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Candida Spondylodiscitis: Diagnostic Dilemmas and Treatment Strategies

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What is already known on this topic?

- *Candida spondylodiscitis accounts for < 5 % of spinal infections yet still carries ~10 % mortality in some studies because diagnosis is often delayed.*
- *MRI is the most sensitive imaging modality, whereas blood cultures are often negative; therefore, CT-guided biopsy remains essential for microbiological confirmation.*
- *Management typically entails prolonged azole therapy with or without surgery, but the optimal antifungal agent and treatment duration are not well defined.*

What does this study add on this topic?

- *Introduces the newly validated IFSD prognostic score, providing the first bedside tool for risk stratification in invasive fungal spondylodiscitis.*
- *Summarises emerging multidrug-resistant species (e.g., Candida auris) and evaluates next-generation antifungals such as rezafungin within an evidence-based diagnostic–treatment algorithm.*

Abstract

Spondylodiscitis is a serious and potentially life-threatening infection that affects the vertebrae and intervertebral discs. *Candida* spp. is a fungus that normally exists as a commensal organism in the human body but can become an opportunistic pathogen in individuals with weakened immune systems. Risk factors such as immunodeficiency, prolonged antibiotic use, intravenous drug use, diabetes, and alcohol dependency can contribute to the development of fungal spondylodiscitis. Fungal spondylodiscitis has a more insidious onset and presents with more ambiguous symptoms compared to bacterial cases, which can lead to delays in diagnosis and treatment. Patients typically present to the clinic with non-specific symptoms such as back pain, limited mobility, and sometimes fever. Because laboratory findings are generally non-specific, magnetic resonance imaging is considered an effective method for diagnosis. Definitive diagnosis typically relies on biopsy and culture results; however, cultures may be negative, and situations where biopsy is not always feasible make diagnosis more challenging. Conservative treatment is the gold standard; however, surgery can be performed when necessary. A multidisciplinary approach and individualized treatment plans are critically important in enhancing the effectiveness of therapy. In conclusion, *Candida* spondylodiscitis is a rare but severe infection. Mortality and morbidity rates can be reduced with early diagnosis and appropriate treatment strategies. In clinical practice, the possibility of fungal infection should not be overlooked, especially in patients with risk factors and should be actively investigated during the diagnostic process. This article aims to contribute to a better understanding of spondylodiscitis caused by *Candida* spp.

Keywords: *Candida*, fungal agents, spondylodiscitis, vertebral infection

Introduction

Spinal infections can be classified as spondylitis, discitis, spondylodiscitis, or epidural abscesses. However, due to anatomical relationships, disc involvement accompanies vertebral osteomyelitis; therefore, vertebral osteomyelitis and spondylodiscitis are considered synonymous in this article. Spondylodiscitis or vertebral osteomyelitis refers to infectious conditions that can affect the vertebrae and discs. Spondylodiscitis, which generally has a bacterial etiology, is most commonly triggered by *Staphylococcus aureus*; however, other bacterial species, fungi, and rarely tuberculosis agents can also cause the disease.[1] Pyogenic involvement is often bacterial, while granulomatous involvement is observed in tuberculosis and fungal infections. The pathogen can spread via hematogenous routes, contiguity, or direct inoculation. Often, the source of the vertebral inflammation is indicated as urinary system infections.[2] Patients most commonly present to the clinic with back pain; however, symptoms such as limited mobility, fever, and local tenderness can also be observed. Blood cultures and imaging are important in the diagnosis of the disease, but none are specific unless a biopsy is taken. Although infections are seen in many parts of the spine, they are least commonly observed in the cervical region, but it has been reported that their effects can be much faster and more severe.[3]

Although bacterial-origin spondylodiscitis is most commonly seen, the possibility of a fungal-origin infection should not be overlooked. Fungal-origin spondylodiscitis may have a more insidious onset compared to bacterial spondylodiscitis, and if not detected and treated with appropriate

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antifungal agents or surgical intervention, it can negatively affect mortality and morbidity. The presence of an immunocompromised state, long-term antibiotic use, alcohol dependency, diabetes mellitus, intravenous drug use, prolonged intensive care history, and the presence of surgical interventions should also suggest fungal spondylodiscitis.[4] Fungal infections generally have a chronic course and do not respond to standard antibiotic treatments, which can make the diagnosis and treatment process more complex.

Candida is a fungus that lives in a commensal relationship within the human body. It contains 15 different subgroups, and the most common is *Candida albicans*. Under normal conditions, *Candida* spp. does not cause serious infections in the human body but can act as an opportunistic pathogen in individuals with weakened immune systems. *Candida* spp. are especially prominent in hospital-acquired infections, and their resistance to antifungals is increasing day by day. For example, *Candida auris* is a multidrug-resistant yeast that has emerged as a hospital-acquired pathogen.[5] *Candida* spondylodiscitis is rare (in <5% of cases) and is seen in immunocompromised patients with risk factors, but can also occur in individuals with completely normal immunity.[6] *Candida* spp. spreads mostly hematogenously and accounts for more than half.[7] Recognizing and managing spondylodiscitis can be difficult due to its nonspecific symptoms; in this review, the etiology, epidemiology, diagnosis, and treatments of spondylodiscitis caused specifically by *Candida* spp. will be emphasized.

Epidemiology and Etiology of Spondylodiscitis

Vertebral osteomyelitis infections can present differently among various pathogens and patient populations. While the most common pathogen is *S. aureus*, they can also be caused by gram-negative bacilli, tuberculosis, Brucella, and fungal agents. Grammatico et al[8] estimated the incidence of vertebral osteomyelitis in France as 2.4 per 100 000 people. According to American data from 1998 to 2013, the incidence increased from 3/100 000 to 5-6/100 000.[9] Fungal vertebral osteomyelitis accounts for 2.5% of all spinal infections.[10]

Sepsis and endocarditis are the most common comorbidities, and the incidence increases with age.[8] Mylona et al,[2] in their study examining 1008 patients and 14 studies, stated that diabetes was the most common comorbidity. In a retrospective study conducted on 253 patients with vertebral osteomyelitis, it was reported that 11% of patients died, more than one-third of survivors developed permanent disability, and recurrence was observed in 14%. Additionally, surgical treatment achieved improvement in 86 out of 109 patients (79%); early diagnosis and an appropriate treatment process are critical for achieving optimal outcomes in spondylodiscitis.[1] Asperges et al),[11] in their systematic review on fungal osteomyelitis, stated that *Aspergillus* and *Candida* are the most common pathogens, vertebral osteomyelitis is the most frequently observed type, and that early diagnosis, longer antifungal therapy, and surgical intervention improve treatment outcomes, but mortality continues to remain significant at 10.5%. The recovery rate in patients with *Candida* spondylodiscitis was 92.3%, whereas it was determined as 70.2% in patients with *Aspergillus* spondylodiscitis.

Candida osteomyelitis is a rare infection generally associated with surgery and broad-spectrum antibiotics; the species most frequently causing infection include *C. albicans* (69%), *Candida tropicalis* (15%), and *Candida glabrata* (8%).[12] *Candidal* discitis can be a late complication of candidemia (Table 1); in one study, it was reported that vertebral osteomyelitis caused by *C. glabrata* emerged 25 months after candidemia.[13] Long-term antibiotic use or anti-MRSA antibiotics use are also important risk factors.[14] Although it is most commonly observed in the spine and sternum bones, it has also been reported in the talus bones of an elderly patient.[15]

Diagnosis

Spondylodiscitis, especially when associated with *Candida* spp., can lead to severe neurological and spinal complications due to delays in diagnosis.[16] *Candida* infections primarily affect the vertebrae in adults, while the femur is more commonly involved in children.[7] Most patients exhibit involvement of the lower thoracic and lumbar spine, and erythrocyte sedimentation rate may be elevated.[17] A thorough history should include previous candidemia or infections, antibiotic usage, travel history, and invasive procedures (e.g., discography).[18] Its incidence has increased following prolonged SARS-CoV-2 infection.[19]

Imaging plays a significant role in the diagnosis and treatment follow-up of the disease. Magnetic resonance imaging (MRI) remains the most effective imaging tool in diagnosing vertebral osteomyelitis. Typical findings such as decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images are important for reliably showing abscesses and phlegmons.[21,22] If MRI is not performed, nuclear medicine methods can be preferred. For example, 18-F-fluorodeoxyglucose - positron emission tomography (FDG-PET) can be a highly sensitive imaging procedure in detecting spondylodiscitis because, compared to other nuclear medicine procedures, PET offers rapid imaging, acceptable radiation dose, and high spatial resolution.[23] Consequently, gadolinium-enhanced MRI is the best option for diagnosis. In MRI imaging, focal partial soft tissue abnormalities and partial involvement of the disc/endplate are more likely in the fungal group.[23]

Diagnosis can be made with culture and biopsy. However, biopsy provides much more accurate information than blood culture.[2] Blood cultures may be negative, but direct vertebral biopsies may be positive.[24] In the absence of positive blood cultures, computed tomography (CT)-guided biopsy is indicated.Table 1

For mortality and morbidity, studies by Kowalski et al[25] have shown that applying a simple grading scale to follow-up imaging examinations, along with the evaluation of inflammatory biomarkers and clinical status, stratifies the risk of treatment failure. It was

Table 1. Complications of Candida spondilodiscitis[1,20]

Type of Complication	Complications
Infection-related	Epidural abscess Paravertebral abscess Disc space abscess Skull base osteomyelitis Subarachnoid spread
Neurological	Radiculopathy Myelopathy Para- or tetraplegia
Structural	Spinal instability Scoliosis Kyphosis
Systemic	Sepsis Systemic spread Bacterial superinfections
Functional	Chronic pain Loss of function

found that patients with improved imaging had a 100% survival within 1 year without microbiologically confirmed failure.

In conclusion, MRI and biopsy are essential for diagnosis. However, in cases where the culture is negative and the biopsy cannot be performed, diagnosis can be made based on clinical and typical radiological findings and increased inflammatory markers. For prognosis prediction, the invasive fungal spondylodiscitis prognosis determination model developed by Yang et al,[26] which considers 5 criteria—immunosuppressed status, presence of radiculopathy or myelopathy, leukocyte count, hemoglobin level, and presence of candidemia—can be used.

Treatment

Conservative management remains the gold standard in spondylodiscitis, typically involving analgesics (nonsteroidal anti-inflammatory drugs or opioids) to alleviate pain, alongside targeted antifungal therapy.[27] Azole derivatives (e.g., fluconazole, ketoconazole, voriconazole), echinocandins, and amphotericin B are commonly used agents in the treatment of *Candida*-related vertebral infections. Identification of *Candida* spp. is essential due to significant variations in antifungal susceptibility across species. For example, while *C. albicans* is typically susceptible to fluconazole, non-albicans *Candida* spp. such as *C. glabrata* and *Candida krusei* often exhibit reduced susceptibility or resistance to fluconazole, necessitating the use of alternative agents like echinocandins or amphotericin B. In addition, some multidrug-resistant pathogens, including *C. auris*, may show resistance to multiple antifungal classes, including azoles and, in certain cases, echinocandins, highlighting the importance of accurate species identification for optimizing treatment. In the absence of species identification, empirical antifungal therapy may be less precise, potentially affecting clinical outcomes.

In cases following spinal surgery, an infection developed in a patient due to the use of artificial nails by an operating room staff member, so paying attention to operating room cleanliness is very important. However, a patient treated with amphotericin B combined with fluconazole has yielded successful outcomes.[28] Ketoconazole has been proposed as a less toxic alternative to amphotericin B in certain cases, and combination regimens (e.g., amphotericin B plus 5-flucytosine and rifampicin) have also produced favorable results.[29-31]

The treatment strategy published in 2016 by the Infectious Diseases Society of America is important for guiding therapeutic approaches.[32] Adaptation of therapy based on fungal species and resistance profiles is essential. For example, when fluconazole-resistant *C. glabrata* spondylodiscitis developed, long-term amphotericin B was required, followed by surgical intervention due to spinal instability.[4] Similarly, for *C. albicans* infections in immunocompromised patients or those with chronic renal disease, modifications in the antifungal regimen are often needed.[33] Improvement in clinical symptoms and inflammatory markers generally occurs within the first month of treatment.

Prolonged antifungal therapy (6-12 weeks or longer) is common, often guided by clinical response, species sensitivity, and the presence of complications such as epidural abscesses or spinal instability.[34] Surgical debridement is frequently indicated, particularly when conservative measures fail, or when neurological deficits, sepsis, or structural instability occur. Surgical intervention enhances the efficacy of antifungal agents by reducing the fungal burden and addressing mechanical instability or compression. Hosameldin et al[35] reported that surgical debridement and fixation provided high efficacy in the management of spontaneous thoracic and lumbar spondylodiscitis, with full motor function recovery in 95% of cases in 3 months. Surgical treatment is required when compression of the nerve root, spinal cord, or dura mater is seen on MRI; serious deformities like spinal instability or kyphosis due to bone destruction are also clear indicators for surgical treatment and are recommended in cases of spinal instability or epidural abscess. Anterior or posterior approaches are preferred depending on the location of the abscess.[35]

The choice of antifungal therapy depends on susceptibility patterns. Fluconazole is generally well-tolerated for long-term use but may not be effective against azole-resistant strains, and some patients, such as those with renal impairment, may not tolerate amphotericin B.[36] In these cases, echinocandins or newer agents like rezafungin may be utilized.[19,37-41] Emerging data also support the use of combination therapies, prophylactic antifungals in high-risk groups, and the importance of catheter removal in improving clinical outcomes. Additionally, superinfection may occur in some patients.[42]

Aggressive treatment may be important in the presence of comorbid conditions; however, it should be noted that if the patient needs to start chemotherapy as soon as possible, direct surgical intervention may be necessary instead of long-term antifungal therapy.[43] In a study related to invasive candidiasis, 2 factors were associated with better survival and higher clinical success: the use of echinocandins and the removal of the central venous catheter.[44] Adelhoefer et al,[45] in their systematic review on *Candida* spondylodiscitis, found that most patients were treated with a median 6-month fluconazole therapy. The lumbar spine was the most affected region, and despite aggressive therapy, 12% did not survive within a year. Age, high Charlson comorbidity index, and shorter treatment duration are among the risk factors associated with 1-year mortality.[46] However, younger age and longer antifungal therapy improved survival rates. Ultimately, the optimal drug and treatment duration for fungal spondylodiscitis are unknown.

In summary, the management of Candida spondylodiscitis typically involves initial broad antifungal coverage followed by a long-term azole regimen once susceptibility is known. Echinocandins and novel antifungals are considered for resistant strains or in patients with significant comorbidities. Surgical intervention is necessary for spinal instability, neurological compromise, or failure of conservative treatment. While medical therapy is often successful, ongoing research is needed to define the optimal treatment duration, agent selection, and use of novel antifungal agents to improve outcomes in this challenging condition.

Conclusion and Discussion

The treatment of *Candida* spondylodiscitis requires a multidisciplinary approach when *Candida* spp. infect the spinal discs and surrounding bone tissues. First, the diagnosis should be made based on the patient's clinical symptoms and appropriate imaging methods, followed by the determination of the infectious agent through biopsy and culture tests. Additionally, the indiscriminate use of antibiotics should be avoided, as antibiotics create an even more ideal environment for the exponential growth of fungi.

Especially, the biofilm-forming abilities and antifungal resistance of *Candida* spp. complicate the diagnosis and treatment processes, and successful outcomes require surgical debridement and the use of advanced antifungal agents. Moreover, patients' immune status, prolonged hospital stays, and existing health conditions play a critical role in determining treatment strategies. Cervical spine spondylodiscitis caused by *Candida* spp. is extremely rare in immunocompetent patients and typically presents with non-specific symptoms that delay treatment. This situation can lead to serious complications such as permanent spinal cord damage and

sepsis. Surgical debridement is recommended; however, there is no standard antimycotic treatment regimen, and treatment generally involves a combination of surgery and long-term antifungal therapy. Prognosis largely depends on timely intervention. The use of MRI for early diagnosis, application of biopsy and culture methods for definitive diagnosis, and determination of appropriate treatment strategies are vital in effectively managing vertebral osteomyelitis. In clinical practice, approaching with a high suspicion towards fungal pathogens plays a critical role in improving patient outcomes.

Long-term antifungal use and surgical interventions may be necessary for treatment efficacy. The aim of surgical intervention is to prevent infection, correct spinal function, eliminate neurological deficits and pain, and obtain a larger sample for biopsy. Supportive therapy includes applying physical therapy and pain management to preserve the patient's mobility and quality of life. Antifungal resistance development should be considered during the treatment process, and the treatment plan should be revised according to culture results. Additionally, an individualized treatment plan should be created considering the patient's overall health status and comorbidities, and long-term follow-ups should be conducted to assess whether the infection is under control.

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