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REVIEW ARTICLE

Native vs Prosthetic Valve *Histoplasma capsulatum* Infective Endocarditis: A Case Report and Systemic Literature Review Comparing Patient Presentation, Treatment Modalities, Clinical Outcomes, and Diagnostic Laboratory Testing

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Histoplasma capsulatum is a rare cause of fungal endocarditis that affects both native and prosthetic valves. It is associated with a high mortality rate if not diagnosed early and treated with a combination of antifungal therapy and surgical intervention. We present a case of a 47-year-old man with histoplasmosis infective endocarditis. He was successfully treated with antifungal therapy and surgical replacement of the infected bioprosthetic aortic valve. Our systemic literature review includes 52 articles encompassing 60 individual cases of *H. capsulatum* infective endocarditis from 1940 to 2020. Patient presentations, diagnostic laboratory testing accuracy, treatment modalities, and patient outcomes comparing and contrasting native and prosthetic valve infection are described.

Keywords. endocarditis; *Histoplasma capsulatum*; histoplasmosis; native valve; prosthetic valve.

Histoplasma capsulatum var. *capsulatum* (*H. capsulatum*) is a dimorphic fungus that exists as a mold in the environment and a yeast in tissue. Geographically, it occurs throughout the world. In Canada, it is primarily seen in Quebec and Ontario along the St. Lawrence Seaway and the Great Lakes Drainage Basin [1]. It is seen in the entire Eastern half of the United States, with a hyperendemic focus along the Ohio and Mississippi River Valleys [1]. It is also seen throughout most of Central and South America and the Southern half of Africa. In Asia, it occurs along the Yangtze River in Southeastern China and throughout India, Indonesia, Japan, Malaysia, Singapore, Thailand, and Vietnam [1]. Acquisition occurs when individuals are active (for occupational or recreational purposes) in these areas, especially when soil contaminated with bird and bat guano is disrupted. The majority of infected individuals are asymptomatic or have mild illness; about 1% develop pulmonary or disseminated infection [1]. For those with disseminated infection, *H. capsulatum* endocarditis is a rare complication, with ~80 cases reported in the medical literature from 1940 to 2020 [2–53]. Over this 80-year period, published case series have summarized characteristics such as patient clinical features, patient treatment modalities and outcomes, and the utility of diagnostic laboratory tests [7, 12, 19, 26, 29, 30, 32, 38, 41, 44, 48]. However, these case series did not consider stratifying these characteristics by native vs prosthetic valve infection. Herein, we present an additional case of *H. capsulatum* prosthetic valve endocarditis and, following a systematic literature review, compare the clinical features, treatment modalities and outcomes, and accuracy of diagnostic laboratory tests for individuals with native valve vs prosthetic valve *H. capsulatum* endocarditis. In addition, previous case series did not have large enough numbers to analyze outcomes data in an early period (1940–1970) and the more modern period (1970–2020), when more effective medications and surgical techniques became available.

CASE REPORT

A 47-year-old man presented to the emergency room of William Beaumont Hospital (Royal Oak, MI, USA) with a 1-month history of severe, sharp, left-sided thoraco-abdominal pain, fever, intermittent chills, fatigue, malaise, night sweats, and 60-lb weight loss. He procrastinated seeking medical attention because of inadequate health insurance. His medical history was significant for congenital aortic coarctation with patch repair and bicuspid aortic valve with bioprosthetic porcine aortic valve replacement (age 11) and aortic coarctation redo-patch repair (age 34). He reported outdoor activities that included cutting

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down tree branches. He was also exposed to bats, birds, and their droppings in the weeks before the onset of his symptoms.

In the emergency department, he was febrile (38.8°C) with normal white blood cell count and liver enzymes. He had elevated ferritin (1259 ng/mL) and LDH (434 U/L). A fourth-generation HIV antigen/antibody test (Architect, Abbott Laboratories) was negative. Physical examination was unremarkable other than his cardiac examination, which revealed a grade 2 out of 6 diastolic blowing murmur along the left sternal border, as well as a soft systolic murmur at the base. In addition, he was splinting the left side of his chest secondary to severe pain. Computed tomography (CT) scan of the abdomen/pelvis showed hepatosplenomegaly with a splenic infarction involving 75% of the spleen. A CT angiogram of the coronary arteries and thorax showed a proximal descending thrombus in his previous aortic patch. A transesophageal echocardiogram showed severe aortic regurgitation with 2 mobile vegetations on the bioprosthetic aortic valve leaflet and a thrombus in the descending thoracic aorta. He was empirically started on cefepime and vancomycin.

Eight days after admission, he underwent redo-sternotomy, redo aortic valve replacement with a mechanical prosthesis, and thoracic graft thrombectomy. *Histoplasma capsulatum* was cultivated from the porcine aortic valve leaflet and aortic valve thrombus using Sabouraud dextrose agar (Remel, Lenexa, KS, USA). Routine histopathology of the explanted heart valve tissue showed extensive necrosis, chronic inflammation, and numerous small yeast forms of *H. capsulatum* (Figure 1). Fungal stain (Grocott methenamine silver) highlighted budding yeast and the presence of large, bizarre yeast forms and hyphae (Figure 2). *Histoplasma* antigen, performed by MiraVista Diagnostics, was elevated in both serum (3.16; normal <0.39 ng/mL) and urine (0.84; normal <0.39 ng/mL). *Histoplasma* serum complement fixation antibodies, performed by ARUP Laboratories, were positive (*Histoplasma* mycelia 1:1024, normal <1:8; *Histoplasma* yeast 1:256, normal <1:8). Immunodiffusion testing was not performed. β-D-glucan, performed by MiraVista Diagnostics, was positive at 122 (normal 31–59 pg/mL). Three sets of aerobic and anaerobic blood cultures (Bactec FX, Becton Dickinson) were negative. After the preliminary pathology report suspected *Candida*, antibiotic treatment with cefepime and vancomycin was discontinued; he was started on intravenous (IV) voriconazole. This was later switched to IV liposomal amphotericin B (AmBisome) for 3 months, followed by oral itraconazole for long-term suppression therapy once it was determined conclusively that his infection was due to *H. capsulatum.*

He clinically improved and was eventually discharged to an extended care facility for rehabilitation and treatment completion. Six weeks later, he was seen in the infectious disease clinic. Although he continued to demonstrate clinical improvement, residual tremors, left upper extremity weakness, and contracture remained. These were the consequence of a period of asystole postoperatively, suspected anoxic encephalopathy, and status epilepticus. Several months later, he died due to a fall at home, resulting in head trauma and intracranial hemorrhage; he was on warfarin therapy. At the time of his death, he had been clinically improving and had no signs or symptoms of infection. *Histoplasma* antigen levels continually declined over his treatment course. The last antigen level, which was near the time of his death, was "detected" but below the threshold level of quantitation. The family refused an autopsy.

LITERATURE SEARCH AND INCLUSION CRITERIA

We conducted a comprehensive computerized literature search using OVID and PUBMED (last search 1/1/2021), using the

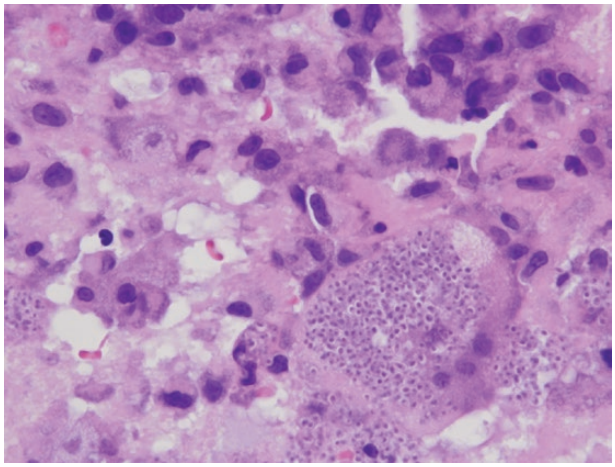

Figure 1. Histopathology of explanted heart valve tissue demonstrating typical small yeast forms of *H. capsulatum.* Small yeast are round-to-oval, 2–4 μm in diameter, and have a pseudocapsule (clear space surrounding the blue "basophilic" cytoplasm—an artefact of formalin fixation; hematoxylin & eosin, 1000× magnification).

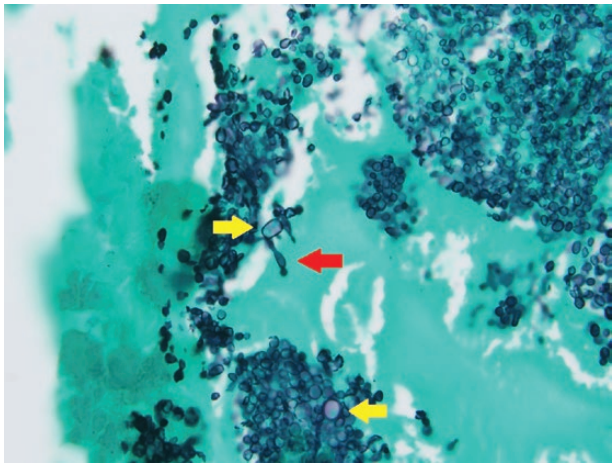

Figure 2. Histopathology of explanted heart valve tissue demonstrating typical and atypical forms of *H. capsulatum*. Numerous typical, small yeast (2–4-μm diameter) with and without budding are present. Atypical large (10–30-μm diameter) yeast forms (yellow arrows) and hyphal elements (red arrow) are present (Grocott methenamine silver, 1000× magnification).

keywords endocarditis, *Histoplasma capsulatum,* and histoplasmosis. For study inclusion, each case had to (1) designate if the infected heart valve was native or prosthetic and (2) provide evidence of valve involvement by *H. capsulatum* either by (a) histopathology and/or microbiologic culture of the valve and/or embolic tissue following surgery or autopsy or (b) clinical evidence of valve involvement (ie, vegetation(s) seen by transthoracic or transesophageal echocardiogram) in conjunction with positive microbiology culture, serum/urine antigen, and/or serology (complement fixation and/or immunodiffusion). Included manuscripts were reviewed by 2 authors (B.L.B., H.B.) to extract the following: location where infection was likely acquired, the valve(s) infected, infected valve type (native or prosthetic), patient age and gender, the specific presence of these symptoms (fever, chills, weight loss, fatigue/weakness, malaise, night sweats, and embolic disease), other symptoms and comorbidities (dyspnea, heart murmur, mental status, organomegaly, etc.), duration of symptoms before diagnosis, treatment (surgery and/or antifungal therapy) and outcomes (death or recovery), and accuracy of diagnostic tests including histopathology and specific morphologic forms of *H. capsulatum* in the heart valve, vascular emboli, or other tissues (spleen, liver, kidney, etc.), microbiology culture (heart valve, vascular emboli, aerobic/anaerobic blood cultures, fungal blood cultures, bone marrow, other locations), serum/urine antigen testing, serology (complement fixation, immunodiffusion), and β-D-glucan data.

RESULTS

Literature Search

A total of 307 manuscripts were obtained. After exclusion of nonpertinent and duplicate manuscripts, 57 underwent review. Four of these (Smith 1972, PMID 4640314; Seriki 1975, PMID 1223326; Melgar 1997, PMID 9100737; Siciliano 2018, PMID 30248465) were excluded due to absence of clinical and laboratory data or valve type designation (native or prosthetic). One (Rogers 1978, PMID 645733) was excluded as it described an infected left atrial myxoma but did not document valve involvement. Thirteen of 14 cases by Riddell [48] were excluded: 10 did not designate the valve type (native or prosthetic); 2 were previously reported by Boland [41] and Moncada [46]; 1 described an infected left atrial myxoma but did not document valve involvement. Fifty-two manuscripts encompassing 60 unique cases from 1940 to 2020 were included. Including our case report, a total of 61 cases of *Histoplasma capsulatum* endocarditis were included in this review. Clinical presentation, clinical treatment modalities and outcomes, and diagnostic laboratory testing data are provided in Supplementary Table 1 (detailed) and Table 1 (summary).

Patient Demographics

Thirty-six cases of native valve endocarditis were included (Table 1). The mean age (range) was 49 (17–67) years, with a male predominance (83%). Infection acquisition location (number) included Buenos Aries, Argentina (1), Georgia (1), Iowa (1), Illinois (1), Ivory Coast/Marseille, France (1), Kentucky (2), London, England (1), Ohio (3), Oklahoma (1), Maryland (1), Michigan (4), Midwest United States (1), Missouri (2), Minnesota (1), not specified (4), Ontario, Canada (1), Tennessee (2), Tennessee/Maryland (1), Tennessee/North Carolina (1), Texas (2), Vandoeuvre Les-Nancy, France (1), Virginia (2), and Virginia/West Virginia/Maryland (1). The frequency of valve involvement was aortic (50%), mitral (25%), aortic and mitral (8.3%), tricuspid (11.1%), pulmonic (2.8%), and not specified (2.8%). Symptom duration before

Table 1. Summary of Patient Presentation, Clinical Outcomes, and Diagnostic Yield of Tests for Native vs Prosthetic Valve *Histoplasma capsulatum* Endocarditis

Patient Presentation & Clinical Outcomes		Native (n = 36)	Prosthetic (n = 25)
Infected heart valve, No. (%)	Aortic	18/36 (50)	18/25 (72)
	Mitral	9/36 (25)	26/25 (24)
	Aortic and mitral	3/36 (8.3)	1/25 (4)
	Tricuspid	4/36 (11.1)	0/25 (0)
	Pulmonic	1/36 (2.8)	0/25 (0)
	Not specified	1/36 (2.8)	0/25 (0)
Age, mean (range), y		49 (17–67)	60 (25–87)
Gender, No. (%)	Male	30/36 (83)	19/24 (79)
Symptom duration before diagnosis, mean (range), mo		9.8 (0.5–41)	5.7 (1–24)
Symptom frequency, No. (%)	Fever	28/32 (88)	18/19 (95)
	Embolic complications	25/32 (78)	11/17 (65)
	Weight loss	24/32 (75)	11/18 (53)
	Intermittent chills	16/32 (50)	9/17 (53)
	Fatigue/weakness	14/31 (45)	7/17 (41)
	Night sweats	7/31 (23)	6/18 (33)
	Malaise	7/32 (22)	5/18 (28)
Mortality, No. (%)	Surgery (no), antifungals (no)	15/15 (100)	3/3 (100)
	Surgery (no), antifungals (yes)	4/8 (50)	2/4 (50)
	Surgery (yes), antifungals (yes)	0/9 (0)	0/13 (0)
Laboratory Testing Methods		**Native (n = 36)**	**Prosthetic (n = 25)**
Tissue morphology of *H. capsulatum* by histopathology, No. (% Positive)	Heart valve ± vascular emboli		
	Small yeast	31/32 (97)	21/21 (100)
	Large yeast ± hyphae	15/31 (48)	10/20 (50)
	Other locations		
	Small yeast	26/26 (100)	2/3 (67)
	Large yeast ± hyphae	4/26 (15)	0/3 (0)
Culture, No. (% Positive)	Heart valve or vascular emboli	7/14 (50)	13/13 (100)
	Blood—aerobic & anaerobic	4/27 (15)	3/21 (14)
	Blood—fungal	2/13(15.4)	5/10 (50)
	Bone marrow	4/12 (33)	2/5 (40)
	Other locations	12/19 (63)	1/4 (25)
Antigen, No. (% Positive)	Serum	0/1 (0)	2/4 (50)
	Urine	2/3 (67)	9/10 (90)
Serology, No. (% Positive)	Complement fixation—mycelia	11/12 (92)	13/15 (87)
	Complement fixation—yeast	10/12 (83)	13/15 (87)
	Immunodiffusion—M band	4/4 (100)	9/11 (82)
	Immunodiffusion—H band	3/4 (75)	9/11 (82)
Other, No. (% Positive)	β-D-glucan	0	1/1 (100)

diagnosis was available for 27 cases (average [range], 9.8 [0.5–41] months). Symptom frequency was available for 87% of cases and included fever (88%), embolic complications (78%), weight loss (75%), intermittent chills (50%), fatigue/weakness (45%), night sweats (23%), and malaise (22%).

Twenty-five cases of prosthetic valve endocarditis were included (Table 1). The mean age (range) was 60 (25–87) years, with a male predominance (79%). Infection acquisition location (number) included Alabama (1), Bangkok, Thailand (1), California (1), Illinois (1), Ohio (2), Maryland (1), Mexico City, Mexico (1), Michigan (3), Midwest United States (1), Minnesota (1), not specified (9), and Ontario, Canada (3). The frequency of valve involvement was aortic (72%), mitral (24%), aortic and mitral (4%), tricuspid (0%), pulmonic (0%), and not specified (0). Symptom duration before diagnosis was available for 18 cases (average [range], 5.7 [1–24] months). Symptom frequency was available for 70% of cases and included fever (95%), embolic complications (65%), weight loss (53%), intermittent chills (53%), fatigue/weakness (41%), night sweats (33%), and malaise (28%).

Embolic complications were similar for both native or prosthetic valve infection and were neurologic (altered mental status, ataxia, coma, confusion, slurred speech, transient hemiparesis) and/or vascular (acute onset of limb ischemia, paresis and/or weakness, and organ infarction) in nature. Additional signs and symptoms included congestive heart failure, cough, dysphagia, dyspnea, headache, heart murmur, hepatomegaly, hepatosplenomegaly, hoarseness, splenomegaly, and ulcers

(larynx, mouth, pharynx and/or tongue). Thirty-three cases were from 1980 or later and would potentially contain HIV-positive individuals. Of these, only 6 were tested for HIV. One of these 6 was HIV-positive (case 37) [35], yielding an estimated HIV positivity rate of 16.7%.

Patient Treatment Modalities and Clinical Outcomes

Clinical treatment and outcomes data were available for 32 of 36 (89%) native valve and 20 of 25 (80%) prosthetic valve cases (Table 1). Surgical intervention consisted of valve replacement and/or embolectomy. Antifungal therapy consisted of standalone or combination therapy with amphotericin B, liposomal amphotericin B (AmBisome), itraconazole, isavuconazole, ketoconazole, and/or voriconazole (Supplementary Table 1). Patient mortality was identical between native and prosthetic valve cases: 100% mortality without antifungal therapy and without surgical intervention; 50% mortality with antifungal therapy and without surgical intervention; 0% with antifungal therapy and with surgical intervention (Table 1). From 1940 to 1970, there were 25 cases in our study. Of these, the overall mortality was 88% (22 died, 3 survived). There was only 1 prosthetic valve case in this time frame (1/25 = 4%). From 1971 to 2020, there were 36 cases in our study. Of these, 2 cases did not report clinical outcomes. Of the remaining 34 cases, the overall mortality was 21% (7 died, 27 survived). There were 24 prosthetic valve cases in this time frame (24/34 = 70.5%) (Supplementary Table 1).

Laboratory Testing

Histopathology

H. capsulatum was consistently identified by routine histopathology. Microscopic evaluation of heart valve ± embolectomy tissue demonstrated small yeast forms in 97% and 100% and large yeast forms ± hyphae in 48% and 50% of native and prosthetic valves, respectively. In other locations (mucosal ulcer, spleen, liver, kidney, etc.), microscopy demonstrated small yeast forms in 100% and 67% and large yeast forms ± hyphae in 15% and 0% of native and prosthetic valve individuals, respectively (Table 1).

Culture

Culture of heart valve ± embolectomy tissue was performed on 27 of 61 cases, with positivity rates of 50% (native) and 100% (prosthetic). Culture techniques included Sabouraud dextrose agar (n = 4), cornmeal agar (n = 1), Malt agar (n = 1), RPMI-1640 plus fetal bovine serum with 1% Noble agar (n = 1), and unspecified (n = 20). Routine blood cultures (aerobic ± anaerobic) were performed on 48 of 61 cases with a positivity rate of 15% (native) and 14% (prosthetic). Culture techniques included Becton Dickinson Bactec (n = 1), bioMerieux BacTAlert (n = 2), and unspecified (n = 45). The number of sets per patient was 3 (n = 15), 6 (n = 6), 13 (n = 1), 14 (n = 1), 20 (n = 1), 39 (n = 1), and unspecified (n = 27). Fungal blood cultures were performed on 23 of 61 cases with a positivity rate of 15.4% (native) and 50% (prosthetic). Culture techniques included brain heart infusion and yeast phosphate agar (n = 1), biphasic Castaneda media (n = 1), Becton Dickinson Bactec (n = 1), lysis centrifugation/Isolator (n = 4), unspecified (n = 12), RPMI-1640 plus fetal bovine serum with 1% Noble agar (n = 2), and Sabouraud dextrose agar (n = 3). The number of cultures per patient was 1 (n = 1), 3 (n = 1), and unspecified (n = 21). Bone marrow culture was performed on 17 of 61 cases, with a positivity rate of 33% (native) and 40% (prosthetic). Culture techniques included Becton Dickinson Bactec (n = 1), Sabouraud dextrose agar (n = 1), and unspecified (n = 15). Culture from other sites (mucosal ulcer, spleen, liver, kidney, etc.) was performed on 23 of 61 cases, with a positivity rate of 63% (native) and 25% (prosthetic). Culture techniques included Becton Dickinson Bactec (n = 1), RPMI-1640 plus fetal bovine serum with 1% Noble agar (n = 1), Sabouraud dextrose agar (n = 3), and unspecified (n = 18) (Table 1).

Antigen

Serum *Histoplasma* antigen testing was performed on 5 of 61 cases, with a positivity rate of 0% (native) and 50% (prosthetic). Urine *Histoplasma* antigen testing was performed on 13 of 61 cases, with a positivity rate of 67% (native) and 90% (prosthetic). In case 53 [46], urine antigen testing was negative (laboratory unknown), but positive (MiraVista Laboratory) upon repeat analysis. Antigen testing for these 18 cases was performed at ARUP laboratories (n = 2), MiraVista Diagnostics (n = 7), and unspecified (n = 9) (Table 1).

Serology

Complement fixation was performed on 27 of 61 cases with a positivity rate of 92% (mycelia)/83% (yeast) and 87% (mycelia)/87% (yeast) for native and prosthetic valve cases, respectively. Testing for these 27 cases was performed by LabCorp (n = 1), ARUP Laboratories (n = 1), unspecified (n = 24), and the US Centers for Disease Control and Prevention (n = 1). Immunodiffusion was performed on 15 of 61 cases, with a positivity rate of 100% (M band)/75% (H band) and 82% (M band)/82% (H band) for native and prosthetic valve cases, respectively. Testing for these 15 cases was performed by Coccidiomycosis Serology Laboratory (n = 1; Davis, CA, USA), Institute Pasteur of Paris (n = 1), LabCorp (n = 1), and unspecified (n = 12) (Table 1).

Other

β-D-glucan was only performed on the current case report (n = 1) for a positivity rate of 100%; testing was performed by MiraVista Diagnostics.

DISCUSSION

The diagnosis of *H. capsulatum* infective endocarditis is challenging, as health care providers may not ask pertinent

questions regarding acquisition risk factors (occupation, travel, and exposure sources). In this review, infected adults were predominantly male for both native (83%) and prosthetic (79%) valve infection, consistent with previous case series [26, 29, 32, 38, 41, 44, 48]. This is not surprising, as male-predominant occupations and activities (construction, farming, home repair, tree trimming, etc.) increase exposure to the source of this infectious agent. However, histoplasmosis endocarditis will likely be observed more frequently in females as traditional, gender-specific occupations and activities become less common. All individuals in this review acquired their infection from regions within the United States and other countries known to harbor this infectious agent [1]. The duration of symptoms before diagnosis was on average (range) 4.1 (0.5–17) months sooner in individuals with prosthetic valve infection. This novel finding likely reflects heightened surveillance of endocarditis in this population. Prosthetic tricuspid or prosthetic pulmonic valve endocarditis was not observed. This novel finding was likely obscured in previous case series as native and prosthetic valve involvement were presented in aggregate [26, 29, 32, 38, 41, 44, 48]. To our knowledge, individuals in this review did not have prosthetic tricuspid or pulmonic valves or risk factors (ie, intravenous drug use) predisposing them to have undergone native tricuspid or pulmonic valve replacement. There was only 1 intravenous drug user in this review, but he had native valve infection [35]. In this review, there were only 33 cases from 1980 or later whereby HIV infection could have been possible. Of these, only 6 individuals had HIV testing performed; the 1 positive individual was the aforementioned intravenous drug user [35].

Serologic (complement and/or immunodiffusion) and *Histoplasma* antigen testing (serum and urine) are critical diagnostic tools. We observed a high positivity rate for complement fixation (83%–92%) and immunodiffusion (75%–100%), which is consistent with previous data [29, 38, 44, 48]. This reflects (a) the immunocompetent status of the individuals in this review and (b) their prolonged duration of disease (0.5 to 41 months) before testing, allowing sufficient time for a robust humoral immune response. The positivity rate of serum antigen testing was 0% (native) and 50% (prosthetic). In contrast, urine antigen testing had a positivity rate of 67% (native) and 90% (prosthetic). The observed higher positivity rate for urine antigen testing and antigen testing in individuals with prosthetic valve infection is a novel observation. This suggests that (a) antigen levels are higher in urine as compared with serum, (b) the concentration of *H. capsulatum* is higher in prosthetic valve infection, and/or (c) *H. capsulatum* is less adherent to prosthetic valve material, thereby allowing higher circulating concentrations of organism or cell wall components to be available for detection by antigen testing. This observation could be an artifact since it was not possible to determine the temporal relationship of serum vs urine antigen testing relative to each individual's disease course. However, it is reasonable to assume that both serum and urine testing would have been performed concurrently. Additionally, pretreatment of serum with heat in the presence of EDTA became the norm around 2009, as this process demonstrated an improved detection rate of *Histoplasma* antigen [54]. In our review, all serum antigen testing was performed in 2010 or later. Therefore, it is unlikely that the observed lower positivity rate for serum antigen testing is related to suboptimal testing protocols. Finally, antigen testing is crucial early in the disease course and for immunocompromised individuals who will likely have false-negative serologic test results due to a blunted humoral immune response.

Culture plays a pivotal diagnostic role and facilitates antifungal susceptibility testing when indicated. We observed a higher positivity rate of culture on heart valve ± vascular embolus tissue, fungal blood cultures, and bone marrow for individuals with infected prosthetic vs native valves. This is a novel observation and, similar to urine antigen testing, supports the ideas that (a) higher microorganism concentrations are present in infected prosthetic valves and/or (b) *H. capsulatum* is less adherent to prosthetic valve material, thereby allowing higher circulating concentrations of organism to be available for detection by culture. Alternately, it is possible that improved culture detection methods were used in those with prosthetic valve infection. The majority of published studies failed to disclose the culture methods employed, thereby precluding the ability to investigate further (Supplementary Table 1). Interestingly, we observed a higher positivity rate of culture from other tissues (mucosal ulcer, spleen, kidney, liver, etc.) in native vs prosthetic valve infections. A possible explanation is that individuals with native valve infection release larger infective embolic thrombi, therefore increasing the organism concentration "inoculum density" in these tissues, with the added benefit of a higher diagnostic yield by culture. Again, the majority of culture methods used in this review were not specified, precluding the ability to determine if differences in cultivation techniques are responsible for this observation (Supplementary Table 1). To enhance the recovery of fungal pathogens from blood, it is highly recommended to use lysis centrifugation (Isolator) or specialized fungal blood culture bottles in conjunction with automated instrumentation (ie, Bactec, BacTAlert3D). For the majority of individuals in this review, bacterial endocarditis was highly suspected. As such, standard-of-care routine blood cultures were performed, with the total number of sets per individual ranging from 3 to 39. The *H. capsulatum* positivity rate was 15% (native) and 14% (prosthetic). This is an expected finding as routine blood culture media are not designed to readily support the growth of fungi [48]. The addition of fungal-specific blood cultures should be considered in individuals with geographic and/or occupational/recreational risk factors for mycotic infection, as this would greatly improve the time to detection of this elusive disease.

Only 1 patient (current case) in this review had β-D-glucan testing, and the result was positive. β-D-glucan is not specific, as the polysaccharide is found in the cell wall of most fungi, except *Cryptococcus*, zygomycetes, and *Blastomyces dermatitidis*. β-D-glucan has demonstrated utility in the diagnosis of invasive fungal infections and monitoring of treatment efficacy [55]. However, the utility of β-D-glucan in *Histoplasma* endocarditis is unclear at this time.

Routine histopathology should be performed on excised tissues. The observation of typical, small *H. capsulatum* yeast forms confirms the diagnosis in nearly 100% of cases. However, as was our experience, the presence of atypical (large "globose" yeast and hyphal) forms poses diagnostic challenges to the inexperienced pathologist and/or clinical microbiologist, who might mistake them for *Candida* or other fungal species. Atypical forms are primarily observed in intravascular tissue (ie, heart valve, vascular emboli) [9, 10, 33]. Occasionally, atypical forms are observed in the adrenal gland, renal papillae, lung, skin, or other tissues [9, 10]. In our review, atypical forms were observed in 50% of heart valve ± vascular emboli tissue and up to 15% in other tissues. Nucleic acid techniques (DNA sequencing, in situ hybridization, and polymerase chain reaction) are being used more frequently on excised tissues to facilitate rapid, definitive diagnoses [1, 36, 40, 46, 48–50].

H. capsulatum infective endocarditis is invariably fatal without combined surgical intervention and antifungal treatment [26, 29, 32, 38, 41, 44, 48]. As observed in this review, individuals failing to receive both antifungal therapy and surgical intervention for native or prosthetic valve endocarditis had a mortality rate of 100%. Mortality for native or prosthetic valve endocarditis was 50% for individuals receiving antifungal therapy alone. Antifungal therapy coupled with surgical intervention had 0% mortality for both native and prosthetic valve endocarditis. These observations are consistent with previous case series despite native and prosthetic valve data being presented in aggregate [26, 29, 32, 38, 41, 44, 48]. In addition, we noted a significant improvement in overall mortality in individuals with disease in the time period of 1940–1970 (88% mortality, n = 25) vs the time period of 1971–2020 (21% mortality, n = 34). This observation highlights the improvements in both surgical treatment and antifungal therapy between these time periods. However, the possibility of reporting bias exists, such that cases with favorable outcomes were preferentially reported. This is a known limitation of retrospective literature reviews. Lipid formulations of amphotericin B, which have reduced toxicity, are commonly used for 4–6 weeks and in combination with surgical intervention. After completing treatment with amphotericin B, most individuals are also treated with itraconazole for at least 1 year and potentially longer.

CONCLUSIONS

We present a case of a 47-year-old man with bioprosthetic aortic valve *Histoplasma* infective endocarditis who following surgical valve replacement and treatment with liposomal amphotericin B (AmBisome) for 3 months and long-term suppression therapy with itraconazole made significant improvement both clinically and via laboratory monitoring of both serum and urine antigen test values. In conjunction with our case report, our systemic literature review highlighted similarities and differences in clinical presentations, clinical outcomes, and the utility of diagnostic testing between individuals with native vs prosthetic valve *H. capsulatum* endocarditis.

For individuals with native or prosthetic valve infection, several key similarities are noteworthy: First, the mortality rates for native and prosthetic valve infection are identical: 100% mortality without surgical intervention and without antifungal therapy, 50% mortality with antifungal therapy alone, and 0% mortality with surgical intervention and with antifungal therapy. Based on these data, standard of care for these individuals should be combined surgical intervention and antifungal therapy. Second, the frequency of clinical symptoms (fever, embolic complications, chills, weight loss, fatigue/weakness, night sweats, malaise) are nearly identical. Third, the positivity rates of histopathology (heart valve and/or vascular emboli) and serologic testing (complement fixation, immunodiffusion) are nearly identical. For serologic testing, optimal results will be observed in immunocompetent individuals.

Observed differences in individuals with native vs prosthetic valve infections are likewise highlighted. First, individuals with native valve infection are, on average, 11 years younger. Second, individuals with prosthetic valve infection are, on average, diagnosed about 4 months sooner after the onset of clinical symptoms. Third, the positivity rate of serum or urine antigen testing is higher in individuals with prosthetic valve infection. Fourth, the positivity rate of urine antigen testing is higher than serum regardless of native or prosthetic valve infection. Fifth, the positivity rate of culture (heart valve and/or vascular emboli, fungal blood cultures, and bone marrow) is higher in prosthetic valve infection. Lastly, overall mortality (regardless of native or prosthetic valve infection) has markedly improved over time. The overall mortality rate from 1940 to 1970 was 88%, but only 21% from 1971 to 2020, reflecting marked improvements in surgical intervention techniques and widespread availability of antifungal therapy.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This work is a single case report and systemic literature review. It conforms to the policies of the Beaumont Health Institutional Review Board (IRB) and does not necessitate patient consent or IRB approval.

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