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EDITORIAL

White-nose syndrome: A novel dermatomycosis of biologic interest and epidemiologic consequence

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Abstract Over the past 10 years, the environmental and veterinary communities have sounded alarms over an insidious keratinophilous fungus, *Pseudogymnoascus destructans,* that has decimated populations of bats (yes, bats, chiropterans) throughout North America and, most recently, Northern China and Siberia. We as dermatologists may find this invasive keratinophilous fungus of particular interest, as its method of destruction is disruption of the homeostatic mechanism of the bat wing integument. Although it is unlikely that this pathogen will become an infectious threat to humans, its environmental impact will likely affect us all, especially as recent data have shown upregulation of naturally occurring coronaviruses in coinfected bats. Dermatologists are familiar with keratinophilous dermatophyte infections, but these rarely cause serious morbidity in individual patients and never cause crisis on a population basis. This contribution describes the effects of *P destructans* on both the individual and the population basis. Bringing the white-nose syndrome to the attention of human dermatologists and skin scientists may invite transfer of expertise in understanding the disease, its pathophysiology, epidemiology, treatment, and prevention.

Introduction

Around the world, millions of people are infected with keratinophilous fungi, but human mortality from these pathogens is infinitesimal. Dermatophyte infections might be unsightly, but, even when recalcitrant, they cause few long-term effects. In contrast, keratinophilous fungi that infect other mammals are not always so benign. In particular, wildlife biologists are gravely concerned about an emerging fungal infection they have characterized as a "devastating disease of hibernating bats that has caused the most precipitous decline of North American wildlife in recorded history."[1] Few pathogens are as insidious and lethal as *Pseudogymnoascus* (formerly *Geomyces*) *destructans,* the fungus that causes bat white-nose syndrome (WNS),[2,3] which threatens huge populations of insectivorous bats throughout eastern North America.[4]

To most Americans, other than on Halloween, bats go largely unnoticed. Their nocturnal habits and secretive lairs make them nearly invisible, despite the enormously valuable ecosystem services they provide as insectivores, seed dispersers, and pollinators. Bats jump to the front of a worrisome epidemiologic queue when one considers that they can harbor lyssaviruses, including classic rabies,[5] and that they are the likely reservoir hosts to other viral zoonoses, including coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome, Middle East respiratory syndrome, Ebola, Marburg, Nipah, and Hendra virus diseases.[6]

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At the population level, however, it seems that WNS, which spreads rapidly among insectivorous bats in their hibernacula (underground and above-ground places of overwintering, such as caves and mines), is far more lethal to hibernating bats than bat-borne viruses are to humans. Indeed, since first documented in 2006,[3] WNS has been documented in 7 North American bat species, killing millions of bats, indeed up to 90% of some populations, such as the now-endangered gray bat (*Myotis grisescens*) and Indiana bat (*Myotis sodalis*).[3,7,8] Concern for the consequences of WNS extend beyond preservation of species, but also include loss of consumption of agricultural pests, as well as broader ecologic consequences, including up-regulation of bat-borne viruses.[9]

Epidemiology

WNS was first identified among hibernating bats at five caves in upstate New York.[10] Huge numbers of dead bats were found—and they had peculiar opaque white hyphae around their muzzles, leading to the name WNS. By 2019, the pathologic fungal infections had been detected on bats in 34 states and provinces in North America as well as across Mongolia and northern China.[11,12] The fungus has been isolated in Europe, where it likely has had a long-standing commensal (benign) relationship with European insectivorous bats, which are apparently disease resistant.[10]

Several lines of evidence suggest that the fungus was introduced to North America from Europe. Specifically, after the 2006 discovery of WNS in hibernating bats of New York and subsequent description of *Pseudogymnoascus destructans*, bat researchers reported observations, dating back several decades, of a seemingly benign white fungus on hibernating bats of several species in central Europe. Follow-up investigations confirmed that these bats were colonized by *P destructans*.[13–16] Further analyses show that European bats develop skin lesions similar to North American WNS, although without accompanying mortality. In areas with high mortality rates (eg, North America), bats start to show high burden of the fungus in early winter, compared with European sites with more commensal relationships.[14]

What brought *P destructans* to North America? There is concern that recreational cavers (spelunkers) may have unwittingly spread the fungus from Europe on contaminated clothes, shoes, and equipment. Subsequent spread within North America is mainly due to bats carrying spores into new hibernacula; however, many states require decontamination of caving equipment and limit access to caves. A map of the current distribution of WNS can be found at whitenosesyndrome.org.

P destructans is spread via direct contact among cohibernating bats in contact with fungal environmental reservoirs in soil of caves and mines.[17] *P destructans* is an unusual mammalian pathogen, because it is an obligate psychrophile (ie, it grows only under cold conditions). It infects bats during hibernation, a state of metabolic quiescence when core body temperatures drop to 2 to 10°C.[18] The fungus grows at temperatures as low as 1°C, optimally 12.5 to 15.8°C, with an upper limit ~19.5°C.[19] At suboptimal temperatures, *P destructans* grows slowly.

Under favorable conditions, *P destructans* grows as a mold with exuberant white hyphae on the wing skin and muzzle fur of susceptible bats. Signs of active infection include patches of rough skin on the ears, forearms, wing membranes, and feet. Hyphae may surround hair follicles, creating the appearance of comedones along the muzzle.[20] Unlike true dermatophytes, which infect only the cornified epidermis (ie, the stratum corneum), *P destructans* also invades the Malpighian layer and crosses the basement membrane.

Cutaneous anatomy of the bat

An overview of bat anatomy and histology helps one understand the pathophysiology of WNS. Normal bat muzzles possess small, scattered hairs and vibrissae (sensory whiskers) with richly vascularized, fibrous follicles along the chin. Muzzle hairs are surrounded by sebaceous glands at their follicle bases. The muzzle's reticular dermis has very little underlying subcutaneous fat.[21] The name, WNS, derives from *facial* hyphae, but the condition's morbidity and mortality arise largely from fungal damage to the wings.

Bat wing histopathology has been described in few species, but can be somewhat generalized.[22] The species of bats affected by WNS, all insectivorous, have extremely thin, membranous wings.[23] Their wings fulfill homeostatic duties common to all mammalian skin, for example, to control temperature, prevent desiccation, and resist microbial pathogens (Figure 1). In addition, wing skin, which composes 85% of body surface area of some insectivorous bats, supports gas exchange,[24] a physiologic phenomenon typically associated with amphibian skin, not mammalian. F1

Wing skin of small insectivorous bats consists of a palindromic arrangement of keratinized stratum corneum on

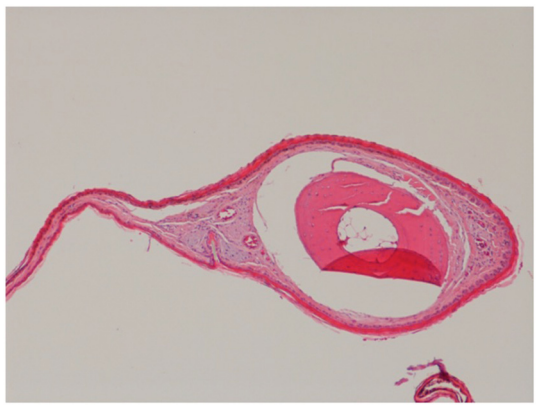

Fig. 1 Bat wing of *Corynorhinus townsendii*, the Virginia big-eared bat. Corynorhinus belongs to the same family, Vespertillonidae, as *Myotis lucifigus* and has nearly identical wing structure.

both outer surfaces, overlying a single-cell layer of basal keratinocytes, separated by a middle zone consisting of a thin layer of connective tissue. The stratum corneum is relatively thick and durable, composing 40% of the epidermal thickness, which withstands the continuous air abrasion that wings experience during flight.[25] Theoretically, there should be a stratum spinosum in between these two epidermal layers, but this cannot be identified on light microscopy and is not described in the veterinary literature. The thin intervening mesenchymal layer, made of indistinguishable dermis and hypodermis (subcutaneous tissue), contains nerves and muscle fibers embedded in an intricate network of elastin and collagen fibers (Figure 2). The mesenchymal zone of bat-wing skin differs from human skin by lacking substantial tissue that produces hair, glands, and other adnexae.[26] Bat wings, in contrast, are largely glabrous.[27]

Pathophysiology of infection (section 4)

Bat wings infected with *P destructans* exhibit variation in gross appearance, ranging from loss of sheen and elasticity (causing a dried-out appearance) to tissue loss and ulcers. WNS-damaged skin resembles human burn injuries, in some ways, with similar complications, such as loss of fluids and electrolytes and a portal for bacterial infection.[26] *P destructans* hyphae traverse the complete thickness of the wing, crossing from the stratum corneum on one side, traversing the basal layer, basement membrane zone, the mesenchymal zone, and on across the epidermal layers on the wing's other side. WNS forms cuplike epidermal erosions and ulcers on the wing's surface, and then destroys the sebaceous glands that moisturize and waterproof the skin. Hyphae do not invade blood vessels, and inflammatory infiltrates are generally absent, even with extensive fungal invasion.

It is proposed that WNS disrupts the skin's homeostatic mechanisms that are necessary for successful hibernation. Like all mammals, bats breathe through conventional respiration, but they can also regulate blood pH by passive release of additional carbon dioxide through wing skin. WNS seems to interfere with this process and with the wing's ability to adjust blood flow to help maintain blood pressure and body temperature.[28] The dermatomycosis disturbs cutaneous regulation of passive transepidermal exchange of oxygen, carbon dioxide, and water vapor.[9,24] This can cause hemoconcentration, hypoglycemia, hypercapnia, and respiratory acidosis—thus disrupting hibernation.[29,30]

Infected bats lose water and electrolytes through damaged skin, leading to hypotonic dehydration. When hibernating, however, the only way that bats can replace fluids is during brief awakenings when they are able to drink cave water, which is largely electrolyte-free. (During active seasons, bats obtain electrolytes by eating insects.)[10,31] When hibernation is repeatedly disrupted, the physiologic costs for bursts of full metabolic activity are high and may fatally deplete energy reserves (ie, subcutaneous fat on nonwinged parts of the body).[32]

The current theory of mortality associated with WNS in progressive stepwise fashion begins with the erosion and ulceration the epidermis. *P destructans* secretes proteolytic endopeptidases, called destructins, that degrade collagen.[27] Ulceration increases blood CO_2 levels, leading to metabolic acidosis and consequent hyperventilation. As the metabolic rate accelerates to maintain body temperature, the bat arouses from hibernial torpor. The combination of dehydration and thermodysregulation is usually fatal.[33]

Most bat-borne pathogens (eg, rabies viruses) proliferate only when the host is metabolically active (ie, nontorpid). *P destructans,* on the other hand, is an obligately psychrophilic pathogen that infects bats only during torpor when core temperatures drop dramatically.[34] Hibernating bats rarely mount significant inflammatory responses to the invading fungi.[35] This initial lack of inflammation during torpor, however, is followed by extensive neutrophilic infiltration when surviving animals emerge in springtime. The robust immune response that accompanies restoration of full metabolic activity resembles the immune reconstitution inflammatory syndrome in HIV-infected humans. The renewed inflammatory vigor—in people and in bats—often creates unanticipated tissue damage.[36] If a WNS-infected bat survives hibernation, metabolic reawakening, and immunologic restoration, full recovery generally ensues.[31]

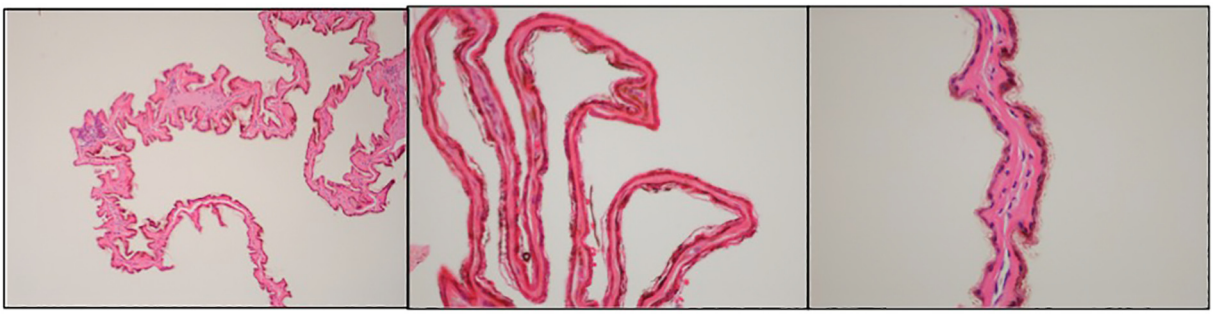

Fig. 2 *Corynorhinus townsendii* wing at **(a)** 100× magnification, **(b)** 200× magnification, and **(c)** 400× magnification. A bilayer of epithelial cells with thin dermis and no subcutaneous tissue is visible. Few endothelial cells are visible lining the dermis.

Ecologic consequence

Although perceived by some as strictly a wildlife conservation challenge, WNS has potentially wide-ranging ecological consequences. WNS may herald the regional extinction of the little brown bat, once among our continent's most abundant bat species, in northeastern North America by 2026.[4] Adaptation among little brown bats has occurred rapidly since WNS was introduced, and drastic genomic shifts have been detected associated with population declines due to the disease.[37] Other species that are moving toward endangered status include tricolored bats (*Perimyotis subflavus*), big brown bats (*Eptesicus fuscus*), Indiana bats, and northern long-eared bats (*Myotis septentrionalis*).

As obligate insectivores, these bats consume literally billions of insect pests each year, contributing ecological services to American farmers valued around $23 billion annually.[10] Bats also consume mosquitoes and other vectors of human pathogens (eg, West Nile virus and other encephalitis-causing arboviruses). Collapse of insectivorous bat populations might permit an increase in vector-borne diseases throughout the former ranges of the decimated species.

Perhaps even more worrisome, especially as the world battles pandemic COVID-19, which is caused by a virus whose natural hosts are insectivorous bats in southern China, is the recent discovery that North American bats that are naturally coinfected with WNS and a different coronavirus shed up to 60-fold more coronavirus RNA than bats without WNS.[38] Although the particular coronavirus studied in the WNS-infected bats did not appear to sicken the bats, other coronaviruses that are commensal in bats have crossed over into human populations several times in the past 20 years, leading to the epidemics of severe acute respiratory syndrome, Middle East respiratory syndrome, and now COVID-19.[39,40]

Conclusions

Much remains to be learned about *P destructans* and WNS—and managing a disease in free-ranging wildlife is challenging. *P destructans* presents unique challenges because its spores can survive in soil, independent of mammalian hosts, allowing it to escape the selective pressures that prevent other host-dependent pathogens (such as viruses) from entirely destroying their reservoir populations. Without population-level infection-control strategies, current efforts to curtail WNS focus on universal precautions, including decontamination of clothing and equipment after exposure to potentially infected animals or contaminated environments, and restricting human access to hibernacula.

Dermatologists appreciate the importance of an intact integument and the disastrous, often fatal, effects when skin cannot accomplish essential homeostatic tasks of temperature control, pathogen resistance, and fluid/electrolyte balance. Can dermatology's scientists help fight WNS by drawing on their understanding of treatment and prevention of skin diseases in another mammalian model, *Homo sapiens*? Due to *P destructans*'s temperature requirements, it is unlikely that it could ever infect *H sapiens;* however, the ecologic consequences of WNS will extend far beyond the bats whose populations are imploding in ways that we are unable to predict.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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