Pediatric Radiology (2023) 53:984–1004
https://doi.org/10.1007/s00247-023-05636-3

REVIEW

# Endemic mycoses in children in North America: a review of radiologic findings

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Received: 13 August 2022 / Revised: 17 February 2023 / Accepted: 17 February 2023 / Published online: 16 March 2023


## Abstract

Clinically significant endemic mycoses (fungal infections) in the United States (U.S.) include *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides immitis/posadasii.* While the majority of infections go clinically unnoticed, symptomatic disease can occur in immunocompromised or hospitalized patients, and occasionally in immune-competent individuals. Clinical manifestations vary widely and their diagnosis may require fungal culture, making the rapid diagnosis a challenge. Imaging can be helpful in making a clinical diagnosis prior to laboratory confirmation, as well as assist in characterizing disease extent and severity. In this review, we discuss the three major endemic fungal infections that occur in the U.S., including mycology, epidemiology, clinical presentations, and typical imaging features with an emphasis on the pediatric population.

**Keywords** Blastomycosis · Children · Coccidioidomycosis · Endemic fungal infection · Histoplasmosis · Imaging

## Introduction

Endemic mycoses are caused by a diverse group of fungi that occur in particular geographic locations. In the United States (U.S.), common endemic mycoses include *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides immitis/posadasii* [1]. Most infections caused by these organisms are asymptomatic. Symptomatic endemic mycoses most commonly present as opportunistic infections in immunocompromised or hospitalized patients, although symptomatic infections occasionally occur in immune-competent individuals. Clinical presentations vary from non-specific symptoms such as fatigue, fever, and weight-loss to more specific symptoms involving the central nervous system (CNS), musculoskeletal system, and skin [2].

Imaging findings, combined with patient history, geographic location, and clinical course can help in reaching an exact diagnosis. Most literature regarding imaging of endemic fungal infections pertains to the adult population, with few publications including pediatric patients [2–5]. As such, our understanding of imaging of pediatric endemic mycoses is largely extrapolated. Yet, emerging research in related fields, such as invasive fungal infections, demonstrates that radiologic manifestations of diseases in children can differ significantly from those in adults, suggesting the need for understanding of the imaging manifestations of endemic fungal infection specific to the pediatric population [6]. In this review, we aim to discuss both the thoracic and extra-thoracic imaging findings that we have observed in children with endemic mycoses. Mycology, epidemiology, common clinical presentations, and diagnostic techniques will also be discussed.

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## Overview of endemic mycoses

All three fungi being discussed are saprophytic, meaning that they feed on decaying organic matter. Exact case numbers are difficult to determine due to differing reporting criteria among states and asymptomatic disease going unrecognized [7–9], but estimated annual incidences of blastomycosis, histoplasmosis, and coccidioidomycosis range between 0 and 121 reported cases per 100,000 population [10–12]. The frequency of hospitalization (4.6 and 28.7 cases per 1 million children and adults, respectively) and mortality (5% and 7% of infected children and adults, respectively) are likely inaccurate [1, 13]. In the pediatric population, emerging research discusses the use of C-reactive protein and procalcitonin to differentiate fungal from bacterial infection, with procalcitonin levels being increased in bacterial infections but not in fungal disease [14, 15].

## Blastomycosis

### Epidemiology

*Blastomyces dermatitidis* is endemic to the Mississippi and Ohio River basin, Great Lakes region, and Southeastern U.S. [16]. Individuals who participate in outdoor activities (e.g., hiking, hunting, fishing) are more likely to be exposed. Incidence in hyperendemic regions, such as Vilas County, Wisconsin, is reported to be 40 cases/100,000 people [15]. Approximately 3–10% of reported cases occur in children [17].

### Mycology

*B. dermatitidis* is a dimorphic haploid ascomycota. In its typical moist soil environment at 22–30 °C, its mycelia exist as septate hyphae with a single conidium (spore) attached to a conidiophore. When disturbed, the fungus' spores fragment from the rest of the hyphae and are released into the air. Mammals in close proximity inhale the aerosolized spores. Once inside the host's lungs, the spores undergo phase transition and convert to a pathogenic multinucleate broad-based budding yeast (Fig. 1) [18, 19].

### Pathogenesis

A number of virulence factors are acquired after *B. dermatitidis* undergoes phase transition. Yeast cells are larger with thicker cell walls, making phagocytosis by the host immune cells more difficult. Adhesion proteins called Blastomyces adhesin-1 (BAD-1) are expressed on the cell surface that possesses a high affinity for human lung tissue and extracellular matrix, allowing for further evasion of the host's immune system, yeast replication, and, potentially, lymphohematogenous dissemination [20–22].

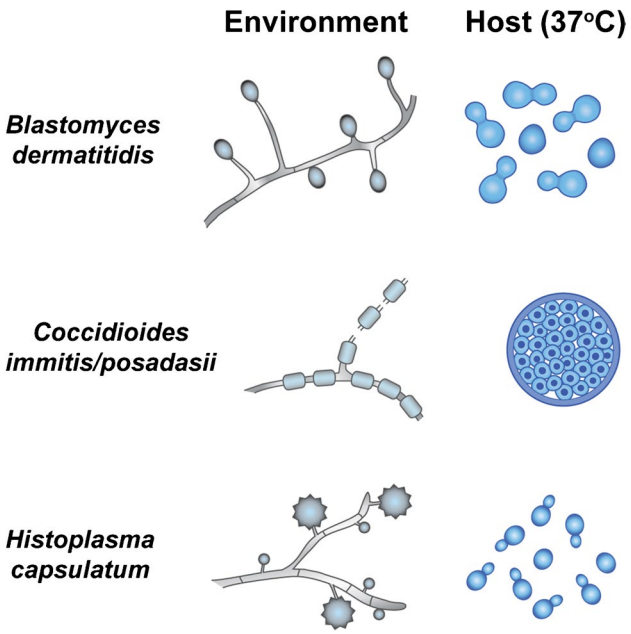


**Fig. 1** Fungal dimorphic states relative to temperature. Copyright permission granted by original artist, Davina H. Murray, and adapted for the manuscript. *Blastomyces* exists as septate hyphae with spores in the environment, and as a broad-based budding yeast in the body. *Coccidiodes* exists as hyphae that link single-cell barrel-shaped spores in the environment, and as spherules in the body that internally contain many endospores that are released upon spherule rupture. *Histoplasma* exists as septate hyphae with spiky macrospores and smooth microspores in the environment, and as an oval budding yeast in the body

### Clinical presentation

*B. dermatitidis* is comparatively less dependent on host immunocompromise than other dimorphic fungi and more frequently causes symptomatic disease in immunocompetent patients. Commonly, blastomycosis presents as a chronic isolated pulmonary disease, with cough being the most sensitive symptom. It is frequently accompanied with dyspnea, sputum production, and systemic signs, such as fever, chills, and fatigue, overlapping with community-acquired pneumonia or tuberculosis [23]. In rare cases, acute respiratory distress syndrome (ARDS) may develop, which is often the cause of death in children with blastomycosis [15, 17, 24].

Extrapulmonary disease is less common and rarely occurs in isolation. The skin is primarily involved, with skin lesions ranging from verrucous to ulcerative in appearance. Dissemination to the bone, causing osteomyelitis, may also occur

[25]. CNS blastomycosis is rare, most commonly affecting immunocompromised patients with acquired immune deficiency syndrome (AIDS). It can manifest with headaches and has a lower mortality rate in children than in the adult population [26].

### Diagnosis

The most common method for diagnosing blastomycosis is multimedia culturing of biopsy or sputum specimens. Cultures can be confirmatory even when histology is negative [27]. Given that yeast growth is rarely apparent before 5 days of culturing and may take as long as 30 days, for prompt identification (less than 1 to 2 days), histologic or cytologic assessment of bronchoalveolar lavage (BAL) can facilitate timely treatment (Fig. 2) [27, 28]. Irrespective of the anatomic site or tissue involvement, classic lesions present as necrotizing granulomas, containing round yeasts with single buds. Their broad-based budding morphology with thick refractile walls is essentially pathognomonic among human pathogens and is highlighted on Grocott methenamine silver (GMS) or periodic acid-Schiff (PAS) stains (Fig. 2) [28, 29]. Occasionally, the yeast morphology overlaps with other fungi requiring confirmation by culture [27, 28]. Alternative methods include serum and urine antigen testing, which has proven reliable for rapid diagnosis, but has limited specificity and should not be used for diagnosis confirmation [30, 31].

### Treatment

Primary treatment goals emphasize early intervention to prevent dissemination (primarily hematogenous) and ARDS.

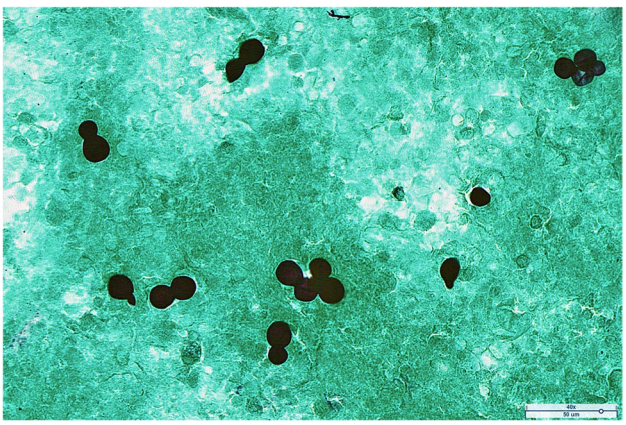

**Fig. 2** Bronchioalveolar lavage (BAL) specimen from a patient with pulmonary blastomycosis. The Grocott methenamine silver (GMS) stain shows numerous *Blastomyces* yeast forms with characteristic broad-based budding and thick cell walls; scale bar 50 µm

Although some cases are self-limiting, persistent mild pulmonary infections may require an oral azole antifungal medication [32]. More severe or disseminated cases will require amphotericin-based compounds that offer better tissue penetrance [33]. Some initial data suggest that serology antigen and antibody levels may be used to track therapeutic response [15, 34–37].

## Coccidioidomycosis

### Epidemiology

*Coccidioides immitis* and *Coccidioides posadasii* are endemic to the Southwestern U.S., northern Mexico, and Brazil [16]. The two are clinically indistinguishable but differ in geographic distribution. In its pathogenic form, coccidioidomycosis, also known as "San Joaquin Sun Valley Fever," has been reported in 22 states. Farmers, military personnel, and excavators are at the greatest risk. Periods of drought that follow heavy rain increase the risk of exposure, because the species reside in dry alkaline soil, where they feed and grow off animals' food and their carcasses [38]. The incidence of coccidiomycosis ranges from 0 to 42.6/100,000 population [12]. Pediatric cases account for 9.2% of the reported annual incidence and have a slightly higher mortality rate compared with adult cases (3.2% in children vs 2.7% in adults) [39, 40].

### Mycology

*Coccidiodes spp.* mycelium exists as septate hyphae that link single-cell barrel-shaped arthroconidia (spores). In mammalian host's lungs, the arthroconidia phase transitions into pathogenic spherules that, internally, grow and host many endospores. Aside from these structural differences, the mycology of *Coccidiodes spp.* is comparable to that of *B. dermatitidis* [38, 39].

### Pathogenesis

Once phase transition has taken place inside the host's terminal bronchioles, coccidioidomycosis primarily relies on its rapid growth ability for virulence to outpace the host's immune system. Spherules undergo synchronous division of nuclei and eventually rupture, releasing hundreds of endospores. Each endospore has the potential to become a new spherule and the process is repeated. Spherules are too large for phagocytosis so the host immune system relies

on antibody-mediated and T-cell immunity [41]. Generally, host cellular immunity can adequately control coccidioidal infection, making virulence greatly dependent on the immune status of the host [40].

## Clinical presentation

Nearly 60% of coccidioidomycosis infections are asymptomatic or self-limited [40]. In the remaining patients, severity usually depends on the patient's immune system status. Coccidioidomycosis can be classified as primary or secondary. The primary disease usually manifests in the lungs with associated flu-like syndrome termed "San Joaquin Sun Valley Fever." Acutely, patients typically develop fever, cough, chest pain, headache, fatigue, and arthralgias, and, on rare occasions, develop pneumonia and respiratory failure. Chronically, especially if left untreated, local lung infections can evolve into diffuse pulmonary disease, pericarditis, mediastinitis, pleural effusions, empyema, and lung abscess [37, 42]. Coccidioidomycosis is commonly mistaken for bacterial pneumonia. In hyperendemic regions, coccidioidomycosis is responsible for up to 25% of community-acquired pneumonia cases [40].

The secondary disease occurs when infection extends or disseminates beyond the primary site to other organs. In addition to primary disease symptoms, the disseminated disease is accompanied by night sweats, weight loss, and lymphadenopathy. In symptomatic pediatric coccidioidomycosis, disseminated disease occurs in up to 81% of cases and is most likely to occur in bones and joints [43, 44]. CNS infection, while uncommon, is the most serious form of secondary disease, with coccidioidal meningitis usually presenting with headache, nausea and vomiting, altered mental status, and fever. While the skin is the most common site of dissemination in adults with secondary disease (occurring in almost 70% of cases), it occurs much less frequently in children (less than 10% of cases). Skin involvement can manifest as erythema nodosum [40, 43].

## Diagnosis

The mainstay method for diagnosis of coccidioidomycosis is the serologic detection of IgG and IgM antibodies [45]. False-negative results are a significant pitfall both in the (severely) immunocompromised and in the setting of new-onset disease, as antibodies may take weeks to develop [35]. False negative serology was reported in approximately 38% of patients with hematogenous infection and 46% of fatal cases in a retrospective study [46]. Histologically, classic lesions present with necrotizing granulomatous inflammation (Fig. 3). Large thick-walled spherules contain numerous endospores and may be seen with routine H&E stains (Fig. 4) [47]. Ruptured spherules spill their endospores into surrounding tissues, which can be highlighted on special stains (GMS and PAS) [48]. A definitive diagnosis of *Coccidioides* requires the unequivocal presence of endospore-containing spherules [49]. Detection by polymerase chain reaction methods is emerging as an alternative rapid diagnostic approach [50].

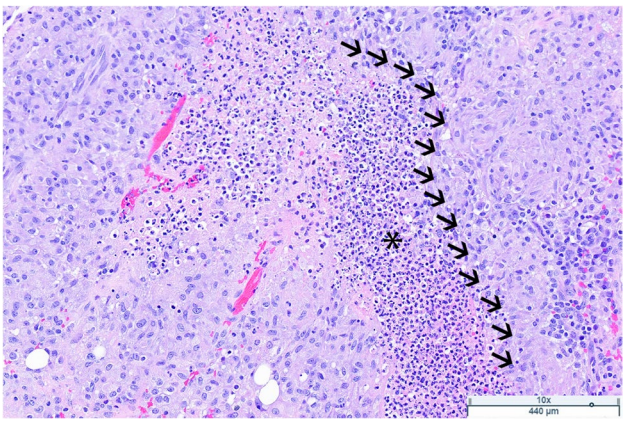


**Fig. 3** Hematoxylin and eosin (H&E) stain showing pulmonary coccidioidomycosis histologic findings. Granulomatous inflammation in pulmonary coccidioidomycosis demonstrating extensive central purulent necrosis (asterisk: collection of neutrophils and cell debris, in a fibrinoid background) surrounded by peripheral palisading/demarcating histiocytes (vague granulomatous lining exemplied by arrows). Scale bar: 440 µm

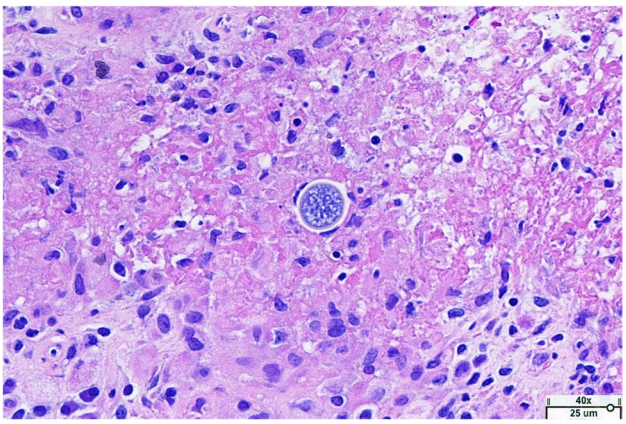


**Fig. 4** Hematoxylin and eosin (H&E) stain showing *Coccidioides* spherule with endospores. Pulmonary coccidioidomycosis with a characteristic spherule containing multiple endospores as highlighted by hematoxylin–eosin in a necrotizing background with loss of nuclear staining. Scale bar 25 µm

### Treatment

Coccidiomycosis treatment typically is focused on patient reassurance and education as most cases are self-limited. Oral azole antifungals are typically reserved for severe disease, including CNS involvement, and in immunocompromised patients. In more severe pulmonary disease or systemic dissemination, pharmacological management may be long-term, sometimes beyond a year, due to the fact that Coccidioidomycosis maintains a high potential for latency. Surgical intervention is more commonly required in children but typically reserved for extreme cavitary pulmonary disease and disease affecting bones and joints [40, 42, 51, 52].

## Histoplasmosis

### Epidemiology

*Histoplasma capsulatum* is endemic to the Mississippi and Ohio River basins of the U.S., Central America, Southeast Asia, and the Mediterranean [16]. Its pathogenic form, histoplasmosis, has been reported in 12 states. People who spend time occupying empty buildings, farms, and caves are at the greatest risk of exposure, as *H. capsulatum* is often found in soils contaminated with bird and bat guano. Occupational risk factors include cleaning, excavating, or exploring said locations [53, 54]. Although annual incidence rates ranged from 0 to 39 cases/100,000 population, histoplasmosis is considered to be the most prevalent endemic mycosis in North America [55]. Incidence in children is difficult to determine as children are more likely to be asymptomatic even with greater exposures [53, 56].

### Mycology

*H. capsulatum*'s mycelium exists as septate hyphae that have spiky macroconidia and smooth microconidia (spores). Inside the mammalian host's lungs, the spores undergo a phase transition and convert to a pathogenic oval budding yeast. Aside from these structural differences, the mycology of *H. capsulatum* is also comparable to *B. dermatitidis* [19, 57, 58].

### Pathogenesis

Due to their small size, *H. capsulatum* spores can bypass the host's mucosal immune system barriers reaching the alveoli, where they phase transition into yeast. Immediately after phase transition, there is an increase in heat shock proteins expression on Histoplasma's cell surface. These proteins promote phagocytosis by acting as a ligand for macrophage cell surface receptors [59]. Other changes in protein production influenced by the phase transition allow histoplasmosis to reduce host pro-inflammatory responses, inactivate reactive oxygen and nitrogen species, and promote nutrition production and transport from within the macrophage [60, 61]. Histoplasmosis outgrows the phagocyte and induces intracellular apoptosis of the cell to result in the release of the yeast. The yeast is then engulfed by other macrophages, allowing for transportation to nearby (and occasionally distant) lymph nodes and then the rest of the reticuloendothelial system (e.g., spleen) for dissemination. An immunocompetent host usually mounts an effective defense once they develop T-cell immunity via dendritic cells, making histoplasmosis virulence generally dependent upon host immune status [62, 63].

### Clinical presentation

Nearly 99% of histoplasmosis cases are asymptomatic [57]. Symptomatic cases are at greater risk of more severe primary and overwhelming disseminated infection. When symptoms do develop, histoplasmosis can be divided into acute, subacute, and chronic infections. Acutely, it presents in severely immunocompromised patients and very young children, usually causing pulmonary disease [63]. If symptomatic, patients most often exhibit cough followed by fatigue, shortness of breath, and fever. Illness severity ranges from self-limiting, mild disease to life-threatening pneumonia and ARDS. If symptoms last for greater than 1 month, the disease is termed subacute pulmonary histoplasmosis. In these cases, patients often develop systemic signs of inflammation such as pericarditis, erythema nodosum, pleuritis, and polyarthritis. After 3 months, the disease is termed chronic pulmonary histoplasmosis [64]. In these instances, cavitary lung disease can occur with associated symptoms of weight loss, productive cough, and hemoptysis. In both acute and chronic infections, both lymphatic and hematogenous dissemination may occur with hilar, mediastinal, and peripheral lymphadenopathy, miliary pneumonia, hepatosplenomegaly, bone marrow suppression, skin and mucosal lesions, and altered mental status. Miliary histoplasmosis, also referred to as disseminated histoplasmosis, presents with the classic military pattern on imaging that can mimic tuberculosis. Hepatosplenomegaly occurs in almost 90% of infants with disseminated disease [53, 57, 65–67].

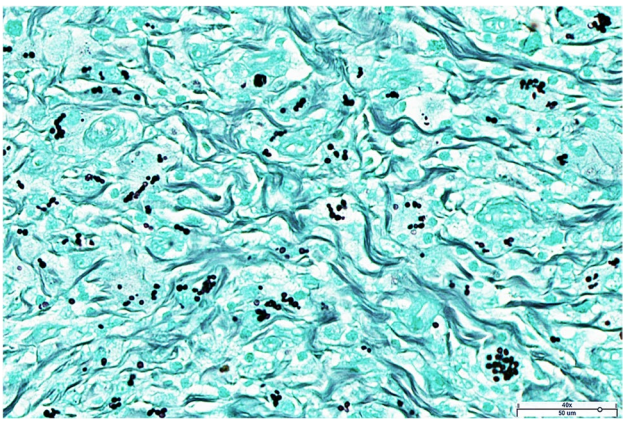

**Fig. 5** Grocott methenamine silver (GMS) stain in histoplasmosis. GMS highlights *Histoplasma* organisms in a patient with pulmonary histoplasmosis, showing numerous clustered small yeasts devoid of a capsule. Scale bar 50 µm

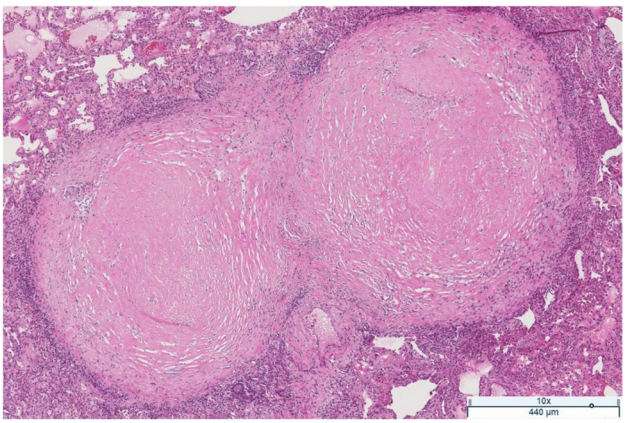

**Fig. 7** Hematoxylin and eosin (H&E) stain showing chronic pulmonary histoplasmosis. Hyalinizing granuloma characterized by a well-circumscribed collection of epitheloid histiocytes with concentric layers of hyalinized collagen which eventually may progress into calcification and fibrosis. The *Histoplasma* organisms cannot be visualized on routine histology and require the use of special stains for identification. Scale bar: 440 µm

## Diagnosis

For rapid diagnosis, Histoplasma antigen detection immunoassays are typically performed on urine or serum samples as well as on BAL and/or cerebral spinal fluid (CSF) [68]. Assays detecting antibodies may show false-negative results (as seen in coccidiomycosis). For confirmatory diagnosis, the organism can be cultured from fluids and in tissue and directly visualized under microscopy [58–60]. Morphologically, *Histoplasma capsulatum* is a round to oval yeast with occasional tapered ends and narrow-based buds that are highlighted by GMS stain (Fig. 5) [48]. In acute disease, variable numbers of yeasts are seen in necrotic areas of distal airspaces, with an interstitial lymphohistiocytic inflammatory response. Chronic pulmonary histoplasmosis demonstrates more classic necrotizing granulomas, ultimately with calcifications and stromal hyalinization (Figs. 6 and 7) [69]. Such inactive burnt-out lesions may be identified radiologically.

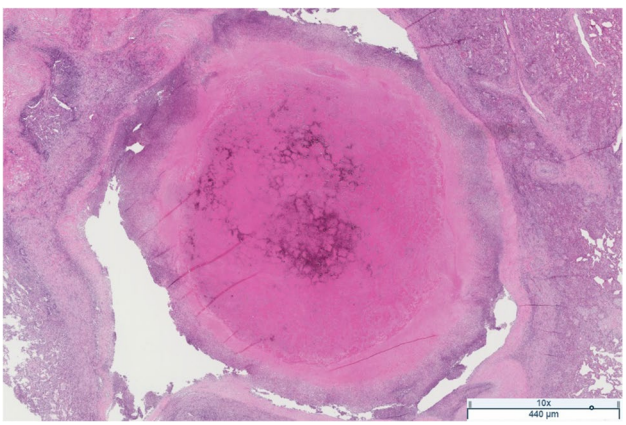

**Fig. 6** Hematoxylin and eosin (H&E) stain showing chronic pulmonary histoplasmosis. Representative lung sections show a discrete palisade of epitheloid histiocytes surrounding a centrally necrotic area. Scale bar: 440 µm

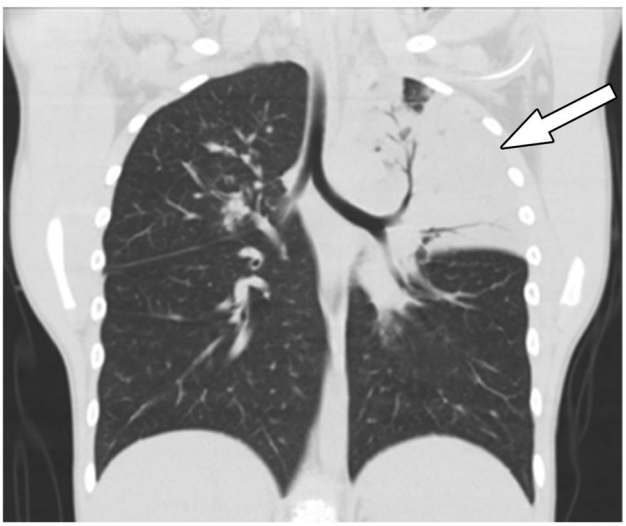

**Fig. 8** 9-year-old with acute fungal infection due to blastomycosis. Coronal reformatted unenhanced chest CT image shows left upper lobe consolidation (arrow) with air bronchograms, mimicking bacterial community-acquired pneumonia

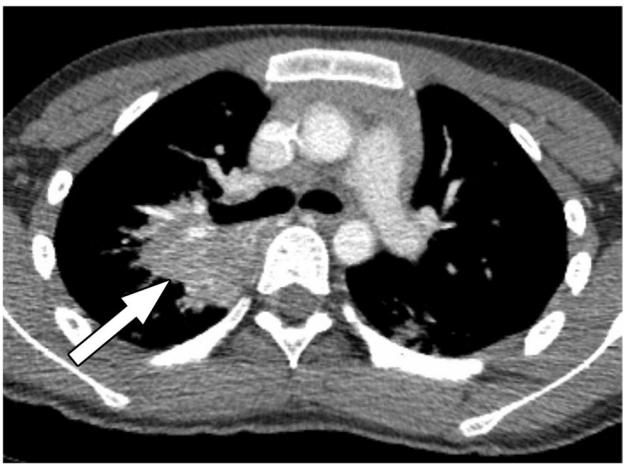

**Fig. 9** 12-year-old boy with acute fungal infection due to blastomycosis. Axial chest CT image with IV contrast material shows right upper lobe consolidation (arrow). Although the morphology of the consolidation is mass-like, the fact that enhancing pulmonary vessels course through the area rather than being displaced by the area suggests consolidated lung parenchyma surrounding bronchovascular bundles rather than a true mass

## Treatment

Treatment approaches are similar to blastomycosis, including oral azoles and amphotericin-based compounds for symptomatic infections [32, 35, 37, 70].

## Imaging findings

Given the limitations of diagnostic testing, the diagnosis and management of endemic fungal infections can be challenging. Imaging can play an important role in prompt diagnosis and intervention. The following section reviews the intra- and extra-thoracic imaging manifestations of endemic mycoses in the pediatric population, with emphasis on findings that are particularly suggestive of endemic fungal infection in general or even specific fungal organisms.

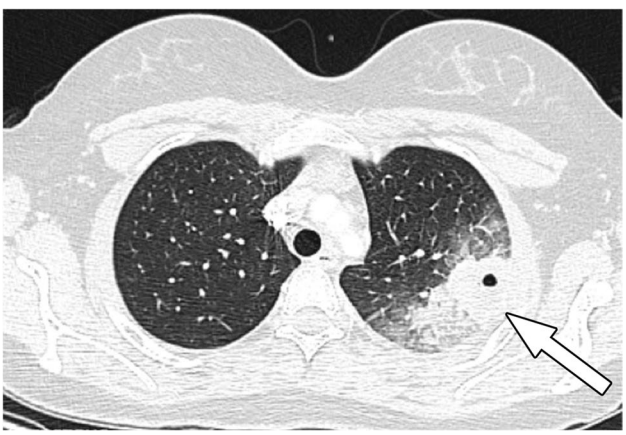

**Fig. 10** 16-year-old girl with acute fungal infection due to coccidioidomycosis. Axial chest CT image with IV contrast material shows left upper lobe consolidation (arrow) with central cavitation and surrounding ground glass opacity

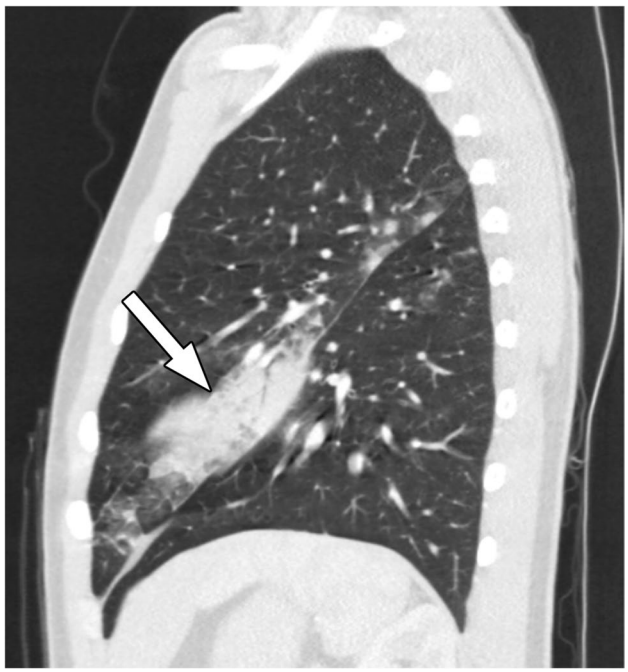

**Fig. 11** 17-year-old boy with acute fungal infection due to histoplasmosis. Sagittal reformatted chest CT image with IV contrast material shows left upper lobe consolidation (arrow) with air bronchograms, mimicking bacterial community-acquired pneumonia

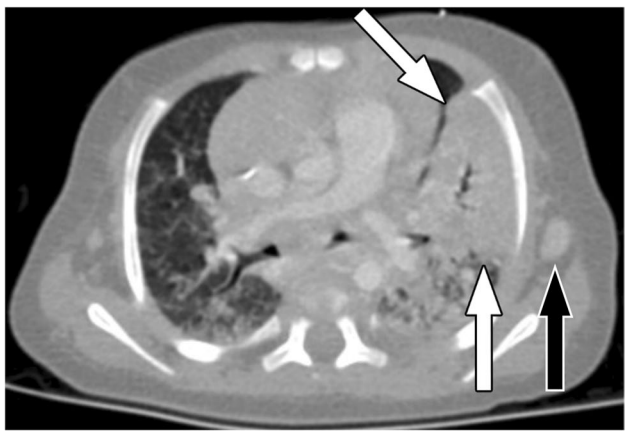

**Fig. 12** 2-month-old boy with acute fungal infection due to coccidioidomycosis. Axial chest CT image with IV contrast material shows left upper lobe consolidation (white arrows) with air bronchograms, mimicking bacterial community-acquired pneumonia, as well as an enlarged left axillary lymph node (black arrow)

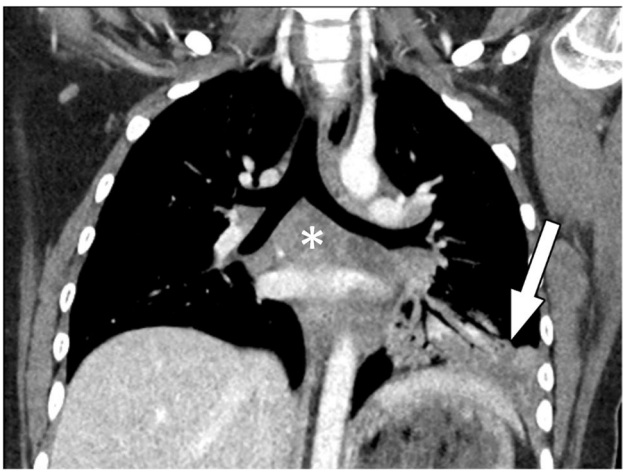

**Fig. 13** 15-year-old girl with acute fungal infection due to coccidioidomycosis. Coronal reformatted chest CT image with IV contrast material shows left lower lobe consolidation (arrow) with air bronchograms. The hypoenhancement of the involved lung differentiates infectious consolidation from atelectasis (the majority of the left lower lobe opacity is hypoenhancing, whereas atelectasis should hyperenhance). Heterogeneously enhancing, mediastinal (asterisk) and hilar lymphadenopathy can also be seen

## Thoracic imaging manifestations

### Consolidation

Lung consolidation can be seen with any endemic fungal infection (Figs. 8, 9, 10, 11, 12, and 13), typically in the setting of acute or initial infection, and is particularly common with blastomycosis (Figs. 8 and 9) [37, 71]. Fungal consolidation appears as variable-sized confluent or patchy lung opacities that obscure the margins of vessels and bronchial walls, often with ill-defined margins and air bronchograms and sometimes with cavitation (Fig. 10) [72].

Consolidation is most often unilateral and segmental or lobar, without any regional predilection [73], frequently mimicking community-acquired pneumonia (Figs. 8, 11, and 12). However, in the setting of severe exposure, histoplasmosis can present with widespread consolidation [74]. Consolidation, particularly that associated with blastomycosis, can also appear mass-like (Fig. 9), mimicking neoplastic processes, pulmonary infarcts, or inflammatory processes, such as granulomatosis with polyangiitis or organizing pneumonia [75] (Tables 1 and 2).

**Table 1** Thoracic imaging manifestations of endemic fungal infection and relative frequency of occurrence with each organism

| Thoracic imaging manifestations | Relative frequency of occurrence |
|---|---|
| Lung consolidation | Blastomycosis > histoplasmosis and coccidioidomycosis |
| Lung nodules | Histoplasmosis and coccidioidomycosis > blastomycosis |
| Lymphadenopathy | Histoplasmosis and coccidioidomycosis > > blastomycosis |
| Calcifications (lung nodules and lymph nodes) | Histoplasmosis > coccidioidomycosis > blastomycosis |
| Fibrosing mediastinitis (rare) | Histoplasmosis > > blastomycosis and coccidioidomycosis |

**Table 2** Extra-thoracic imaging manifestations of endemic fungal infection by body compartment

| Body compartment | Imaging manifestation |
|---|---|
| Abdomen (most common extra-thoracic site of endemic fungal infection) | Splenomegaly<br>Solid organ nodules and mass-like lesions<br>Solid organ abscesses/fluid collections<br>Solid organ calcifications (histoplasmosis)<br>Bowel inflammation<br>Peritonitis |
| Musculoskeletal system | Osteomyelitis (blastomycosis and coccidioidomycosis > > histoplasmosis)<br>Septic arthritis (blastomycosis and coccidioidomycosis > > histoplasmosis)<br>Tenosynovitis |
| Skin and soft tissues (most common extra-thoracic site of blastomycosis) | Skin thickening<br>Subcutaneous soft tissue inflammation<br>Fluid collections |
| Central nervous system (most common extra-thoracic site of coccidioidomycosis) | Meningitis<br>Intra- or extra-axial abscesses<br>Spinal canal involvement |

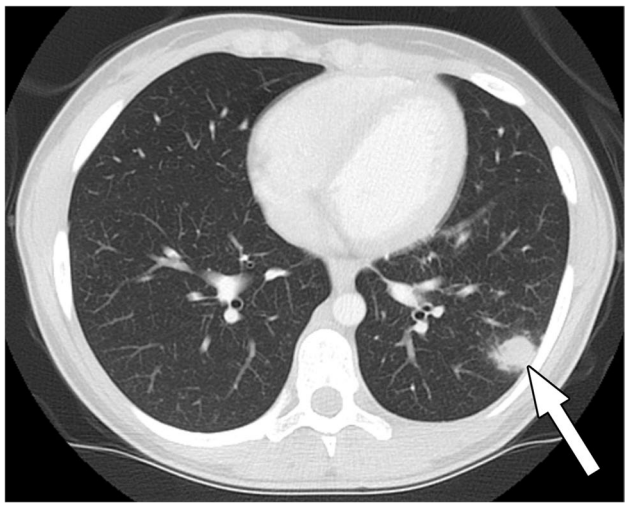

**Fig. 14** 15-year-old girl with acute fungal infection due to histoplasmosis. Axial chest CT image with IV contrast material shows a solitary nodule in the left lower lobe (arrow). The ill-defined margins favor an infectious or inflammatory etiology rather than a malignant etiology

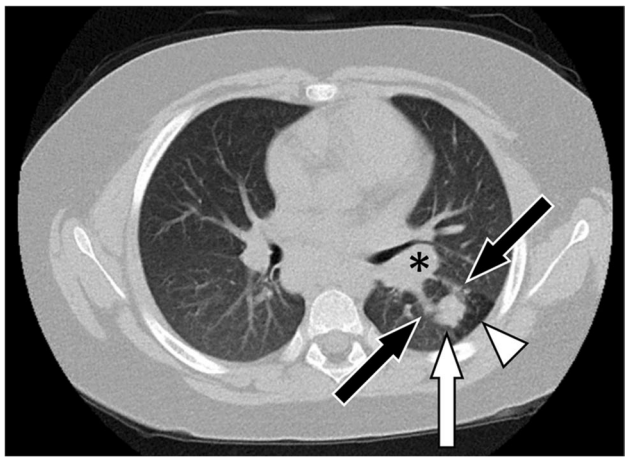

**Fig. 16** 8-year-old girl with sequelae of histoplasmosis. Axial unenhanced chest CT image shows a solitary nodule in the left lower lobe (white arrow) with punctate internal calcifications and associated surrounding satellite nodules, nodularity/beading of the adjacent bronchovascular bundle and pleura (black arrows), peripheral air trapping (arrowhead), and an enlarged left hilar lymph node with punctate calcification (asterisk)

## Nodules

Lung nodules are common in patients with endemic fungal infection, particularly histoplasmosis (Figs. 14, 15, 16, and 17) and coccidioidomycosis (Figs. 18 and 19), and they can be solitary (Fig. 14) or multiple (Fig. 18). Disseminated fungal infection, particularly in immunocompromised patients, may present as numerous tiny lung nodules in a miliary pattern (Fig. 15), an appearance indistinguishable from disseminated tuberculosis [76]. Helpful findings at initial imaging suggesting fungal infection as the cause of a pulmonary nodule rather than lung malignancy or metastatic disease include peribronchovascular nodularity or beading adjacent to the nodule (Figs. 15 and 16) and/or satellite nodules surrounding the dominant nodule [6, 73]. Ill-defined margins also favor an infectious or inflammatory etiology rather than a malignant etiology (Fig. 14). Over time, these nodules tend to decrease in size, and those due to histoplasmosis commonly calcify (Fig. 17) [6, 74]. Fungal lung nodules can also cavitate (Fig. 19), appearing initially with central lucency, and ultimately as a thick or thin-walled cavity with or without mural calcification [6, 71, 74, 76–80].

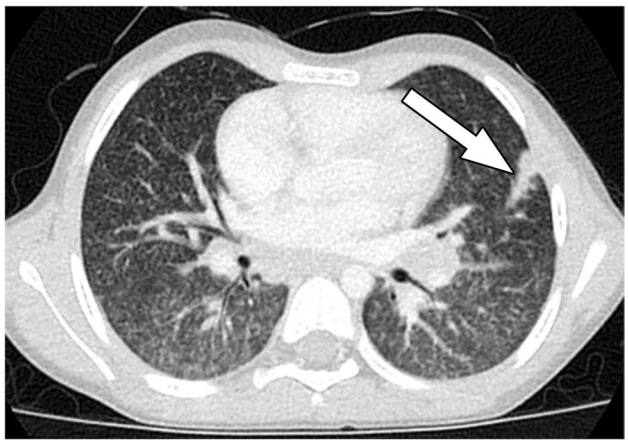

**Fig. 15** 6-year-old girl with history of juvenile idiopathic arthritis and confirmed histoplasmosis. Axial chest CT image with IV contrast material shows a dominant nodule in the lingula with adjacent bronchovascular nodularity/beading (arrow) suggesting the primary site of infection as well as tiny nodules elsewhere in a miliary pattern suggesting disseminated infection

## Lymphadenopathy

Thoracic lymph nodes (Figs. 20, 21, 22, 23, and 24) are frequently involved in the setting of histoplasmosis and coccidioidomycosis and quite uncommonly involved in the setting of blastomycosis, with unilateral hilar lymph nodes most commonly involved (Fig. 20) and sometimes also mediastinal lymph nodes (Figs. 21 and 22) [73]. Lymph nodes are commonly enlarged in the setting of active fungal infection (Fig. 23) and can undergo necrosis and coalescence (Fig. 24) [81]. The nodal disease associated with histoplasmosis commonly calcifies when

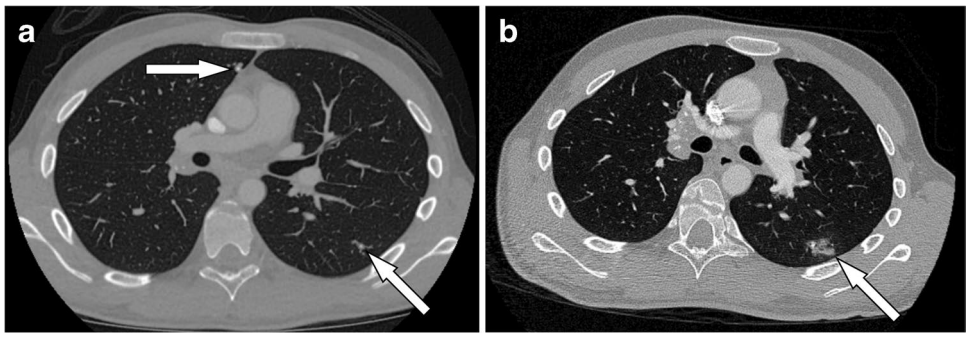


**Fig. 17** 17-year-old boy with prior histoplasmosis infection. **a** Axial chest CT image with IV contrast material shows centrally calcified nodules in the left lower lobe and right upper lobe (arrows). **b** Axial chest CT image with IV contrast material obtained 7 weeks later for worsened cough after a course of steroids shows new clustered ill-defined nodules around the left lower lobe calcified nodule (arrow) compatible with histoplasmosis reactivation. Enlarged right hilar lymph nodes containing calcifications are also present

subacute or healing, an evolution less commonly seen with coccidioidomycosis, rarely seen with blastomycosis, and unlike nodal disease in routine community-acquired pneumonias (Figs. 20, 21, and 22). A variety of patterns of lymph node calcification can be observed in this setting, including speckled or stippled calcifications (Fig. 20), peripheral or "egg-shell" calcification, and dense, confluent calcification (Fig. 22) [82, 83].

### Fibrosing mediastinitis

Fibrosing mediastinitis is a rare, generally late, complication of endemic fungal infection, almost exclusively histoplasmosis although cases due to blastomycosis and coccidioidomycosis have been reported [84, 85]. It involves large amounts of mature, concentrically deposited, dense, paucicellular collagen infiltrate, and that obliterates mediastinal adipose tissue and that can compress or constrict mediastinal and hilar structures in response to fungal antigen in genetically susceptible individuals [86–88]. Fibrosing mediastinitis is best characterized with contrast-enhanced CT and tends to manifest as unilateral mediastinal and/or hilar, relatively localized, infiltrative, variably enhancing, and often calcified soft tissue, but can be extensive and bilateral (Fig. 25) [89–91]. Associated airway obstruction due to tracheal or bronchial narrowing may be especially evident in children due to greater airway compliance, but other potentially affected structures include the pulmonary veins and arteries, superior vena cava and brachiocephalic veins,

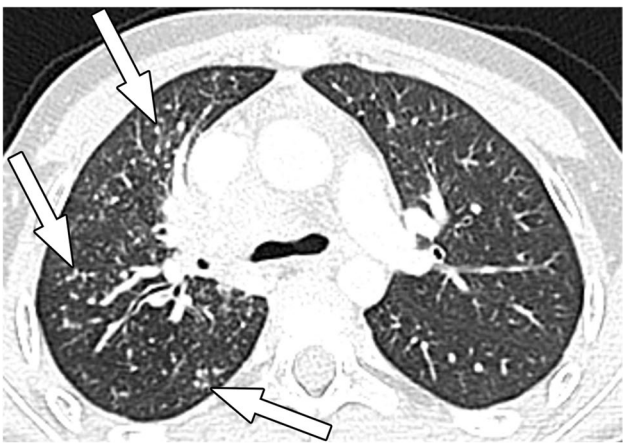

**Fig. 18** 7-year-old boy with acute fungal infection due to coccidioidomycosis. Axial chest CT image with IV contrast material shows multiple scattered small nodules in the right lung (arrows)

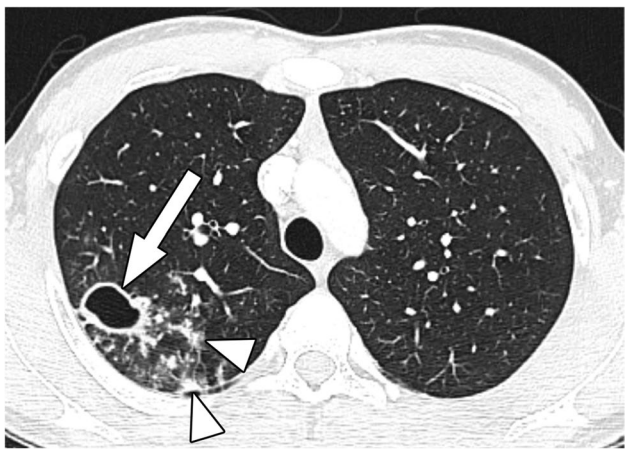

**Fig. 19** 17-year-old boy with acute fungal infection due to coccidioidomycosis. Axial chest CT image with IV contrast material shows a dominant cavitary nodule (arrow) in the right lung and several surrounding satellite nodules (arrowheads)

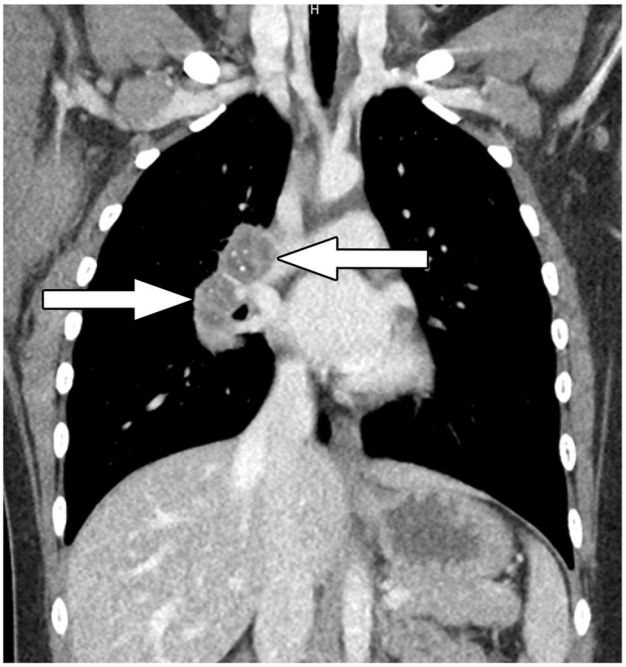

**Fig. 20** 16-year-old girl with active histoplasmosis. Coronal reformatted chest CT image with IV contrast material shows enlarged, predominantly hypoenhancing right hilar lymph nodes with septation-like enhancement (arrows) and internal speckled calcifications

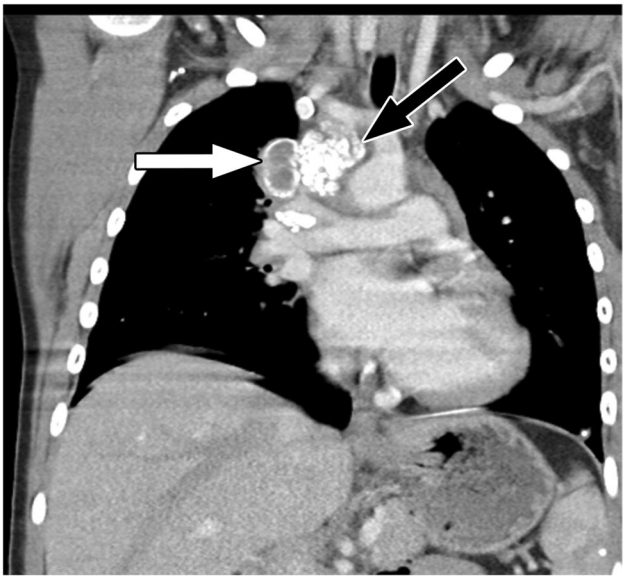

**Fig. 22** 9-year-old girl with active histoplasmosis. Coronal reformatted chest CT image with IV contrast material shows multiple calcified mediastinal lymph nodes. Both eggshell (white arrow) and dense lymph node calcifications (black arrow) are present

aorta and aortic branches, esophagus, thoracic duct, pericardium, recurrent laryngeal and phrenic nerves, and autonomic ganglia [86, 92]. Close follow-up may be sufficient in some cases, but in patients with symptoms attributable to fibrosing mediastinitis nonsurgical (e.g., vascular stenting) or surgical interventions may be required [91].

## Extra-thoracic imaging manifestations

### Skin and soft tissues

Skin and soft-tissue involvement (Fig. 26) is the most common extra-thoracic manifestation of blastomycosis and the most common presenting finding in children [17, 93]. Imaging may show skin thickening, subcutaneous

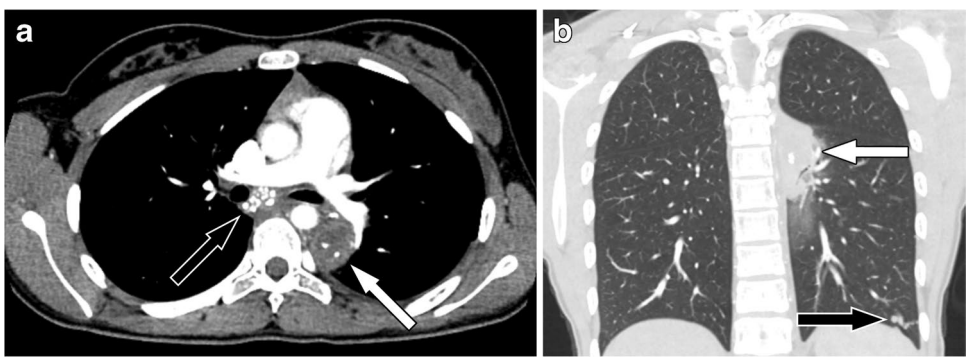


**Fig. 21** 15-year-old girl with chest pain and active histoplasmosis. **a** Axial chest CT image with IV contrast material shows peripheral enhancement of an enlarged left peribronchial lymph node (white arrow). Calcifications within this lymph node in the setting of densely calcified lymph nodes elsewhere (black arrow) suggest possible reactivation histoplasmosis, which was confirmed at work-up. **b** Coronal reformatted chest CT image with IV contrast material shows left lower lobe consolidation and ground-glass opacity around the reactivated lymph node (arrow) as well as clustered small nodules in the lateral basal aspect of the left lower lobe (black arrow), the largest of which is calcified, related to the original infection

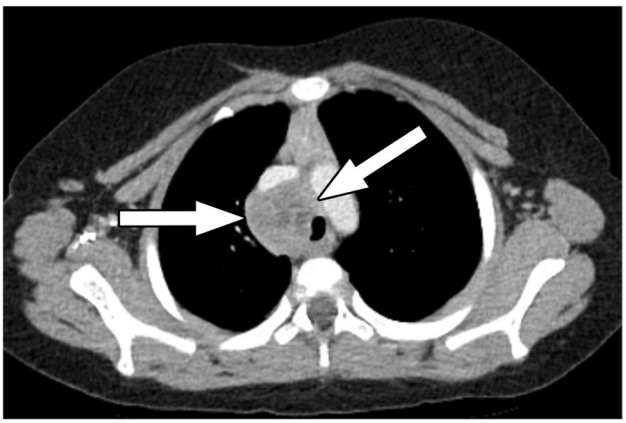

**Fig. 23** 4-year-old girl with active histoplasmosis. Axial chest CT image with IV contrast material shows heterogeneously enhancing right paratracheal lymphadenopathy (arrows). There is mass effect on the superior vena cava anteriorly, and the trachea is deviated to the left. Nodal involvement can be bulky and result in substantial mass-effect

soft tissue inflammation, and fluid collections [73]. In the setting of coccidioidomycosis infection erythema nodosum can be seen, presenting as multiple painful, erythematous, indurated nodules that typically affect the extremities [40]. Imaging generally is not required to evaluate the skin and soft tissue manifestations of endemic fungal infections, but these findings may be the first identified manifestation of disease.

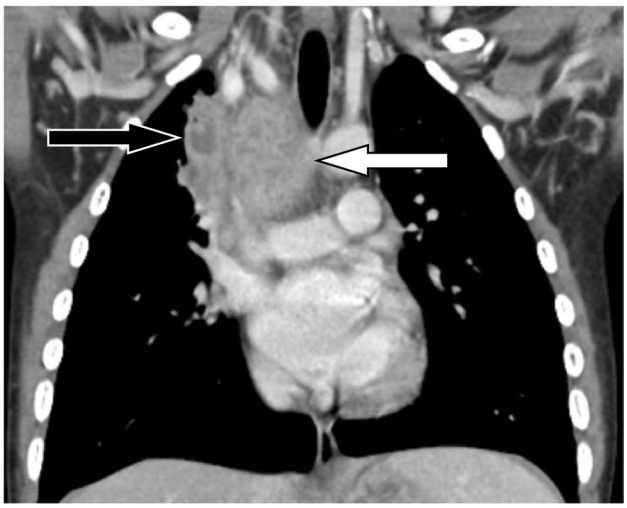

**Fig. 24** 7-year-old boy with active coccidioidomycosis. Coronal reformatted chest CT image with IV contrast material shows heterogeneously enhancing, conglomerate mediastinal lymphadenopathy (white arrow), including a right upper mediastinal lymph node with discrete central necrosis (black arrow)

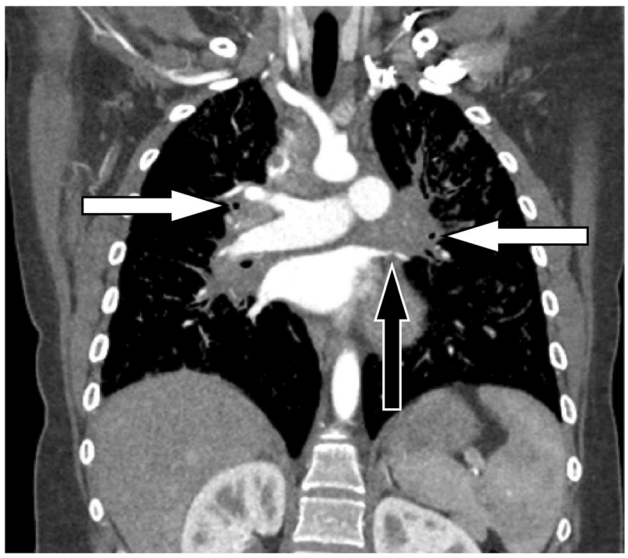

**Fig. 25** 17-year-old girl with fibrosing mediastinitis due to histoplasmosis infection. Coronal reformatted chest CT image with IV contrast material shows confluent, infiltrative soft tissue involving the mediastinum and both hila that encases and narrows bilateral bronchi (white arrows) and the left upper pulmonary vein (black arrow)

### Musculoskeletal system

Fungal bone and joint infections are most commonly seen with coccidioidomycosis (Figs. 26 and 27) and blastomycosis (Figs. 28 and 29) and are rarely seen with histoplasmosis [94, 95]. Bone and joint infections are more commonly unifocal but can be multifocal [94]. Systemic signs and symptoms are often absent and inflammatory markers can be normal [96].

Fungal osteomyelitis can involve the axial or appendicular skeleton. On radiographs and CT fungal osteomyelitis can appear as "punched-out" lytic lesions (Fig. 27 and 30a), permeative pattern lytic lesions, or frank osseous destruction, and periosteal new bone formation is uncommon [95, 97–99]. MRI will show T1-weighted hypointense and T2-weighted hyperintense marrow signal similar to that seen with other forms of osteomyelitis and can show associated findings such as intraosseous abscess formation (Fig. 28), osseous destruction (Fig. 30b), and/or soft tissue findings that are often seen in the setting of fungal osteomyelitis, including inflammation, abscess, or sinus tract [96–99].

Fungal infectious arthritis is most commonly monoarticular, typically involving large joints, with the knee being the most commonly involved joint [94]. Synovial infection is often associated with adjacent bone erosion and/or destruction similar to that seen with tuberculosis

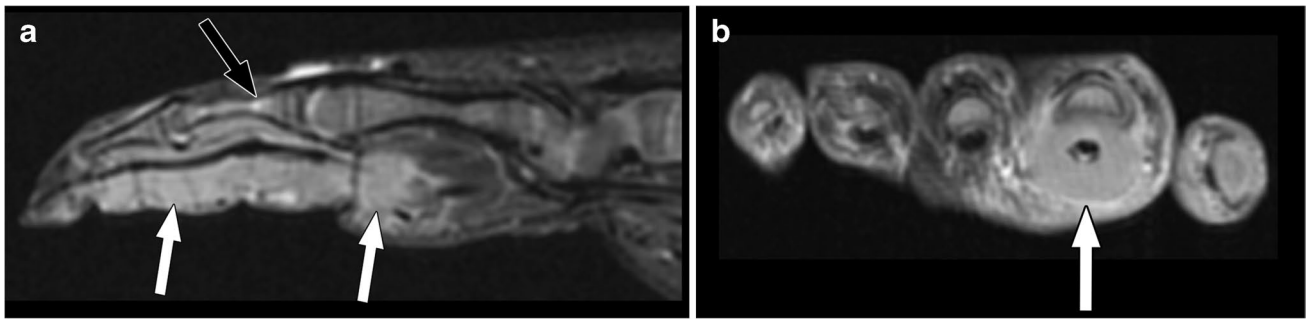


**Fig. 26** 2-month-old boy with tenosynovitis and osteomyelitis due to disseminated coccidioidomycosis. **a** Sagittal T2-weighted MR image of the index finger shows extensive abnormal T2-weighted hyperintense signal in the volar soft tissue of the finger (white arrows) surrounding the flexor tendons, consistent with tenosynovitis, as well as foci of abnormal T2-weighted hyperintense marrow signal in the proximal phalanx, consistent with osteomyelitis (black arrow). **b** Axial contrast-enhanced T1-weighted MR image shows mild enhancement along the periphery of the area of index finger volar soft tissue T2-weighted hyperintense signal abnormality (white arrow)

infection [94, 97, 99]. On the other hand, in the case of blastomycosis, joint infection often results from the spread of infection from an adjacent site of osteomyelitis [95, 96, 98, 99]. When present, radiographic findings of septic arthritis can include effusion, periarticular osteopenia, erosion(s), and/or osseous destruction. MRI findings can include effusion, synovitis, perisynovial edema, cartilage destruction, periarticular bone marrow edema, and/or erosions. In addition to infectious arthritis, both coccidioidomycosis and histoplasmosis can have a sterile, migratory polyarthritis associated with primary pulmonary infection as part of a hypersensitivity syndrome [95, 100].

In addition to osteoarticular infection, histoplasmosis, coccidioidomycosis, and blastomycosis can all cause tenosynovitis that may or may not be adjacent to an area of osteomyelitis, with all reported cases localizing to the hand and wrist [101–105]. In fact, synovitis about the wrist, typically flexor tenosynovitis, seems to be the most common musculoskeletal manifestation of histoplasmosis in healthy patients [106]. On MRI fungal tenosynovitis manifests as thickened, T2-weighted hyperintense signal tenosynovium surrounding tendons with variable enhancement and surrounding soft tissue inflammation (Fig. 26) [101, 103], while on ultrasound it manifests as hypoechoic tissue surrounding tendons that can be hyperemic on color Doppler imaging [107]. When involving the flexor tendons of the wrist associated median nerve thickening can be seen [101, 107].

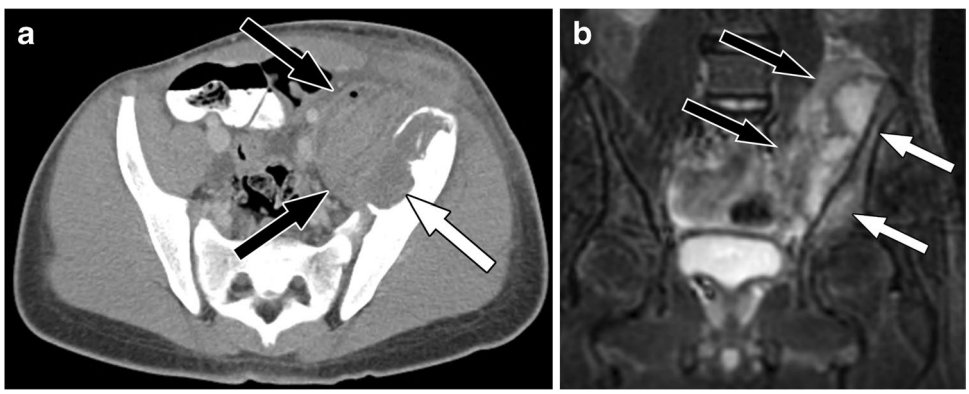


**Fig. 27** 13-year-old boy with osteomyelitis due to disseminated coccidioidomycosis. **a** Axial pelvic CT image with IV and oral contrast materials shows destruction of the left ilium (white arrow) with a contiguous large area of mixed phlegmon and abscess containing a small focus of gas extending centrally into the pelvis (black arrows) and superficially into the overlying soft tissues. The left iliac vessels are displaced medially, and the surrounding fat planes are obscured by edema. **b** Coronal T2-weighted fat-saturated pelvic MR mages shows bone marrow hyperintense signal abnormality in the left ilium consistent with osteomyelitis (white arrows) as well as the large area of mixed phlegmon and abscess in the left iliac fossa seen on CT (black arrows)

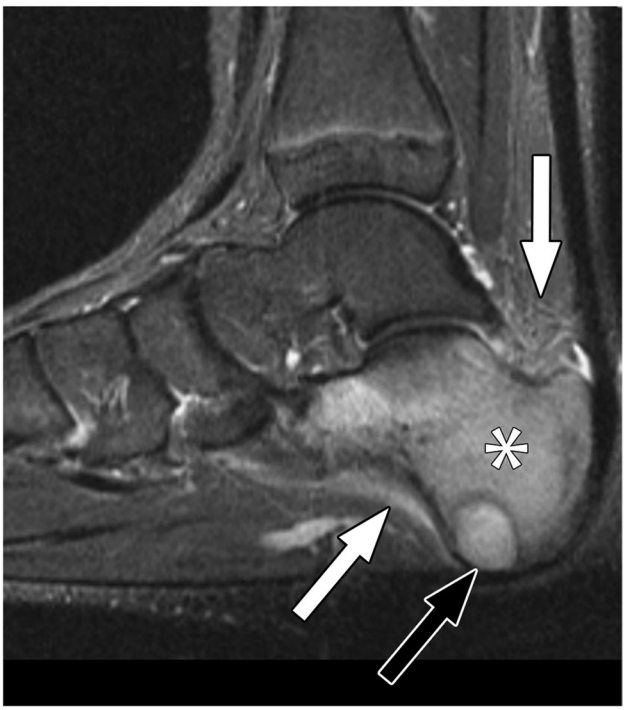

**Fig. 28** 12-year-old girl with osteomyelitis due to disseminated blastomycosis. Sagittal T2-weighted fat-saturated MR image of the foot shows bone marrow edema throughout the calcaneus (asterisk), an intraosseous abscess (black arrow), and mild surrounding soft tissue edema (white arrows)

### Central nervous system

All three endemic mycoses can involve the CNS (Figs. 31, 32, and 33). The CNS is the most common extra-thoracic site of infection for coccidioidomycosis, occurring in over one-third of children with disseminated disease [108]. The most common CNS presentation is meningitis, which appears as leptomeningeal enhancement and sometimes thickening on contrast-enhanced CT and MRI (Fig. 30) [109]. Spinal canal involvement with granulomas and spinal cord syrinx have been associated with coccidioidal meningitis [110, 111].

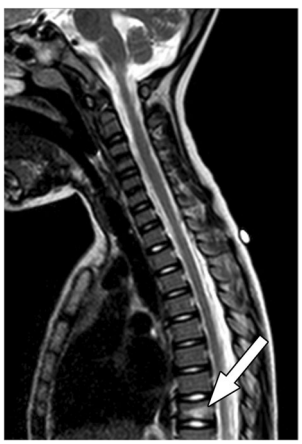

**Fig. 29** 10-year-old boy with osteomyelitis due to disseminated blastomycosis. Sagittal T2-weighted MR image of the thoracic spine shows T8 vertebral body height loss and marrow edema (arrow)

Intraparenchymal and/or extra-axial abscesses can occur in acute disseminated infection [73], and when intraparenchymal, abscesses can be single or multifocal (Fig. 32). Small abscesses can appear as enhancing lesions on contrast-enhanced CT or MRI, whereas larger abscesses present as rim-enhancing fluid collections that can have diffusion restriction on MRI [6, 109, 112]. Extra-axial granulomatous lesions have a propensity to occur in specific areas, such as the basilar cisterns, Sylvian fissures, and chiasmatic region. Depending on the extent of CNS involvement, obstruction of CSF flow may occur and hydrocephalus can develop [109]. Cases of blastomycosis have also been known to cause CNS disease presenting as punctate foci enhancement in the brain (Fig. 32) [113].

### Abdomen

Involvement of the abdomen can occur with all three endemic mycoses and is the most common site of extra-thoracic disease in the setting of histoplasmosis infection. Involvement of the viscera, mesentery, and peritoneal cavity can be due to hematogenous and/or lymphatic dissemination, and it is most common in the immunosuppressed population (e.g., particularly pediatric patients undergoing treatment for malignancy or immunosuppressive therapy for solid organ transplant or autoimmune disorder, such as children with Crohn's disease prescribed biologic therapy) [114–117]. Systemic dissemination and abdominal involvement also have rarely been described in infants with mostly transient immune system deficiencies and exposure to large amounts of the pathogen [118].

The spleen is the most common site of abdominal involvement in children. Splenic involvement due to histoplasmosis (Figs. 34, 35, and 36) may present as splenomegaly or as focal nodules or mass-like lesions in the setting of active infection that commonly calcify upon healing (Fig. 35); fluid collections also may be observed (Fig. 36) [119–122]. Blastomycosis and coccidioidomycosis also may rarely involve the spleen upon dissemination, presenting as splenomegaly and irregular, small nodular and/or mass-like areas of hypoenhancement on contrast-enhanced CT (Fig. 37) and hypoechogenicity on ultrasound that correspond to areas of necrosis/abscess formation at pathology [123–126].

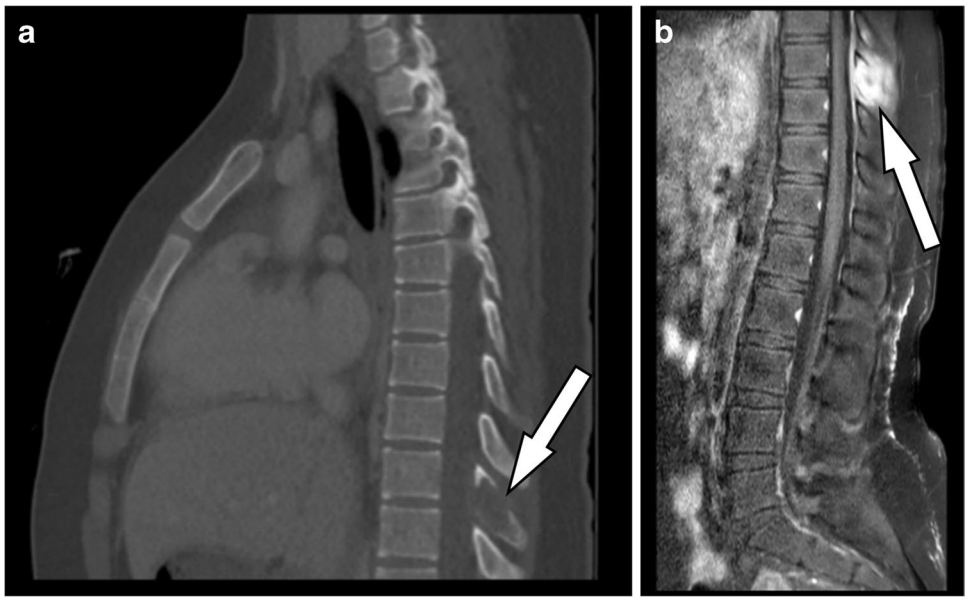


**Fig. 30** 14-year-old girl with osteomyelitis due to disseminated coccidioidomycosis**. a** Sagittal reformatted chest CT image with IV contrast material shows a "punched-out" lytic lesion in the T9 spinous process (arrow). **b** Sagittal T1-weighted fat-saturated MR image with IV contrast material shows an enhancing destructive lesion in the T9 spinous process (arrow) with surrounding soft tissue inflammation and minimal epidural extension

While rare, granulomas of the liver as well as periportal lymphohistiocytic inflammation have been observed in the setting of active histoplasmosis infection [127]. Collins et al. documented that histoplasmosis is the most common cause of hepatic granulomas identified upon liver biopsy in a Midwestern U.S. pediatric cohort [128]. A mass-like liver lesion also has been described in the setting of coccidioidomycosis [129]. Liver involvement by active endemic fungal infections is rarely evident by imaging in our experience, although punctate

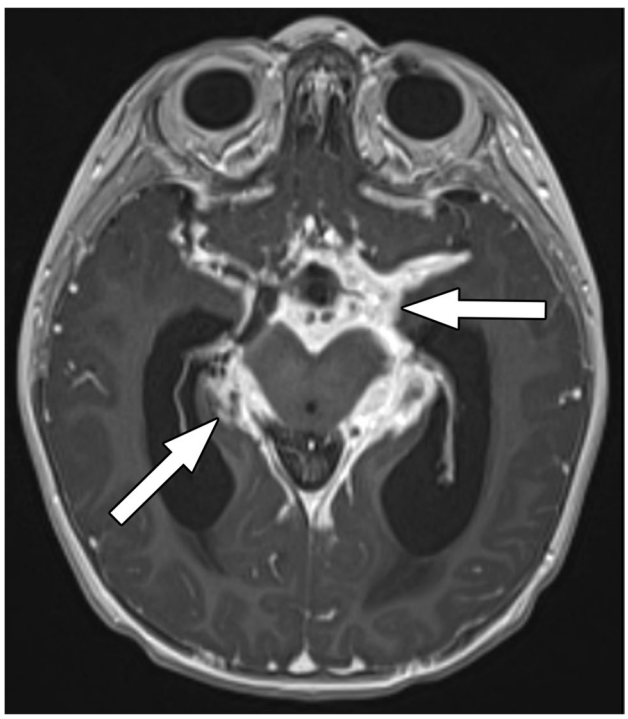

**Fig. 31** 15-month-old boy with meningitis due to disseminated coccidioidomycosis. Axial contrast-enhanced T1-weighted MR image of the brain shows thick, irregular enhancement of the meninges and basal cisterns (arrows). The partially visualized lateral ventricles are dilated due to obstruction of CSF flow

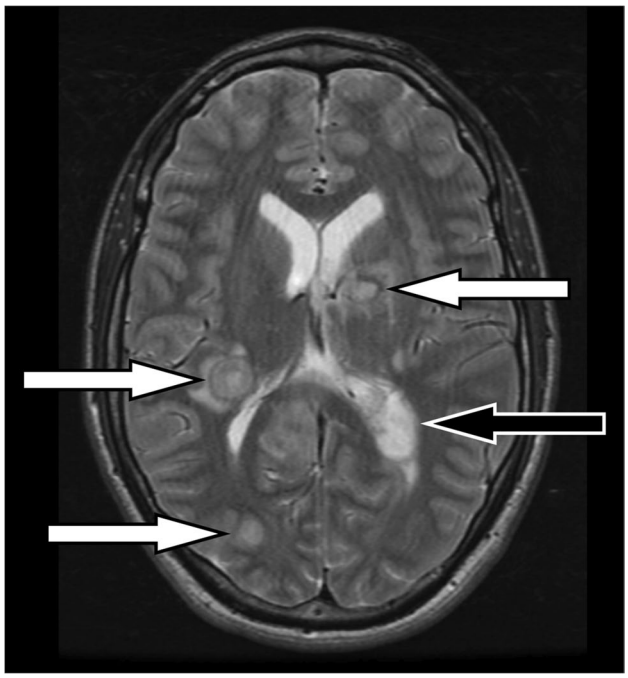

**Fig. 32** 17-year-old boy with brain abscesses due to disseminated histoplasmosis. Axial T2-weighted MR image of the brain shows multiple intraparenchymal abscesses (white arrows) as well as enlargement of the left lateral ventricle choroid plexus consistent with choroid plexitis (black arrow)

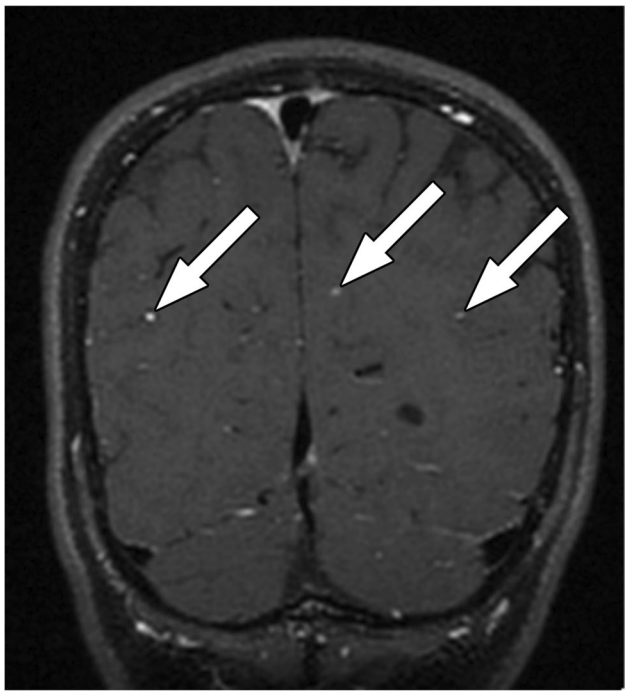

**Fig. 33** 8-year-old boy with brain involvement from disseminated blastomycosis. Coronal contrast-enhanced T1-weighted fat-saturated MR image of the brain shows scattered punctate foci of enhancement throughout the brain (arrows)

calcifications eventually may be observed when the infection is chronic or successfully treated.

The adrenal glands and kidneys also can be rarely involved by these infections, although reports are primarily in adults. Adrenal manifestations in the setting of histoplasmosis include nonspecific adrenal gland

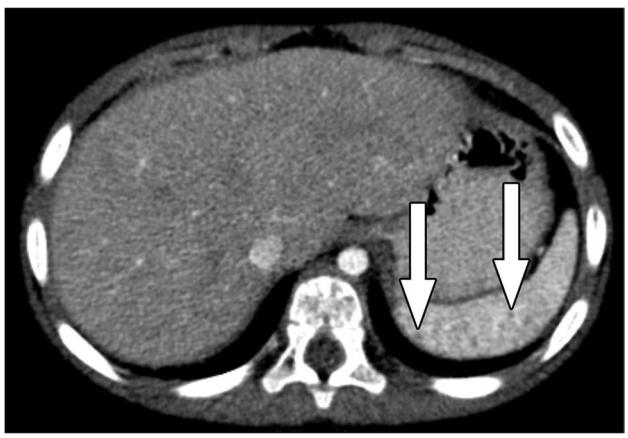

**Fig. 34** 3-year-old girl with disseminated histoplasmosis and splenic involvement. Axial abdominal CT image with IV contrast material shows numerous tiny hypoattenuating nodular foci in the spleen (arrows)

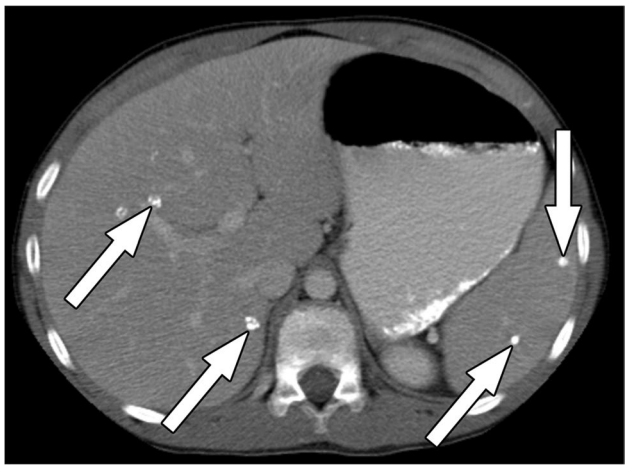

**Fig. 35** 11-year-old boy remote disseminated histoplasmosis and liver and spleen involvement. Axial abdominal CT image with IV contrast material shows multiple coarse calcifications in the spleen and liver (arrows)

enlargement, hypoenhancing areas on contrast-enhanced CT that reflect areas of caseous necrosis, and calcifications as well as clinical adrenal gland insufficiency [130–132]. Renal involvement by histoplasmosis (Figs. 38 and 39) may appear as one or more nonspecific mass-like lesions, potentially mimicking neoplasm, and parenchymal calcifications [133, 134]. There is a general paucity of reports of these infections involving the pancreas in either children or adults, although vary rare instances of mass-like pancreatic lesions due to blastomycosis have been described in adults [125, 135].

There are numerous reports of small and large bowel involvement by these infections in both children and

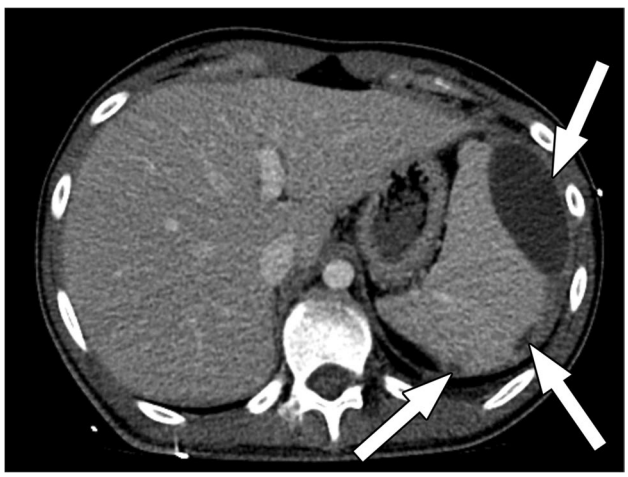

**Fig. 36** 17-year-old boy with disseminated histoplasmosis and splenic involvement. Axial abdominal CT image with IV contrast material shows multiple infectious subcapsular splenic fluid collections (arrows)

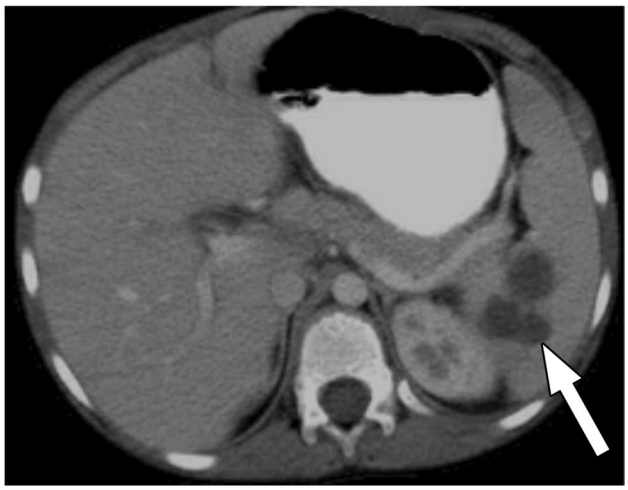

**Fig. 37** 10-year-old boy with disseminated blastomycosis and splenic involvement. Axial abdominal CT image with IV contrast material shows clustered round hypodense lesions in the spleen (arrow).Fine needle aspiration identified budding yeasts

adults. Involvement of the distal small bowel and proximal colon by histoplasmosis can mimic Crohn's disease, with bowel wall thickening, nodularity, and ulcers seen on imaging and granulomas seen at histopathology [136]. A case report also described histoplasmosis involvement of the bowel wall as a cause of recurrent intestinal intussusception in a young child [137]. Segmental involvement of the bowel, including the colon, and associated

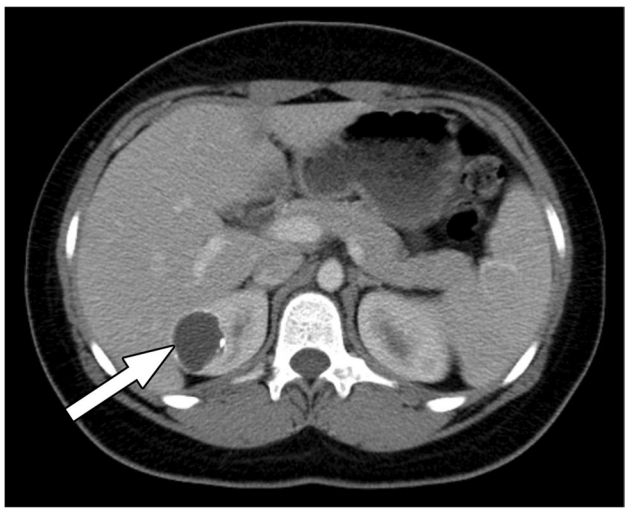

**Fig. 38** 14-year-old girl with remote disseminated histoplasmosis and kidney involvement. Axial abdominal CT image with IV contrast material shows a low attenuation, cystic lesion with a thin rim of calcifications in the upper pole of the right kidney (arrow). Additional images from the same CT (not shown) demonstrated splenic calcifications and a calcified nodule in the imaged right lung lower lobe typical of histoplasmosis

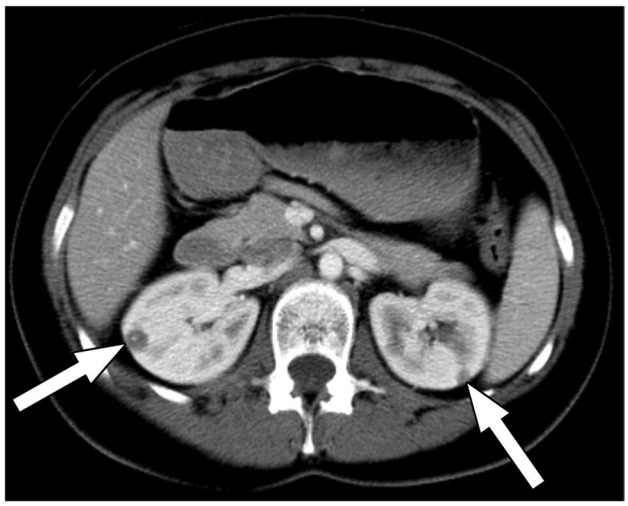

**Fig. 39** 15-year-old girl with disseminated histoplasmosis and kidney involvement. Axial abdominal CT image with IV contrast material shows small round low attenuation lesions in both kidneys (arrows), the one on the right with a punctate central calcification. Additional images of the abdomen and chest from the same CT (not shown) demonstrated splenic calcifications, bilateral calcified lung nodules, and enlarged, calcified mediastinal lymph nodes typical of histoplasmosis

regional lymphadenopathy due to histoplasmosis has been described in the specific setting of untreated human immunodeficiency virus/Acquired Immunodeficiency Syndrome (HIV/AIDS). Infection of the bowel due to blastomycosis and coccidioidomycosis also can occur with dissemination, appearing as bowel wall thickening and hyperenhancement with potential associated adjacent inflammatory fat stranding and prominent vasculature [138–140]. Peritoneal, mesenteric, and omental involvement (i.e., granulomatous peritonitis), including discrete soft tissue lesions and ascites, is a rare manifestation of infection by these organisms, sometimes potentially mimicking malignancy or pelvic inflammatory disease [138–143].

## Conclusion

Endemic fungal infections in the pediatric population are relatively uncommon and remain difficult to accurately and timely diagnose. The clinical manifestations of these infections can range widely and overlap with non-fungal infections as well as other inflammatory processes. Knowledge of the various thoracic and extra-thoracic manifestations, which can be readily identified by imaging, and a maintained high index of suspicion can facilitate timely diagnosis and management of affected children.

**Author contribution** All authors contributed to the drafting and editing of the manuscript.

## Declarations

**Conflicts of interest** None

**Key take-home points**

- The incidences of endemic fungal infections in children remain unknown, as the majority of these infections are asymptomatic or cause only minor illness.
- Severe and/or disseminated endemic fungal infection is most often associated with immunocompromised state but can occur in immunocompetent children.
- Symptomatic endemic fungal infections frequently present with clinical signs and symptoms of pulmonary infection, with radiologic findings potentially mimicking non-fungal community-acquired pneumonia or tuberculosis.
- Endemic fungal infections can spread via the lymphatic system or blood stream, leading to extra-pulmonary sites of disease.
- Imaging, and perhaps most importantly a radiologist with a maintained high index of suspicion for endemic fungal infection, is critical to the prompt diagnosis and treatment of moderate-severe endemic fungal infections, as the diagnosis is commonly delayed due to nonspecific clinical presentation, overlap with non-fungal infections, and slow organism growth upon tissue and/or fluid culture.
- Aside from potentially assisting with diagnosis, cross-sectional imaging (e.g., CT, MRI, or ultrasound) of extra-pulmonary infection can be useful for determining the extent and severity of the disease.
- In general, there is a paucity of studies describing the radiologic features of endemic fungal infections and their associations with clinical outcomes in children, and therefore much of our knowledge is extrapolated from adult medical literature and our clinical experience. Despite this fact, there is likely considerable overlap in pediatric and adult clinical and imaging manifestations.

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