Cardiovascular Topics

Experience with adjunctive corticosteroids in managing tuberculous pericarditis

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Summary

***Objectives*: To compare the efficacy of intrapericardial corticosteroid therapy to either oral corticosteroid therapy or intrapericardial placebo in addition to closed pericardiocentesis and anti-tuberculous therapy in patients with tuberculous pericarditis.**

***Methods*: Patients with large pericardial effusions requiring pericardiocentesis were included. A short-course anti-tuberculous regimen was initiated and patients were randomised to one of three treatment groups: 200 mg intrapericardial triamcinolone hexacetonide; oral prednisone plus intrapericardial placebo; or 5 ml intrapericardial 0.9% saline (placebo). Patients were followed up for at least one year.**

***Results*: Fifty-seven patients were included in the study; 21 tested HIV positive (36.8%). Forty (70.0%) had microbiological and/or histological evidence of tuberculosis, and 17 (30.0%) had a diagnosis based on clinical and laboratory data. All patients responded well to initial pericardiocentesis. However, nine patients (16.0%) were lost to follow up. The hospitalisation duration for the steroid groups was shorter than for the placebo group. This difference was not significant. Complications were similar for all arms.**

***Conclusions*: Intrapericardial and systemic corticosteroids were well tolerated but did not improve the clinical outcome. The standard six-month regimen was effective regardless of HIV infection. The potential benefits from adjunctive corticosteroids in the management of effusive tuberculous pericarditis could not be demonstrated in this three-year study.**

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Pericardial disease accounts for about 10% of all patients who are hospitalised for cardiac impairment in developing countries,[1] the most common cause being tuberculosis (TB). Before the introduction of anti-tuberculous drugs and improved anaesthetic and surgical techniques, tuberculous pericarditis was usually fatal. The mortality has since decreased to between 17 and 40%.[2-4]

Tuberculous pericarditis is routinely treated with pericardiocentesis[5] and chemotherapeutic agents (including isoniazid, pyrazinamide, rifampicin and ethambutol).[6] Although national guidelines recommend six months of intensive therapy,[6] some experts recommend longer regimens ranging from nine[7,8] to 12[9] months. Uncertainty exists as to whether the treatment duration should be altered in human immunodeficiency virus (HIV)-positive individuals. Higher rates of side effects from standard treatment regimens and higher relapse rates have been described in these patients,[10] although this finding has not been consistent.[11]

The use of adjunctive corticosteroid therapy, together with anti-tuberculous drugs remains topical in the treatment of tuberculous pericarditis. Rapid improvement of symptoms and reduced mortality have been suggested following the use of oral adjunctive corticosteroids.[2-4,12-14] However, their use in HIV-positive individuals may increase the risk of bacterial and viral infections.[15,16]

Maisch *et al*.[17] demonstrated that side effects of systemic corticosteroid therapy could be avoided by treating autoreactive pericardial effusion with intrapericardial installation of 200 mg (5 ml) of the relatively nonresorbable corticosteroid steroid triamcinolone hexacetonide. Using a similar approach, Quigg[18] successfully treated patients with uraemic pericardial effusions by pericardiocentesis with an indwelling catheter followed by a stat instillation of triamcinolone hexacetonide into the pericardial space.

Given the potential benefits of adjunctive corticosteroids and the possibility of achieving these benefits without the risk of the systemic effects of an 11-week course of high-dose oral corticosteroids, we decided to test the effects of intrapericardial triamcinolone in patients with tuberculous pericardial effusion who had been on antituberculous therapy for at least 48 hours and the daily aspirate was less than 100 ml. The triamcinolone (5 ml) was installed prior to removal of the indwelling pericardial catheter.

Objectives

The objectives of this study were: (1) to assess the role of adjunctive corticosteroid therapy with regard to mortality and the prevention of constrictive pericarditis; (2) to compare the administration of conventional oral corticosteroid therapy with intrapericardial triamcinolone hexacetonide; and (3) to assess the impact of HIV co-infection on the clinical course of patients with tuberculous pericardial effusions, as well as the effects of therapy in these patients.

Methods

Patients presenting to the Cardiology Unit of Tygerberg Academic Hospital, Western Cape with large tuberculous pericardial effusions requiring diagnostic and/or therapeutic pericardiocentesis from February 1997 to June 2000 were screened for possible enrolment into this study. The study was approved by the ethics committee of Stellenbosch University and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent and received counselling for HIV antibody testing. Baseline demographic, clinical, echocardiographic and electrocardiographic data were also obtained.

Patient selection and management

All patients met the following inclusion criteria: (1) age 13 to 75 years; (2) large pericardial effusion on echocardiography (epi-pericardial distance > 10 mm); (3) pericardial aspirate with protein content > 30 g/l; (4) pericardial fluid adenosine deaminase (ADA) activity > 35 U/l. Patients with CD4 counts < 200 cells/µl were excluded due to uncertainty as to the effects of corticosteroids on immuno-compromised patients with TB with regard to risk for disseminated disease. In addition, patients presenting with signs of constrictive pericarditis or requiring pericardial surgery within the first five days of admission were excluded.

The pericardial effusion was drained by echocardiographically guided aspiration via an indwelling pigtail catheter;[19,20] the intention of this procedure was complete pericardial drainage. Chest radiography (CXR) was performed thereafter to exclude a pneumothorax and to evaluate the lung fields. The patient was then admitted into a general medical ward. The catheter was kept *in situ* to allow daily intermittent drainage and was removed when the daily aspirate was < 100 ml, when it became blocked, or when there was evidence of localised skin infection. During hospitalisation, patients were examined twice daily for fever, change in haemodynamic status, and clinical evidence of localised skin and/or pericardial infection.

A standard short-course anti-tuberculous regimen was initiated according to national guidelines, namely a combination of rifampicin, isoniazid, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid for a further four months.[6] Patients were then randomly assigned as per a predetermined randomisation schedule for 100 patients on a 3:3:4 basis. Numbers were drawn from a hat, stored on a list on a computer and provided to the treating physician with the assigned treatment by a non-clinical administrator. The randomisation code remained concealed and was not revealed to the investigators or the study subjects until completion of the study. The unblinded, independent physician administered one of the following randomly assigned treatment options:

- Triamcinolone: 200 mg (5 ml) intrapericardial triamcinolone hexacetonide ($n = 17$).
- Prednisone: oral prednisone plus intrapericardial placebo (5 ml 0.9% saline solution; $n = 16$). Oral prednisone was started at 60 mg/day for four weeks, followed by 30 mg/day for four weeks, 15 mg/day for two weeks and 5 mg/day for one week.
- Placebo: 5 ml intrapericardial 0.9% saline ($n = 24$).

Triamcinolone was injected directly into the pericardium just prior to the removal of the indwelling catheter. Due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone.

Patients were discharged on anti-tuberculous therapy and pyridoxine, with or without adjunctive prednisone. HIV-positive patients also received daily oral cotrimoxazole; due to the prevailing national policy at the time of this study, none of these patients received antiretroviral therapy.

Laboratory investigations

Pericardial fluid was analysed for biochemistry,[21] ADA activity,[22] cytology, differential leukocyte count, and microbiology (Gram and auramine staining followed by microscopy and TB culture). Two morning samples of expectorated sputum were collected for direct microscopy and TB culture. *Mycobacterium tuberculosis* isolates were tested for susceptibility to isoniazid and/or rifampicin. Blood was analysed for haematology (full-blood cell count and differential leukocyte count), biochemistry (urea, creatinine, liver function tests and thyroid function tests), and serology [C-reactive protein (CRP), rheumatoid factor, antinuclear factor and antistreptolysin-O titre (ASOT)]. All patients were tested for HIV. CD4 lymphocyte counts were requested in all HIV-positive patients.

Follow-up assessment

Patients were assessed one month after discharge and thereafter at three-monthly intervals for a minimum of one year. At follow-up visits, patients were assessed clinically for features of ongoing TB, immunodeficiency, pericardial disease (effusion, tamponade and constriction), side effects of medication (anti-tuberculous drugs and prednisone), general sense of wellbeing, and functional capacity. Therapeutic response was assessed as: (1) absence, improvement, or worsening of exercise tolerance, dyspnoea, cough, ankle swelling, abdominal discomfort, chest pain, fever, night sweats, and/or weight loss; (2) absence, improvement, or worsening of oedema, ascites, hepatomegaly, pleural effusion, raised jugular venous pressure (JVP), tachycardia, hypotension, pulsus paradoxus, Kussmaul's sign, pericardial rub, and/or pericardial knock; (3) evidence of infection at the puncture site and/or the pericardial space; and (4) echocardiographic

evidence of persisting or re-accumulated pericardial fluid or pericardial constriction and the subsequent need for pericardiectomy. Echocardiography was performed at baseline, at the first follow-up, and thereafter as clinically indicated.

Outcome measures

The primary endpoint was all-cause mortality. Secondary endpoints included: (1) death attributed to pericarditis; (2) disability related to pericardial disease at one-year follow-up visit, where disability was defined as a history of restricted physical activity [using New York Heart Association (NYHA) functional class]; (3) development of effusive constriction; and (4) development of fibrous constrictive pericarditis requiring pericardiectomy. The diagnosis of constrictive pericarditis was made on the basis of a combination of clinical[23] and echocardiographic features.[24] These included abrupt posterior motion of the interventricular septum in early diastole, abrupt posterior motion during atrial systole, reduced amplitude of left ventricular posterior wall motion, premature pulmonary valve opening, dilatation of the hepatic veins and inferior vena cava, and characteristic Doppler patterns of transvalvular and central venous flow velocities during respiration.[25] Patients did not undergo routine cardiac catheterisation to establish evidence of constriction.

TABLE I. DEMOGRAPHIC AND CLINICAL DATA OF STUDY POPULATION

Demographic data	*Prednisone* (n = *16*)	*Triamcinolone* (n = *17*)	*Placebo* (n = *24*)
Females	7	4	12
Males	9	13	12
HIV-seropositive patients	9	6	6
Mean age (SD) in years	34.4 (9.86)	38.6 (10.16)	33.3 (15.86)
Range of age (in years)	17–58	22–66	17–66
Symptoms			
Fever (%)	13 (81)	12 (71)	18 (75)
Night sweats (%)	7 (44)	7 (41)	10 (42)
Weight loss (%)	13 (81)	13 (76)	19 (79)
Anorexia (%)	12 (75)	12 (71)	19 (79)
Dyspnoea (%)	15 (94)	16 (94)	22 (92)
Chest pain (%)	6 (38)	4 (24)	7 (29)
Cough (%)	14 (88)	15 (88)	20 (83)
Physical signs			
Lymphadenopathy (%)	5 (31)	4 (24)	7 (29)
Soft cardiac sounds (%)	13 (81)	14 (82)	20 (83)
Hepatomegaly (%)	10 (63)	11 (65)	16 (67)
Peripheral oedema (%)	6 (38)	6 (35)	11 (46)
Ascites (%)	2 (13)	2 (12)	3 (13)
Tachycardia (%)	13 (81)	13 (76)	20 (83)
Pulsus paradoxus (%)	3 (19)	5 (29)	7 (29)
Kussmaul's sign (%)	2 (13)	2 (12)	3 (13)
Jugular venous pressure > 4 cm (%)	13 (81)	15 (88)	20 (83)
Systolic BP < 100 mmHg (%)	1 (6)	1 (6)	1 (4)

SD = standard deviation; BP = blood pressure; HIV = human immunodeficiency virus.

Statistical analysis

Interval (continuous) variables are expressed as mean (standard deviation, SD). Statistical analysis of continuous variables was done with the Mann-Whitney *U*-test. Non-parametric data were expressed as median (range). Statistical analysis of these variables was done with the Kruskall-Wallis one-way ANOVA tests and chi-square testing to establish statistical significance. A p-value < 0.05 was considered statistically significant. Bonferroni (all pair-wise) multiple comparison and the Kruskall-Wallis multiple-comparison z-value tests were used to establish statistically significant differences between groups. For the Kruskall-Wallis test, medians were regarded as being significantly different if the z-value exceeded 1.960; for the Bonferroni test, medians were considered significantly different if z-values were > 2.394. All statistical analyses were done using Statistica version 6.0.

Results

A total of 134 patients were admitted to Tygerberg Academic Hospital with large pericardial effusions requiring pericardiocentesis between February 1997 and June 2000. Ninety-five individuals (70.9%) were diagnosed with pericardial TB, including 47 who tested HIV positive (49.5%). Based on pre-determined eligibility criteria, 57 patients (60.0%) were enrolled in the study. The age of study subjects ranged from 17 to 66 years, and included 23 females and 34 males. Demographic and clinical data are summarised in Table I. Reasons for patient ineligibility and the clinical outcomes of these patients are shown in Table II. The mean (SD) follow-up period was 14.2 (2.3) months. Each patient received the randomly assigned treatment and results were evaluated on an intent-to-treat basis.

Forty of the 57 patients (70.0%) had microbiological and/or histological evidence of TB, the remaining 17 patients (30.0%) were diagnosed by clinical and supportive laboratory data. Twenty-one of these patients (37.0%) were HIV positive. Baseline demographic, radiographic, electrocardio-

TABLE II. SUMMARY OF INELIGIBLE PATIENTS PRESENTING WITH TUBERCULOUS PERICARDITIS (*n* = 38)

Exclusion criteria	*Number of patients* (n = *38*)	*Baseline constriction* (n = *6*)	*Deaths* (n = *16*)
CD4 cell count < 200 cells/µl	21	3	4
Lymphocyte count < 0.8×10^9/l	4	0	3
Disseminated TB/ lymphocyte count < 0.8×10^9/l	1	0	1
Early death/lymphocyte count < 0.8×10^9/l	1	0	1
Early pericardial surgery	5	2	1
Blocked drainage tube	1	0	1
Left ejection fraction < 35%	2	1	2
Severe lung disease	3	0	3

TABLE III. COMPLICATIONS AND OBSERVATIONS OF TRIAL PATIENTS AT FOLLOW UP (*n* = 57)

	Prednisone (n = *16)*	*Triamcinolone* (n = *17)*	*Placebo* (n = *24)*
Complications in hospital			
Local pain	3	3	4
Repeat pericardiocentesis	1	0	1
Leakage at skin insertion	1	1	2
Local skin infection	0	1	1
Duration of hospitalisation			
Mean (SD) days	9.9 (5.1)	10.5 (4.4)	11.2 (5.3)
Range in days	4–21	4–19	4–30
Complications as out-patient			
Herpes labialis	1	0	1
Varicella zoster	1	1	0
Local skin infection	1	1	0
Effusive constriction	1	1	0
Fibrous constriction	1	0	0
Left ventricular aneurysm	0	1	0
Surgical intervention			
Pericardial fenestration	1	0	0
Total pericardiectomy	1	0	0
Status at 1-year follow-up			
Reduced level of activity	2	2	3
Raised JVP	1	1	2
Hepatomegaly	0	1	0
Failure to attend follow-up visit	4	1	4

JVP = jugular venous pressure.

graphic and echocardiographic findings were similar between the three treatment groups, as were baseline diagnostic and other laboratory findings (including ADA results).

Clinical endpoints and complications

Complications and observations of study patients at follow-up are presented in Table III. All patients had a good clinical response to initial pericardiocentesis. The duration of hospitalisation ranged from four to 30 days; although the hospitalisation duration was slightly shorter in the two steroid groups compared to the placebo group, the difference was not statistically significant.

There were no significant differences in the number of patients in each group that experienced minor complications such as localised pain, leakage at wound site, and local skin infection. Two patients developed transient jaundice but still completed six months of anti-tuberculous therapy. Thirteen cases of infection were recorded during the follow-up period, including oral candidiasis (n = 5), local skin infection (n = 4), *Herpes labialis* (n = 2), and *Varicella zoster* (n = 2). Although these events occurred more frequently in the combined corticosteroid group (n = 9; 27.2%) than in the placebo arm (n = 4; 16.7%), the difference was not statistically significant (p = 0.07).

Two male patients (both HIV negative) developed effusive-constrictive pericarditis, which was diagnosed clinically and confirmed echocardiographically at the first follow up. Both patients were over 40 years of age with a positive smoking history; in addition, they both had evidence of pulmonary infiltrates on CXR and had been investigated for pulmonary TB in the month preceding pericardial aspiration, suggesting the possibility of a more chronic form of pericardial TB. One patient (prednisone group) underwent surgical pericardial fenestration at six weeks, followed by total pericardiectomy at four months, and was entirely well at his one-year follow up. The other patient (triamcinolone group) had relatively mild features and refused surgery. He was managed conservatively, and the features of constriction improved progressively and had subsided by the one-year follow up. Echocardiography demonstrated pericardial thickening, which was still present at the two-year follow up, but not accompanied by features of constriction.

Seven patients (12.0%) complained of reduced levels of activity at their one-year follow up. Three of these patients (42.9%, all HIV positive) had no cardiac abnormalities, and tests for disseminated TB and other opportunistic infections were negative. The other four patients (57.1%, of which one was HIV positive) were found to have an increased JVP. Echocardiography confirmed cardiac abnormalities: two had pericardial thickening but no definitive evidence of constriction; the other two had left ventricular impairment with mild to moderate mitral and tricuspid regurgitation.

The distribution of complications was similar between the three treatment arms (Table III). No deaths were recorded for the study population, but nine patients (16.0%) failed to attend their follow-up appointments at six and 12 months. None of these patients were admitted to Tygerberg Academic Hospital or any other public hospitals in the region for a period of two years after enrolment and all efforts to trace them failed. In addition, their names did not appear on the national death registry. The age distribution of these 'non-attendees' ranged from 17 to 58 years. Four of the nine patients were HIV positive with baseline CD4 counts of 392, 214, 256 and 243 cells/µl, respectively.

An analysis of the outcomes of the 38 TB patients who were excluded from the study is presented in Table II. All of these patients were treated by closed pericardiocentesis and concurrent early initiation of anti-tuberculous therapy. Patients with effusive constrictive pericarditis were treated by pericardial fenestration and adjunctive oral prednisone based on published recommendations.[13,14]

Discussion

The present study suggests that echocardiographically guided closed pericardiocentesis with intermittent daily aspiration in combination with early initiation of directly observed antituberculous therapy results in excellent outcomes in patients with effusive pericardial TB, irrespective of HIV status. Only two cases of effusive constrictive pericarditis developed during the first six months after enrolment. Both patients did well; one required total pericardiectomy due to symptomatic constriction, whereas the other improved without surgical intervention. The study was underpowered to detect significant effects of adjunctive corticosteroids and a multi-centred study or a meta-analysis of similar studies would be required

to assess larger numbers of patients in order to evaluate the potential benefit of adjunctive corticosteroids.

The study also demonstrated that secondary skin infection occurs rarely when an aseptic technique is applied and no differences in the frequency of skin sepsis were noted between the various treatment groups. The incidence of systemic infections or HIV-associated complications, such as opportunistic infections or malignancies was also similar in the three treatment categories. The use of adjunctive corticosteroids led to shortened hospitalisation with a mean (SD) duration of days in hospital for the prednisone, triamcinolone and placebo groups of 9.9 (5.1), 10.5 (4.4) and 11.2 (5.3), respectively. Differences between the two adjunctive corticosteroid and the placebo groups were statistically insignificant.

The results of this study support the use of routine antituberculous therapy for six months in both HIV-positive and -negative patients. There were no associated cases of multi-drug resistance, reactivation, or dissemination of TB. HIV-infected patients had very similar outcomes to those who were HIV negative and based on our results, there is no reason to support prolonged treatment duration in individuals who have CD4 counts > 200 cells/µl.

There are a number of published reports of small series of patients demonstrating the beneficial effect of prednisone in patients with tuberculous pericarditis.[13,14,26,27] Contrary to these reports, the use of adjunctive steroids did not result in improved clinical outcome in this series of patients with effusive tuberculous pericarditis. Effusive-constrictive pericarditis was an exclusion criterion in the present study, whereas other studies have described features suggestive of established or threatening effusive-constrictive pericarditis.[13,14] In the former Transkei, effusive constriction was considered to be a more common clinical variety than pericardial effusion or classical fibrous constrictive pericarditis.[28]

It is therefore necessary to recognise that different interventions may be required for specific clinical phases of the same disease. In an observational study, patients who had only 80 to 100 ml of fluid aspirated before treatment with high doses of oral prednisolone (including four weeks of 120 mg daily), and where standard TB therapy was initiated, had rapid resolution of their effusions.[29] A potential place for adjunctive corticosteroids may therefore possibly be for those patients who present relatively late and have features of effusive-constrictive disease at presentation,[13,14] or those in whom pericardiocentesis is unsuccessful.[30] It has also been suggested that corticosteroids be reserved for critically ill patients with recurrent large effusions who do not respond to pericardial drainage and anti-tuberculous drugs alone. In view of the results of our series of patients, no benefit was observed by using intrapericardial triamcinolone.

The present study also suggests that the mortality of HIV-infected individuals (CD4 counts > 200 cells/µl) does not differ significantly from those who are HIV negative. This contradicts earlier reports suggesting a significantly higher mortality in HIV-infected individuals.[31] In the present study, adjunctive steroids resulted in a tendency towards a higher number of minor infections; however, none of the patients developed oesophageal candidiasis, cryptococcal meningitis, or other more serious opportunistic infections, malignancies, septicaemia or pneumonia.

Other researchers have found potentially harmful side effects related to the use of steroids in HIV-infected individuals, including a higher incidence of bacterial infections, *Herpes simplex* and *Herpes zoster* reactivation, and potentially the development of Kaposi's sarcoma.[15,16,32] In a non-randomised study of TB in HIV-positive patients, Elliott and colleagues[16] reported increased risk for *Herpes zoster* and Kaposi's sarcoma in patients treated with prednisone, but in the study of Hakim and colleagues,[33] Kaposi's sarcoma occurred only in patients who were not on steroids.

None of the HIV patients in the present study developed constriction and it has been postulated that the rate of constriction is reduced by HIV infection.[33] Hakim and colleagues[33] observed a trend towards improved survival but no reduction in the occurrence of constriction in the adjunctive steroid group. In keeping with our results, an updated version of the *Cochrane Systematic Review* (which includes Hakim's study) revealed that the results of all published studies are still inconclusive and that there is uncertainty regarding the effectiveness of steroids in patients with tuberculous pericarditis.[34]

Our study has a number of weaknesses; most notably the fact that 16.0% of patients did not attend their six-month and/or one-year follow-up visits and that data on mortality and constriction may therefore be incomplete. The poor follow-up rate probably reflects the impact of migratory lifestyles on healthcare in poorer socio-economic regions of South Africa. It could also be argued that an oral placebo should have been used in combination with the intrapericardial placebo.

At the time of planning the study, the role of corticosteroids in HIV-infected patients was unclear and it was decided to expose only those with CD4 counts > 200 cells/µl. Twenty-one potential patients were not enrolled due to this reason. An analysis of these patients confirmed an increased rate of morbidity and mortality due to non-cardiac complications. There was a dramatically increased mortality in patients who had been excluded from the trial on the basis of low CD4 and/or total lymphocyte counts. Retrospectively, it could be argued that these patients should have been included in the study.

Conclusion

Intrapericardial and systemic corticosteroids were well tolerated, but did not improve the outcome in these selected patients. The standard six-month treatment regimen was effective regardless of HIV infection. This single-centre study was underpowered to detect significant effects of adjunctive corticosteroids. Further placebo-controlled trials are warranted but should be conducted at several centres using the same protocol, as single-centre studies are unlikely to answer these questions. Patients with effusive constrictive disease should be included, as well as those with CD4 counts < 200 cells/µl. At present, there is no conclusive evidence for the routine use of adjunctive corticosteroids, which should

be reserved for critically ill patients with recurrent large effusions who do not respond to pericardial drainage and anti-tuberculous drugs alone.[30]

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References

1. Maharaj B. Causes of congestive heart failure in black patients at King Edward VIII Hospital, Durban. *Cardiovasc J S Afr* 1991; **2**: 31–32.
2. Rooney JJ, Crocco JA, Lyons HA. Tuberculous pericarditis. *Ann Intern Med* 1970; **72**: 73–78.
3. Desai HN. Tuberculous pericarditis: A review of 100 cases. *S Afr Med J* 1979; **55**: 877–880.
4. Bhan GL. Tuberculous pericarditis. *J Infect* 1980; **2**: 360–364.
5. Harvey AM, Whitehill MR. Tuberculous pericarditis. *Medicine* 1937; **16**: 45–94.
6. South African Department of Health. Practical guidelines for the diagnosis and treatment of tuberculosis in South Africa. 1996.
7. Sagrista-Sauleda J, Permanya-Miralda G, Soler-Soler J. Tuberculous pericarditis; Ten year experience with a prospective protocol for diagnosis and treatment. *J Am Coll Cardiol* 1988; **11**: 724–728.
8. Fowler NO. Tuberculous pericarditis. *J Am Med Assoc* 1991; **266**: 99–103.
9. Koh KK, Kim EJ, Cho CH, *et al*. Adenosine deaminase and carcinoembryonic antigen in pericardial effusion diagnosis, especially in suspected tuberculous pericarditis. *Circulation* 1994; **89**: 2728–2735.
10. Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries. *Lancet* 1990; **335**: 387–390.
11. De Cock KM, Soro B, Coulibaly IM, *et al*. Tuberculosis and HIV infection in sub-Saharan Africa. *J Am Med Assoc* 1992; **268**: 1581–1587.
12. Spodick DH. Tuberculous pericarditis. *Br Med J* 1994; **308**: 61.
13. Strang JIG, Gibson DG, Nunn AJ, *et al*. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987; **2**: 1418–1422.
14. Strang JIG, Gibson DG, Mitchison DA, *et al*. Controlled clinical trial of complete open surgical drainage and of presnisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988; **ii**: 759–764.
15. Gill PS, Loureiro C, Bernstein-Singer M, *et al*. Clinical effects of glucocorticoids on Kaposi's sarcoma related to the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989; **110**: 937–940.
16. Elliott AM, Halwiindi B, Bagshawe A, *et al*. Use of prednisolone in the treatment of HIV positive tuberculosis patients. *Q J Med* 1992; **85**: 855–860.
17. Maisch B, Risti AD, Pankuweit S. Intrapericardial treatment of autoreactive pericardial effusion with triamcinolone: the way to avoid side effects of systemic corticosteroid therapy. *Eur Heart J* 2002; **23**: 1503–1508.
18. Quigg RJ, Idelson BA, Yoburn DC, *et al*. Local steroids in dialysis-associated pericardial effusion. *Arch Intern Med* 1985; **145**: 2249–2252.
19. Louw VJ, Reuter H, Smedema JP, Katjitae I, Burgess LJ, Doubell AF. Clinical experience with echocardiographically guided pericardiocenthesis and extended drainage in a population with a high prevalence of HIV infection. *Neth Heart J* 2002; **10**: 399–406.
20. Reuter H, Doubell AF. The management of tuberculous pericardial effusions. *Cardiol Forum* 2002; **2**: 50–59.
21. Burgess LJ, Reuter H, Carstens ME, Taljaard F, Doubell AF. The use of adenosine deaminase and interferon-γ as diagnostic tools for tuberculous pericarditis. *Chest* 2002; **122**: 900–905.
22. Burgess LJ, Reuter H, Taljaard F, Doubell AF. Role of biochemical tests in the diagnosis of large pericardial effusions. *Chest* 2002; **121**: 495–499.
23. Strang JIG. Tuberculous pericarditis in Transkei. *Clin Cardiol* 1984; **7**: 667–670.
24. Feigenbaum H. Pericardial disease. In: Feigenbaum H, ed. *Echocardiography*. Philadelphia: Lea and Febiger, 1986: 548–578.
25. Oh JK, Hatle LK, Seward JB, *et al*. Diagnostic role of Doppler echocardiography in constrictive pericarditis. *J Am Coll Cardiol* 1994; **23**: 154
26. Alzeer AH, Fitxgerald JM. Corticosteroids and tuberculosis: risks and use as adjuvant therapy. *Tubercle Lung Dis* 1993; **74**: 6–11.
27. Senderovitz T, Viskum K. Corticosteroids and tuberculosis. *Respir Med* 1994; **88**: 561–565.
28. Commerford PJ, Strang JIG. Tuberculous pericarditis. In: Coovadia HM, Benatar SR, eds. *A Century of Tuberculosis: South African Perspectives*. Cape Town: Oxford University, 1991: 123–136.
29. Strang JIG. Rapid resolution of tuberculous pericardial effusion with high dose prednisolone and antituberculous drugs. *J Inf* 1994; **28**: 251–254.
30. Lorell BH. Pericardial diseases. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia: WB Saunders, 1997: 1478–1534.
31. Pozniak AL, Weinberh J, Mahari M, *et al*. Tuberculous pericardial effusion associated with HIV infection: a sign of disseminated disease. *Tubercle Lung Dis* 1994; 75: 297–300.
32. Schulhafer EP, Grossman ME, Fagin G, *et al*. Steroid induced Kaposi's sarcoma in a patient with pre-AIDS. *Am J Med* 1987; **82**: 313–317.
33. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000; **84**: 183–188.
34. Mayosi BM, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. *Cochrane Review*. The Cochrane Library. Oxford: Update Software, 2002.