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Emergence of *Aspergillus terreus* as a Notable Fungal Pathogen of Human and Animal Health

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Abstract *Aspergillus terreus*, historically considered an environmental saprophyte, is now known to be an important opportunistic pathogen in human and veterinary medicine. Its increasing occurrence, particularly in immunocompromised individuals, emphasises its clinical relevance. Importantly, *A. terreus* demonstrates inherent resistance to the key antifungal, amphotericin B, which further complicates treatment options and is associated with increased morbidity and mortality. The virulence of the pathogen is enhanced by its production of various mycotoxins, another type of secondary metabolite that may alter host–pathogen interactions, and statins. Here, we review the current understanding of the taxonomy, ecology, and pathogenicity of *A. terreus* and its specific morphologic characteristics and resistance profiles. We explored their transmission dynamics, highlighting their environmental reservoirs and possible zoonotic routes. Infections caused by this fungus can cause a variety of clinical manifestations, from superficial to invasive diseases; therefore, a high index of suspicion is required to make a diagnosis. The phenotypic diversity of the organism along with traditional identification methods is a challenge for diagnosis." Therapeutically, the resistance of *A. terreus* to amphotericin B requires alternative antifungal regimens, with voriconazole and posaconazole demonstrating variable activity. This review further discusses breakthroughs in diagnostic modalities and therapeutic approaches with the potential to improve patient outcomes. We also highlight preventive strategies, such as environmental control and infection surveillance, to reduce the risk of *A. terreus* infection. This review intends to bring together the current knowledge and offer valuable insights related to the emerging pathogen *A. terreus* and its clinical importance.

Keywords: *Antifungal resistance, Aspergillus terreus, Emerging fungal pathogen, Invasive aspergillosis, Public health*

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1. Introduction

Aspergillus terreus was first recognised as an opportunistic, ubiquitous environmental saprobe and was initially known to colonise ecological niches present in soil, decaying vegetation, and compost, and as such, played an essential role in recycling organic matter. Originally considered to be of limited clinical relevance, it has now become one of the most relevant opportunistic pathogens in immunocompromised hosts and is a frequent cause of life-threatening infections in patients receiving chemotherapy, organ transplants, or prolonged corticosteroid therapy [1]. Traditionally deemed an incidental contaminant of clinical specimens, increasing evidence supports the role of *A. terreus* as a pathogen initiating severe infections, including invasive aspergillosis (IA), particularly in haematological malignancy and transplant populations. This paradigm shift mirrors a greater appreciation for the organism's distinguishing pathogenic factors, including inherent resistance to amphotericin B, as well as the production of biologically active metabolites such as terreic acid, which may influence host immunity and microbiota competition [2]. Basic taxonomic classification places *A. terreus* in the section Terrei, characterised by biseriate conidiophores and smooth-walled conidia, but morphological similarities with other *Aspergillus* species in clinical identification can lead to misidentification [3].

The setting of *A. terreus* as an emerging pathogen is within the synchronising of the One Health paradigm, which is defined as seeking equitable improvement and optimal health for humans, animals, and the environment, and recognising the interrelationship among these three components [4]. Isolations of this ubiquitous fungus from veterinary patients have been on the rise, particularly among canines and equines, suggesting both zoonotic potential and environmental persistence across multiple ecosystems [5]. Nosocomial presence, particularly in construction-affected healthcare settings, underscores the role of environmental disruption in pathogenic emergence.

Comparative studies have shown important differences between *A. terreus* and the more common *A. fumigatus*, which causes over 90% of IA worldwide [6]. *A. fumigatus* is heat-tolerant and capable of fast sporulation, whereas *A. terreus* has slow growth but is resistant to oxidative damage, antifungals, and clearance by the immune system. In addition, *A. terreus* displays intrinsic amphotericin B resistance, in contrast to A. *fumigatus* which is usually susceptible to polyenes, with concrete implications for standard antifungal regimens and treatment failure. These species differences require accurate diagnostics and species-level identification in clinical mycology to facilitate species-tailored antifungal courses and appropriate surveillance approaches [7].

2. Etiology

Aspergillus terreus is taxonomically situated in the phylum *Ascomycota*, class *Eurotiomycetes*, order *Eurotiales*, and family *Trichocomaceae* in the *Aspergillus* section *Terrei*. Phylogenetically, it is a well-resolved clade separated from other medically relevant Aspergilli with *A. fumigatus*, *A. flavus*, and *A. niger*, as indicated by multilocus sequence analysis of β-tubulin, calmodulin, and ribosomal internal transcribed spacer (ITS) regions. Despite having a different phylogenetic lineage, morphological distinction from other species in the section Terrei is largely obscured by overlapping colony characteristics and conidial morphology. The classical phenotypic identification is based primarily on the observation of compact biseriate conidiophores, smooth to finely roughened hyaline conidia, and characteristic cinnamon-brown pigmentation on Czapek-Dox agar; its limitations such as non-specificity and non-reproducibility in clinical diagnosis are discussed [8]. Sequencing of ITS and β-tubulin genes is therefore the gold standard for accurate species-level resolution based on molecular techniques. A complementary approach is the use of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, which has emerged as a rapid diagnostic tool for fungal pathogens, demonstrating excellent discriminatory power with the support of high-quality reference libraries [9].

Aspergillus terreus virulence is determined by a panoply of virulence determinants that increase its fitness in the environment and promote host invasion. Central to these functions are conidial surface proteins, including hydrophobins that enhance immune evasion by covering pathogen-associated molecular patterns (PAMPs), and catalases that provide strong resistance to reactive oxygen species (ROS) generated by host immune cells [10]. *A. terreus* has a secondary metabolome comprising a diverse range of bioactive molecules, including terreic acid, lovastatin and citreoviridin, many of which are immunomodulatory or cytotoxic and are synthesized in a tightly regulated manner by biosynthetic gene clusters (BGCs). Unique pathogenicity islands coding for NRPS, PKS, and other virulence-related regulators have been described through genomic screening [11]. Comparative genomics provides further evidence of expanded gene families associated with cell wall remodelling, iron acquisition, and antifungal resistance, consistent with adaptive evolution towards a pathogenic lifestyle. An interesting feature of *A. terreus* is that, while it lacks genes for the production of common toxins, it does have genes involved in thermotolerance, an important factor in survival in febrile hosts, and a key stepping-stone to the behaviour of this fungus in pulmonary tissue colonisation [12]. These findings highlight the molecular complexity of *A. terreus* as an emerging fungal pathogen and support the application of integrative genomic and proteomic strategies to understand its pathobiology.

3. Transmission

Aspergillus terreus is found in many ecological niches, and environmental reservoirs include soil, compost, decaying plant material, and indoor environments such as hospital air-handling units and ventilation systems. It is found in rural and urban environments alike, allowing for continuous aerosol release of infectious conidia— small, hydrophobic spores (2–3 μm diameter) that are easily carried by wind or air currents and can remain airborne for an extended period [13]. Upon inhalation, these conidia evade mucociliary defences by residing in the alveolar spaces, where they can germinate, notably in immunocompromised hosts. Fungi may be disseminated in the environment, and high spore burdens have been found in areas undergoing hospital renovation or construction. Interestingly, *A. terreus* conidia are thermotolerant and more resistant to desiccation than many other *Aspergillus* species, which may permit them to persist in nosocomial environments and are of concern in clinical settings involving neutropenic patients [14]. The isolation of *A. terreus* from air and dust samples from hospital wards (including intensive care unit [ICU]/oncology wards) has been described in surveillance across multiple institutions and may contribute to its role as an airborne pathogen capable of causing iatrogenic transmission [15].

Recent evidence indicates that *A. terreus* has zoonotic potential and can be transmitted between species, but these interspecies transmission events have not been studied as extensively as bacterial zoonoses. The observed cases of systemic aspergillosis in dogs and horses, especially in immunosuppressed and/or stressed animals, suggest a common environmental source or potential cross-species infection in human-animal interaction environments [16]. *A. terreus* has been isolated from nasal cavities, lungs, and cerebrospinal fluid in veterinary contexts, which parallels the tropism seen in human infections. Given that we live indoors with domestic animals, the One Health approach is critical with respect to domestic animal cases as potential sentinels of human risk. Additionally, nosocomial outbreaks of aspergillosis have been linked to contaminated medical equipment, air filters, and hospital construction dust, indicating that iatrogenic transmission routes may exceed environmental exposure alone [17]. People with a weakened immune system, such as during haematopoietic stem cell transplantation, are particularly susceptible to invasive diseases after low-level exposure. The importance of the implementation of strict infection control measures such as high-efficiency particulate air (HEPA) filtration, air sampling, and antifungal prophylaxis in high-risk periods

has been emphasised in previous studies [18]. Together, these findings support a multifactorial model of *A. terreus* transmission based on environmental persistence, airborne dispersal, zoonotic back-acquisition, and healthcare-associated vectors.

4. Epidemiology

While the global incidence of *Aspergillus terreus* infections was previously thought to be relatively low compared to of that *A. fumigatus*, there has been a notable increase in the disease in recent years, particularly among immunocompromised populations. Based on multicentre surveillance studies, including TRANSNET and SEIFEM, *A. terreus* was noted as the second or third most frequent cause of invasive aspergillosis (IA) in Europe and North America, with prevalence ranging from 4% to 9% depending on geographic location and patient population [19]. This trend is in part explained by the wider adoption of diagnostic modalities able to make accurate species-level identification and the growing recognition of antifungal resistance in non-*fumigatus* Aspergilli. Clinical isolates of *A. terreus* are most frequently isolated from the respiratory tract, followed by blood, central nervous system, and skin specimens, mostly in individuals with haematologic malignancies, solid organ transplant, or neutropenia, primarily prolonged [20]. Nosocomial clustering of species distribution is also observed, suggesting that localised environmental features such as airborne spore burden and bioaerosol management in health-care settings can modulate the dynamics of infection.

Compared with the typical immunocompromised host, where *A. terreus* infection is a consideration, the at-risk population includes certain veterinary species, especially dogs and horses. In these animals, infections are often caused by sinonasal, pulmonary, or disseminated mycoses, and such infections are increasingly observed in Europe and North America, raising concerns about cross-kingdom transmission routes or shared environmental exposures [21]. Epidemiological studies from these regions have identified significant variations: *A. terreus* can account for up to 7% of *Aspergillus* isolates in India; in the US, incidence has been reported in construction-related hospital outbreaks; in Europe, Austria, and Germany, comparably high incidence rates have been reported, which may be attributable to local environmental reservoirs and advanced diagnostic modalities for fungi [22]. *A. terreus* is especially significant from an epidemiological standpoint due to its intrinsic resistance to amphotericin B, associated with increased mortality rates than *A. fumigatus*-related IA in the absence of routine antifungal susceptibility testing. These changing trends exemplify the need for integration of *A. terreus*–specific surveillance into both institutional antifungal infection control programs and multicentre epidemiological systems [23].

5. Clinical Spectrum

5.1. In Humans

Aspergillus terreus was increasingly isolated from heavily immunocompromised patients with a wide range of clinical features. IA is still the most common presentation, with the lung being the most affected organ because conidia enter through the inhalational route. CT usually shows nodular infiltrates with halo or air crescent signs, but these radiological patterns are non-specific and overlap with those of other fungal pathogens. Dissemination to extrapulmonary sites, including the paranasal sinuses and central nervous system (CNS), is well documented beyond the lungs, especially in those with persistent neutropenia or allogeneic haematopoietic stem cell transplantation (HSCT) [24]. CNS infection manifests with meningitis or space-occupying lesions and is linked to high mortality, partly due to diagnostic delay and poor antifungal CNS penetration across the blood–brain barrier. Cutaneous infections, although rarer, can occur from direct inoculation or haematogenous spread, particularly in intensive care patients with indwelling catheters or traumatic disruption of the skin barrier [25]. Importantly, mortality rates for invasive forms of *A. terreus* are higher (as high as 80%) than those of A. *fumigatus*, largely owing to inherent resistance to amphotericin B, delayed diagnosis, and poor treatment response in disseminated disease. *Aspergillus terreus* can cause primary cutaneous aspergillosis in immunocompetent individuals following traumatic inoculation, particularly in agricultural settings. Itraconazole therapy has been effective in resolving such cutaneous infections caused by *A. terreus* when promptly administered [26].

5.2. In Animals

Aspergillus terreus is an emerging veterinary pathogen, particularly of canines and equines, where both localized and systemic disease may occur. Sinonasal aspergillosis is the most common type in dogs, which is typically characterised by nasal discharge, facial swelling, or epistaxis and diagnosed via rhinoscopic examination, culture, and imaging [27]. Disseminated forms, although less common, have been observed in immunosuppressed or genetically predilected breeds, affecting the kidneys, vertebrae, or CNS. *A. terreus* has been described in reported equine cases as pulmonary pathogens and, less frequently, as the etiology of guttural pouch mycosis, a life-threatening condition that results from hematomas caused by vascular erosion contribute [28]. Therefore, these infections may not be straightforward to diagnose because the clinical signs overlap with those related to bacterial and non-*terreus* fungal pathogens. There has also been a new interest in the zoonotic potential of *A. terreus*, particularly in human animal contact settings. While direct zoonotic transmission has not been definitively demonstrated, the finding of identical genotypes within the same geographical areas in human and animal isolates highlights the need for consideration of environmental reservoirs and a One Health approach for effective surveillance and control strategies [29]. This case represents the first documented report of primary cutaneous aspergillosis due to A. terreus in an immunocompetent individual in Gujarat, India, following traumatic exposure. The cinnamon-brown colonies on Sabouraud agar and compact biseriate conidial heads in

Narayan stain confirmed the diagnosis [30].

6. Diagnosis

Infections caused by *Aspergillus terreus* require multiple diagnostic steps, including the use of routine mycology, molecular techniques, and immunological tools. Conventional diagnostics, such as potassium hydroxide (KOH) mounts or calcofluor white staining, can provide initial visualisation of septate hyphae with acute-angle branching, but cannot achieve species-level identification. Cultural examination on Sabouraud dextrose or Czapek-Dox agar (Figure 1) at standard incubation conditions results in colonies with diagnostic cinnamon-brown pigmentation and a powdery texture, but differentiation and correlation with morphologically analogous Aspergilli is difficult to accomplish [31]. The invasive nature of *A. terreus*, as well as its ability to invade blood vessels (angioinvasion), which are characteristic of invasive aspergillosis, can be confirmed by histopathological examination of tissue biopsies stained with periodic acid–Schiff (PAS) or Grocott's methenamine silver (GMS), but sensitivity remains insufficient to differentiate *A. terreus* from other *Aspergillus* species. However, the yield of culture-based methods is hindered by the fastidious nature of *A. terreus* growth in clinical specimens, warranting the use of complementary nonculture-based diagnostics to obtain higher detection rates and facilitate timely intervention [32].

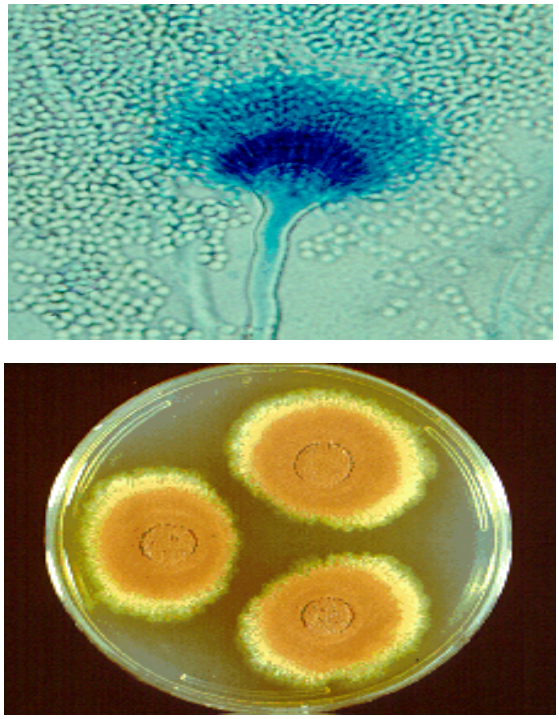

Figure 1. *Aspergillus terreus* conidial head with spores and Colonies grown on Czapek dox agar; Source [48]

Molecular techniques, especially polymerase chain reaction (PCR) assays based on the internal transcribed spacer (ITS) and β-tubulin gene regions, are particularly prominent in increasing the specificity and sensitivity of diagnostics. These facilitate species-level identification directly from clinical specimens with turnaround times much shorter than those of standard cultures [33]. Galactomannan enzyme immunoassay (GM-EIA) is the most widely used serum or broncho-alveolar lavage (BAL) antifungal biomarker for established invasive aspergillosis, but its sensitivity for *A. terreus* has some variability depending on species in terms of antigen productions [34]. Likewise, the identification of (1→3)-β-D-glucan, a pan-fungal cell wall element, also aids diagnostic efforts; however, in this case, it is not genus-specific, and false-positives can occur because there can be cross-reactivity with other fungi or contaminants. More recently, matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF MS) has developed into a rapid and reliable approach for the identification of *A. terreus* from culture isolates, although accuracy is highly dependent upon the quality of reference spectra databases. Point-of-care detection of fungal biomarkers using innovative biosensing technologies, including electrochemical and nanomaterial-based sensors, is being developed to transform early diagnostics, especially in resource-limited or high-risk environments [35]. Collectively, the incorporation of these diagnostic modalities will increase the accuracy and timing of *A. terreus* detection, which is critical for timely antifungal initiation and improved clinical outcomes.

7. Treatment

Aspergillus terreus infections are known to be a therapeutic challenge because of their unique antifungal susceptibility profile. Among other important features, *A. terreus* displays intrinsic resistance to one of the mainstay systemic antifungal agents, amphotericin B (AmB), which has been linked to poor clinical outcomes and high mortality rates in cases of invasive disease [36]. Changes in the ergosterol biosynthesis pathways responsible for the reduced affinity of AmB when binding to the fungal cell membranes are mainly responsible for that resistance, resulting in decreased fungicidal activity [37]. In addition, *A. terreus* possesses elevated antioxidative defences which counter the oxidative insult normally caused by polyenes through the production of reactive oxygen species (ROS), with several catalases, superoxide dismutases, and peroxidases upregulated in this organism [38]. Reports of minimum inhibitory concentration (MIC) testing of international isolates have confirmed high-level resistance to AmB, with MICs commonly above established clinical breakpoints. This illustrates the importance of antifungal susceptibility testing in treatment decisions. Conversely, the triazole antifungal agents voriconazole and posaconazole exhibited variable but overall good in vitro activity against this rare pathogenic species, making them the drugs of choice, particularly for upper or disseminated pulmonary infections of *A. terreus* [39].

Second-generation triazoles, such as voriconazole, have emerged as first-line recommendation options because of their reliable fungistatic activity, excellent bioavailability, and documented efficacy demonstrated in randomised clinical studies. However, the outcomes of treatment might differ owing to strain-specific susceptibility differences, as well as patient pharmacogenetics and drug–drug interactions, which are common in haematologic

patients receiving polypharmacy regimens [40]. Posaconazole is an alternative with enhanced activity against some resistant isolates and has utility in salvage therapy or prevention in high-risk individuals, including recipients of haematopoietic stem cell transplantation. Combination antifungal therapies, including voriconazole combined with echinocandins (e.g. caspofungin), have also been investigated to overcome such treatment limitations; however, clinical data remain inconclusive, mainly based on case reports or small series [41]. Furthermore, adjunctive immunomodulatory approaches such as granulocyte transfusions and cytokine therapy (that is, IFN-γ) have been studied in an attempt to bolster host immunity among prostaglandin Fmax and markedly neutropenic patients, producing variable outcomes. Owing to the considerable morbidity and mortality associated with *A. terreus*, especially in patients with invasive disease and delayed diagnosis, tailored treatment approaches combining rapid diagnostics, susceptibility testing, and pharmacodynamic monitoring are critical in improving clinical outcomes.

8. Control and Prevention

The control and prevention of *Aspergillus terreus* infections requires an integrated approach that focuses on environmental, clinical, and veterinary aspects of exposure. This universal soil-dwelling fungus can be found in organic-rich substrates; therefore, environmental decontamination is very important for both community and healthcare settings. Filters with high-efficiency particulate air (HEPA) units are widely used as routine air filters in haematology wards and transplant units and have been shown to reduce airborne conidial concentrations and subsequent fungal infections [42]. During such construction or renovation periods, when fungal spores are disseminated, strict decontamination protocols must be equivalent. This includes construction zone sealing, negative air pressure systems, and the use of portable HEPA filters in nearby patient care areas [43]. Traditional indoor air quality monitoring with volumetric spore trapping and environmental culture is still a mainstay of preventive mycology; however, real-time molecular detection assays are progressively being promoted owing to their greater sensitivity and promptness [44].

While infection control strategies play an important role in the setting of high-risk cohorts, such as haematopoietic stem cell transplant (HSCT) recipients, acute leukaemia patients, and patients with prolonged neutropenia, targeted prophylaxis with antifungal agents is required in clinical practice. Although posaconazole has demonstrated broad-spectrum prophylactic activity against several species of *Aspergillus*, variable activity against *A. terreus* may occur, warranting both therapeutic drug monitoring and surveillance for resistance. Voriconazole is still regarded as the drug of choice for empirical or pre-emptive therapy, highlighting the importance of antifungal stewardship programs due to emerging resistance [45]. Preventive measures in veterinary medicine are not well developed and are urgently needed, particularly in breeds predisposed to disseminated aspergillosis. Minimising exposure to contaminated hay, compost, and dusty stables is recommended alongside prompt isolation and treatment of animals infected with *Candida auris* to reduce the burden of spores in the environment [46]. In this regard, the One Health concept of integrating human/animal/environmental health strategies from the home to the hospital, to the field, and beyond is critical for developing large fungal management frameworks that integrate health systems and regulatory structures across a wide range of sectors [47,49]. A holistic prevention strategy, which is based on data from multiple sectors, will be the most successful way to reduce the incidence of *A. terreus* infections and improve outcomes in humans and veterinary populations.

9. Conclusion

The emergence of *Aspergillus terreus* as a clinically relevant pathogen highlights a paradigm shift in fungal epidemiology and diagnostic and therapeutic strategies in man and veterinarian medicine. Once a saprophyte of obscure environmental importance, *A. terreus* is now recognised as one of the most important opportunistic fungal pathogens in humans, with its unique blend of intrinsic resistance to amphotericin B, extensive dispersal of conidia, and capacity to result in fatal invasive disease, particularly in immunocompromised patients. Its pathogenicity is intimately related to its genetic background, including biosynthetic gene clusters coding for virulence-related natural products and signalling molecules, such as terreic acid and statins, and strategies of immune evasion. As a member of the section Terrei, *A. terreus* is phylogenetically distinctive and has become progressively more isolated from both clinical and environmental niches. Awareness of the importance of species-level diagnostics will help delineate the burden of *A. terreus* infection and inform its management.

Clinical manifestations of *A. terreus* diseases in humans and animals include a wide range of diseases, from localised sino-pulmonary infections to life-threatening disseminated aspergillosis. A high case fatality rate of the disease complicated by diagnostic ambiguity and limitations in therapy underscores an urgent need for accurate, rapid, and species-specific detection tools. Additionally, advanced molecular assays, antigen-based diagnostics, and MALDI-TOF platforms hold great potential in augmenting clinical decisions and improving patient outcomes. Simultaneously, prophylactic antifungal regimens, particularly among high-risk haematology and transplant populations, should be adjusted to reflect *A. terreus*-specific antifungal resistance patterns. Infection prevention and environmental decontamination efforts (for example, HEPA filtration and real-time air quality surveillance) are foundational pillars of protective strategies in healthcare facilities. *A. terreus* is zoonotic at all boars, and its environmental ubiquity makes it both a One Health and a One Environment problem that speaks to the need for integrated surveillance and collaborative mitigation programs across the medical and veterinary and environmental sectors. With this fungal species continuously emerging through geographies and hosts, ongoing research, prompt clinical detection, and evolving public health strategies are essential to contain the

growing burden on global health.

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Contribution of Authors

All authors contributed equally. They read the final manuscript and approved the final submission for publishing.

Conflict of Interest

The authors declare no conflicts of interest.

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