Tuberculosis and the Heart

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INTRODUCTION
Recognized since antiquity, tuberculosis (TB) still contributes significantly to the global burden of disease, with an estimated 9.6 million new cases of the disease worldwide in 2014.1 This is especially true in the developing world where human immunodeficiency virus (HIV) infection and AIDS, socioeconomic deprivation, and poor health systems infrastructure interact to make TB a significant public health problem.2 Although it remains primarily a disease of the lungs, the classic lesion of TB—the acid fast Mycobacterium tuberculosis (Mtbb) bacilli in a necrotic core bound by aggregates of various inflammatory cells (granuloma)—can be found in virtually any part of the body (Fig. 1). Autopsy studies performed in the pre-HIV/AIDS era suggest that the heart is involved in approximately 2% of cases of patients who died from TB.3 Similar studies of patients who died of TB and were coinfected with HIV demonstrate multisystemic dissemination in up to 80% of patients.4,5 Of all the extrapulmonary manifestations of TB, involvement of the heart is second only to central nervous system TB in terms of its devastating morbidity and mortality.

It has been almost a decade since there was a comprehensive review of the main form of tuberculous heart disease.6 That review focused on the pathogenesis, diagnosis, and management of tuberculous pericarditis and concluded by noting that there remained major gaps in our understanding of tuberculosis as it affects the heart.
understanding of the subject. The identified gaps included the need for improved diagnostic tools, a better understanding of the impact of HIV, and determination of the effectiveness of adjuvant therapy on clinical outcomes. Since then, much data, predominantly from sub-Saharan Africa, have been generated to address some of these gaps. An updated comprehensive overview of TB and the heart with a summary of the new insights is therefore timely and hopefully of value to the general physician and cardiologist on the front lines of patient care.

The search strategy for this review involved a comprehensive search of MEDLINE, EMBASE and the Cochrane library of systematic reviews with the MeSH terms: “tuberculosis and the heart,” “cardiac tuberculosis,” “cardiovascular tuberculosis,” “myopericarditis and tuberculosis,” “tuberculous pericarditis,” “tuberculous aortitis,” and “HIV and the heart” from January 2005 to December 2015. The reference lists of selected articles were searched for articles deemed to be of relevance to the subject. Appropriate English language studies were retrieved and reviewed.

There have been a number of important advances in our understanding of tuberculous pericarditis over the last decade. Most of the new information has been generated from sub-Saharan Africa and Asia, where TB is endemic, HIV is epidemic, and the majority of patients with TB are also coinfected with HIV. The Investigation of the Management of Pericarditis in Africa (IMPI) registry was a prospective observational cohort of consecutive patients with suspected TB pericarditis across multiple sites in sub-Saharan Africa. Important questions related to the immunopathogenesis, clinical manifestations, diagnosis, and outcomes of TB pericarditis in the HIV era were investigated in the registry.17–18

The IMPI immunotherapy trial was a double-blind, randomised control trial of 1400 patients with definite or probable TB pericarditis who were randomised to receive adjunctive corticosteroids or Mycobacterium indicus pranii versus placebo in a 2 × 2 factorial design.19 These studies, which were conducted between 2004 and 2015, form the backbone of new insights gained since 2005.

There are 3 predominant clinical manifestations of tuberculous heart disease. In descending order of frequency, these include TB pericarditis, myocardial TB with or without aneurysm formation, and TB aortitis with or without mycotic aneurysms and pseudoaneurysms involving the aortic valve and/or sinuses of Valsalva. Important clinical, diagnostic, and management aspects of each are reviewed.

TUBERCULOUS PERICARDITIS

Tubercle bacilli access the pericardium via 3 main mechanisms. These include retrograde lymphatic spread from mediastinal, paratracheal and peribronchial lymph nodes, hematogenous spread (dominant in immunocompromised hosts), and, rarely, direct contiguous spread from adjacent structures such as the lungs, pleura, and spine. In the presence of a competent immune system, tuberculous pericardial disease is usually localized to the pericardial space. It is typically a paucibacillary condition; tubercle proteins trigger a vigorous cell-mediated hypersensitivity response with T-helper cell (subtype 1) predominant cytokine release, leading to an inflammatory exudative effusion and its hemodynamic sequelae. In patients with dysfunctional immunity as occurs in HIV/AIDS, there is evidence that mycobacterial replication is active, bacillary loads are high, and the

**Fig. 1. Mycobacterium tuberculosis.** Tuberculous granuloma (A) showing an aggregation of lymphocytes, monocytes, multinucleate giant cells with a central area of caseous necrosis. Ziehl-Neelsen stain (B) demonstrating acid-fast M tuberculosis (arrow). (Courtesy of Dr Craig Jamieson, formerly of Anatomical Pathology Department, University of Cape Town, Observatory, Cape Town, South Africa.)
clinical manifestations of tuberculous pericarditis are related to the impact of the infectious and virulent nature of the Mtb itself in addition to the hemodynamic sequelae. Tuberculous pericarditis typically presents as 1 of 4 clinical syndromes, namely, acute pericarditis, effusive pericarditis and its complications, myopericarditis, and constrictive pericarditis. Although it is convenient to review them as distinct clinical entities, it is important to understand that there is much overlap in the clinical manifestations.

The triad of severe pericarditic chest pain, a pericardial friction rub, widespread ST-segment and T wave abnormalities and PR segment depression typical of acute pericarditis is an uncommon clinical presentation of tuberculous pericarditis, accounting for only 3% to 8% of patients who present with tuberculous pericarditis. The syndrome is thought to occur soon after inoculation of tubercle bacilli into the pericardium, and is characterized pathologically by polymorphonuclear leukocytosis with abundant bacilli and granuloma formation. The diagnosis of a tuberculous etiology depends on the presence of constitutional symptoms, lack of evidence of conventional bacterial infection, and the demonstration of concurrent TB infection elsewhere in the body; easily accessible pericardial fluid is typically absent in acute pericarditis. The resolution of symptoms with initiation of empiric antituberculous therapy in TB endemic areas is also suggestive. A diagnostic index score that uses 6 clinical and laboratory variables has been developed for use in endemic areas. These variables and their weighted score are outlined in Table 1. A summed score of 6 or more has a sensitivity of 86% and specificity of 85% for the diagnosis of tuberculous pericarditis. Acute tuberculous pericarditis is managed in similar fashion to effusive tuberculous pericarditis as discussed elsewhere in this article.

Effusive pericarditis is the commonest form of pericardial TB in patients with and without HIV. In the developing world, 40% to 70% of large pericardial effusions are tuberculous in origin. This is in contrast with the developed world, where less than 4% of cases are tuberculous. The clinical presentation of this group of patients is determined by the rate of fluid accumulation, magnitude of pericardial fluid-induced cardiac compression, and the severity of the inflammation, edema, and loss of visceral pericardial compliance. Where cardiac compression is significant or rapid, cardiac filling and stroke volume can be compromised significantly. If hemodynamic compensatory mechanisms are adequate, the symptoms are usually those of congestive heart failure without hypotension, and the clinical signs of a large pericardial effusion (Table 2). Where pericardial fluid accumulation is relatively quick and compensatory mechanisms are inadequate, patients present with evidence of hypotension and tachycardia typical of tamponade. A subset of patients may have sizable effusions with little evidence of cardiac compression, such that the constitutional symptoms of active TB predominate and the effusion may be an incidental finding (Videos 1 and 2). Where the visceral pericardium is rendered noncompliant by inflammation and postinfectious injury, patients present with a combination of the compressive hemodynamics of tamponade and the physiology of constrictive pericarditis—a syndrome aptly termed effusive constrictive pericarditis. Invasive hemodynamic studies suggests that effusive constrictive pericarditis is common in patients with TB.
pericarditis occurring in up to 50% of cases.14 The implication of a diagnosis of effusive constrictive pericarditis is not clear, although there are some observational data to suggest that long-term outcomes may be worse.29,30 Chest radiography, an electrocardiogram, and echocardiography remain essential clinical aids in the evaluation and management of patients with suspected effusive TB pericarditis. The characteristic findings are shown in Box 1. Echocardiography is especially important to confirm the presence and determine the size of the effusion and its suitability for safe diagnostic or therapeutic pericardiocentesis.31

The early and accurate diagnosis of a tuberculous etiology of pericardial effusion has remained an important obstacle to optimal patient care. Although empiric therapy in high TB prevalence parts of the world has been advocated by some, it is important to recognize that the price to pay for missing treatable alternative causes is high.32 Traditionally, the definitive diagnosis of tuberculous pericarditis depends on the demonstration of tubercle bacilli in the pericardial fluid or tissue by either direct examination or culture.22,27,33 This approach yields a positive diagnosis in 57% of patients in historical series and in less than 20% of patients in contemporary series.19,27,34 The most recent advance in the diagnosis of TB pericarditis relates to the usefulness of unstimulated gamma interferon (uIFN-γ, a pericardial fluid biomarker of TB infection) and polymerase chain reaction–based methods of identifying Mtb genetic material in pericardial fluid. Pandie and colleagues15 compared the accuracy of the Xpert Mtb/RIF quantitative polymerase chain reaction assay to pericardial fluid adenosine deaminase (ADA) and uIFN-γ measurement in the diagnosis of tuberculous pericarditis. Using a cutoff value of 44 pg/mL, uIFN-γ had a sensitivity and specificity of 95.7% and 96.3%, respectively, for a diagnosis of TB, making it superior to both Xpert Mtb/RIF (sensitivity, 63.8%; specificity, 100%) and ADA at a cutoff value of 35 IU/L (sensitivity, 95.7%; specificity, 84%).18 Despite the superiority of pericardial fluid uIFN-γ over both ADA and Xpert Mtb/RIF as a diagnostic biomarker of tuberculous pericarditis, its widespread use in clinical practice is hindered by its high cost. Given the low yield from fluid culture and the proven usefulness of modern diagnostic biomarkers, the modern diagnostic strategy in patients with suspected TB pericarditis in TB endemic areas should be to (1) exclude alternative deadly causes of an inflammatory exudative effusion (eg, bacterial, malignant, and uremic pericarditis), (2) use biomarkers of TB such as pericardial fluid uIFN-γ and ADA, (3) confirm TB at sites other than the pericardium (eg, sputum, lymph nodes, pleural or ascitic fluid), and (4) have a low threshold to treat for TB where no obvious alternative is apparent and the clinical picture fits.18,31,35

Although the safety and efficacy of a 6-month course of 4-drug antituberculous chemotherapy in the management of effusive tuberculous pericarditis has long been established, the role of adjunctive therapies in improving survival and pericarditis-related outcomes has been unclear until recently.36–38 The results of the adequately powered IMPI Immunotherapy trial have provided the best evidence to date that, although adjunctive steroids decrease the incidence of constrictive pericarditis and subsequent rehospitalization by close to 45%, they do not reduce mortality rates compared with placebo.19 In patients who were infected with HIV, steroids were associated with an increase in incidence of HIV-related malignancies, making firm recommendations about their use in this subset of patients difficult.19 Other adjunctive therapies whose efficacy has been tested include Mycobacterium indicus pranii, which was neutral in the IMPI immunotherapy trial19; intrapericardial corticosteroids, which are neutral19; intrapericardial thrombolysis, which has shown promising results in a small case series40; and routine pericardial evacuation, which is recommended by most authorities.31,41 Given the very close association of tuberculous pericarditis and HIV,2 patients in whom the diagnosis is suspected should undergo HIV testing with the

<table>
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<th>Box 1 Clinical diagnostic aids and characteristic findings in tuberculous effusive pericarditis</th>
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<tr>
<td><strong>Chest radiograph</strong></td>
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<tr>
<td>Cardiomegaly, pulmonary infiltrates, pleural effusion, mediastinal lymphadenopathy</td>
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<tr>
<td><strong>Electrocardiogram</strong></td>
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<tr>
<td>Sinus tachycardia, diffuse ST-segment and T wave changes, QRS microvoltage, QRS alternans, atrial fibrillation</td>
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<tr>
<td><strong>Echocardiogram</strong></td>
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<td>Pericardial effusion (with or without fibrin stranding), pericardial thickening, caval vessel distension with diminished inspiratory collapse, paradox parietal motion, right atrial/ventricular diastolic collapse, exaggerated respiratory transvalvular Doppler flow, expiratory diastolic hepatic vein flow reversal</td>
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<tr>
<td><em>Indicative of cardiac tamponade.</em></td>
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intention of starting combination antiretroviral therapy where HIV coinfection is confirmed. Although direct comparisons are practically impossible to make, it is likely that the large difference in the use of combination antiretroviral therapy in the IMPI immunotherapy trial versus the IMPI registry (>70% vs <10%) had a significant bearing on the large differences in survival in those who were HIV infected in the 2 studies.

The natural history of patients with effusive pericarditis is variable and the clinical course in the individual patient unpredictable. Short-term complications include tamponade; the main longer term complication is fibrotic fusion of the 2 layers of the pericardium and the development of constrictive pericarditis. In the anti-TB therapy only arm of the 1400 patient IMPI Immunotherapy trial where close to 60% of participants underwent pericardiocentesis, approximately 18% of patients were dead at 12 months, 8% progressed to develop constrictive pericarditis, 4% had a reaccumulation of the pericardial effusion with the development of tamponade, and 40% to 60% recovered fully with no long-term clinical sequelae. Data from the IMPI registry suggests that the disease may present more aggressively in patients who are HIV infected as this group of patients tend to have more significant dyspnea (New York Heart Association functional classes III and IV), hemodynamic instability, and more evidence of myocardial involvement compared with their HIV-uninfected age- and sex-matched controls. Finally, data from the IMPI registry suggest that the incidence of constrictive pericarditis may be significantly lower in HIV-infected participants; an explanation for this observation remains to be elucidated.

The diagnosis of posttuberculous constrictive pericarditis requires a combination of a high index of suspicion, meticulous clinical evaluation for what are often subtle signs (Table 3), and integration of data from imaging (echocardiography, computed tomography, MRI; Fig. 2), and, occasionally, invasive hemodynamic evaluation. Once the diagnosis of constrictive pericarditis has been made, establishing a tuberculous etiology is less straightforward (Fig. 3). This is because a significant proportion of patients present for the first time with established constriction and have no prior history of TB. Whether or not a course of anti-TB therapy is required in these patients who do not have evidence of active TB is not known. Where there are recent symptoms or signs of TB or microscopic evaluation of postoperative pericardial tissue reveals active inflammation, an empiric course of anti-TB therapy is reasonable. However, where this evidence of active TB is absent, there is little evidence of any benefit.

The only definitive treatment for tuberculous constrictive pericarditis remains surgical pericardectomy, even though it is associated with a perioperative mortality of between 5% and 14%. In some instances of tuberculous pericarditis, the underlying myocardium can become inflamed and edematous as a complication of the disease process. Evidence for this myopericarditis takes the form of elevated biomarkers of myocardial injury (troponins, creatinine kinase, etc), dynamic electrocardiographic changes consistent with myocardial injury, and evidence of mild impairment of left ventricular systolic function by direct imaging. Where cardiac MRI is available, gadolinium enhancement of both the pericardium and myocardium is characteristic of tuberculous myopericarditis (Fig. 4). The sparse number of case reports in the literature suggests that myopericarditis is a rare complication of tuberculous pericarditis among HIV-negative, immunocompetent patients. However, data from the IMPI registry suggests that, among HIV-infected patients with advanced immunosuppression and CD4 counts of less than 100 cells/μL, TB myopericarditis is much more common.

<table>
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<th>Physical Sign</th>
<th>Prevalence, n (%)</th>
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<tr>
<td>Sinus tachycardia</td>
<td>47 (70)</td>
</tr>
<tr>
<td>Pulsus paradoxus (&gt;12 mm Hg)</td>
<td>32 (48)</td>
</tr>
<tr>
<td>Increased central venous pressure</td>
<td>67 (100)</td>
</tr>
<tr>
<td>Palpable apical impulse</td>
<td>39 (58)</td>
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<tr>
<td>Increased cardiac dullness</td>
<td>17 (25)</td>
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<tr>
<td>Pericardial knock</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Muffled heart sounds</td>
<td>51 (76)</td>
</tr>
<tr>
<td>Sudden inspiratory S2 splitting</td>
<td>24 (36)</td>
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<tr>
<td>Third heart sound</td>
<td>30 (45)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>67 (100)</td>
</tr>
<tr>
<td>Ascites</td>
<td>60 (89)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>63 (94)</td>
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a S2 – Second heart sound.

Tuberculosis myocarditis (a separate entity from myopericarditis) is a very rare manifestation of cardiovascular TB with an occurrence rate of 0.14% in more than 13,000 autopsies performed over 27 years by Rose and colleagues. Myocardial spread of TB is presumed to occur via mechanisms similar to those giving rise to TB pericarditis and aortitis. For reasons that are not clear, there is an apparent predilection to the right heart, particularly the right atrium. Pathologically, it manifests as either nodular tuberculomas with central caseation, miliary tubercles of the heart, or a diffuse infiltrative pattern associated with pericarditis. Case reports suggest that tuberculous

**Fig. 2.** Tuberculous constrictive pericarditis. A 31-year-old woman with right heart failure. Cardiac MR T1-weighted half Fourier acquisition single shot turbo spin echo image (A) showing large right pleural effusion, bilateral pulmonary interstitial changes, and fibrocavitary lesions in the left lung apex and atelectasis of the right lower lobe. (B) Short T1 inversion recovery imaging with a normal myocardial signal intensity ratio, but a markedly thickened pericardium measuring 15 mm. (C) Enhancement after administration of gadolinium contrast. (Courtesy of Dr Ntobeko Ntusi, Division of Cardiology, Groote Schuur Hospital/University of Cape Town, Observatory, Cape Town, South Africa.)

**Fig. 3.** Tuberculous constrictive pericarditis. (A) Postmortem macroscopic appearance showing pericardial thickening and adherence to myocardium. (B) Microscopic appearance of heart in A demonstrating a thickened and fibrotic pericardium with extension of fibrosis into the myocardium. (Courtesy of Dr Craig Jamieson, formerly of Anatomic Pathology Department, University of Cape Town, Observatory, Cape Town, South Africa.)
myocarditis has a high case fatality rate in part because the diagnosis is difficult to make ante mortem.\textsuperscript{50–54}

The clinical presentation of tuberculous myocarditis includes atrial and ventricular tachyarrhythmias, conduction defects, ventricular aneurysms and pseudoaneurysms, dilated cardiomyopathy with heart failure, and sudden cardiac death.\textsuperscript{53,55–57} The diagnosis requires a high index of suspicion, an appropriate imaging modality (echocardiogram, computed tomography scan, or MRI) and demonstration of caseous granulomatous inflammation with or without Mtb bacilli in myocardial tissue obtained at endomyocardial biopsy.\textsuperscript{53} To date, there is little to offer patients beyond the standard 4 drug anti-TB therapy.\textsuperscript{55,56}

**TUBERCULOUS AORTITIS**

Tuberculous infection of the aorta is an exceedingly rare manifestation of TB with an occurrence rate of 0.004% in 22,792 postmortem examinations over 50 years.\textsuperscript{58} Mtb bacilli can access the aortic wall via contiguous extension from an adjacent infective focus (eg, tuberculous mediastinal lymphadenitis), via the vasa vasorum as part of systemic seeding of bacilli and direct implantation of bacilli on preexisting atheromatous plaques.\textsuperscript{59,60} Tuberculous aortitis usually presents with mycotic aneurysms of the aorta with both the thoracic and abdominal aorta affected equally.\textsuperscript{59} Aneurysms may be true or false and within the ascending aorta, can extend to the aortic root and involve the sinus of Valsalva.\textsuperscript{59,61} Rarely, tuberculous aortitis can present as stenotic lesions of the aorta causing acquired aortic coarctation and hypertension.\textsuperscript{62}

The clinical manifestations of tuberculous mycotic aneurysm relate to its mass effect on adjacent organs or the complications of rupture. Common symptoms include chest or back pain, hoarseness, and stridor. Acute aortic regurgitation and cardiac tamponade have also been reported in patients with aneurysms involving the aortic root and sinus of Valsalva.\textsuperscript{59,61} Owing to its exceeding rarity, a high index of suspicion is required to make the diagnosis of tuberculous aortic mycotic aneurysm in patients from TB endemic areas. Where available, computed tomography angiography is a fast and sensitive modality to aid with diagnosis and is useful to delineate the size and nature of aneurysm and its relation to surrounding structures. Demonstration of contrast extravasation indicates aneurysm rupture and is an indication for emergency surgery.\textsuperscript{61} Surgery with in situ reconstruction with prosthetic graft or extraanatomic bypass added

![Fig. 4. A 16-year-old boy with disseminated tuberculosis (TB) with heart failure owing to TB myopericarditis. Cardiac MR steady state free precession images w (A, B) with short axis and horizontal long axis view showing small pericardial effusion; short T1 inversion recovery image (T2-weighted imaging) showing increased myocardial signal intensity ratio, in keeping with myocardial edema (C). Late gadolinium enhancement images showing mid-wall to subepicardial enhancement, in keeping with myocarditis (D–F); the pericardium also enhances. (Courtesy of Dr Ntobeko Ntusi, Division of Cardiology, Groote Schuur Hospital/University of Cape Town, Observatory, Cape Town, South Africa.)](image-url)
to standard 4-drug antituberculous therapy is the current standard of care.\textsuperscript{59} Without either form of treatment, tuberculous aortitis is uniformly fatal.\textsuperscript{58} Confirmation of a tuberculous etiology is usually made on histology of the resected or biopsied aorta showing the typical granulomatous inflammation with caseation with or without demonstration of Mtb bacilli.

**SUMMARY**

TB remains a significant health problem in the developing world. Cardiovascular TB is a potentially devastating presentation of this ancient infection. The last 2 decades have witnessed tremendous progress in our understanding of the disease, including our ability to recognize and diagnose it, and our capacity to alter its natural history and improve survival through the use various therapeutic options. Most patients present with well-recognized, stereotypical clinical syndromes, and where there is timely diagnosis and prompt optimal treatment, survival has improved from a universally fatal condition before the use of 4-drug anti-TB therapy in the past century to greater than 90% in the IMPI immunotherapy trial. Despite this progress, challenges remain. Chief among them is making the evidence based interventions discussed, which should be the standard of care (such as echocardiography, pericardio-centesis kits, ulIFN-\(\gamma\) assays, MRI for complex cases, and surgical pericardiectomy) available and accessible to the poorest and most vulnerable communities where cardiac and other forms of TB are most prevalent.

**SUPPLEMENTARY DATA**

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ccl.2016.08.007.

**REFERENCES**


