bacterial pneumonia were thought to have contributed to the death of a California sea lion. This organism was also found in the eye of a horse with keratitis; however, several bacteria were also detected, and its contribution to the condition is uncertain.

C. magnus was the causative agent in an immunocompetent cat that had a recurrent painful mass lesion of the foreleg, together with enlargement of the regional lymph node. Convulsions, seen in this cat during the early stage of treatment, suggested CNS involvement but resolved with continuing therapy. *C. magnus* was also isolated from the ear of a cat with otitis externa, but the inflammation was attributed to *Aspergillus fumigatus*, and the role of *C. magnus* is uncertain.

C. laurentii was detected a dog with panniculitis and osteomyelitis. This organism was also found in the stomach of aborted equine fetuses. A subcutaneous infection with *C. flavescens* in a dog appeared as abscessed lesions on the muzzle, jaw and eyelid.

Communicability

Avian guano is an important source of *C. neoformans* in the environment. This organism proliferates especially well in pigeon droppings, where it might also mate and produce infectious spores. Both *C. neoformans* and *C. gattii* have been detected occasionally in droppings or cloacal swabs from other avian species. Short-term colonization of the intestinal tract seems to be possible. Canaries that were fed *C. neoformans* shed viable organisms in feces for up to 8 days, and pigeons for as long as 36 days.

Animals with clinical cryptococcosis are not thought to transmit these organisms by casual contact. Encapsulated yeasts found in the tissues are unlikely to be small enough to enter the alveoli of the respiratory tract. Nevertheless, infected animals can contaminate the environment with yeasts, which could proliferate if they find a suitable niche. Organisms from lesions or blood might also cause localized cryptococcosis if they are accidentally inoculated into tissues.

There is one reported of transplacental transmission, in a harbor porpoise infected with *C. gattii*.

Post Mortem Lesions

The gross lesions may appear either as granulomas or as gelatinous masses with minimal inflammation.

In cats, lesions can occur in any organ system. A viscous exudate is often found in the nasal passages and sinuses. Small gelatinous nodules may be scattered on the viscera of the abdominal and thoracic cavities. In cases with CNS involvement, the meninges can be congested and thickened. They sometimes have a cloudy, gelatinous appearance, and they may be covered by a scant mucoid exudate. Gray, gelatinous masses (cryptococcomas) may also be found in the brain and spinal cord. Ocular lesions

including chorioretinitis or panophthalmitis can be seen in some cats. CNS disease in cats may be associated with only minimal inflammation.

Many dogs with fatal cryptococcosis have disseminated disease, with granulomas throughout the body. Pulmonary involvement is common, even in dogs with no signs of respiratory disease. Lesions may also be found on other organs including the kidneys, lymph nodes, spleen and liver. The CNS lesions resemble those in cats, with meningoencephalitis and mass lesions in the brain and spinal cord; however, in dogs the lesions are more often accompanied by granulomatous inflammation.

Similar lesions may be seen in other species.

Diagnostic Tests

Cryptococcosis is usually diagnosed by detecting these organisms in blood, or in other samples from biopsies, impression smears, aspirates or swabs of affected sites. Nasal secretions, bronchial washings, skin exudates, CSF and urine are among the samples that may contain cryptococci. In one unusual case, organisms found in the feces of a dog led to a diagnostic workup for cryptococcosis. When diagnosing cryptococcosis in birds, the possibility of asymptomatic colonization must be considered. Organisms can also be detected occasionally in the nares of some healthy mammals.

Cryptococcus spp. can sometimes be found in clinical samples by direct observation. *C. neoformans* and *C. gattii* are round to oval yeasts, surrounded by large capsules that stain strongly with Mayer's mucicarmine. In an India ink preparation, the capsule appears as a clear halo around the yeast cell. Unless budding is observed, it can be confused with a fat droplet or other artifact. Other useful stains include Alcian blue, Gomori methenamine silver, colloidal iron, periodic acid-Schiff (PAS), Masson-Fontana silver stain, Gram's stain, new methylene blue and Wright's stain. Although pathogenic cryptococci are expected to form capsules in the body, non-encapsulated organisms were apparently observed in the tissues of one cat infected with *C. magnus*. *Cryptococcus* spp. can also be identified in the tissues by immunofluorescence or immunohistochemistry. Some species of *Cryptococcus* do not appear to stain well with certain antibodies.

A latex cryptococcal agglutination test can detect *C. neoformans* capsular antigens in blood, CSF or urine. False negatives are possible in animals with localized disease. In the human literature, cross-reactivity (false positivity) has been reported occasionally with organisms in the genus *Trichosporon* and more rarely with *Histoplasma, Penicillium marneffei* (penicilliosis) and members of the Mucoromycotina (mucormycosis).

A definitive diagnosis can also be obtained by culture. Although *C. neoformans* and *C. gattii* can form colonies on most media, growth is best on fungal media such as Sabouraud dextrose agar without cycloheximide. Colonies usually appear within 2 to 5 days, but growth may be delayed in samples with few organisms. The organism is identified by its appearance, ability to grow at 37°C and biochemical tests; by molecular methods such as DNA sequencing; or with commercial yeast identification systems. Differential media can also aid identification. Both *C. neoformans* and *C. gattii* produce melanin and usually form brown colonies on Niger (birdseed) agar. Canavanine-glycine-bromthymol blue agar can distinguish *C. gattii* from *C. neoformans*. If needed for epidemiological analyses, genetic types can be identified by techniques such as multilocus sequence typing (MLST) or amplified fragment length polymorphism (AFLP). However, veterinary diagnostic laboratories may not identify *Cryptococcus* even to the species level.

Treatment

Cryptococcosis in animals is treated with antifungal drugs such as amphotericin B, flucytosine, itraconazole, fluconazole and ketoconazole. Flucytosine is not used alone, as this results in rapid development of resistance; instead, it is typically combined with amphotericin B. The choice of antifungal agent varies with the species of animal and drug side effects, and with the ability of the drug to penetrate into the affected site(s). Cost considerations can also be a factor, especially in larger animals. Short courses of anti-inflammatory drugs have been prescribed concurrently in certain cases, to decrease inflammation in critical sites such as the brain.

Drug treatment is sometimes combined with surgical debulking or excision of a mass. Two upper respiratory tract infections in horses, which are challenging to treat, were apparently eliminated with such combination therapies.

Prevention

Whether there are any effective methods of preventing cryptococcosis is uncertain, as *C. gattii* and *C. neoformans* are widespread in environments such as avian feces, rotting wood and soil, and risk factors for illness are still poorly understood. Although some factors (e.g., soil disturbances) seem to increase the risk of cryptococcosis, clinical cases occur even in pets kept indoors. It should be kept in mind that many animals are probably exposed frequently, but do not become ill.

Environmental modifications may be considered in certain situations. Some sources suggest that eucalyptus mulch should be avoided with kiwis, as *C. gattii* caused fatal cryptococcosis in several of these birds. Environmental modification was also used at the Antwerp Zoo, when cryptococcosis occurred in an indoor exhibit, and *C. neoformans* var. *neoformans* was detected in a tree-trunk, tree-stumps, and decaying wood in that exhibit, but not in surrounding areas. In this case, the contaminated objects were removed and replaced.

Cryptococcal mastitis in cattle is usually associated with treatment of the mammary gland for another condition.

Care should be taken not to contaminate syringes, cannulas or antibiotic preparations. The teat ends should also be adequately prepared before treatment.

Morbidity and Mortality

Mammals and marsupials

Risk factors for cryptococcosis in animals are poorly understood. One study suggested a link between veterinary cases caused by *C. gattii* in Canada, and soil disturbances or logging with 10 km. Pathogenic *Cryptococcus* spp. have been found in the nares of a small percentage of animals. Studies from Vancouver Island, Canada, detected *C. gattii* in the nasal passages of 1.1% of dogs, 4.3% of cats and 1.5% of horses. A study that followed a small number of asymptomatically infected or colonized dogs and cats found that some animals remained persistently colonized for months, while other seemed to clear the organism, and a few cats became ill. In this study, 2 of 7 nasally colonized cats with antigens in the blood developed clinical signs within 4-6 months. The remaining cats and all 5 dogs remained asymptomatic. Persistent colonization with *Cryptococcus* spp., as well as clinical cases, have also been reported in koalas.

Clinical cases are reported more often in cats than other domesticated animals, but the reason for this is unknown. It was once thought that cats immunosuppressed by retroviruses were more likely to develop cryptococcosis. However, newer studies do not support this idea, and some recent reviews consider it to be doubtful. There is currently no evidence that immunosuppression plays a significant role in susceptibility in ferrets and dogs. Cryptococcosis seems to be uncommon in horses in many areas (although other factors could be responsible for the small number of reported cases); however, this species is affected relatively often by *C. gattii* in Western Australia.

Although animals with cryptococcosis can be treated successfully, the prognosis can be guarded, particularly in animals with CNS disease. Relapses can also occur after apparent cure. The prognosis may vary with the species. Cats often respond well to treatment, especially when the brain is not involved. However, clinical cases in horses are often fatal. Cryptococcal mastitis in cattle is usually a mild condition, but some infections can cause the death of the cow. Cattle with this disease rarely recover spontaneously.

Birds

Despite the high prevalence of *C. neoformans* in some avian environments, cryptococcosis is an uncommon disease in birds. In pigeons, this has been attributed to their high body temperature, which is expected to inhibit replication of the organism. Why the organism remains confined to the upper respiratory tract in many clinically affected birds, but disseminates in others, is unknown. Most of the psittacine birds in a case series from Australia had localized upper respiratory disease, but published cases in Europe and the Americas often described disseminated cases. Some authors speculate that, in kiwis, dissemination might be related to the lower body temperature of ratites. Immunosuppression or the disruption of the normal bacterial flora by antibiotics have also been proposed as possible predisposing factors in some birds.

Infections in Humans

Incubation Period

The incubation period for *C. neoformans* infections is uncertain, as this organism is ubiquitous and it is often impossible to determine when the person was exposed. Some clinical cases can occur months or years after exposure.

The *C. gattii* organisms responsible for the Vancouver Island outbreak have a distinctive molecular type, which has allowed the incubation period to be determined in visitors to the island. Illnesses caused by this organism have appeared 6 weeks to 13 months after exposure, with an estimated median incubation period of 6-7 months.

Clinical Signs

The consequences of infection with *C. neoformans* or *C. gattii* range from asymptomatic colonization of the airways to respiratory signs of varying severity, or disseminated infections that may involve the CNS, eye, skin and other organs. While there seem to be some differences between the syndromes caused by *C. neoformans* and *C. gattii*, both species can affect any organ. In immunosuppressed hosts, *C. neoformans* may cause little inflammation, and the symptoms can be mild even with extensive disease. Only a small percentage of the people exposed to either organism become ill.

In most patients, *Cryptococus* spp. enter the body via the respiratory tract and replicate first in the lungs. Many pulmonary infections are asymptomatic in both immunocompetent and immunosuppressed hosts, although lesions may be apparent on x-ray. In clinical cases, the signs vary from a nonspecific cough alone, to more significant symptoms that can include dyspnea or shortness of breath, pleuritic chest pain or hemoptysis. Other signs may include low-grade fever, weight loss, anorexia and malaise. Pleural effusions can occur, but are uncommon, and adult respiratory distress syndrome has been reported. Serious respiratory syndromes and progressive pulmonary disease are more likely to occur in immunocompromised patients. Many infections in healthy patients may be self-limited.

From the lungs, *Cryptococcus* spp. may spread to other organ systems, particularly in immunosuppressed patients. Respiratory symptoms can either precede or occur concurrently with other syndromes. Disseminated disease can also be seen in individuals who had asymptomatic pulmonary infections.

CNS disease is the most common form of disseminated cryptococcosis. The typical syndromes are subacute or

chronic meningitis and meningoencephalitis, or mass lesions (cryptococcomas) in the brain. The development of the illness is often insidious, with initial signs such as headache, fatigue, drowsiness or changes in behavior. A persistent headache, often of several weeks' duration, is a common presentation. Although some patients may have a fever, body temperature can also be only slightly elevated or normal. Neck stiffness is often minimal or absent. Other signs, such as abnormalities in vision, seizures, vomiting, impaired consciousness and paralysis, can develop with the progression of the disease. Cranial nerve paralysis is common. Cryptococcomas may cause focal signs such as aphasia, cerebellar syndrome or paresis, especially in immunocompetent patients. Elevated cerebrospinal fluid (CSF) pressure from cryptococcomas or chronic meningoencephalitis can lead to hydrocephalus and further neurological signs, including dementia. Other syndromes, such as spinal cord lesions or ischemic stroke, have also been seen. Untreated infections in the brain are eventually fatal, but the course of the disease varies between patients. These infections may be rapidly fatal in some immunocompromised individuals.

The eye is also a common site of dissemination, resulting in lesions such as optic neuritis, chorioretinitis and endophthalmitis. Ocular signs, including vision loss, can also be caused by intracranial hypertension from CNS disease.

Dissemination of organisms to the skin can cause a variety of lesions, which may mimic other diseases. Papules, which may ulcerate or evolve to other forms, are often seen initially. Other reported lesions include pustules, vesicles, bullae, ulcers, palpable purpura, superficial granulomas, plaques, subcutaneous tumor-like masses, cellulitis, abscesses or sinus tracts, and even rare cases of necrotizing fasciitis. AIDS patients may have umbilicated papules that resemble molluscum contagiosum. Cutaneous involvement often occurs concurrently with cryptococcosis in the brain or other organs.

Less frequent or rare syndromes include osteomyelitis, septic arthritis, myocarditis, lymphadenitis, hepatitis, peritonitis, abdominal cryptococcomas, gastrointestinal involvement, renal abscesses, prostatitis, myositis, endocarditis and septic shock. In AIDS patients, invasion of the adrenal glands may cause adrenal insufficiency. Urogenital involvement is often asymptomatic.

Residual deficits including visual impairment or persistent neurological defects can be seen in some patients after treatment.

Primary cutaneous cryptococcosis

Direct inoculation into the skin (primary cutaneous cryptococcosis) is an uncommon presentation, and typically results in a localized lesion such as a nodule, tubercle or abscess at the inoculation site. The lesions of primary cutaneous cryptococcosis sometimes regress spontaneously.

Other Cryptococcus spp. infections

Few infections with *Cryptococcus* species other than *C. neoformans* or *C. gattii* have been documented in the literature. Reported syndromes included fungemia or localized infections associated with medical devices such as indwelling catheters; as well as pulmonary infections, osteomyelitis, cutaneous lesions and septicemia. Several species of *Cryptococcus* can cause meningitis. A bone marrow infection with *C. uzbekistanensis* occurred in an elderly man with a T-cell lymphoma.

Communicability

Person-to-person transmission is very rare and has occurred only in unusual circumstances. A few cases were linked to transmission in transplanted tissues or organs, including internal organs and a cornea. A health care worker developed localized skin disease after accidental self-inoculation with contaminated blood. Possible nosocomial transmission was also reported in a case from an intensive care unit in Taiwan. In this incident, a mechanically ventilated, long term patient with pulmonary carcinoma apparently became infected from the patient in the adjacent bed, who had disseminated cryptococcosis. There are no reports of transmission during casual contact.

Rare cases of possible or probable mother-to-child transmission have been seen in HIV-positive women, but there are no documented cases in infants born to immunocompetent women.

Diagnostic Tests

Cryptococcosis is usually diagnosed by detecting the organism or its antigens in blood, or in tissues and fluids from affected sites (e.g., cerebrospinal fluid, bronchial washings, urine).

Cryptococcus spp. can sometimes be found in clinical samples by direct observation or culture, using methods such as those described under diagnostic tests for animals. Microscopy may detect nonviable yeasts, which appear intact, in the tissues for several months after treatment. During culture, human diagnostic laboratories do not always differentiate *C. gattii* from *C. neoformans*.

A latex agglutination test (or less frequently used ELISA) can detect capsular antigens in blood or CSF. Antigens may not be found if the infection is localized to the lungs. False positive reactions can be seen occasionally with *Trichosporon* infections, or less frequently in cases of mucormycosis, penicilliosis or histoplasmosis. Antigen levels fall very slowly after treatment, as capsular material from non-viable organisms may persist in the body for a time.

Other helpful tests include CT and MRI in patients with CNS disease, and x-rays in patients with pulmonary signs. Serology to detect specific antibodies is not generally used in diagnosis, as healthy people are often seropositive.

Treatment

Cryptococcosis can be treated with various antifungal drugs including amphotericin B □, flucytosine (5-fluorocytosine), fluconazole and itraconazole. Standardized treatment recommendations have been published for illnesses caused by *C. neoformans* and *C. gattii*. The recommended drugs and duration of treatment vary with the site affected and the immune status of the individual. Supportive therapy may be needed to treat conditions such as dangerously elevated intracranial pressure in patients with CNS disease. Surgery is occasionally used to reduce the size of a mass lesion. Immunocompetent, asymptomatic patients may or may not be treated if the infection is confined to the lungs, as these infections are usually self-limiting.

There is still little experience in treating infections with other *Cryptococcus* species, but antifungal drugs were used successfully in some cases. Removal of any predisposing cause, such as an indwelling catheter, is expected to help the condition resolve.

Immune reconstitution syndrome can sometimes complicate the treatment of cryptococcosis. This syndrome occurs when immunity is boosted in a patient who was previously immunosuppressed (e.g., a pregnant patient after delivery, or an HIV-infected person treated with antiviral drugs). The subsequent overly robust immune response to *Cryptococcus* can exacerbate the symptoms and may even be fatal. Concurrent anti-inflammatory medications are sometimes needed to treat this condition.

After treatment, some immunosuppressed patients must be maintained long term or lifelong on antifungal drugs, to prevent latent infections from recurring.

Prevention

Complete prevention of exposure is probably impossible. *C. neoformans* is ubiquitous, while *C. gattii* has now been identified in a variety of climates, in and around many species of trees. Despite the frequency of exposure, most people do not become ill.

In some circumstances, it might be possible to decrease the level of exposure from some environmental sources, such as bird droppings (especially pigeon droppings), trees during logging and cutting, eucalyptus trees in bloom, and soil disturbances. Removal of guano should be preceded by chemical decontamination or wetting with water or oil to decrease aerosolization.

Although no cases of animal-to-human transmission have been reported (except via avian feces in the environment), it is prudent to use caution when handling animals with cryptococcosis. People handling such animals should use appropriate barrier precautions, including avoidance of accidental inoculation into breaks in the skin. Cages and litter boxes should be decontaminated regularly.

Targeted screening of immunosuppressed individuals, using tests that detect cryptococcal antigens, might identify disseminated infections in the early stages when they are most readily treated.

Morbidity and Mortality

Cryptococcus neoformans

In most parts of the world, *C. neoformans* is an opportunist that mainly affects people with depressed cell-mediated immunity. AIDS patients and organ transplant recipients are particularly susceptible. An estimated 5-10% of HIV-infected persons developed cryptococcosis early in the AIDS epidemic; however, the incidence has decreased with the development of more effective retroviral therapy. Sarcoidosis, some forms of cancer and prolonged treatment with corticosteroids also increase the risk of serious illness. In the U.S., the annual incidence of cryptococcosis is currently 0.4-1.3 cases per 100,000 persons in the general population, 2 to 7 cases per 1,000 AIDS patients, and 0.3 to 5.3 cases per 100 transplant patients. A few reports suggest that, in some locations, *C. neoformans* might also be an important pathogen of immunocompetent people. In one large study from China, both *C. neoformans* and *C. gattii* mainly affected healthy patients with no chronic conditions or other underlying illnesses. In Vietnam, *C. neoformans* var. *grubii*, rather than *C. gattii* was reported to be the most common cause of cryptococcal meningitis in immunocompetent people. Whether local *C. neoformans* variants or other factors might affect the pattern of illness is unknown.

The outcome of a *C. neoformans* infection depends on the health of the host, the form of the disease and the treatment. Healthy people seem to be exposed frequently to this organism without becoming ill. Serological surveys suggest that many individuals encounter it in early childhood, and pulmonary granulomas containing *C. neoformans* can be an incidental finding in people with no history of cryptococcosis. Symptomatic pulmonary infections in healthy people may resolve without treatment. In contrast, untreated cryptococcosis affecting the CNS is fatal even if the person is immunocompetent.

The survival rate for *C. neoformans* cryptococcosis is poorer if the person is immunosuppressed or the disease is advanced. The 10-week case fatality rate is 10-25% among HIV-infected patients in developed countries, despite the availability of highly active antiretroviral therapy. In countries with limited resources, mortality in this population is 37–43%, even with the use of amphotericin B, and it can reach 100% in some case series. Case fatality rates of 20-100% have been reported in organ transplant patients.

Cryptococcus gattii

The incidence of illness caused by *C. gattii* varies significantly between geographic regions and populations. As with *C. neoformans*, most people exposed to *C. gattii* do not become ill. In Australia, where this organism is relatively common in the environment, the average annual incidence of cryptococcosis caused by *C. gattii* is ≤ 1 case per million population. Aboriginal populations in Australia have a much higher rate of illness, with one study reporting

up to 140 cryptococcosis cases per million population (77% caused by *C gattii*). Whether the elevated risk in this group is caused by increased environmental exposure, genetic susceptibility or other factors is still uncertain. The incidence of *C. gattii* cryptococcosis is also high in central Papua New Guinea (43 cases per million population), and it has been elevated on Vancouver Island, Canada (25 cases per million population) and in neighboring regions of Canada and the U.S. since 1999. *C. gattii* is uncommonly linked to clinical cases in most parts of North America, and the reason for its emergence on Vancouver Island is still uncertain. Some authors suggest that a localized population of organisms might have become more virulent and spread. Even on Vancouver Island, the number of clinical cases represents only a small fraction of the exposed population.

Most studies report that the majority of patients affected by *C. gattii* do not have underlying illnesses and are not immunosuppressed. One recent analysis from the U.S. found that 76% of patients either smoked, were taking immunosuppressive medications, were infected by HIV, or had underlying chronic health conditions including cancer, various respiratory and cardiac conditions, liver disease or diabetes. Cigarette smoking was also identified as a risk factor in an Australian study. In two Australian studies, approximately 9% or 28% of *C. gattii* cases occurred in HIV-negative patients with other illnesses or risk factors including cancer, idiopathic CD4 lymphopenia or the use of long term immunosuppressive drugs.

Estimates of the case fatality rates for *C. gattii* cryptococcosis in Australia, British Columbia, the U.S., and Papua New Guinea vary from 9% to 36%. Reported case fatality rates for *C. gattii* meningoencephalitis were 0-20% in Australia and 41% in Papua New Guinea. Fatal illness may be more likely in older patients, people with underlying illnesses, and those who are immunosuppressed. Some reports suggest that *C. gattii* infections might respond more slowly to treatment than *C. neoformans*.

Other Cryptococcus species

Clinical cases caused by organisms other than *C. neoformans* or *C. gattii* are rarely reported. As of 2007, approximately half of these cases occurred in people who had impaired cell-mediated immunity due to immunosuppressive drugs or illnesses such as cancers, and 16% were seen in HIV-infected patients. Some cases were associated with invasive medical devices (e.g., indwelling catheters). However, illnesses have also been seen in people who apparently had no underlying conditions. For example, *C. uniguttulatus* meningitis occurred in a healthy, HIV-negative man.

Internet Resources

Centers for Disease Control and Prevention (CDC). *Cryptococcus neoformans*
http://www.cdc.gov/fungal/cryptococcosis-neoformans/

CDC. *Cryptococcus gatti*
http://www.cdc.gov/fungal/cryptococcosis-gattii/

eMedicine.com - Cryptococcosis
http://emedicine.medscape.com/article/215354-overview

eMedicine.com - Imaging in CNS Cryptococcosis
http://emedicine.medscape.com/article/339576-overview.

International Veterinary Information Service (IVIS)
http://www.ivis.org

Material Safety Data Sheets –Canadian Laboratory Center for Disease Control
http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com

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