CONTEMPORARY REVIEW

Tuberculosis and the Heart

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ABSTRACT: Acquired tuberculosis continues to be a challenge worldwide. Although tuberculosis has been considered a global public health emergency, it remains poorly controlled in many countries. Despite being primarily a pulmonary disease, tuberculosis could involve the heart. This systematic review is part of the "Neglected Tropical Diseases and Other Infectious Diseases Involving the Heart" (the NET-Heart Project) initiative from the Interamerican Society of Cardiology. This project aims to review the cardiovascular involvement of these heterogeneous diseases, advancing original algorithms to help healthcare providers diagnose and manage cardiovascular complications. In tuberculosis, pericardium involvement is relatively common, especially in AIDS, and tuberculosis is the most common cause of constrictive pericarditis in endemic countries. Myocarditis and aortitis by tuberculosis are rare. Clinical manifestations of cardiovascular involvement by tuberculosis differ from those typically found for bacteria or viruses. Prevailing systemic symptoms and the pericarditis diagnostic index should be taken into account. An echocardiogram is the first step for diagnosing cardiovascular involvement; however, several image modalities can be used, depending on the suspected site of infection. Adenosine deaminase levels, gamma interferon, or polymerase chain reaction testing could be used to confirm tuberculosis infection; each has a high diagnostic performance. Antituberculosis chemotherapy and corticosteroids are treatment mainstays that significantly reduce mortality, constriction, and hospitalizations, especially in patients with HIV. In conclusion, tuberculosis cardiac involvement is frequent and could lead to heart failure, constrictive pericarditis, or death. Early detection of complications should be a cornerstone of overall management.

Key Words: heart ■ myocarditis ■ pericarditis ■ tuberculosis ■ vessels

Tuberculosis is a communicable disease caused by the bacillus Mycobacterium tuberculosis. It is the leading cause of mortality from an infectious disease and is among the top 10 leading causes of death worldwide, particularly in low- and middle-income countries (LMIC) where it generates a significant burden of disease. Although tuberculosis has been considered a global public health emergency for the past 25 years, it remains poorly controlled. For this reason, in September 2018, the United Nations held its first-ever high-level meeting on tuberculosis to assess the state of the epidemic and seek to combat it from a global perspective. As a result, the target 3.3 strategy, which will try to end the tuberculosis epidemic by 2030, was established. The goal will be a reduction by 90% of tuberculosis mortality and 80% of tuberculosis incidence rate compared with 2015.2

Despite being primarily a pulmonary disease, M tuberculosis can affect any organ of the body, and often presents with cardiac involvement. After the central nervous system, cardiovascular involvement is one of the most common extrapulmonary manifestations of tuberculosis. Cardiovascular involvement in tuberculosis portends an unfavorable prognosis (for example, tuberculous pericarditis is associated with a mortality rate close to 40%).3 The "Neglected Tropical Diseases and Other Infectious Diseases Involving the Heart" (the NET-Heart Project), an initiative of the "Emerging Leaders" section of the Interamerican Society of Cardiology, aims to expand knowledge about the...
Cardiovascular complications in these types of diseases, to help to identify barriers, and to look for possible solutions. The main objective of this systematic review is to generate a useful and applicable algorithm to be used by general physicians and cardiologists, mainly from LMIC.

**Methods**

We conducted a systematic review of the literature following the design and rationale of the NET-Heart Project. Initially, the databases from PubMed, EMBASE, and LILACS were screened to identify articles containing the MESH terms "tuberculosis" and "heart," "cardiac," "heart failure," "pericarditis," "pericardium," "endocardium," "conduction disorders," "arrhythmias," "syncope," and "vessels" published between January 1955 and June 2020, limited to human studies and restricted to English. The construction of the search obtained 764 references, and 256 duplicated references were eliminated. Two authors (J.P.L. and E.L.P.) reviewed the title and abstracts of all articles. The initial selection was made according to the inclusion criteria: randomized clinical trials, case series, observational studies, systematic reviews, and case reports. Nonhuman studies and off-topic articles were excluded. Narrative reviews and nonsystematic reviews were also excluded. After applying inclusion and exclusion criteria, 51 articles were detected to be qualitatively analyzed: 9 clinical trials, 25 case reports, 5 case series, 3 observational studies, and 9 systematic reviews. Seven articles were found directly by review of reference lists (Figure S1).

**Results**

**Epidemiology**

According to the global tuberculosis report from the World Health Organization, in 2019, around 10 million people (between 9 and 11) acquired tuberculosis, with >87% of the cases belonging to LMIC mostly from South Asia (44%), Sub-Saharan Africa (24%), and Western Pacific (18%) regions, indicating a close relation with poverty (Figure 1). Tuberculosis leads to a significant burden of disease and increased mortality; for example, in LMIC it leads to 40% to 70% of pericardial effusion cases, and in 2018 caused 1.5 million deaths worldwide. Immunosuppression is a crucial risk factor for acquiring tuberculosis. The advent of the HIV epidemic in the past decades has put many additional people at risk. It has been shown that people with HIV have a 9 to 16 times higher risk compared with individuals without HIV. Indeed, the World Health Organization report showed that 8.6% of people with tuberculosis had HIV coinfection. Other risk factors for tuberculosis include glucocorticoid use, poor nutritional status, and chronic noncommunicable diseases, including cardiovascular diseases.

**Physiopathology and Cardiac Involvement**

The cardiovascular structures usually involved in tuberculosis are the pericardium, the myocardium, and the aorta. Table 1 summarizes the frequency and types of cardiovascular involvement in tuberculosis. Pericardial involvement is relatively common, especially in patients with AIDS where pericardial effusion caused by *M. tuberculosis* reaches 85% or higher. Conversely, in immunocompetent patients with acute pericarditis, tuberculosis accounts for <5% of cases. Myocarditis and aortitis are relatively rare cardiac manifestations of tuberculosis (<2% in different series). Mycotic aneurysms are the typical lesions, but pseudoaneurysms have been reported.

Pericardial compromise includes (1) acute pericarditis, (2) pericardial effusion, (3) myopericarditis, and (4) constrictive pericarditis. These presentations may overlap and are not exclusive. *M. tuberculosis* can reach the pericardium through different pathways. Because the lungs are the principal entrance for the bacillus, it typically has a lymphatic spread from mediastinal, parapharyngeal, and peribronchial lymph nodes or a direct spread from the lung or the pleura. If miliary tuberculosis occurs, hematogenous spread is possible. Hematogenous spread mainly occurs in immunocompromised subjects where higher bacilli loads and increased mycobacterial replication are present. Immunocompetent subjects typically generate a paucibacillary condition because of cell-mediated hypersensitivity with T-helper cells (sub-type 1) that attenuate the severity of the disease. Tuberculosis is the most common cause of constrictive pericarditis, in endemic countries, accounting for 38% to 83% of the cases. Transient constriction occurs in 10% of tuberculosis-related pericarditis, while progression to overt constrictive pericarditis occurs in 20% to 50% of patients despite being on antituberculosis treatment. Furthermore, constrictive...
Pericarditis can persist for several years, leading to heart failure.\(^{17,25,26}\) Figure 2 shows a case of a patient with HIV presenting with constrictive pericarditis.\(^{27}\) Also, cardiac tamponade with tuberculosis pericarditis can occur.\(^{25}\)

In contrast, myocardium compromise is generated mostly by hematogenous spread, and less frequent by retrograde lymphatic spread from mediastinal lymph nodes or directly from the pericardium. Tuberculosis has an anatomical predilection for the right-sided mediastinal lymph nodes; therefore, the right heart is the myocardium that is the most vulnerable area because of contiguous spread.\(^{18,19}\) Less than 50 cases of tuberculous endocarditis have been described in the literature.\(^{28}\) Moreover, few cases of tubercular pancarditis have been reported, mainly in young people.\(^ {29}\) The aortic wall is infected by contiguous spread from an adjacent infective focus via the vasa vasorum, and directly implants on atheromatous plaques.\(^ {30}\) The vast majority of the reported cases of tuberculosis vascular involvement are related to disease of the aorta; however, cases of tuberculosis involvement in smaller arteries have been described.\(^ {20,31}\)

**Symptoms**

Classic symptoms and signs of acute pericarditis such as stabbing pain and pericardial rubbing are not common in tuberculosis pericarditis (between 3% and 8%).\(^ {15,31}\) Conversely, the presentation tends to be insidious and systemic signs and symptoms as described in Tables 2 and 3 are more frequent.\(^ {32,33}\) Clinical manifestations depend on the rate of fluid accumulation, the hemodynamic effect on cardiac contraction, and the degree of inflammation triggered by the infection.\(^ {34}\) If fluid accumulation is progressive, general systemic symptoms or heart failure will be the prevailing symptom.\(^ {8,35}\) If fluid accumulation is rapid and there are no compensatory mechanisms, the patient will clinically manifest with tachycardia and hypotension. If no treatment is received or the treatment is inadequate, up to half of patients may progress to cardiac tamponade and mortality may be as high as 85% at 6 months.\(^ {16,36}\)

Acute clinical manifestations of tuberculous myocarditis may become apparent as disturbances of the conduction system, causing prolonged QT syndrome, ventricular fibrillation, or cardiac arrest. On the other hand, chronic myocardial involvement may manifest with gradual heart failure symptoms or even as an asymptomatic patient who is diagnosed postmortem.\(^ {18}\) Subacute endocarditis presents as constitutional symptoms similar to pericarditis. Dyspnea and heart failure symptoms appear when vegetations generate hemodynamic compromise leading to severe valve insufficiencies.\(^ {28}\)
In the aorta, clinical manifestations are produced by the formation of pseudoaneurysms or mycotic aneurysms, which manifest mainly as a pulsatile or palpable mass or chest or abdominal pain caused by mass effect, and will depend on the location and the rate of growth of the lesions.\textsuperscript{20,30} Commonly, most aneurysms do not produce symptoms and are only diagnosed after an autopsy is performed.\textsuperscript{37,38} Cases of complications caused by aneurysm perforation leading to exsanguination, acute aortic insufficiency, or cardiac tamponade have been described, and usually have a fatal outcome.\textsuperscript{39–41}

### Diagnostic Tests

A definitive diagnosis of cardiac tuberculosis requires isolation of the tubercle bacillus from the pericardial fluid or heart or vessel tissue by either direct examination or culture, but this isolation is often difficult in practice. We propose a diagnostic algorithm to apply in all settings (Figure 3). Pericardiocentesis is usually indicated for the diagnostic approach of patients with suspected tuberculous pericarditis. Table 4 shows the indications for pericardiocentesis.

Several tests, with different diagnostic performance, can be carried out to confirm infection. Test selection should be based on the suspected site of the cardiovascular compromise and the test availability in the local setting.

An integrated approach including clinical examination and specific pericardial fluid tests with adenosine deaminase (ADA) levels, gamma interferon (IFN-γ), and/or polymerase chain reaction testing for \textit{M tuberculosis} is required for the diagnosis of tuberculosis.\textsuperscript{36} High clinical suspicion in endemic areas is necessary. Reuter et al\textsuperscript{36} developed a diagnostic score index that

### Table 1. Type and Frequency of Cardiac Involvement in Tuberculosis

| Type of Cardiac Involvement | Frequency   |
|-----------------------------|-------------|
| Pericarditis                 | 2%–5%\textsuperscript{15} |
| Myocarditis                  | 0.14%–2%\textsuperscript{16} |
| Aortitis                     | 0.3%\textsuperscript{20} |

### Figure 2. A case of a patient with HIV presenting with constrictive pericarditis.

A 35-year-old man with HIV infection was diagnosed with disseminated \textit{Mycobacterium tuberculosis} infection from bronchial, pericardial fluid, and pericardium samples (red arrowhead in A). Two months later, he presented with right-sided heart failure. Echocardiography was compatible with constrictive pericarditis as shown by pericardial thickening (red arrowheads in B), and reduction of left ventricular inflow (E wave) >25% with inspiration (red arrow in C). Computed tomography of the chest also showed thickened pericardium and mild pericardial effusion (red arrows and red star, respectively, in D). Courtesy of Dr. Andres F. Miranda-Arboleda, Department of Cardiology, Clinica CardioVID, Hospital Pablo Tobón Uribe, Universidad de Antioquia, Colombia. Modified from Miranda-Arboleda et al\textsuperscript{27}.
combines 6 variables (both clinical and laboratory) for endemic areas (Table 5); a score higher than 6 has a sensitivity of 86% and specificity of 85% for tuberculous pericarditis diagnosis.

In high-income countries, where tuberculosis prevalence is low, patients with acute pericarditis should initially be stratified into high or low risk based on features of poor prognosis in pericarditis such as fever >38.8°C, subacute onset, large pericardial effusion, cardiac tamponade, and lack of response to anti-inflammatory drugs after at least 1 week of therapy. Those with low risk could be managed as an outpatient with anti-inflammatory drugs; meanwhile, those with high risk should be hospitalized for further studies, and pericarditis caused by tuberculosis, neoplasia, or connective tissue diseases should be ruled out.42,43

ADA is an enzyme required for the conversion of adenosine to inosine. It can be found in any tissue, but the largest concentrations are present in the lymphoid tissue. High ADA activity in tuberculosis appears to be indirectly related to the activated lymphocytic antigenic response. In a systematic review and meta-analysis, ADA testing yielded a sensitivity and specificity of 88% and 83%, respectively, with an area under the receiver operating characteristic curve of 0.9539 compared with mycobacterium cultures; therefore, ADA activity has a significant diagnostic value for pericardial tuberculosis. The unstimulated IFN-γ is a pericardial fluid biomarker of tuberculosis infection. Its utility is based on the fact that T lymphocytes release IFN-γ when are exposed to specific antigens.44 A cut-off of 50 pg/mL results in 92% sensitivity and 100% specificity compared with the criterion standard. Despite its adequate diagnostic performance, the test is not broadly used because of its high cost, especially in LMIC. Polymerase chain reaction is a molecular biology technique that obtains a large number of copies of a particular DNA fragment. The polymerase chain reaction technique has a high specificity for the diagnosis of tuberculosis in pericardial fluid (between 96% and 100%); however, different series have shown a low sensitivity (15%–20%).38,45 When the performance of the 3 tests for the diagnosis of pericardial tuberculosis was compared, IFN-γ had the best accuracy with a sensitivity of 95.7% and specificity of 96.3%, suggesting that IFN-γ is the most useful diagnostic test if it is available.46 Recently, Mutyaba proposed an attractive diagnostic strategy for tuberculosis pericarditis in endemic areas, as follows: (1) exclude alternative deadly causes of an inflammatory exudative effusion (eg, bacterial, malignant, and uremic); (2) obtain biomarkers such as pericardial fluid IFN-γ or ADA; and (3) confirm tuberculosis in other sites (eg, lymph nodes, sputum, or pleural fluid).19 For the diagnosis of constrictive tuberculosis pericarditis, a high clinical suspicion and an integrated approach with different imaging methods such as echocardiography, computed tomography, or cardiac magnetic resonance is required. As mentioned before, transient constrictive pericarditis can occur in 10% of patients with acute tuberculous pericarditis; although diagnosis and clinical follow-up is usually made with an echocardiogram, Chang et al demonstrated in 16 patients with constrictive pericarditis (50% tuberculous pericarditis) that positron emission tomography/computed tomography using 18F-labeled fluorodeoxyglucose is a useful tool to detect early stages of pericardial inflammation and predict which subjects will respond to steroid therapy or reverse constriction.47 Consideration should be given to the fact that direct identification of the microorganism is often not achieved.

If cardiovascular symptoms appear and myocarditis is suspected, an evaluation with transthoracic echocardiogram or cardiac magnetic resonance is preferred. However, a definitive diagnosis requires

### Table 2. Clinical Features of Acute Tuberculous Pericarditis

| Clinical Feature                  | Prevalence (%) |
|----------------------------------|----------------|
| Chest pain                       | 41%            |
| Cough                            | 46%            |
| Dyspnea                          | 44%            |
| Fever                            | 73%            |
| Pericardial rub                   | 39%            |
| Paradoxical pulse                 | 39%            |
| Hepatomegaly                      | 44%            |
| Chest radiography                | 98%            |
| Cardomegaly                      | 98%            |
| Pleural effusion                  | 41%            |
| Parenchymal lung lesion           | 15%            |
| Hilar lymphadenopathy             | 10%            |

Data derived from Gooi and Smith.33

### Table 3. Clinical Signs Observed in 67 Patients With Tuberculous Constrictive Pericarditis

| Physical Sign                    | Prevalence (%) |
|----------------------------------|----------------|
| Sinus tachycardia                | 70%            |
| Pulsus paradoxus                 | 48%            |
| Increased central venous pressure| 100%           |
| Palpable apical impulse          | 58%            |
| Increased cardiac dullness       | 25%            |
| Pericardial knock                | 21%            |
| Muffled heart sounds             | 76%            |
| Sudden inspiratory S2 split      | 36%            |
| Third heart sound                | 45%            |
| Hepatomegaly                     | 100%           |
| Ascites                          | 89%            |
| Peripheral edema                 | 94%            |

Data derived from Strang.8 S2 indicates second heart sound.
the demonstration of caseous granulomatous inflammation with or without tuberculosis bacilli in myocardial tissue.\textsuperscript{18,48} For aortitis, computed tomography is the most widely used imaging technique because it allows the precise localization of the aneurysm and characterizes its size and relation with surrounding structures, as well as helping with surgical planning. A typical granulomatous lesion with caseation from the resected aorta gives a definitive diagnosis of tuberculous aortitis.\textsuperscript{48}

### Treatment

Most of the data on the management of tuberculous pericarditis come from the sub-Saharan African population, where the coexistence of tuberculosis and HIV is frequent. Thus, several studies have been conducted depending on the individual serological status. Tuberculous pericarditis treatment is based on 4-drug conjugated antituberculosis chemotherapy associated with corticosteroids and, in certain situations, drainage, either open or percutaneous. Antituberculosis chemotherapy has shown a significant decrease in mortality, especially in patients with HIV.\textsuperscript{49} This 4-drug regimen includes isoniazid (300 mg daily), rifampicin (600 mg daily), ethambutol (15–25 mg/kg daily), and pyrazinamide (15–30 mg/kg per day). The regimen does not...
differ from pulmonary tuberculosis treatment and should be given initially for 2 months. Then, it should be continued with rifampicin and pyrazinamide for another 6 months regardless of the patient’s immune status. Opposite to high-income countries, in LMIC where tuberculosis is endemic, increasing multidrug-resistant to first-line antituberculosis chemotherapy is worrisome. Multidrug-resistant tuberculosis denotes bacillary resistance to at least isoniazid and rifampicin; meanwhile, extensively drug-resistant adds multidrug-resistant tuberculosis bacillary resistance to any fluoroquinolone and at least 1 of the 3 second-line injectable drugs (namely, kanamycin, amikacin, and capreomycin).50 Table 6 describes the principal antimicrobial agents used in the management of tuberculosis.

In the past decades, the role of corticosteroids has been controversial. Contradictory results from trials demonstrated a decrease in mortality and need for pericardiectomy, while others did not.49,51–53 In 2017 a systematic review and meta-analysis of interventions to treat tuberculosis pericarditis was conducted to help answer this question, which included the results of the IMPI (Investigation of the Management of Pericarditis in Africa) trial.31,54 Corticosteroids were shown to have a positive effect, decreasing the incidence of death from pericarditis, development of constrictive pericarditis, and subsequent hospitalizations. The suggested prednisone dose is 1 mg/kg per day for 4 weeks, then 0.5 mg/kg per day for 4 weeks, 0.25 mg/kg per day for 2 weeks, and finally 0.125 mg/kg per day for 2 weeks. As mentioned above, between 20% and 50% of patients may develop constriction; in those cases, pericardiectomy may be necessary. The precise moment when the procedure should be carried out is still unclear; however, usually, 6 to 8 weeks of antituberculosis treatment should be given before performing the procedure.52

In the case of cardiac tamponade, emergency drainage should be performed. Compared with percutaneous pericardiocentesis, the efficacy of open surgical drainage was assessed in 1 trial that included 122 South African subjects with tuberculous pericardial effusion. Open surgical drainage showed a reduction in the risk of reaccumulation of fluid requiring repeat pericardiocentesis (relative risk, 0.23; 95% CI, 0.07–0.76). However, there was no difference in the measured outcomes such as death or the need for pericardiectomy, and there was possible publication bias. Given the lack of strong evidence favoring open drainage, percutaneous pericardiocentesis is a reasonable and recommended option, especially under echocardiographic guidance.52,54,55 Other interventions, such as immunotherapy with *Mycobacterium indicus pranii*,31 colchicine,56 or intrapericardial fibrinolysis,57 have not shown significant effects on mortality or pericarditis complications.

Because CV complications of tuberculosis are not frequent, there are still insufficient data to guide a specific treatment for myocarditis beyond standard chemotherapy for miliary or pulmonary tuberculosis. In the case of endocarditis, surgical replacement of the damaged valve or removal of the cardiac implantable electronic device should be performed.58,59

The standard of treatment in patients with tuberculous aortic involvement (aneurysm or pseudoaneurysm) is the reconstruction plus implantation of a prosthetic graft or an extra-anatomic bypass in addition to antibiotic treatment.30 Aneurysm size does not influence the need for treatment, and surgery should not be delayed. If aneurysm rupture is evident, the surgical indication is emergent. Open surgery has been

### Table 5. Tuberculous Pericarditis Diagnostic Index

| Variable                  | Score |
|---------------------------|-------|
| Night sweats              | 1     |
| Weight loss               | 1     |
| Fever >38°C               | 2     |
| White blood cell count <10×10⁹ | 3     |
| Serum globulin >40 g/L    | 3     |

A score of 6 or greater suggests tuberculous pericarditis. Data derived from Reuter et al.36

### Table 6. Antituberculosis Drugs: Classification and Dosages Used in Multidrug-Resistant Tuberculosis Treatment

| Group: Description | Components |
|--------------------|------------|
| First-line oral drugs | Isoniazid |
|                    | Rifampicin |
|                    | Ethambutol |
|                    | Pyrazinamide |
| Fluoroquinolones   | Levofloxacin |
|                    | Moxifloxacin |
|                    | Gatifloxacin |
| Injectable agents   | Capreomycin |
|                    | Kanamycin |
|                    | Amikacin |
|                    | Streptomycin |
| Oral bacteriostatic second-line agents | Ethionamide |
| Agents with efficacy that is not totally clear | Linezolid |
|                    | Amoxicillin-clavulanate |
|                    | Clavulanic acid |
|                    | Ceftriaxone |
|                    | Cefotaxime |
|                    | Meropenem-clavulanate |

Data derived from Chang and Yew.50
the standard of care, but the current trend is to use an endovascular approach given its technical facilities. If the patient is unstable with acute bleeding, first-line management is arterial transcatheter embolization.60

Cardiovascular adverse events because of antituberculosis treatment are rare, while hepatotoxicity is frequent and requires continuous monitoring of transaminases, bilirubins, and alkaline phosphatase. Furthermore, individuals with tuberculosis may be prone to develop immune reconstitution inflammatory syndrome. This syndrome is characterized by a paradoxical deterioration of a preexisting infectious process after the start of treatment and usually manifests with pulmonary involvement, but cardiovascular adverse effects have also been described, mainly heart failure.61

**DISCUSSION**

Tuberculosis is a public health problem, particularly in LMICs, and efforts to decrease its incidence have progressed in recent years. Part of these efforts focused on improving knowledge of the disease to obtain an earlier diagnosis and offer timely treatment, especially in extrapulmonary involvement where the clinical manifestations are diverse. Most of the information on tuberculous heart disease management and prognosis comes from sub-Saharan Africa, where a significant effort has been made to improve understanding of the disease, especially with the IMPI registry and trial.15,31 However, the more frequent use of immunosuppressive therapies for chronic diseases increases the risk of tuberculosis worldwide.2

Clinical manifestations of tuberculosis pericarditis are different from those typically found for bacteria or viruses; systemic signs must be sought, and the pericarditis diagnostic index should be taken into account. Once pericardial involvement has been diagnosed, the use of antituberculosis chemotherapy with adjunctive corticosteroids, particularly in individuals with HIV, is essential to substantially improve outcomes such as mortality and the need for pericardiectomy. Furthermore, a high clinical suspicion of tuberculosis should prevail when approaching a patient with signs of endocarditis, myocarditis, or aortitis in endemic areas, and the use of diagnostic tools should be based on the site of involvement.

**CONCLUSIONS**

Cardiac involvement in tuberculosis is frequent and can lead to heart failure, constrictive pericarditis, or death; hence early detection of these complications should be a cornerstone of overall management. Efforts should focus on improving the availability of diagnostic tools with both laboratory tests (such as the ADA or IFN-γ) and imaging (echocardiogram or cardiac magnetic resonance). Combined treatment with antituberculosis chemotherapy and close follow-up to ensure adequate adherence and avoid immune reconstitution inflammatory syndrome are necessary.

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None.

**Supplementary Material**

Appendix S1

Figure S1

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Supplemental Material
Appendix

List of IASC Emerging Leaders - NET-Heart Project members

Macarena Cousirat (Argentina), Cristhian Ramírez (Colombia), Diego Araiza Garaygordobil (México), Carlos Eduardo García (Guatemala), Cristhian Emmanuel Scatularo (Argentina), Oswaldo Andrés Ballesteros (Ecuador), Ana Laura Sauce Pérez (México), Juan Ignacio Cotella (Argentina), Héctor Isaac Ortiz (Guatemala), Juan Farina (Argentina), Shyla Gupta (Canada), Naomi Gazendam (Canada), Luis Gerardo González (México), Cynthia Yeung (Canada), Dennys Franco (México), Lucrecia Burgos (Argentina), Gonzalo Perez (Argentina).
Figure S1. Flow diagram demonstrating search strategy used.

References identified in database searches (n= 764)

Abstracts analyzed to decide eligibility (n= 518)

Total studies included in the qualitative synthesis of the systematic review (n= 51)

- Clinical trials (n= 9)
- Case reports (n= 25)
- Series of cases (n= 5)
- Observational studies (n= 3)
- Systematic reviews (n= 9)

Number of duplicate references removed (n= 246)

Number of abstracts excluded, and reasons for their exclusion (n= 467)

- Non-systematic reviews (n= 41)
- Unrelated publication (n= 420)
- Not available article (n= 6)