Non-Candida Yeasts and Dimorphic Fungi in Cetaceans

Subjects: Microbiology

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This encyclopedia entry addresses the overlooked presence of non-*Candida* yeasts in cetaceans, key to marine ecosystems yet threatened by human activity, climate change, and pollution. Highlighting the importance of cetaceans as indicators of ocean and human health, it examines the distribution, pathogenicity, and ecological impact of specific yeast species, including *Cryptococcus* spp. and *Paracoccidioides* spp. The entry explores the balance between yeast commensalism and pathogenicity, influenced by environmental stressors like pollution and climate alterations, and its effects on marine host health and ecosystem dynamics. The unique physiological and ecological aspects of cetaceans are considered, with a focus on potential effects on their behavior, reproduction, and survival. The entry identifies key research gaps and advocates for advanced molecular studies on the cetacean mycobiome, emphasizing the need for a One Health approach. It underscores the urgency of further research into non-*Candida* yeasts in cetaceans for marine conservation and public health.

Keywords: cetacean mycobiome ; fungal infection ; dolphin ; one health ; zoonosis ; fungal pathogen

1. Introduction

Cetaceans play a critical role in marine ecosystems. Marine mammals are consumers of production at most trophic levels, and this position in the trophic hierarchy directly affects both predator and prey dynamics, thereby influencing marine biodiversity and nutrient cycling ^{[1][2][3]}. However, the environment is being increasingly affected by severe anthropogenic impacts such as climate change and pollution, among others. In this regard, cetaceans are considered sentinel species for both ocean and human health ^[4]. They are ideal indicators of ecosystem health due to their extended lifespan, enduring coastal residence, high-trophic level feeding, and distinct fat reserves that accumulate anthropogenic toxins. As many marine mammals inhabit coastal regions alongside humans and share dietary sources, they can also act as reliable indicators of potential human health concerns ^[5]. In fact, they face numerous environmental challenges, such as chemical pollution, temperature and salinity fluctuations, and algal toxins. Importantly, they play a significant role in the emergence and spread of both new and re-emerging pathogens ^[6].

Non-*Candida* yeasts might play a conspicuous role in the complex microbiota ecology of cetaceans ^[Z]. Current research, despite being considerably limited, points to the considerable biodiversity of these yeasts within different cetacean hosts, and there is still a significant knowledge gap on the role of these microorganisms in the ecology and pathology of their hosts. Although several studies on bacterial microbiota have been conducted in cetacean populations, the fungal microbiome and fungal-related pathologies have been largely ignored ^{[B][9][10][11]}. Notably, the distribution of these yeasts is not homogeneous and demonstrates significant intraspecies variation, as well as distinct anatomical niches within the same individual, including the skin, blowhole, and gastrointestinal tract, among others. These findings underscore the intricate interplay of host-specific and location-specific factors in shaping the composition of the fungal community. Several genera and species have been identified in both wild and captive cetacean populations. However, efforts in research have neglected fungal pathology and the mycobiome; therefore, the related evidence is considerably limited.

2. Identified Species of Non-Candida Yeasts in Cetaceans

2.1. Cryptococcus spp.

Cryptococcosis, caused by the fungi *Cryptococcus neoformans* or *C. gattii*, is increasingly significant in healthcare. *Cryptococcus neoformans* primarily affects immunocompromised individuals, often leading to central nervous system (CNS) complications and subsequent meningoencephalitis. In contrast, *C. gattii* infection typically results in severe lung disease. Globally, cryptococcosis sporadically impacts a broad range of species, from Acanthamoeba to large mammals ^{[12][13]}. While domesticated animals are well documented in the literature, free-living wildlife is often overlooked. The disease's prevalence varies and is notably higher in parts of Australia, Brazil, and the Pacific Northwest. This fungal

infection affects diverse wildlife, pets, livestock, and humans and can cause both overt disease and subclinical infection [14].

Cetacean species exhibit enhanced susceptibility to *Cryptococcus* spp. infections. Both *C. neoformans* and *C. gattii* have been identified in these animals (**Table 1**). While *C. neoformans* is ubiquitously distributed and frequently found in environments with minimal exposure to solar radiation, with a significant reservoir being shielded avian guano accumulations, *C. gattii* has a more restricted distribution and is commonly linked to the Eucalyptus camaldulensis tree, among others $\frac{[14][15]}{2}$.

Unlike other fungal species, *Cryptococcus* spp. is not believed to be a normal colonizing organism in cetaceans, and mainly all reported cases are related to invasive diseases with high mortality rates ^[16]. This vulnerability is particularly pronounced during coastal migrations, while in captivity or in situations of proximity to terrestrial regions that allow the individuals to encounter infectious propagules present in effluents and runoff entering marine environments ^[14]. Additionally, these infections can occur as outbreaks and can be associated with the detection of cases in humans or other animal species ^[12]. In fact, previous cryptococcal epizootics that cause remarkable mortality in odontocetes are clustered around terrestrial hotspots ^[16]. The emergence of *C. gattii* in North America in 1999 marked a multispecies cryptococcosis outbreak across British Columbia, Washington State, and Oregon. Since the early 2000s, the Pacific Northwest of the USA and Canada, witnessed an upsurge in such infections among marine mammals and humans. Significantly, animal cases outnumbered human cases by approximately 75%, with a substantial impact on marine mammals ^{[16][127][18]}.

The primary mode of transmission in cetaceans is through the inhalation of basidiospores. This susceptibility arises from the large intake of these infective propagules, which are transported deep into the lower respiratory system as a consequence of the inspiration of a large tidal volume after explosive exhalations, as well as the absence of sinonasal filtration mechanisms ^[14]. Furthermore, given the anatomical absence of a cribriform plate in cetaceans, direct inoculation and consequent neurological diseases are less frequent than in humans, in whom the prevalence of meningoencephalitis is considerably greater ^[19]. Pneumonia is the predominant clinical manifestation in cetaceans and can potentially escalate to disseminated systemic infections. It appears in the context of direct fungal invasion of the lung parenchyma and destructive inflammatory infiltration, sometimes associated with granulomatosis ^[20], bronchitis, and pleuritis ^[21]. It is usually followed by generalized lymphadenopathies and, in some cases, multiorgan affectation with gastric, renal, splenic, or even adrenal involvement ^{[22][23]}. A unique case of maternal–fetal transmission of *C. gattii* in a harbor porpoise (*Phocoena phocoena*) was also reported ^[24]. While some cutaneous lesions have been described ^{[22][25]}, nearly all cases in the literature report pulmonary cryptococcosis.

Cryptococcal invasive disease can occur both in wild and captive animals ^{[23][26]}. On the one hand, *C. neoformans* infections have been reported in baleen whales such as the southern right whale (*Eubalaena australis*) coinfected with *Candida zeylanoides*. However, the majority of related studies have focused on odontocetes, specifically Dall's porpoises (*Phocoenoides dalli*) and harbor porpoises. These investigations primarily involve necropsies conducted on wild stranded animals ^{[17][25][26][27][28]}. On the other hand, *C. gatti* infections have affected bottlenose dolphins (*Tursiops truncatus*), spinner dolphins (*Stenella longirostris*), Dall's and harbor porpoises, and Pacific white-sided dolphins (*Lagenorhynchus obliquidens*) ^{[16][17][18][21][22][24]}. These isolations have been reported worldwide, in the West and East Atlantic, East Pacific, and Indian Ocean, and from the outbreaks of British Columbia to South Africa or Western Australia (**Table 1**).

Although *Cryptococcus* species are not typically considered standard colonizer in these species and are frequently associated with invasive cases during outbreaks, findings from two distinct studies employing both culture-based and molecular methodologies could challenge this understanding ^{[29][30]}. In 1990, an investigation into the microbiota obtained from cultures of healthy and lesional skin tissue samples from 19 bowhead whales (*Balaena mysticetus*) near Barrow, Alaska, identified two isolates of *C. neoformans* in lesioned skin. Additionally, several other species, including *C. gastricus*, *C. luteolus*, *C. albidus*, *C. laurentii*, *C. terreus*, and *C. uniguttulatus*, were detected in both healthy and lesional skin samples ^[29]. In a more recent study examining the gastrointestinal microbiota of East Asian finless porpoises (*Neophocaena asiaeorientalis sunameri*) using high-throughput sequencing, *Cryptococcus* spp. was very frequently detected in stomach, hindgut, and fecal samples. This was in stark contrast to the findings of the fecal microbiota of Californian blue whales (*Balaenoptera musculus*), where *Metschnikowia* spp. predominated.

While the strains of the fungus detected across various hosts have shown temporal and spatial consistency in known epizootics, the literature on this topic is fragmented. The validity of these studies is often contingent upon the diagnostic methods used. A notable research gap exists in antifungal susceptibility, with limited data available, as exemplified by a

single report on itraconazole susceptibility in a bottlenose dolphin with cryptococcal bronchopneumonia ^[21]. This indicates a crucial area for further investigation to enhance the understanding and treatment of fungal diseases.

Moreover, the role of human activities, such as construction and deforestation, in the epidemiology of cryptococcal disease across species, including cetaceans, other animals, and humans, in environmental alterations demands attention. These activities can disturb habitats and facilitate the aerosolization of fungal spores, potentially contributing to disease proliferation, as observed in *C. gattii* outbreaks $\frac{[16]}{1}$. This connection accentuates the need for an interdisciplinary approach, integrating environmental, animal, and human health considerations to address the complex interplay between anthropogenic activities and disease dynamics, ultimately fostering a healthier coexistence between humans and their environment.

2.2. Paracoccidioides ceti: The Etiologic Agent of Lacaziosis or Lobomycosis

Paracoccidioidomycosis, previously known as lacaziosis or lobomycosis, was first documented by Jorge de Lobo in 1931 in a man from the Amazonia who presented with enduring sacral nodular lesions ^[31]. By 1971, a similar condition was observed in dolphins ^[32]. Given their phenotypic parallelism and cultivation challenges, both of these conditions were believed to be caused by a shared fungal agent, referred to as *Lacazia loboi*, by Taborda in 1999. Molecular studies subsequently revealed that the uncultivable pathogens causing this disease in dolphins and humans were distinct species: *P. ceti* and *P. lobogeorgii*, respectively ^{[33][34]}. However, *P. ceti* is assumed to be a zoonotic pathogen, as shown by recorded cases of human–dolphin transmission ^[35]. While such cases exist, they appear infrequently ^{[36][37]}. Unintended transmissions in research settings ^[38] and deliberate experimental infections in animals and humans have been documented ^{[39][40]}.

Although human cases occur mainly in the rainforest regions of Central and South America, especially in the Brazilian Amazon basin ^[41], most dolphin infections have been reported along Florida's coastline ^[42]. Nevertheless, there are accounts from distant areas, encompassing the Eastern and Western Atlantic, Eastern and Western Pacific, and Indian Ocean. It has been recognized in various locations in the Americas, including Brazil ^{[43][44]}, Costa Rica ^[45], Venezuela ^[46], and Surinam ^[47]. Importantly, outside of the Americas, paracoccidioidomycosis has been reported in France ^[35], Spain ^[48], Madagascar ^[49], South Africa ^[50], and Japan ^{[51][52]} (**Table 1**). Nonetheless, all human cases in nonendemic countries have been imported.

To date, all cases of paracoccidioidomycosis have occurred in species of the *Delphinidae* family, while there are no reports on this phenomenon in platanistoid dolphins or mysticetes. Moreover, both captive and wild dolphins are susceptible to this infection, and serological studies have demonstrated that the seroprevalence against *P. ceti* in captive dolphins is 61.0%, while that in wild Dall's porpoises is 26.9% ^[53]. Evidence of paracoccidioidomycosis has been reported in bottlenose dolphins (*T. truncatus*) in the West Atlantic ^{[43][46][54][55][56]}, in the East Atlantic ^[35], and in the Eastern Pacific ^{[45][57]}, and in Indo-Pacific bottlenose dolphins (*Tursiops aduncus*), both in the Indian Ocean ^[49] and in the Western Pacific ^{[52][58]}. Furthermore, there have been cases in Indian Ocean humpback dolphins (*Sousa plumbea*), in Australian snubfin dolphins (*Orcaella heinsohni*), and in Guiana dolphins (*Sotalia guianensis*) in the Western Atlantic ^{[50][59]} (**Table 1**).

The disease manifests through distinct clinical features, and it is often influenced by environmental factors, especially in epizootic instances observed in the coastal regions of Florida and North Carolina ^[60]. Its typical lesions, white to reddish and occasionally gray, are raised and adopt a nodular or verrucous profile, resembling the appearance of a cauliflower. They might ulcerate or become expansive plaques prone to bleeding upon minor trauma. Commonly impacted anatomical areas include the dorsal cranial surface, anterior dorsum, and fins ^{[42][51][56][58][60][61]}. Pathological features include acanthosis, hyperkeratosis, hyperpigmentation, profound fibrosis ^{[42][52][58]}, lymphohystiocytic infiltration, and microabscesses replete with yeast-like cells connected by short and thin isthmuses ^[60].

However, many of the reports in the literature describing this disease involve only phenotypic characterizations of the lesions, both in wild and captive environments, and lack a proper microbiological identification of the etiological agents. Therefore, results must be carefully interpreted, especially considering the taxonomical chaos that governs the definition of the disease and considering that other fungal pathogens may be the cause of similar cutaneous diseases, such as *Trichosporon* spp. [62][63]. In fact, in many previous reports, lesions have been characterized as lobomycosis-like disease or lacaziosis-like disease—or, currently, paracoccidioidomycosis-like disease—when the histological or molecular detection of the pathogen has not been feasible [43][49][57][63].

Table 1. *Cryptococcus* spp. and *Paracoccidioides ceti* in cetaceans. Colonization was considered when there was no attributable evidence of infection or fungus-associated lesions reported.

Fungal Species	Cetacean Species	Colonization or Infection	Location	Isolation Origin	Captivity of Free- Living	Antifungal Resistance	Reference
Non-identified <i>Cryptococcus</i> spp.	Neophocaena asiaeorientalis sunameri Stenella coeruleoalba, Tursiops truncatus	Infection or colonization	China Western Australia	Lung, lymph nodes, stomach	Captive and free- living	No data	[<u>23][26][30]</u>
C. neoformans	Eubalaena australis, Balaena mysticetus. Phocoena phocoena, Phocoenoides dalli	Infection	Alaska British Columbia South Africa	Skin, lung, lymph nodes	Free- living	No data	[<u>17][25][27]</u> [29]
<i>C. gattii—</i> VGI and VGIIa	Lagenorhynchus obliquidens, Stenella longirostris, T. truncatus, P. dalli, P. phocoena	Infection	Atlantic coast of Canada British Columbia California Hawaii South Africa Washington	Skin, lung, lymph nodes, stomach, adrenal gland, kidney, spleen, pleura, placenta, brain and meninges	Captive and free- living	One isolate in <i>T. truncatus</i> susceptible to itraconazole	[<u>16][17][18]</u> [<u>21][22][24]</u>
C. albidus	B.mysticetus	Probable infection	Alaska	Skin	Free- living	No data	[<u>29]</u>
C. gastricus	B.mysticetus	Probable infection	Alaska	Skin	Free- living	No data	[<u>29]</u>
C. luteolus	B.mysticetus	Probable infection	Alaska	Skin	Free- living	No data	[<u>29]</u>
C. laurentii	B. mysticetus	Colonization	Alaska	Skin	Free- living	No data	[29]
C. terreus	B.mysticetus	Colonization	Alaska	Skin	Free- living	No data	[29]
C. uniguttulatus	B.mysticetus	Colonization	Alaska	Skin	Free- living	No data	[29]
Paracoccidioides ceti	Orcaella heinsohni, P. dalli, Sotalia guianensis, Sousa plumbea, Stenella frontalis, T. truncatus, Tursiops aduncus	Infection	Australia Belize Brazil Colombia Costa Rica Ecuador Florida Japan Madagascar Mayotte Mexico Peru South Africa Surinam Venezuela	Skin	Captive and free- living	No data	(35)(42)(43) [46)(48)(49) [51)(52)(57) [61)(63)

2.3. Other Dimorphic Fungi

In addition to *P. ceti*, other dimorphic fungi responsible for endemic systemic mycoses in other animals and humans have been reported in cetaceans, as seen in **Table 2**.

Fungal Species	Cetacean Species	Colonization or Infection	Location	Isolation Origin	Captivity of Free- Living	Antifungal Resistance	Reference
Blastomyces dermatitidis	Tursiops truncatus	Infection	Gulf of Mexico	Skin, lung, kidney, lymph nodes, heart, spleen, liver, gastrointestinal tract,	Free- living	No data	[64]
Coccidioides immitis	T. truncatus	Infection	California	Lung, lymph nodes, brain	Free- living	No data	[65]
Coccidioides posadasii	Phocoena phocoena, Phocoenoides dalli	Unknown	Japan	Serological evidence	Free- living	No data	[53]
Histoplasma capsulatum	T. truncatus	Infection	California	Lung	Captive	No data	[27][66]

3. The Significance of Non-*Candida* Yeasts in Cetacean Health and Disease

The diverse microbial communities within cetaceans, notably including non-*Candida* yeasts, are pivotal in shaping the health and disease dynamics of these marine mammals. This exploration transcends the immediate sphere of veterinary medicine and cetacean health, shedding light on broader ecological interactions and health implications. By delving into these intricate relationships, we not only contribute to cetacean conservation and well-being but also gain insights into the delicate balance of marine ecosystems. Such research underscores the symbiotic relationship between animal health and environmental integrity and, by extension, the well-being of human populations, aligning with a comprehensive approach to health that acknowledges the interconnectedness of all life forms and their shared environment.

As previously shown, several yeast species have been isolated from cetaceans, both from healthy and diseased individuals. While many of these yeasts, such as *Trichosporon* spp. and *Rhodotorula* spp., have been identified as environmental saprophytes, their detection in healthy cetaceans suggests potential commensal or even mutualistic relationships. For instance, they might play roles in nutrient absorption, immune system modulation, or protection against pathogenic microbes by outcompeting them or producing inhibitory compounds. Indeed, high-throughput sequencing in the gastrointestinal tract of East Asian finless porpoises revealed a high abundance of *Malassezia* spp. in the foregut, suggesting potential roles in digestion or maintaining gut homeostasis ^[30].

However, the separation between symbiosis and pathogenicity can be tenuous. While *Trichosporon* spp. have been isolated from healthy cetacean skin, they have also been implicated in cutaneous diseases, as noted in cases involving bottlenose dolphins $^{[62]}$. Furthermore, *Coccidioides* spp., known to thrive in terrestrial environments, are responsible for respiratory infections in cetaceans, with fatal consequences in some cases $^{[65][67]}$. Importantly, other fungal species such as *Cryptococcus* spp. and *Paracoccidioides* spp., as well as other dimorphic fungi, stand out for their potentially severe impact on cetacean well-being and might also be considerably misidentified and highly underdiagnosed, possibly due to the lack of access to these wild populations, among others $^{[14][60]}$.

Environmental disturbances, immune suppression due to pollution or climate alterations, or stress might facilitate these transitions from harmless colonization to disease. Understanding the triggers for this shift is critical for managing the health of both wild and captive cetaceans ^{[G][68]}. The diverse interactions of non-*Candida* yeasts with cetaceans might have profound implications for both conservation and veterinary medicine. Recognizing the potentially pathogenic role of some yeasts, especially in immunocompromised individuals, as well as the immune responses to these diseases and the host–pathogen relationship, emphasizes the importance of regular health assessments and monitoring, particularly in captive settings where animals might be exposed to various stressors or immunosuppressive therapies. Moreover, understanding cetacean mycobiome composition and function, which is still limited in the scientific literature beyond limited studies ^{[30][69]} could illuminate broader ecological dynamics, including how pollution, climate change, or human interventions affect marine ecosystems.

The health of cetaceans often reflects the health of their ecosystems ^[5]. Disturbances leading to increased susceptibility to yeast infections, for instance, may signify broader ecological issues that need to be addressed. Alterations in the prevalence or pathogenicity of particular yeast species could serve as early warning signs of environmental changes, and preemptive fungal biomarkers could serve as valuable and useful indicators of individual, population, or ecosystem

changes. For example, an increase in pathogenic fungi or a decrease in beneficial fungi might suggest that environmental stressors or contaminations affect the health of the marine ecosystem. Furthermore, for conservation efforts, understanding these dynamics becomes crucial. can be drawn.

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