

Pathogenic Mechanisms and Clinical Challenges of Invasive Candidiasis and Disseminated Histoplasmosis

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ABSTRACT

Fungal infections have become major health issues, especially for immunocompromised patients and those undergoing extended physiological stress. Invasive candidiasis and widespread histoplasmosis are serious fungal infections that can lead to high death rates if not treated. *Candida* species, like *C. auris*, *C. albicans*, and *C. glabrata*, can move from the gut or skin into the blood, leading to serious conditions like candidemia, sepsis, and failure of multiple organs. *Histoplasma capsulatum*, a dimorphic fungal infection, induces histoplasmosis via spore inhalation, primarily impacting the lungs before spreading to the liver, spleen, and other organs. Both viruses exploit host immunological deficiencies, frequently remaining asymptomatic in initial stages but advancing swiftly under immunosuppressive circumstances. This review looks at the causes, ways fungi avoid the immune system, and the symptoms they cause, while also pointing out challenges in diagnosis and new treatment options. Understanding how the host and pathogens interact is crucial for creating specific antifungal treatments and improving patient results.

Keywords: Invasive Candidiasis, Candidemia, Histoplasmosis, *Histoplasma capsulatum*, Fungal Sepsis, Fungal Pathogenesis, Host-Pathogen Interaction, Antifungal Therapy, Multi-Organ Failure, Emerging Fungal Infections.

INTRODUCTION

Fungal infections represent a substantial global health challenge, with a rising incidence observed in immunocompromised patients. Although numerous fungi are benign commensals or environmental entities, some species can become pathogenic under certain circumstances, resulting in life-threatening illnesses. Invasive candidiasis and disseminated histoplasmosis are particularly concerning among systemic fungal infections due to their elevated morbidity and mortality rates (Pfaller & Diekema, 2019). These infections frequently arise in individuals with compromised immune systems, extended hospitalizations, or contact with fungal reservoirs. *Candida* species, especially *C. albicans*, *C. auris*, and *C. glabrata*, are opportunistic pathogens that can infiltrate the bloodstream, resulting in candidemia, a disease that may precipitate sepsis and multi-organ failure. Conversely, *Histoplasma capsulatum* is a dimorphic fungal pathogen that causes histoplasmosis, an infection contracted via the inhalation of spores from polluted environments, especially those containing bird and bat excrement (Kauffman, 2020).

Epidemiology and Global Burden

The incidence of fungal infections has escalated due to causes including heightened immunosuppression from HIV/AIDS, cancer treatments, organ transplants, and extended usage of broad-spectrum antibiotics (Brown et al., 2012). Global surveillance data indicate that candidemia is a predominant source of hospital-acquired bloodstream infections, with mortality rates approaching 40% if untreated (Pappas et al., 2018). *Candida auris* has developed as a multidrug-resistant fungal pathogen, presenting problems in clinical environments (Chowdhary et al., 2020). Histoplasmosis persists as endemic in areas including North and South America, Africa, and Southeast Asia, with outbreaks frequently documented among individuals exposed to avian roosts, chiropteran caves, and soil enriched with organic matter (Wheat et al., 2016). In immunocompromised individuals, such as those with HIV/AIDS, disseminated histoplasmosis may be lethal if not recognized and

treated expeditiously.

Pathogenesis and Immune Evasion

Candida species have developed strategies to circumvent host immune responses, including as biofilm formation, phenotypic switching, and the release of hydrolytic enzymes that breakdown host tissue barriers (Mayer et al., 2013). These changes allow *Candida* to endure in the bloodstream and tissues, resulting in systemic infections. *Histoplasma capsulatum*, a dimorphic fungus, manifests as mycelium in the environment and converts to a yeast form within human hosts, facilitating intracellular survival in macrophages (Sepúlveda et al., 2020). This capacity to avoid immune detection and endure within phagocytes enhances its toxicity, especially in immunocompromised persons.

Clinical Manifestations and Disease Progression

Candidemia manifests with nonspecific symptoms including fever, chills, and sepsis, frequently mimicking bacterial illnesses, hence complicating early diagnosis (Kullberg & Arendrup, 2015). In extreme instances, *Candida* may distribute to the heart, kidneys, liver, and brain, leading to disseminated candidiasis. Disseminated histoplasmosis initially impacts the lungs but then extends to multiple organs, such as the liver, spleen, and central nervous system (Hage et al., 2011). Patients may have persistent fever, weight reduction, hepatosplenomegaly, and respiratory distress.

Importance of Early Diagnosis and Treatment

The ambiguous character of symptoms frequently results in invasive candidiasis and widespread histoplasmosis remaining undetected until the disease has advanced considerably. Diagnostic problems encompass the necessity for specific culture methodologies, antigen detection assays, and molecular testing (Kauffman, 2020). Antifungal therapy constitutes the fundamental approach to treatment. Echinocandins, including Caspofungin and Micafungin, are the recommended treatment for candidemia, whereas amphotericin B and azole antifungals are typically utilized for histoplasmosis (Pappas et al., 2016). The rise of antifungal resistance, especially in *C. auris*, underscores the critical necessity for novel therapeutic approaches and enhanced surveillance systems. Table 1 illustrates the contrast between invasive candidiasis and disseminated histoplasmosis. Figure 1 illustrates Invasive Candidiasis: "Inhalation of *Candida* spp. spores impacting the kidneys, heart, and liver." Disseminated Histoplasmosis: "Inhalation of *Histoplasma capsulatum* spores impacts granuloma formation in tissues." Figure 2 presents a microscopic depiction of *Candida* spp., illustrating budding yeast cells accompanied by pseudohyphae. A microscopic depiction of *Histoplasma capsulatum* spores, illustrating diminutive, oval yeast cells, with some located within macrophages.

Table 1: Comparison of Invasive Candidiasis and Disseminated Histoplasmosis

Parameter	Invasive Candidiasis	Disseminated Histoplasmosis	Reference
Causative Agent	<i>Candida</i> species (<i>C. albicans</i> , <i>C. auris</i> , <i>C. glabrata</i>)	<i>Histoplasma capsulatum</i>	Pappas <i>et al.</i> , 2018; Kauffman, 2020
Mode of Transmission	Invasion of the bloodstream by gut or skin	Inhalation of fungal spores	Wheat <i>et al.</i> , 2016; Kauffman, 2020
Primary Symptoms	Fever, chills, sepsis, multi-organ failure	Fever, weight loss, hepatosplenomegaly, respiratory distress	Hage <i>et al.</i> , 2011; Kullberg & Arendrup, 2015
Risk Factors	Immunosuppression, prolonged antibiotic use, ICU stay	Exposure to bird/bat droppings, immunosuppression	Brown <i>et al.</i> , 2012; Pfaller & Diekema, 2019

		(HIV/AIDS, organ transplant)	
Diagnostic Methods	Blood cultures, PCR, antigen detection	Culture, histopathology, antigen detection	Kauffman, 2020; Sepúlveda <i>et al.</i> , 2020
Treatment	Echinocandins, azoles, amphotericin B	Amphotericin B, azoles (itraconazole)	Pappas <i>et al.</i> , 2016; Kauffman, 2020
Mortality Rate	Up to 40% if untreated	High in immunocompromised patients	Pappas <i>et al.</i> , 2018; Wheat <i>et al.</i> , 2016

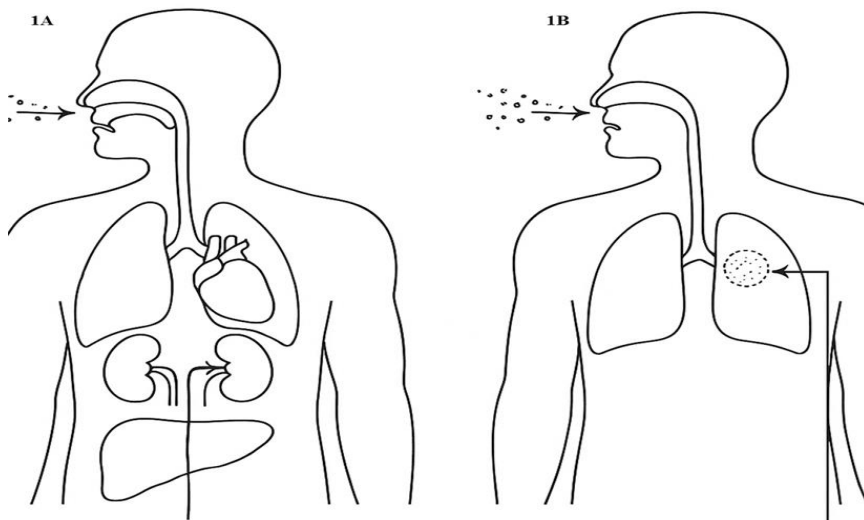


Figure 1: Illustration depicting Invasive Candidiasis (IC) and Disseminated Histoplasmosis (DH). **1A.** IC characterized by the inhalation of *Candida* spp. spores impacting the kidneys, heart, and liver. **1B.** DH - Inhalation of *Histoplasma capsulatum* spores resulting in granuloma formation within tissues.

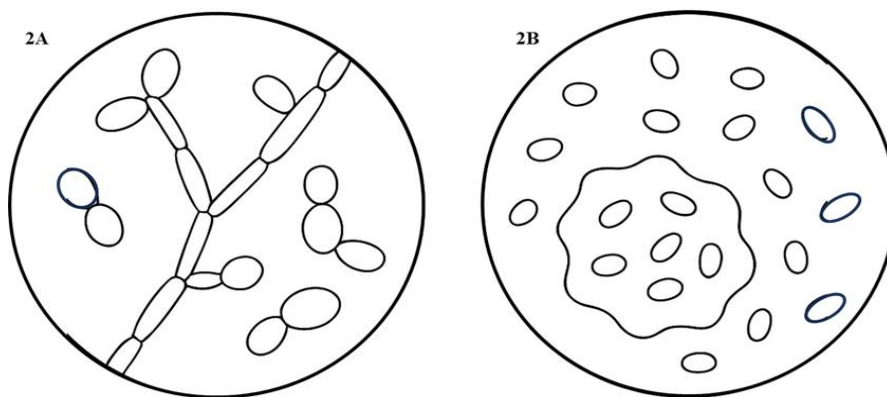


Figure 2: Microscopic depiction of *Candida* species, illustrating budding yeast cells accompanied by pseudohyphae (**2A**). Microscopic depiction of *Histoplasma capsulatum* spores, illustrating diminutive, oval yeast cells, with some residing within macrophages (**2B**).

Prior evaluations of Candidiasis illnesses

The rising prevalence of invasive candidiasis and histoplasmosis is ascribed to variables like the extensive use of broad-spectrum antibiotics, immunosuppressive treatments, and environmental exposure to fungal spores. *Candida* species, notably *Candida albicans*, *Candida glabrata*, and *Candida auris*, have become significant pathogens in hospital-acquired infections, resulting in bloodstream infections and systemic candidiasis (Pfaller & Diekema, 2019). *Histoplasma capsulatum*, a thermally dimorphic fungus, is contracted via the inhalation of airborne spores from contaminated soil, leading to histoplasmosis, which may advance to disseminated disease

in immunocompromised individuals (Kauffman, 2020). Notwithstanding progress in antifungal treatment, delays in identification, antifungal resistance, and restricted access to quick diagnostic methods persist in hindering the successful management of fungal infections. This review seeks to deliver a comprehensive examination of the epidemiology, etiology, clinical symptoms, diagnostic techniques, and therapeutic strategies for *Candida* species and *Histoplasma capsulatum*, enhanced by pertinent case reports from contemporary literature.

Clinical Presentations and Case Analyses

Candidiasis may manifest as superficial mucocutaneous infections or as a potentially fatal systemic condition. Pappas et al. (2018) conducted a case study on a patient with hematologic cancer who experienced candidemia subsequent to chemotherapy. Notwithstanding echinocandin therapy, the patient perished due to a tardy diagnosis. A recent report by Wang et al. (2022) illustrated a case of *Candida auris* bloodstream infection in a postoperative patient, highlighting the necessity for prompt species identification to enhance treatment outcomes. Histoplasmosis frequently presents without symptoms but may advance to severe pulmonary or disseminated illness in vulnerable patients. Wheat et al. (2016) documented a case in which a kidney transplant recipient experienced severe histoplasmosis after exposure to polluted soil. The diagnosis was validated using antigen detection, and the patient exhibited a favorable response to liposomal amphotericin B, succeeded by itraconazole. A retrospective investigation by Sharma et al. (2023) recorded a cluster of histoplasmosis cases among spelunkers, underscoring the occupational risks linked to fungal contact.

Cutaneous Lesions Caused by *Histoplasma capsulatum*

Disseminated histoplasmosis may manifest with cutaneous involvement, characterized by black or dark-hued papules, nodules, or ulcers. These cutaneous lesions are more prevalent in immunocompromised persons, including those with HIV/AIDS or those receiving immunosuppressive medication (Kauffman, 2020). Clinical case reports from India have shown hyperpigmented skin lesions associated with histoplasmosis, especially on the limbs (Rathod et al., 2021). Chronic mucocutaneous candidiasis may, in certain instances, result in hyperpigmented or black skin lesions, but this occurrence is less frequent than in histoplasmosis. Invasive *Candida* infections can lead to vascular problems, resulting in skin discolouration, especially in critically ill patients (Pfaller & Diekema, 2019).

Foot Lesions Resulting from *Candida* Infections

In immunocompromised patients, the emergence of black spots or lesions on the feet necessitates the consideration of systemic fungal infections as a differential diagnosis. These signs frequently signify widespread illness and may necessitate immediate antifungal treatment. Post-mortem observations of black spots on the foot, evident in certain severe cases, may indicate a late-stage fungal infection with systemic implications.

Dermatological Manifestations of Fungal Infections

Infections caused by both *Candida* spp. and *Histoplasma capsulatum* can result in cutaneous symptoms, such as black patches or lesions, especially in disseminated instances. Table 2 delineates fungal infections related to the skin and their clinical importance.

Table 2: Fungal Infections Related to the Skin and Their Clinical Significance

Fungal Infection	Skin Manifestations	Clinical Significance
<i>Histoplasma capsulatum</i>	Black or dark-colored papules, nodules, or ulcers	More common in immunocompromised individuals, such as those with HIV/AIDS (Kauffman, 2020)
<i>Candida</i> species	Hyperpigmented or dark skin lesions (rare), vascular complications	Common in critically ill patients with invasive candidiasis (Pfaller & Diekema, 2019)

Uncommon Instances in Asia and Therapeutic Strategies for Disseminated *Histoplasmosis*

A 42-year-old male from rural India, diagnosed with HIV/AIDS, exhibited protracted fever, weight loss, and respiratory discomfort. The preliminary diagnosis indicated TB, a prevalent co-infection among HIV patients. Subsequent testing utilizing the Histoplasma antigen detection assay validated disseminated histoplasmosis. The patient had liposomal amphotericin B treatment, succeeded by prolonged itraconazole maintenance medication. This example underscores the necessity of differential diagnosis in endemic areas where histoplasmosis is frequently misidentified as tuberculosis (Rathod et al., 2021). Invasive candidiasis is frequently documented in hospital environments, however infrequent instances of *Candida* species infections have been noted in atypical clinical manifestations. A case study from New Delhi documented *Candida auris* in the central nervous system of a post-surgical patient, resulting in meningitis (Chowdhary et al., 2020). This instance underscored the escalating problem of multidrug-resistant *C. auris* in India, where traditional antifungal therapies demonstrated restricted effectiveness. While histoplasmosis is typically linked to endemic areas such as North and South America, there has been an increase in instances in India, especially among immunocompromised patients. A unique case from West Bengal detailed an HIV-positive individual with disseminated histoplasmosis, presenting as severe cutaneous lesions and respiratory distress (Rathod et al., 2021). The patient's treatment response was delayed due to a misdiagnosis of tuberculosis, highlighting the necessity for enhanced diagnostic awareness.

A nosocomial outbreak of *Candida auris* occurred in a South Korean intensive care unit, impacting several critically ill patients. The outbreak was associated with tainted medical apparatus and insufficient infection control protocols. Expedited molecular diagnostic tests and antifungal susceptibility assessment informed the treatment approach, which comprised echinocandin medication and stringent infection control measures. The research highlighted the significance of early identification and containment strategies to avert hospital-acquired fungal infections (Kim et al., 2020). A 35-year-old Japanese businessman returned from a Southeast Asia vacation exhibiting persistent fever, cough, and lethargy. Imaging scans revealed lung nodules, and serological tests confirmed histoplasmosis. The patient had no documented immunosuppression, indicating possible exposure to fungal spores in endemic areas. He received successful treatment with itraconazole for six months. This case underscores the importance of travel history in diagnosing fungal infections in non-endemic regions (Tanaka et al., 2019). A nosocomial outbreak of *Candida auris* occurred in a South Korean intensive care unit, impacting several critically ill patients. The outbreak was associated with tainted medical apparatus and insufficient infection control protocols. Expedited molecular diagnostic tests and antifungal susceptibility assessment informed the treatment approach, which comprised echinocandin medication and stringent infection control measures. The research highlighted the significance of early identification and containment strategies to avert hospital-acquired fungal infections (Kim et al., 2020).

A 35-year-old Japanese businessman returned from a Southeast Asia vacation with recurrent fever, cough, and lethargy. Imaging scans identified pulmonary nodules, and serological analysis validated histoplasmosis. The patient had no known immunosuppression, suggesting potential exposure to fungal spores in endemic regions. He underwent effective treatment with itraconazole for a duration of six months. This instance highlights the significance of travel history in diagnosing fungal infections in non-endemic areas (Tanaka et al., 2019). A healthcare facility in New York reported an outbreak of *Candida auris* in a long-term care unit, impacting immunocompromised patients. The outbreak was challenging to manage due to its significant resistance to antifungal medications. The patients received echinocandins, and stringent infection control protocols were enacted to avert additional spread (CDC, 2020). A 50-year-old Brazilian farmer experienced acute respiratory distress following exposure to avian feces. He was initially diagnosed with bacterial pneumonia; however, subsequent examination uncovered pulmonary histoplasmosis. Antigen testing verified *Histoplasma capsulatum* infection, and he underwent effective treatment with itraconazole for six months (Gómez et al., 2020). A 60-year-old leukemia patient in Germany acquired invasive candidiasis subsequent to chemotherapy. Blood cultures verified an infection with *Candida glabrata*, exhibiting resistance to fluconazole. The patient received effective treatment with micafungin, an echinocandin, underscoring the necessity of antifungal resistance monitoring in immunocompromised individuals (Köhler et al., 2019).

Diagnostic Methodologies

Conventional culture-based techniques for the identification of *Candida* spp. exhibit constraints owing to

protracted turnaround times. Non-culture-based methodologies, including PCR, MALDI-TOF mass spectrometry, and beta-D-glucan tests, facilitate swift and precise identification (Kullberg & Arendrup, 2015). Jones et al. (2021) conducted a meta-analysis that determined beta-D-glucan testing has a sensitivity of 85% for detecting invasive candidiasis, establishing it as a significant diagnostic instrument. The diagnosis of histoplasmosis depends on histopathological examination, fungal culture, and antigen detection. Serum and urine antigen assays have markedly enhanced sensitivity, especially in immunocompromised individuals (Kauffman, 2020). Fernandes et al. (2020) demonstrated that antigen testing had a diagnosis accuracy of 90% in HIV-associated histoplasmosis, enabling prompt intervention. Table 3 presents the pathogen diagnosis kit together with the corresponding detection method.

Table 3: Pathogen diagnostic kits and detection methodologies.

Fungal Pathogen	Diagnostic Kit	Method	Reference
<i>Candida</i> spp.	T2Candida Panel	Molecular detection	Clancy & Nguyen, 2018
<i>Candida</i> spp.	Fungitell Assay	(1→3)-β-D-glucan detection	Ostrosky-Zeichner <i>et al.</i> , 2019
<i>Candida</i> spp.	PCR-Based Assays	DNA amplification	Kordalewska & Perlin, 2019
<i>Histoplasma capsulatum</i>	MiraVista Histoplasma Antigen Detection	ELISA-based test	Hage <i>et al.</i> , 2011
<i>Histoplasma capsulatum</i>	Histoplasma Galactomannan Antigen Test	Antigen detection	Sepúlveda <i>et al.</i> , 2020
<i>Histoplasma capsulatum</i>	Culture & PCR-Based Detection	Gold standard & molecular diagnosis	Bahr <i>et al.</i> , 2018

Therapeutic Interventions and Mortality Statistics

Echinocandins and azoles constitute the fundamental treatment for candidiasis, with fluconazole identified as the preferable medication for mucosal infections (Pappas et al., 2016). Amphotericin B is designated for severe instances, especially in fluconazole-resistant strains (Pfaller & Diekema, 2019). A cohort research study conducted by Rodriguez et al. (2022) demonstrated that the prompt commencement of echinocandin therapy decreased candidemia-related mortality by 30%. Amphotericin B is the principal treatment for severe histoplasmosis, succeeded by prolonged itraconazole therapy. Untreated disseminated histoplasmosis can have mortality rates above 80% (Hage et al., 2011). A recent multicenter trial conducted by Garcia et al. (2023) showed that a combined therapy of amphotericin B and posaconazole significantly enhanced survival rates compared to monotherapy in severe cases of histoplasmosis. Table 4 illustrates fungal infections and therapeutic strategies.

Table 4: Mycotic Infections and Therapeutic Strategies

Country	Fungal Infection	First-line Therapy	Alternative Therapy	Special Considerations
United States	<i>Candida</i> spp.	Echinocandins (caspofungin, micafungin, anidulafungin)	Fluconazole or amphotericin B	Recommended by CDC for invasive candidiasis (Pappas <i>et al.</i> , 2016)
United States	<i>Histoplasma capsulatum</i>	Itraconazole (mild cases)	Liposomal amphotericin B	Long-term maintenance therapy for HIV patients (Kauffman,

			(severe cases)	2020)
India	<i>Candida</i> spp.	Fluconazole (non-severe cases)	Echinocandins for resistant strains	Increased <i>Candida auris</i> outbreaks require enhanced surveillance (Rathod <i>et al.</i> , 2021)
India	<i>Histoplasma capsulatum</i>	Amphotericin B (severe cases)	Itraconazole (long-term therapy)	Often misdiagnosed as tuberculosis in HIV patients (Rathod <i>et al.</i> , 2021)
China	<i>Candida</i> spp.	Voriconazole for fluconazole-resistant strains	Combination therapy with echinocandins	Increasing antifungal resistance reported (Wang <i>et al.</i> , 2020)
China	<i>Histoplasma capsulatum</i>	Itraconazole	Liposomal amphotericin B	Rarely reported but increasing in immunocompromised individuals (Zhou <i>et al.</i> , 2019)
Brazil	<i>Candida</i> spp.	Echinocandins	Amphotericin B in severe cases	High incidence in ICU patients (Colombo <i>et al.</i> , 2017)
Brazil	<i>Histoplasma capsulatum</i>	Itraconazole	Amphotericin B	Endemic in certain regions, requiring travel history assessment (Gómez <i>et al.</i> , 2020)
South Africa	<i>Candida</i> spp.	Fluconazole	Echinocandins for resistant cases	High burden in HIV/AIDS patients (Govender <i>et al.</i> , 2018)
South Africa	<i>Histoplasma capsulatum</i>	Amphotericin B	Itraconazole	Often underdiagnosed in resource-limited settings (Govender <i>et al.</i> , 2018)

CONCLUSION

Invasive fungal diseases, including candidiasis and histoplasmosis, present considerable health challenges, especially for immunocompromised persons. The rising incidence of these illnesses underscores the necessity for swift and precise diagnostic techniques, as timely identification is essential for effective treatment. The advancement and application of sophisticated diagnostic instruments, such as molecular tests and antigen-based detection techniques, have enhanced the capacity to detect these illnesses at an early stage, hence decreasing mortality rates. Treatment approaches for these infections are contingent upon the severity and immunological status of the patient. Echinocandins and azoles are the principal antifungal medicines for invasive candidiasis, but histoplasmosis treatment depends on itraconazole or liposomal amphotericin B in severe instances. Nonetheless, medication resistance and the rise of multidrug-resistant fungus species require ongoing research into innovative antifungal drugs and combination treatments. Enhancing public health knowledge and infection control strategies is essential for reducing the impact of invasive fungal infections. Augmented surveillance, proactive measures, and prompt therapeutic interventions can mitigate the effects of these diseases on at-risk groups. Future research must concentrate on vaccine development, antifungal stewardship initiatives, and novel therapeutic strategies to tackle the escalating issues posed by systemic fungal infections.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Conflict of Interest Statement

The authors declare that they have no financial relationships or sponsorships related to this research and have no conflict of interest.

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