Review Article

A Review on Fungal Myocarditis: The Agents, Predisposing Factors and Treatments

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Abstract

Background and Aim: Myocarditis is an inflammatory disease of the heart muscle. It has many symptoms, from mild chest tenderness to cardiogenic alarm. Fungal myocarditis is a disseminated infection that mostly occurs in immunocompromised patients, especially in the intensive care unit (ICU). It has similar symptoms to coronary disease. The exact diagnosis of fungal myocarditis is complex and may be caused by different fungal agents.

Materials and Methods: A review of the literature on fungal myocarditis using PubMed and Google Scholar was conducted. This review collected case reports of fungal myocarditis from 2010 to 2023 worldwide to provide current prevalence in different sex categories and ages. Case reports were reported from North America, Asia, and Europe.

Results: According to results, *Aspergillus* myocarditis was more commonly reported in men (71.4 %) and had the highest mortality rate among the other fungi (close to 57%). Generally, there are no case reports from South America, Africa, and Australia. Amphotericin B is the first drug choice for *Aspergillus* myocarditis. Despite qualifying voriconazole treatment, voriconazole use is still under research and has not been confirmed for childcare. Fungal myocarditis mainly occurs in immunocompromised patients who have been hospitalized in ICU.

Conclusion: Regarding morbidity and mortality rate, myocarditis is an alarming disease. Misinterpreting signs and symptoms with other diseases often make diagnosing this disease complex. Delayed diagnosis often leads to failure of the multiple organs and can directly affect the treatment protocol.

Keywords: Myocarditis, Mycoses, Mortality

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Introduction

Myocarditis is an inflammatory heterogeneous heart muscle disease with a broad range of symptoms from mild chest tenderness to cardiogenic alarm and variable clinical patterns worldwide[1]. Infectious agents, noxious substances, drugs, or autoimmune disorders are the causes of most myocarditis reports[1].

The histological diagnosis of myocarditis is classified into different forms according to the type of inflammatory cell infiltrate: lymphocytic, eosinophilic, polymorphic, giant cell myocarditis, and cardiac sarcoidosis[2].

Fungal myocarditis is defined as a generally disseminated infection. Sometimes, it can be complicated to figure out disseminated fungal infections. It mainly occurs in immunocompromised patients, and the incidence is enhanced when patients have been hospitalized in ICU. However, immunocompetent patients are hardly affected[3-5].

Since myocarditis appears with non-specific symptoms containing chest pain, dyspnea, and palpitations, it often acts like more frequent disorders such as coronary artery disease[6]. The clinical patterns may range from negligible symptoms to heart failure, lethal arrhythmias, or cardiogenic shock[7].

Although acute myocarditis usually has an excellent short-term prognosis, it varies extensively by cause[6]. Clinically, acute myocarditis indicates a short time between the arrival of symptoms and the detection (generally <1 month)[8].

Invasive fungal pathogens contain primary mycotic agents, valid pathogenic and intrinsic virulent entities such as *Histoplasma spp.* and *Blastomyces spp*. Secondary mycotic organisms such as *Candida* and *Aspergillus* species, *actino*, and *Mucorales* are opportunistic, less infectious pathogens. Also, some gram-positive bacteria that perform like fungi in terms of their growth pattern, such as *Nocardia* and *Actinomyces* species, can cause fungal-like myocarditis; therefore, The survey of these organisms is included in this review[9].

Physical examination, laboratory testing, chest X-ray, transthoracic echocardiography, cardiac MRI, bronchoscopy with alveolar lavage (BAL), and abdominal ultrasonography were used to diagnose fungal myocarditis.

As mentioned above, myocarditis is a cause of cardiovascular diseases, and cardiovascular diseases are the main provider of the total mortality rate[10]. Hence, we should consider its costs and the burden created for patients and healthcare services. The economic burden of myocarditis is related to diagnostic methods (MRI, CT scan), hospitalizations, drug consumption during treatment, and autopsy issues after death.

This review aimed to provide an update on the reported cases of fungal myocarditis worldwide to assess different factors in these patients and the connection of myocarditis to underlying disease and investigate the prevalence of fungal myocarditis in different sex categories.

Materials and Methods

A review was conducted of the literature available on fungal myocarditis caused by different species using PubMed and Google Scholar. Additionally, the following terms were searched: fungal myocarditis, *Aspergillus* myocarditis, *Candida* myocarditis, *Histoplasma* myocarditis, *Cryptococcus* myocarditis, Blastomycosis, Mucormycosis, Actinomycosis, *Nocardia* myocarditis. All articles in a language other than English were excluded from the study.

Results

Aspergillosis: Aspergillosis can be defined as a wide range of diseases, including severe, invasive disorders affecting almost the main organs. *Aspergillus* pancarditis, defined as inflammation of the whole parts of the heart, including epicardium, myocardium, and endocardium, is specifically uncommon and has a poor prognosis[11]. Its incidence has been assessed as approximately 10% - 14%. In the Middle East, invasive Aspergillosis rates continue to increase, bringing considerable morbidity and mortality[12]. The total mortality rates may be evaluated as 27% - 60% despite antifungal therapy (Table 1)[13]. In Aspergillosis cases, a blood culture is admitted to determine the disease[3]. The galactomannan (GM) enzyme immunoassay and (1–3)-Beta-D-glucan tests were used to diagnose Aspergillosis. [5]

Candidiasis: Heart *Candida* invasion considerably makes the procedure difficult in systemic Candidiasis. When a person without a history of heart disease has a positive culture test for *Candida*, a notable arrhythmia, conduction disorder, or another remarkable quick-release system (QRS) change and is admitted to the hospital, we should be suspected of heart Candidiasis. The influence of treatment on *Candida* invasion of the heart is undetermined (Table 2)[14].

Table 1. Cases of *Aspergillus* myocarditis.

Age	Gender	Case fatality	Blood culture	Underlying diseases	Manifestations	Reference	Species
23	M	died	negative	occupational risk factors	necrotizing fungal pancarditis and aortitis fungal abscesses in the lungs	5	NM.
24	M	died	negative	NM.	leptospirosis	5	*A. fumigatus*
76	M	died	negative	asymptomatic anemia	Invasive Aspergillosis involving the lungs, heart, liver, and gastrointestinal tracts	13	NM.
81	F	died	negative	rheumatoid arthritis	chronic renal failure, multiple cerebral infarctions,	13	NM.
30	M	survived	negative	acute fever	malignant lymphoma, infective endocarditis	11	NM.
70	M	died	negative	acute leukemia progressive shortness of breath and peripheral edema allogeneic hematopoietic cell transplantation	disseminated Aspergillosis in the heart, brain, kidney, spleen, stomach, bladder, and lung	15	*A. udagawae*
60	F	died	positive	diabetes mellitus eosinophilic granulomatous with polyangiitis	invasive myocarditis multiple myocardial abscesses	16	*A. fumigatus*
57	M	survived	positive	pansinusitis with recurrent polypectomies	eosinophilic myocarditis	17	NM.
9	F	survived	positive	acute leukemia	infection in the paranasal sinuses, skin, and lungs	18	*A. fumigatus*
42	M	survived	positive	macrophage-	myocardial abscesses,	19	*A. fumigatus*

				dominated myocarditis	myocardial wall rupture, and septic shock		
68	M	died	negative	orthotopic liver transplantation	septic shock, multiple organ failure, multiple Aspergillosis abscesses	20	*A. fumigatus*
18	M	survived	negative	idiopathic fulminant hepatic failure, orthotopic liver transplantation	Malnutrition, large pericardial effusion	21	*A. fumigatus*
63	F	survived	positive	aplastic anemia, fever, and malaise	the pulmonary lesion, a lesion within the left ventricular anterolateral wall	22	*A. fumigatus*
62	M	died	negative	AIDS, pneumocystis carinii pneumonia, fever, shortness of breath, productive cough	extensive right basal ganglia infarct, bilateral facial asymmetry, and right-extremities paralysis	23	*A. fumigatus*

NM: not mentioned; M: male; F: female

Table 2. Cases of *Candida* myocarditis.

Age	Gender	Case fatality	Underlying diseases	Manifestations	Reference	Species
63	M	died	white sticky sputum, shortness of breath and chest tightness, allergic cough, previous smoking history	diffuse myocardial dyskinesia	24	NM.
42	M	survived	fulminant macrophage-dominated myocarditis,	myocardial abscess	19	*C. glabrata*
16	F	NM.	fever, chest, and back pain	lymphocytic infiltrate, biventricular	25	NM.

				akinesis		
40	M	NM.	subjective fevers, exertional dyspnea, and a non-productive cough, gout	myocardial infarction	26	*C. albicans*

NM: not mentioned; M: male; F: female

Histoplasmosis: Histoplasmosis is an autochthonal mycosis, most common in North America. All presented patients have a background of immunosuppression (Table 3)[27].

Histoplasma capsulatum is a dimorphous and opportunistic organism that mainly causes infection in immunosuppressed patients, especially in HIV/AIDS patients, infants due to their immature immune systems, rheumatologic disorders in children, or organ-transplant patients who are getting immunosuppressive treatments. Nevertheless, other immunosuppressed can also be at risk[28].

Disseminated Histoplasmosis is uncommon in immunocompetent infants. Prominent cardiac problems in immunocompromised elderly encompass endocarditis and pericarditis, though, in medical reports, myocarditis rarely has been presented[29].

Cryptococcosis: Cryptococcosis is exceedingly uncommon in immunocompetent individuals. Cardiac Cryptococcosis is rarely reported in disseminated Cryptococcosis form by spreading through blood. It is an opportunistic infection that results from encountering the microorganisms *C. neoformans* or *C. gattii*, usually passed infection by aspiring bird feces, primarily pigeons. In 20.7 % of pigeons, *C. neoformans* has been isolated in Mexico. The disease is not transmitted from one individual to another. However, there is also a risk of affliction in organ recipients (Table 4)[30].

Table 3. Cases of *Histoplasma* myocarditis

Age	Gender	Case fatality	Underlying diseases	Manifestations	Reference	Species
16	F	survived	malaise, fever, vomiting, and diarrhea	myocarditis and multi-organ failure	29	*H. capsulatum*
49	F	survived	progressive painful weakness of proximal muscles ,‹inflammatory polyarthritis of small joints	dilated cardiomyopathy, pedal edema, and transaminitis despite diuretics	27	*H. capsulatum*
37	F	died	Neurofibromatosis type 1 (NF1), hypertension, schizophrenia, seizure disorder, upper respiratory symptoms, nausea, and myalgia	cardiomyocyte hypertrophy and myocarditis	31	*H. capsulatum*
44	M	survived	crohn's disease, diabetes mellitus, hypothyroidism, and COVID-19 infection exacerbated weakness, myalgias, fevers and diarrhea	myocarditis	28	*H. capsulatum*

M: male; F: female

Table 4. Cases of *Cryptococcus* myocarditis

Age	Gender	Case fatality	Underlying diseases	Manifestations	Reference	Species
NM.	M	survived	progressive dyspnea, rapid progression to paroxysmal nocturnal dyspnea	lethargic, painful facies, cold, clammy, and pale skin, jugular venous distention, Kussmaul sign positive	30	*C.neoformans*
50	M	died	NM.	autoimmune disorder, connective tissue disorder	32	NM.
54	M	survived	palpitations and activity-related presyncope, as well as influenza-like symptoms	hilar lymph glands and multiple nodular lesions in the lungs, edema, and nodular structures in the heart	33	*C.neoformans*

NM: not mentioned; M: male

Blastomycosis: Blastomycosis is a rare infection that mostly appears in North America. The annual prevalence of Blastomycosis in North America varies from 0.2 to 1.94 cases per 100,000 individuals (Table 5)[34]. Etiologic organisms of Blastomycosis are *Blastomyces dermatitidis* and *Blastomyces gilchristii*. Nowadays, analyzing sequences by PCR is the only technique for distinguishing these species. Investigation of Blastomycosis needs visualization and culture from a specimen[35].

Mucormycosis: Generally, Mucormycosis involves immunocompromised patients such as people with diabetes, people who suffer from malignancies, organ stem cell recipients, and people involved in pandemic diseases such as COVID-19. Due to clinical difficulties, misdiagnoses, and similarity in symptoms with other diseases, Mucormycosis diagnosis is usually postponed (Table 6)[36].

Table 5. Cases of *Blastomyces* myocarditis

Age	Gender	Case fatality	Underlying diseases	Manifestations	Reference	Species
36	M	survived	right arm weakness and tingling, cough with blood-streaked sputum, fever, and unintentional 8 pounds of weight loss	hemoptysis and night sweats	34	NM.
44	M	survived	dyspnea, cough, night sweats, and associated 20 pounds weight loss	subjective fevers, tachycardic but with a regular rhythm	35	NM.

NM: not mentioned; M: male

Table 6. Cases of *Mucormycoces* myocarditis

Age	Gender	Case fatality	Underlying diseases	Manifestations	Reference	Species
47	M	died	diabetes mellitus, decompensated liver cirrhosis ،non-alcoholic steatohepatitis, hepatocellular carcinoma (HCC)، underwent living donor liver transplantation (LDLT) with splenectomy using a right hemi-liver graft procured from his son	fungal endocarditis multiple bleeding infarctions due to arterial septic emboli caused by fungi	37	*C. bertholletiae*

M: male

Actinomycosis and Nocardiosis: Bacterial myocarditis is uncommon and frequently isolated in the background of acute sepsis or is related to particular bacterial pathogens[38]. Mortality emerges to be elevated, as is observed with all bacterial myocarditis, and ICU admission is necessary in many cases[39]. Cardiac Actinomycosis is an uncommon disease frequently demonstrated as pericardial, making up nearly 70%–80% of cardiac cases. Endocarditis and myocarditis are extremely uncommon[40]. Risk factors include malnutrition, masculinity, immunosuppression by any reason, and low level of general and oral hygiene. Infection is common in planters who work in areas with uncoated feet and hands after surgical procedures(Table 7)[41]. *Nocardia* species are environmental gram-positive, filamentous bacteria, a complicated group of agents considered to pertain to aerobic *Actinomycetes*. They can be found everywhere and account for lethal, uncommon, and acute opportunistic human contagions, particularly in immunocompromised patients[42,43].

Treatments: The first drug choice for *Aspergillus* myocarditis is amphotericin B. Systemic infection frequently appears during the period of diagnosis, and because the infection quickly develops, it has a poor prognosis[11].

Considering treatment, isavuconazole has unapproved use in children. However, sometimes, it is the basis chosen for the patients' antifungal therapy because of coexisting acute renal failure that prevents the usage of voriconazole or posaconazole because of possible cyclodextrin accumulation, even though constant replacement treatment can efficiently eliminate cyclodextrin. Despite qualifying voriconazole treatment, voriconazole use is still under research and has not been confirmed for childcare[18].

Table 7. Cases of Actinomycosis and *Nocardia* myocarditis

Age	Gender	Case fatality	Underlying diseases	Manifestations	Reference	Species
53	M	survived	breathlessness, fatigue, right lower limb swelling, a vague abdominal bloating sensation decreased appetite, weight loss	well-defined lytic lesions, cardiomegaly with features of right atrial enlargement, mild tricuspid regurgitation	41	NM.
14	M	survived	acute rheumatic fever	cardiomegaly with pulmonary congestion, severe aortic valve regurgitation	44	*A. oris*
56	M	survived	dyspnea, hypotension, Parkinson's disease with psychosis, cough, tachycardia	thick-walled cavitary lung lesion	45	*A. meyeri*
33	M	survived	productive cough, worsening dyspnea on exertion, and diarrhea	*Nocardia* infection	46	*N. asiatica*

NM: not mentioned; M: male

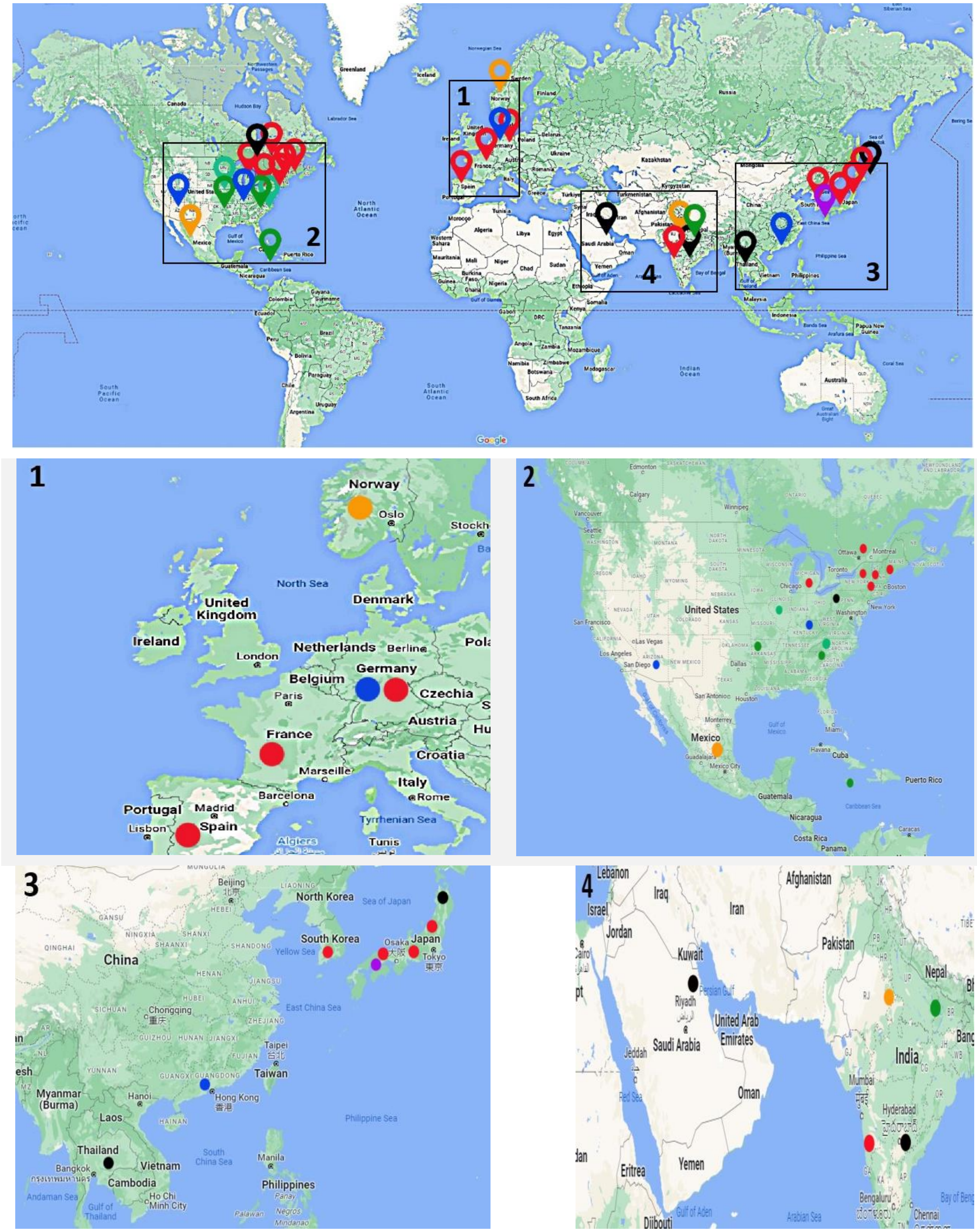

Figure 1. Distribution of fungal myocarditis cases in the world; (●Aspergillosis, ● Candidiasis, ● Histoplasmosis, ● Cryptococcosis, ●Blastomycosis, ●Mucormycosis, ●Actinomycosis and Nocardiosis).

Discussion

Myocarditis is an alarming disease due to its morbidity and mortality rate. Diagnosis of this disease is often difficult due to the misinterpretation of signs and symptoms with other diseases. Delayed diagnosis directly affects the treatment protocol and often leads to failure of the multiple organs.

Myocarditis affects immunocompromised patients, including diabetes, hematological malignancy, organ transplant, and AIDs patients.

Although infection treatment has been developed since the dawn of time, the number of cases reported gradually increased. Therefore, exact and new tests to diagnose each disease are essential. We may identify more cases of fungal myocarditis in the future, as well as with the advancement and acceleration of clinical diagnoses. Therefore, there is a possibility that the mortality rate of these patients will decrease, especially in *Aspergillus* myocarditis.

Several cases have been performed for myocarditis in the United States, Japan, India, Spain, Germany, France, Michigan, South Korea, Canada, and other geographical areas. Despite this, no complete report gathers all the cases together. This study collected all the cases from 2010 to 2023 (Figure 1).

Different fungal pathogens can lead to myocarditis. It can be caused as a result of invasive systemic or pulmonary infection.

Conclusion

Regarding morbidity and mortality rate, myocarditis is an alarming disease. Misinterpreting signs and symptoms with other diseases often make diagnosing this disease complex. Delayed diagnosis often leads to failure of the multiple organs and can directly affect the treatment protocol.

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None.

Conflict of interest

The authors further declare that, they have no conflict of interest.

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