RICKETTSIAL DISEASE

Rickettsial infections are caused by a variety of bacteria from the genera *Rickettsia, Orientia, Ehrlichia, Neorickettsia, Neoehrlichia*, and *Anaplasma*. *Rickettsia* spp. are classically divided into the typhus group and spotted fever group (SFG). *Orientia* spp. make up the scrub typhus group. The rickettsial pathogens most likely to be encountered during travel outside the United States include *R. africae* (African tick-bite fever), *R. conorii* (Mediterranean spotted fever), *R. rickettsii* (known as both Rocky Mountain spotted fever and Brazilian spotted fever), *O. tsutsugamushi* (scrub typhus), and *R. typhi* (murine typhus).

Transmission

Most rickettsial pathogens are transmitted by ectoparasites such as fleas, lice, mites, and ticks. Organisms can be transmitted by bites from these ectoparasites or by the inoculation of infectious fluids or feces from the ectoparasites into the skin. Inhaling or inoculating conjunctiva with infectious material may also cause infection for some of these organisms. Transmission of some rickettsial diseases after transfusion or organ transplantation is rare but has been reported.

Epidemiology

All age groups are at risk for rickettsial infections during travel to endemic areas. Both short and long-term travelers are at risk for infection. Transmission is increased during outdoor activities in the spring and summer months when ticks and fleas are most active. However, infection can occur throughout the year. Because of the 5- to 14-day incubation period for most rickettsial diseases, tourists may not necessarily experience symptoms during their trip, and onset may coincide with their return home or develop within a week after returning. Although the most commonly diagnosed rickettsial diseases in travelers are usually in the spotted fever or typhus groups, travelers may acquire a wide range of rickettsioses, including emerging and newly recognized species.

R. typhi and *R. felis*, which are transmitted by fleas, are widely distributed, especially throughout the tropics and subtropics and in port cities and coastal regions with rodents. Humans exposed to flea-infested cats, dogs, and peridomestic animals while traveling in endemic regions, or who enter or sleep in areas infested with rodents, are at most risk for fleaborne rickettsioses.

Clinical Presentation

Rickettsioses are difficult to diagnose, even by health care providers experienced with these diseases. Most symptomatic rickettsial diseases cause moderate illness, but some Rocky Mountain and Brazilian spotted fevers, Mediterranean spotted fever, scrub typhus, and epidemic typhus may be fatal in 20%–60% of untreated cases, so prompt treatment is essential.

Clinical presentations vary with the causative agent and patient; however, common symptoms that typically develop within 1–2 weeks of infection include fever, headache, malaise, rash, nausea, and vomiting. Many rickettsioses are accompanied by a maculopapular, vesicular, or petechial rash or sometimes an eschar at the site of the tick bite. African tick-bite fever is typically milder than some other rickettsioses, but recovery is improved with treatment. Patients with murine or epidemic typhus usually present with a severe but nonspecific febrile illness, and approximately half will also present with a rash. Ehrlichiosis and anaplasmosis should be suspected in febrile patients with leukopenia with an exposure history.

Diagnosis

Diagnosis is usually based on clinical recognition and serology; the latter requires comparison of acute- to convalescent-phase serology, so is only helpful in retrospect. Etiologic agents can generally only be identified to the genus level by serologic testing. PCR and immune histochemical analyses may also be helpful.

Treatment

Treatment of patients with possible rickettsioses should be started early and should never await confirmatory testing, which may take weeks when serology is used. Immediate empiric treatment with a tetracycline is recommended, most commonly doxycycline. Broad-spectrum antibiotics are not usually helpful. Chloramphenicol may be an alternative in some cases, but its use is associated with more deaths, particularly for *R. rickettsii*. Expert advice should be sought if alternative agents are being considered.

Prevention

No vaccine is available for preventing rickettsial infections. Antibiotics are not recommended for prophylaxis of rickettsial diseases.

Travelers should be instructed to minimize exposure to infectious arthropods during travel (including lice, fleas, ticks, mites) and animal reservoirs (particularly dogs) when traveling in endemic areas. The proper use of insect or tick repellents, self-examination after visits to vector-infested areas, and wearing protective clothing are ways to reduce risk. These precautions are especially important for people with underlying conditions that may compromise their immune systems, as these people may be more susceptible to severe disease.

FUNGI AS POTENTIAL PATHOGENS

Fungi that are pathogens are usually plant pathogenic Fungi. There are comparatively few species that are pathogenic to animals, especially mammals. According to Hawksworth (1992), there are approximate a little 1.5 million described species of fungi. A little more than 400 of these species are known to cause disease in animals, and far fewer of these species will specifically cause disease in people. Many of the latter will only be superficial types of diseases that are more of a cosmetic than a health problem. Thus, there are not many species of fungi that are pathogenic to human that will be fatal. The study of Fungi as animal and human pathogens is **medical mycology**.

The diseases of warm-blooded animals caused by fungi are known as **mycoses** (sing.=mycosis). The successful treatment of fungal diseases is more difficult than those caused by bacteria. Because bacteria are prokaryotes, the makeup of their cells are very different than our own eukaryotic cells and pharmaceutical products, such as antibiotics, are able to successfully destroy

bacteria without harming our cells, tissues and organs. The most widely used drug for treating systemic mycosis and other fungal infections that do not respond to other drugs is Amphotericin B. Azole drugs are also widely used, but these only inhibited fungal growth and do not kill the fungus.

There are a number of diseases that specifically cause human diseases. However, fungi can vary in their host specificity.

The majority of most human pathogenic fungi appear to be soil inhabiting species where they live as saprobes, but given the appropriate conditions, i.e. if the person is not healthy, an open wound is present, direct injection of fungus into your system, a particular life-style, AIDS, etc., they will aggressively attack people. Thus, many fungal infections may be due to **opportunistic fungi** (=facultative parasites) rather than fungi that specifically cause human diseases.

Fungal Human Pathogens

In discussing fungal diseases, the most convenient way of classifying them is to categorize them according to the type of infection that has occurred:

1. **Superficial infections**, are caused by fungi that attack the skin or its appendages (nail, feathers and hair). Some examples of these infection include ringworms, jock-itch and athlete's foot. These fungi are known as **dermatophytes**.

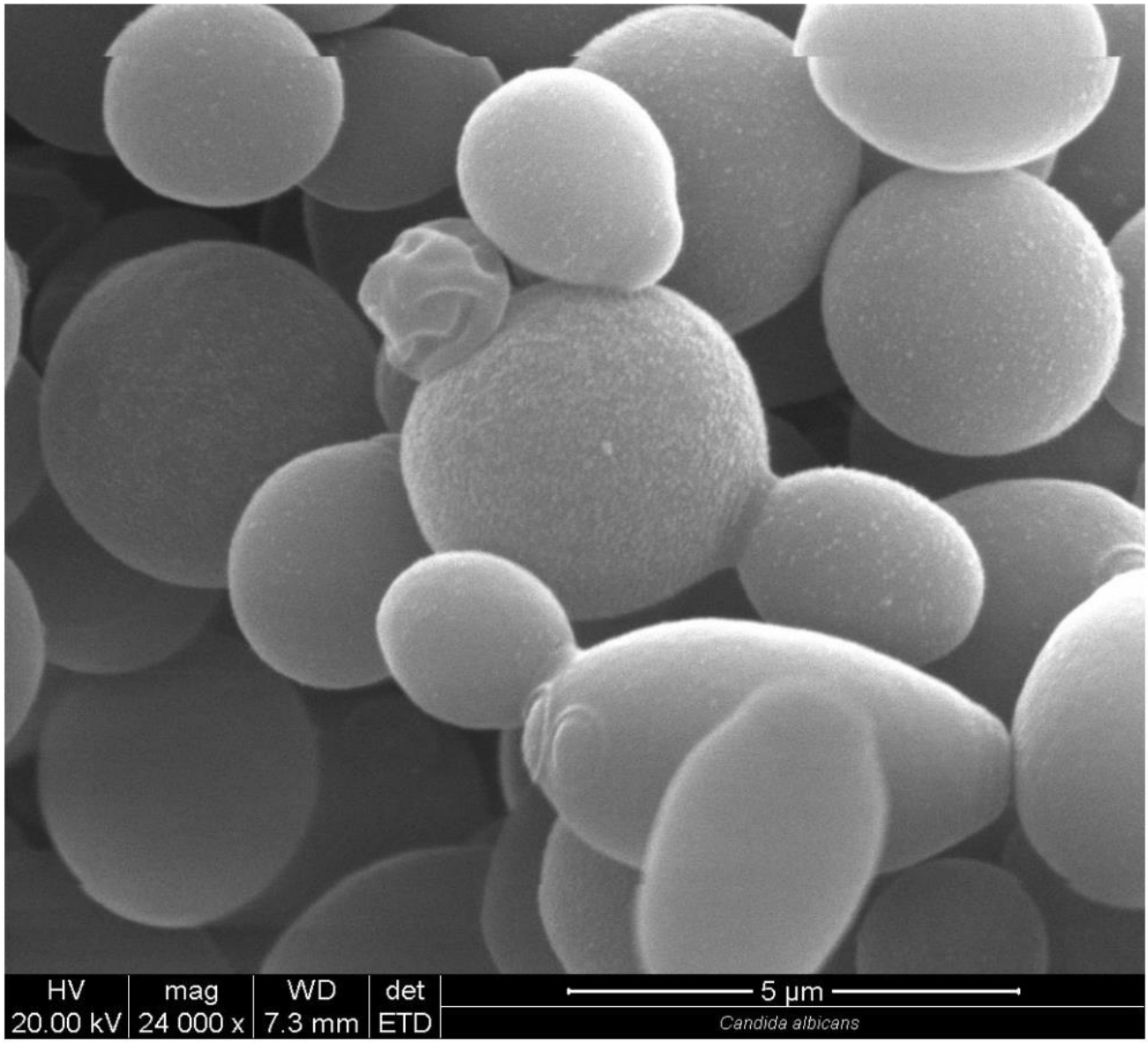
2. **Systemic infections**, diseases that occur deep within the tissues, involving vital organs and/or the nervous system, and which may be fatal, but may also be chronic. Entry into the body is usually through inhalation of spores or open wounds. Blood circulation or respiratory system may then transmit fungus throughout body and additional infection of internal organ may occur. These fungi, are usually saprotrophic fungi, growing in the soil.

A third, **Intermediate infection**, is sometimes also recognize and is intermediate between the two just discussed. The infection will occur below the skin, but will remain localized

***Candida albicans* and Candidiasis**

Candida albicans is a dimorphic fungus. That is, it grows as both mycelium and yeasts. This is one reason why there were so many names given to this fungus. This fungus normally occurs in the mouth, digestive tract, and vagina of perfectly healthy people, but under some circumstances, and for reasons unknown, it may cause severe and even fatal infections, with lesions and eruptions of the skin, nails, mouth, bronchial tubes and lungs. There are suggestions that there are special strains of this species that are pathogenic. This is suggested by the fact that this

disease can be contagious and epidemics have occurred. Predisposition may also play a role in infection. Oral infections known as thrush are relatively common. Infections can occur on various parts of the body.



Chromoblastomycosis

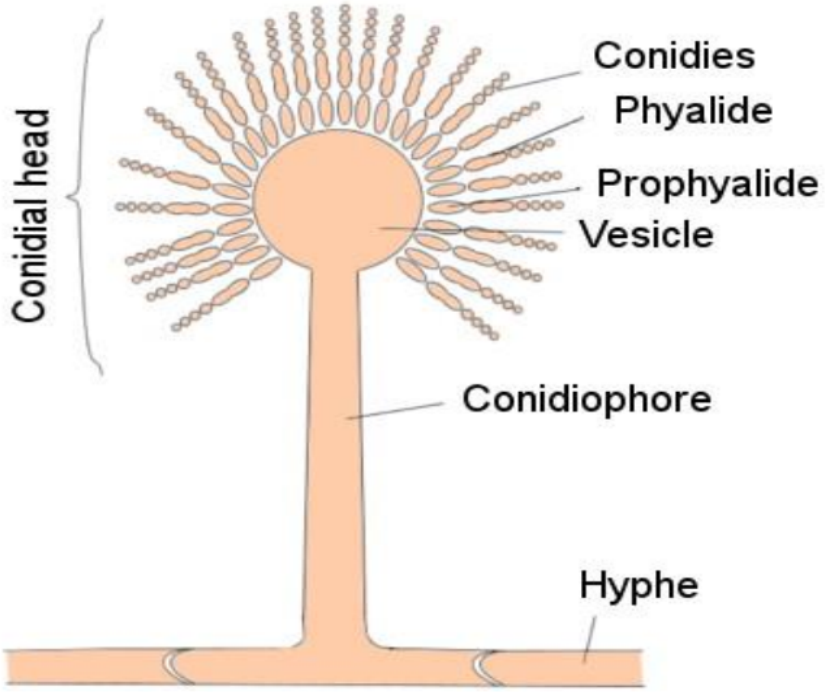
Disease is mostly tropical to subtropical, but was first reported from Boston in 1915 and may be caused by several species of fungi. Species causing this disease are mostly soil inhabiting or on decaying vegetation and typically enter the foot or lower part of the leg through wounds from walking bare-footed. Early treatment involves excision of infected area or cryosurgery. Chemical treatments vary in their success of controlling this disease.

***Aspergillus fumigatus* and Aspergillosis**

Aspergillus fumigatus is a species complex rather than a single species. It is actually composed of ten species. These species are commonly found in decaying vegetation, especially when the latter is undergoing microbiological heating, because this complex is **thermophilic**, adapted to growing at high temperatures 50 - 55ºC (120 -130ºF).

Aspergillus fumigatus sometimes parasitizes animals, especially birds, infecting mainly lungs and causing heavy mortality - up to 50% in young turkeys and up to 90% in young chicks. Heavy losses have also been reported in herring gulls, ostriches and diving ducks in the wild and in penguins in zoos. The fungus can also invade the embryos of eggs in incubators, and probably does the same in eggs in nest in the wild. It also invades the uterus of pregnant cattle and grows through the placenta into the fetus, which then dies and is aborted. It has been estimated that 64% of bovine abortion investigated were due to infection of *A. fumigatus*.

In people, the disease can lead to a chronic lung infection which is apparently very contagious. The fungus is thought to cause death, but that is not certain. In patients that have died and *A. fumigatus* has been isolated, many have also had underlying disease that possibly lowered their resistance to the fungus. However, it is also possible that the fungus had lowered their resistance to the other infective agents. It is difficult to know what came first.



Mechanism of pathogenecity

Diseases Caused by Human Pathogenic Fungi

Fungal diseases can be broadly classified on the basis of causative agents as:

(a) dermatophytosis,

(b) histoplasmosis,

(c) blastomycosis,

(d) coccidiomycosis,

(e) candidiasis,

(f) cryptococcosis,

(g) aspergillosis,

(h) hyalohyphomycosis, and

(i) zygomycosis,

These diseases differ in their nature, causative agents, and distribution. Candidiasis encompasses secondary or opportunistic infections ranging from acute, sub-acute, and chronic to life-threatening mycoses. Infections are localized to mouth, throat, skin, vagina, fingers, bronchi, lungs, and gastrointestinal tract, or sometimes become systemic as candidemia, endocarditis, and meningitis. A number of Candida spp are encountered in candidiasis such as C. albicans, C. glabrata, C. tropicalis, C. krusei, C. dubliniensis, C. parapsilosis. C. albicans is a member of the commensal microflora of the intestine. It is pleomorphic and undergoes reversible morphogenic transitions between budding yeast, pseudohyphal, and hyphal growth forms. Healthy persons generally encounter superficial infections but in immunocompromised patients invasive infections could also occur. Approximately 70% of woman experience vaginal candidiasis once in a life, and 20% suffer from recurrence. Among other Candida spp, C. glabrata has emerged as a frequent pathogen due to increased use of immune suppressive agents. C. krusei is a pathogen of importance in patients with hematological malignancies and transplants. C. parapsilosis is frequently isolated from blood cultures due to insertive medical devices. C. tropicalis is one of the causative agents of candidemia and isolated from patients with leukemia and those who have undergone bone-marrow transplantation. C. dubliniensis is found associated with systemic infections in AIDS patients.

Host–Fungi Interaction: The Process of Infection

Like any other microbial pathogen, fungal infection also involves some basic steps such as

(1) Entry and adherence to the host tissue, (2) invasion of the host tissue,

(3) Multiplication, colonization and dissemination in the tissues, and

(4) Evasion of the host immune system and damage to the tissues.

Host Factors

Considering the interaction between host and pathogen, immune cells are the major antagonists to the survival of fungal pathogens inside the host. However, primary resistance to fungal invasion and colonization is contributed by cutaneous and mucosal physical barriers. The non-specific host defenses include

(1) The antifungal activity of saliva and sweat,

(2) The competition for space and nutrients by the normal microbiota of the skin and mucous membranes, which limits the growth of potential pathogens, and

(3) The mechanical barrier of the skin and mucous membranes which prevent entry of fungi.

Inflammatory systems to combat fungal proliferation involving the action of neutrophils, mononuclear phagocytes, and other granulocytes are also considered to be nonspecific. The specific host defenses or acquired immunity consist basically of the cell-mediated immunity regulated by T-lymphocytes. In humans, mycoses acquired by exposure to fungal spores through the respiratory tract are checked primarily by the first line of defense, i.e., mucociliary clearance. Overall, severity of disease depends on factors such as inoculum size of the attacking pathogen, magnitude of tissue damages, ability of fungi to multiply in the tissue, and the immune status of the host cells.

Fungal Factors

Production of extracellular enzymes such as keratinases, collagenases, gelatinases, phospholipases, lipases, and acid proteinases by dermatophytes, Aspergillus sp, Candida sp, and Cryptococcus sp is considered to be the fungal-associated factor that helps fungi in nutrient uptake, tissue invasion, adherence, and dissemination inside the host. In some fungi such as C. neoformans, the presence of capsule may be an important factor.

Virulence and Pathogenicity

Pathogenesis is the ability of a microorganism to infect the host and produce disease resulting from interaction of pathogen with host via expression of certain factors on both sides.

Pathogenicity of a fungus depends on its ability to adapt to the tissue environment and to withstand the lytic activity of the host's defenses. Several determinants including genes or gene products such as enzyme molecules known as virulence factors are involved in this relationship, producing superficial to invasive infections in humans. Virulence refers specifically to a property of the pathogen and, according to modern definitions, virulence is the ability of a pathogen to multiply and cause harm to its host. Diseases caused by fungi without invasion of live tissues include mould allergies and cutaneous dermatophyte infections (ringworm), in which fungi invade and damage only the nonviable epidermis. Many human fungal pathogens are dimorphic and the morphogenetic transition between these forms is often stimulated by growth in the host and correlated with host invasion.

Determinants of pathogenicity are called virulence factors. Pathogenic microbes often possess a number of virulence factors and mechanisms. These factors determine whether the organism (the host) lives or dies during host–microbe interactions. The factors can be inducible or constitutive, the direct product of genetic elements (proteins), or the products of complex biosynthetic pathways such as polysaccharides or lipid mediators. The virulence factor can be assessed by comparing biological response in fungi with and without the factor. The most convincing evidence for a factor to be considered as a virulence determinant is the simultaneous loss of the factor and loss of virulence, and the regaining of virulence when the factor is restored. Virulence factors must help the pathogen to grow at elevated temperatures, facilitate adherence, penetration and dissemination, or assist in resistance against innate immune defenses, e.g., phagocytosis and complement.