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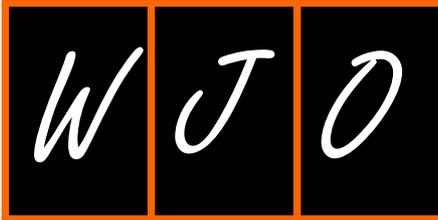
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## Fungal arthritis: A challenging clinical entity

Anjali Mishra, Deven Juneja

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### Abstract

There has been an increasing incidence of fungal infections in recent years. Rarely joints are also affected by fungal infections. Mainly, these infections develop in prosthetic joints, but sometimes native joints are also involved. *Candida* infections are mostly reported, but patients may also develop infections secondary to non-*Candida* fungi, especially *Aspergillus*. Diagnosis and management of these infections is challenging and may involve multiple surgical interventions and prolonged antifungal therapy. Despite this, these infections are associated with high morbidity and mortality. This review described the clinical features, risk factors, and therapeutic interventions required to manage fungal arthritis.

**Key Words:** *Aspergillus*; *Candida*; Fungal arthritis; Invasive fungal infections; Osteomyelitis

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**Core Tip:** Fungal arthritis and osteomyelitis are rare diseases, but their incidence is increasing with the rising prevalence of predisposing factors. Most infections are secondary to *Candida spp.*, especially *Candida albicans*, but patients rarely develop infections secondary to other fungi, including *Aspergillus*, *Histoplasma*, *Cryptococcus* and *Coccidioides*. Fungal biomarkers may aid in rapid diagnosis in high-risk patients, but definitive diagnosis requires bone or synovial culture or biopsy. Surgical intervention and prolonged antifungal therapy form the mainstay of therapy, with azoles and echinocandins providing a safe and effective therapeutic option.

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## INTRODUCTION

Fungal septic arthritis is a rare but severe and sometimes even life-threatening infection. It requires long-term medical and, in most cases, surgical management. During the past few years, there has been a dramatic surge in invasive fungal infections (IFIs). This is majorly attributable to the rise in the number of immunocompromised patients, including those on immunosuppression or broad-spectrum antibiotics, neutropenia, indwelling prosthesis, Human immunodeficiency virus (HIV), diabetes mellitus, burns, and long-term parenteral alimentation. A marked improvement in diagnostic techniques, including molecular methods, has also contributed to the early and rapid detection of these infections[1-3]. The course of bone and joint fungal infection can vary from indolent to highly aggressive. Spread is usually hematogenous (due to the high vascularity of synovial tissue), direct extension from a nearby infective focus or direct inoculation[4]. An indolent infection may be challenging to diagnose due to a lack of systemic inflammatory response and the absence of typical imaging features. However, the absence of a periosteal reaction and new bone formation at the site of osteomyelitis may indicate fungal etiology[5]. Therefore, diagnosing such cases may be highly dependent on a thorough history and physical examination. The clinical course and outcomes vary depending on the specific fungal species and the host factors.

## PATHOPHYSIOLOGY

Hematogenous dissemination is the most frequent route of spread for IFIs. The other common route is direct inoculation from an exogenous source, such as surgery, prosthetic implantation, intra-articular corticosteroid injection, arthrocentesis, trauma, and open fractures[4,6]. The most common presenting complaint is localized pain followed by signs of local inflammation (swelling, erythema, and effusion), fever, and decreased range of motion. The large weight-bearing joints such as knees are most frequently affected[7]. However, there are no distinct clinical clues that may help differentiate fungal from bacterial arthritis. Hence, a detailed histopathological diagnosis is needed to elucidate a definitive pathogen in cases of high suspicion. In some cases, lytic lesions, cortical erosions, or adjacent osteoporosis and osteomyelitis may be seen on imaging scans. Findings of necrotizing granulomas on pathological examination make tubercular arthritis a close differential diagnosis (Table 1)[5,7].

## DIAGNOSIS

Diagnosis of fungal arthritis can be quite challenging because of insidious disease onset with slow progression and lack of characteristic findings. The typical stains and smears used for fungal identification, such as potassium hydroxide or gram stain, may fail to identify the organism, and routine cultures are often non-diagnostic. The routine biochemistry and synovial fluid leukocyte count resemble a picture suggestive of non-infectious arthritis[7]. The demonstration of fungi on synovial, bone, or tissue culture and biopsy can be more indicative of an actual infection. However, the biggest limitation is the time taken to grow, especially in filamentous fungi cases, which potentially delays the treatment [3,8]. The fungal cultures are plated on Sabouraud dextrose agar at 24 °C-25 °C and should not be reported negative for growth until 4 wk after incubation[8].

As a consequence of difficult diagnosis and rising uncertainty of the classical phenotypic methods of fungal identification, there is now an increased focus on the use of molecular methods and antigen detection methods as surrogates for histopathology and cultures. The non-culture-based serological testing techniques that detect antibodies include enzyme immunoassay, immunodiffusion, and complement fixation. Among the molecular diagnostic tests, only a few tests, such as Film Array Blood Culture Identification (BioFire Diagnostics, Inc.), which is a PCR-based test, has been approved by the Food and Drug Administration. The matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) assay is a new test rapidly gaining popularity. It is a non-nucleic acid sequence-based molecular diagnostic assay for fungi, especially filamentous fungi such as *Aspergillus spp.*, and its strength lies in speed and accuracy[9].

There is an increasing interest in the use of biomarkers for diagnosing IFIs.  $\beta$ -D-glucan (BDG) is a non-specific fungal marker that may be positive in many fungal infections like *Candida*, *Aspergillus*, *Pneumocystis jirovecii*, and *Fusarium*. However, BDG may be negative in patients with *Cryptococcus*, *Blastomyces* (yeast form), or Zygomycetes (*Absidia*, *Mucor*, or *Rhizopus*) infection. Galactomannan is more

Table 1 Differential diagnosis for fungal arthritis

No.	Diagnosis
1	Bacterial arthritis
2	Tubercular arthritis
3	Sarcoidosis
4	Ewing's sarcoma
5	Osteogenic sarcoma
6	Langerhans cell histiocytosis
7	Malignant metastasis

specific to *Aspergillus* infections. These biomarkers have the advantage of rapid turn-around time and hence, if applied in high-risk patients with a moderate to high chance of IFI, may enable an early diagnosis. However, these biomarkers may also be falsely elevated in many patients, especially those on intravenous beta-lactam antibiotics (amoxicillin-clavulanate and piperacillin-tazobactam) and those on hemodialysis.

## MANAGEMENT

### **Surgical**

In cases of fungal native joint arthritis, a combined approach using medical and surgical therapy is typically desired for optimal results. Most cases of fungal osteomyelitis and septic arthritis need irrigation and surgical debridement. At the same time, tissue or fluid specimens can be collected for histopathological examination. Drainage and debridement are often unnecessary in the established diagnosis of cryptococcal infections.

The surgical process involves debridement of bony and soft tissues, removal of sinus tracts, and insertion of antifungal beads, if required[4]. Many cases of fungal vertebral osteomyelitis are associated with spinal instability and nerve root compression; hence spinal stabilization and arthrodesis are typically required. Early surgical interventions have been shown to prevent neurological injury in such patients[10].

### **Pharmacological management**

Antifungal therapy, along with surgical intervention, forms the mainstay of therapy for fungal arthritis. Historically, the primary clinical experience treating invasive fungal arthritis has been with amphotericin B (Amp B), with or without flucytosine. However, recently azoles (fluconazole and extended-spectrum triazoles such as voriconazole, posaconazole, and isavuconazole) and echinocandins (casposungin, micafungin, and anidulafungin) have been added to the list of available therapeutic options[11]. The recent clinical practice guideline for the management of osteoarticular candidiasis updated by the Infectious Diseases Society of America (IDSA) in 2016 recommends fluconazole and echinocandins as the first drugs of choice for *Candida* infections, given good efficacy and a better safety profile. Liposomal Amp B has been recommended as an alternative[12].

### **Azoles**

The azole group blocks ergosterol synthesis in the cell membrane by inhibiting the enzyme lanosterol 14A demethylase and alters the functions of the membrane enzymes resulting in its dysfunction[13]. Fluconazole has good bone and tissue penetration, as indicated by the synovial fluid levels. Except for *Candida (C.) krusei*, *C. glabrata*, and some strains of *C. auris*, the majority of the *Candida* species are susceptible to fluconazole[14]. However, it has poor activity against *Aspergillus*. Voriconazole is the drug of choice for *Aspergillus* infections and has good bone penetration.

### **Polyenes**

Amp B belongs to the polyene class of antifungal drugs that binds to ergosterol and results in the formation of pores, leakage of ions, and cell death. Additionally, Amp B also causes lipid peroxidation and oxidation reaction. The drug's newer lipid formulations are less nephrotoxic than conventional Amp B deoxycholate and have a better tolerability and toxicity profile. However, because of the better safety profile of azoles and echinocandins, it is typically reserved for invasive and resistant fungal infections. The toxicity profile of Amp B is directly related to its affinity and interaction with cholesterol. The most common adverse effects include infusion-related reactions (fever, chills, malaise, and hypotension), hypokalemia, hypomagnesemia, thrombocytopenia, leucopenia, normochromic, and

normocytic anemia with long-term use. Renal toxicity is dose-related, and renal failure is generally reversible after discontinuation of the drug. Adequate hydration and avoiding concomitant use of other nephrotoxic drugs may decrease the incidence of nephrotoxicity. The infusion-related toxicity can be reduced by administering a slow infusion over an extended period[4,15].

### **Echinocandins**

Echinocandins inhibit the synthesis of 1,3  $\beta$ -glucan, a major polysaccharide component of the cell wall and cause osmotic instability. This class of antifungals has a better tolerance profile with fewer adverse effects and ease of dosing in renal and liver dysfunctions. Echinocandins are active against most triazole-resistant pathogens and demonstrate fungicidal activity towards *Candida* species and fungistatic against mold (*Aspergillus* species)[16]. They are relatively less active against *C. guilliermondii* and *C. parapsilosis* and lack any activity against *Cryptococcus neoformans*, Zygomycetes and *Trichosporon* species due to the absence of  $\beta$ -glucan in the cell walls of these organisms[17]. Echinocandins are most effective against the biofilm formed by certain fungal species like *C. albicans* on retention hardware and medical devices. Studies have demonstrated the effectiveness of caspofungin and micafungin in killing preformed *Candida*-related biofilms at concentrations achievable *in vivo*[18].

### **Pyrimidine analogue**

Flucytosine is an antimetabolite agent, approved by the Food and Drug Administration in 1971, for treating invasive cryptococcal and *Candida* infections. The drug carries a high risk of resistance to its use and is almost always used in combination with other antifungals, such as Amp B, for systemic and IFIs. It can cause acute hepatitis and severe hematological adverse effects, including pancytopenia, agranulocytosis, aplastic anemia, and bone marrow suppression[19].

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## **COMMON PATHOGENS**

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Several different fungi may cause arthritis with varying clinical presentations. It is pertinent to make a pathological diagnosis as therapeutic options, the duration of therapy, and patient prognosis vary. Many risk factors have been identified for infection with different fungi, which may aid in raising suspicion and enabling early diagnosis (Table 2)[20,21].

### ***Candida* species**

*Candida* species are the most common cause of fungal arthritis and osteomyelitis, especially in immunocompromised patients. An episode of candidemia, despite adequate antifungal treatment, may cause invasive joint and bone disease even after a long latent period of several months and sometimes even years[22]. *C. albicans* is the most commonly isolated species. *Candida* osteomyelitis often involves vertebrae, sternum, femur, humerus, and tibia. It usually starts as synovitis, eventually involving the adjacent bone causing osteomyelitis[4,5,23]. *Candida* arthritis, however, targets large-weight joints such as the knee, hip, shoulder, and ankle[20]. Joints affected by rheumatoid arthritis are predisposed to *Candida* infection. Infection can occur during aspiration, intra-articular steroid injection, or arthroscopy [11].

Surgical findings are cartilage erosion, thickening and hyperemia of the synovium with fibrosis, scarring, and purulence. Radiographically, *Candida* osteomyelitis of the spine shares certain findings with bacterial infections such as disc space narrowing, end plate destruction of adjacent vertebral bodies, and demineralization and mottled trabecular pattern in cases of long bone infections[5,24].

Treatment of *Candida* joint disease includes antifungal therapy and surgical debridement. Fluconazole remains the mainstay of medical management as most *C. albicans* are still susceptible. For septic arthritis, it is a 6-wk course of treatment with fluconazole or an echinocandin for 2 wk, followed by oral fluconazole for at least 4 wk. Lipid formulation of Amp B is another alternative, with therapy for 2 wk before transitioning to fluconazole. For osteomyelitis, a longer course of 6 mo of fluconazole is generally required. Alternatively, an echinocandin or liposomal Amp B may be used for 2 wk, followed by 6-12 mo of fluconazole, depending upon the clinical and radiographical improvement (Table 3). Surgical drainage is indicated in all cases of septic arthritis. Removal is recommended in cases of infected prosthetic joints[12].

### ***Aspergillus* species**

*Aspergillus spp.* are ubiquitous saprophytes, and the pathogenic species are *Aspergillus (A.) fumigatus*, *A. niger*, *A. flavus*, and *A. terreus*. Infection most commonly occurs through inhalation of spores or hematogenous spread from a primary pulmonary focus. Extension of infection may involve maxillofacial structures, mastoids, sphenoid bones, or basilar skull, but most cases of *Aspergillus* osteomyelitis involve the vertebrae[25]. The lumbar spine is the most frequently involved site in cases of hematogenous spread[5].

The most common presentation is fever, pain, tenderness, and swelling of the joint. Cases of head and neck infections may present with headache, conjunctivitis, periorbital cellulitis, proptosis, and epistaxis. Radiologically, vertebral aspergillosis may be challenging to distinguish from tuberculosis. Cultures of

Table 2 Risk factors for specific fungal infections

Fungal infections	Risk factors
<i>Candida</i> spp.	Immunosuppression
	Chemotherapy
	Recent surgery
	Uncontrolled diabetes
	Corticosteroids
	Broad spectrum antibiotics
	Intravenous drug abuse
	Indwelling central venous catheters
	Hemodialysis
	Multiple site colonization
<i>Aspergillus</i> spp.	Neutropenia
	Chronic granulomatous disease
	Post-organ transplant
<i>Coccidioides immitis</i>	Uncontrolled diabetes
	Immunosuppression
	Advanced age
	HIV
<i>Histoplasma capsulatum</i>	HIV
	Advanced age
	Post-organ transplant
	Corticosteroids
	Immunosuppression

HIV: Human immunodeficiency virus.

biopsy specimens or synovial fluid growing the characteristic acutely branching hyphae are usually diagnostic of *Aspergillus*[26]. Identification tests for *Aspergillus* also include serum beta-d-glucan, galactomannan antigen test, and PCR testing. Serum assays for BDG are not specific to *Aspergillus*. Galactomannan antigen test has prognostic value with a serial decline in the serum levels indicating an effective antifungal treatment[27].

Triazoles and Amp B have long been used to treat invasive aspergillosis. Voriconazole is recommended as the drug of choice in managing invasive aspergillosis as it has a broad antifungal spectrum of activity and lesser nephrotoxicity than amphotericin[28]. Antifungal treatment is recommended for 6 wk to 8 wk, along with surgical debridement. Surgical debridement of the infected material helps with reducing the infective burden and allowing better drug penetration[13].

### ***Coccidioides* species**

*Coccidioides* species are dimorphic fungi found predominantly in regions of Mexico and central, southern, and southwestern regions of the United States. Extrapulmonary dissemination of the disease is rare, but polyarticular arthritis may occur during primary infection with rash, fever, eosinophilia, and bilateral hilar lymphadenopathy as hypersensitivity syndrome[29]. Although rare, hematogenous dissemination may result in septic arthritis, and weight-bearing joints, like the knee, are at greater risk of involvement. On standard laboratory tests, raised erythrocyte sedimentation rate, C-reactive protein, peripheral eosinophilia, and raised *Coccidioides* complement fixation titer may be seen[4].

Radiological findings include joint space narrowing with effusion, osteopenia, and lytic lesions with bone destruction. Histopathology may show villonodular synovitis, pannus and sinus tract formation, non-necrotizing granulomas, and spherules containing endospores. It is a septic arthritis demonstrating synovial proliferation rather than synovial fluid accumulation[30]. The main antifungal drugs are oral azoles (fluconazole and itraconazole), which have largely replaced the role of Amp B, except in immunocompromised patients and disseminated coccidioidomycosis[31].

Table 3 Therapeutic options for fungal arthritis

Antifungal drugs	Indication/pathogen	Dosage
Fluconazole	Candidiasis	400 mg (6 mg/kg) daily (IV/PO)
	Histoplasmosis	
	Blastomycosis	
	<i>Coccidioides</i>	
	<i>Cryptococcus</i>	
Voriconazole	<i>Aspergillus</i>	4-6 mg/kg BD; 200 mg BD (IV/PO)
	Candidiasis	
	<i>Coccidioides</i>	
	Blastomycosis	
	<i>Cryptococcus</i>	
Itraconazole	<i>Aspergillus</i>	100-400 mg/d (PO)
	<i>Sporothrix</i>	
	Candidiasis	
	<i>Coccidioides</i>	
	Histoplasmosis	
	<i>Cryptococcus</i>	
	Blastomycosis	
Ketoconazole	Blastomycosis (mild to moderate cases)	200-400 mg OD (PO)
	<i>Coccidioides</i>	
	<i>Cryptococcus</i>	
	<i>Histoplasmosis</i>	
Liposomal amphotericin B	<i>Candida species</i> (except <i>C. lusitanae</i> )	3-5 mg/kg/d (IV)
	<i>Cryptococcus</i>	
	<i>Aspergillus</i>	
	<i>Coccidioides</i>	
	<i>Histoplasmosis</i>	
Echinocandins: Caspofungin, anidulafungin, micafungin	Candidiasis (fungicidal)	Caspofungin: 70 mg on day 1 followed by 50 mg OD (IV); anidulafungin: 200 mg on day 1 followed by 100 mg OD (IV); micafungin: 100 mg OD (IV)
	<i>Aspergillus</i> (fungistatic)	
5-Flucytosine	<i>Cryptococcus</i>	100 mg/kg/d divided q 6 h (PO)
	<i>Candida</i>	

IV: Intravenous; PO: Per os (oral administration).

### ***Cryptococcus species***

*Cryptococcus* is a basidiomycete that primarily involves the lungs and central nervous system. The route of infection could be inhalational, hematogenous from infected lungs in cases of disseminated disease, or rarely a direct trauma causing arthritis. Septic arthritis usually results from the contiguous spread of infection from adjacent osteomyelitis[32]. *Cryptococcus neoformans* has a unique polysaccharide capsule that protects it against phagocytosis and opsonization in the host[4].

The stains that aid in diagnosing cryptococcosis include periodic acid Schiff stains and methenamine silver nitrate. The diagnostic and prognostic value of serum cryptococcal antigen in osteoarticular cases needs to be better defined[33]. Histopathologic examination of tissue or bone specimens may demonstrate granulomatous changes with extensive fibrosis and giant cells. Radiological findings elicit

discrete, well-defined lytic lesions, usually without sclerotic or periosteal change. In cases of vertebral osteomyelitis, the intervertebral space is spared despite contiguous vertebral body involvement[26]. In non-complicated single-site infections and the absence of any immunosuppressive risk factors, fluconazole 400 mg (6 mg/kg) OD for 6-12 mo is the antifungal treatment of choice. In case of disseminated disease (at least 2 non-contiguous sites involved or high levels of serum cryptococcal antigen titer  $\geq$  1:512), a combination of liposomal Amp B and flucytosine for 2 wk followed by fluconazole as maintenance therapy for 6-12 mo is recommended by IDSA 2010 guidelines[34].

### ***Histoplasma species***

*Histoplasma (H.) capsulatum* usually causes a self-limited respiratory flu-like illness. The spores of this fungus have a predilection for the reticuloendothelial system and can spread to regional lymph nodes. Patients with impaired cellular immunity, such as HIV AIDS infection, are predisposed to *Histoplasma* primary infection or reactivation disease. It usually causes aseptic arthritis as a spectrum of immunologically mediated diseases. Synovial fluid analysis is inflammatory and demonstrates mononuclear cell predominance. The joint involvement is symmetric but may be migratory, and the most common sites of involvement include the knee, ankle, and small joints of the hands and wrist. Other than osteoarticular disease, *H. capsulatum* may also cause tenosynovitis and carpal tunnel syndrome[4,26,35]. *H. capsulatum*, along with *Coccidioides immitis*, are the two fungi most implicated in immune complex arthritis. This leads to joint swelling secondary to synovial proliferation rather than fluid accumulation, often manifested by symmetrical joint involvement[7]. The treatment recommendation is liposomal Amp B for 12 wk before transitioning to oral itraconazole. For mild cases, oral itraconazole is recommended[35].

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## **PROSTHETIC JOINT INFECTION**

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Prosthetic joint infection (PJI) is a known complication of joint arthroplasty procedures and occurs in 1%-2% of cases of prosthetic joint implantations[36]. Overall, *Staphylococcus* is the most common organism isolated in 50% of cases, and *C. albicans* is the most common cause of fungal PJI. Most cases are encountered after revision arthroplasty. The risk factors include diabetes, immunosuppressive therapy, malignancy, obesity, prior antibiotic use, multiple revision surgeries, and preceding bacterial PJI. The clinical presentation is usually similar to septic arthritis as pain, effusion, erythema, joint tenderness with raised levels of erythrocyte sedimentation rate, C-reactive protein, and possibly a positive aspirate culture in cases of deep PJI[4,36,37].

The management consists of two-stage revision arthroplasty, separated by 3-6 mo with a prolonged systemic antifungal treatment[37]. Even after two-stage revision arthroplasty there may be a significant recurrence rate of 20%[38]. Fungal infections are relatively more difficult to treat and require longer time intervals for reimplantation in order to reduce the risk of infection recurrence. The reimplantation is based on the patient's stability and surgical wound status. Some surgical centers also practice joint re-aspiration before proceeding with reimplantation[3,8]. As updated by IDSA in 2016, drug therapy for *Candida* PJI includes fluconazole, liposomal Amp B and echinocandins, and prosthetic device removal [12]. Echinocandins are a lucrative alternative as they have the potential to penetrate the biofilm with the advantage of better tolerance and safety profile and fewer drug interactions than most antifungals [39].

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## **CURRENT CHALLENGES AND FUTURE DIRECTION**

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In the present era of evolving anti-fungal resistance, treating invasive fungal diseases poses an immense challenge. Due to limited bone penetration for most of the anti-fungal drugs and high relapse and recurrence rates, there is a need for prolonged duration of therapy resulting in increased financial burden and high drop-out rates. Experiments are now being conducted to search for newer potential targets and generate new antifungal combinations to overcome drug resistance. An example of such a new target is heat shock protein 90, which modulates fungal virulence and drug resistance through certain downstream effectors and proteins such as calcineurin. The calcineurin inhibitor analogues have been studied to possess antifungal properties and may hold a promising role in abrogating drug resistance. Similarly, pharmacological inhibition of heat shock protein 90 expression with geldanamycin has been shown to reduce resistance to azoles and echinocandins, including resistance that has already evolved in humans treated with these antifungal drugs[40]. Development of newer drugs like ibrexafungerp, a triterpenoid anti-fungal agent, which has advantages of having oral formulation, broad-spectrum activity, and efficacy against newer strains of *Candida* like *C. auris*, may help in managing difficult and resistant infections[41].

## CONCLUSION

Fungal arthritis and osteomyelitis are rare but difficult to treat conditions. The incidence of fungal disease is increasing as predisposing factors are more prevalent in the general population. The treatment for fungal arthritis requires surgical intervention and a prolonged course of antifungal agents. The treatment targets preservation of joints, eradication of the infection, and protection from future recurrence.

## FOOTNOTES

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