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A Review of Takayasu's Arteritis in Children, in Gauteng

Deirdré Hahn

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Paediatrics.

Johannesburg 1999

DECLARATION

I, Deirdré Hahn declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this University.

18 Day of June, 1999

Deirdré Hahn

DEDICATION

To my parents Emil and Retha Hahn, and my husband
Dr.Bill Monday; for their ongoing
encouragement and support.

PUBLICATIONS AND PRESENTATIONS

A review of Takayasu's arteritis in children in Gauteng, South Africa

Deirdré Hahn, Peter D. Thomson, Udai Kala, Peter G. Beale and
Solomon E. Levin
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ABSTRACT

We have reviewed 31 patients with Takayasu's arteritis followed at two paediatric nephrology units in Gauteng, South Africa over a 15 year period. There were 25 black patients, 4 white patients and 2 patients of mixed race. The mean age at diagnosis was 8.42 ± 3.59 (range 2.4 – 14.5, median 8) years.

The most common presenting sign was hypertension, followed by cardiac failure, bruits and absent pulses. The Mantoux test was strongly positive in 27 patients (90%, control population 5%). Markers of activity included a raised erythrocyte sedimentation rate (23 patients) or Gallium single photon emission tomography (positive in 12 of 16 patients). Angiography revealed type II (abdominal aorta) and III (arch plus abdominal aorta) lesions to be most common (11 in each group). All patients received antituberculous therapy and most low-dose aspirin for it's anti-thromboxane effect. Corticosteroids and further immunosuppression were used to control disease activity. We added total lymphoid irradiation (TLI) or cyclophosphamide. Twenty-six patients in all received further immunosuppression, with 13 patients in each group. Results were similar in the two groups, with similar pre- and post-therapy systolic blood pressures and creatinine clearances. Two patients in each group relapsed, 4 died in the TLI group and 2 in the cyclophosphamide group. Surgical intervention, usually in the quiescent phase, consisted mainly of renal autotransplantation. Because of the problems with TLI and 2 patients with papillary carcinoma of the thyroid with long-term follow-up, we no longer use TLI. We have shown that with active medical and surgical intervention the aggressive course of this disease in children can be modified.

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INTRODUCTION

Takayasu's arteritis is a chronic vasculitis involving the aorta, its proximal branches and the pulmonary arteries. This inflammatory condition results in stenosing, occlusive and aneurysmal lesions of the involved vessels.(1) Initial simultaneous investigation and clinical documentation of this disease in different countries resulted in the confusing terminology, including aortic arch syndrome, occlusive thrombo-aortopathy and non-specific aorto-arteritis. The condition was probably first documented by Savory in 1856, but our current concepts stem from Takayasu's description in 1908. He stressed the unusual ocular findings in a young woman who had associated absent pulses of the upper limbs.(2) Shimuzu and Sano in 1951 described it as 'pulseless disease' after detailing the clinical and pathological findings.(3) The term, Takayasu's disease was coined by Caccamise and Whitman, who thought they were describing the first case outside Japan. (4) Until the 1960's, it was still believed that these were different disease entities, but a unifying theme of all reported cases was that the histological examination proved to be nearly identical. A Research Committee was appointed by the Japanese Ministry of Health and Welfare and the disease was subsequently called Takayasu's arteritis.(5)

The disease is widely prevalent in Asian countries and Central America, but a worldwide distribution is documented. (6, 7) Initial South African documentation was by Isaacson et al in 1959, with successive reports by Isaacson and Schnier in 1961 and Schrire and Asherson in 1964. (8, 9, 10) Takayasu's arteritis has a predilection for young women with peak ages between 10 to 25 years, but it may occur from early childhood to late adulthood. (11)

The aetiology and predisposing factors of Takayasu's arteritis are as yet an enigma although infections such as tuberculosis, genetic factors and an auto-immune component have been invoked. (12, 13, 14, 15)

The clinical presentation, with distinct geographical variation is widely heterogeneous and involves classically two phases. An initial inflammatory process or 'pre-pulseless phase' with variable constitutional features; followed by a later 'pulseless phase' with multiple arterial occlusions producing symptoms of cerebral, visceral or extremity ischemia. (16, 17, 18)

The natural history and adequate therapy in Takayasu's arteritis is uncertain. Widely varying mortality rates are documented; with some recording death within 2 to 5 year. of diagnosis, though some have recorded a 5 year survival rate of 83%. Morbidity and mortality obviously depend on disease severity and therapeutic strategies. Factors related to increased mortality include hypertension, Takayasu's retinopathy, arterial aneurysm and aortic incompetence. (19, 20, 21)

Management of the disease is multifaceted and includes medical and surgical intervention. Medical therapy consists essentially of controlling the inflammatory process with immunosuppressives including corticosteroids and cytotoxics such as cyclophosphamide. (22 - 26) We used Total Lymphoid Irradiation (TLI) as an alternative immunosuppressive, but had not yet compared it to cyclophosphamide. (27) Surgical intervention to improve organ perfusion subsequent to vascular damage is often required. (28)

The diagnosis and optimal management of children with Takayasu's arteritis remains an ongoing challenge. During this review I hope to outline our thoughts regarding the aetiopathogenesis of the disease and to highlight specifically our experience related to the treatment and its potential complications.

PATIENTS AND METHODS

The protocol to this research report was reviewed by the Ethics Committee. The following Ethics Clearance number was issued: M 05/06/97.

Patients identified included those referred to and followed up at the Paediatric Nephrology units of Johannesburg General and Chris Hani Baragwanath Hospitals in whom Takayasu's arteritis was diagnosed. Data from the two units was analysed together as coming from one unit. All the patients involved were fully evaluated including age, clinical examination, laboratory investigations and transfemoral angiography.

Serological testing to exclude other collagen vascular disorders included syphilis, anti-double stranded DNA antibody, antinuclear factor, rheumatoid factor and antineutrophil cytoplasmic antibody.

Additional investigations consisted of Mantoux tests (5u of intradermal purified protein derivative) which were done on all. Investigations assessing disease activity included ESR (erythrocyte sedimentation rate); CRP (c-reactive protein) and often a Gallium spect scan.(27) Serial serum creatinines to measure renal function, and DMSA scan to assess differential function were done, where appropriate.

The extent and anatomical level of vascular involvement as ascertained from angiographic findings was defined according to accepted classification. (29) Some patients were also assessed by CT scanning or MRI. Where possible, specimens were also assessed histologically.

Treatment Profiles

Patients with congestive cardiac failure were managed according to accepted treatment regimens. Hypertension was treated using standard antihypertensives, though ACE-inhibitors were only used when bilateral renal artery stenosis had been excluded. If intractable hypertension occurred with bilateral renal artery stenosis, ACE inhibitors were used cautiously, with frequent assessment of maintenance renal function. All our patients received antituberculous therapy.

Steroids were commenced at a daily dose of 2mg/kg and were gradually weaned according to clinical response. Ten patients included in this review have been described elsewhere. (27, 30)

Due to previous poor outcomes in our region (31), a more aggressive immunosuppressive approach was embarked upon in our units. Patients were managed with either total lymphoid irradiation (TLI) or cytotoxic chemotherapy; namely, cyclophosphamide. All but two of the patients received their treatment allocation according to random numbers, and both units were allocated treatment from the same batch of random numbers. The TLI regimen was modelled on a wide-field low dose irradiation schedule as previously used for immunosuppressive pre-transplant work up. (32) This therapy was also subsequently used in some of our patients with systemic lupus erythematosus (33), and it had been described by Strober et al. (34)

Patients were treated supine in the mantle position, with cobalt 60. Two or three matching fields were used, at an extended source-skin distance. These fields extended from the base of the skull to 2cm below the ischial tuberosities. The upper part of the humerus, as well as the whole chest, trunk and pelvis were treated. Blocks were constructed from half-value layer lead to shield lungs, kidneys and gonads. The dosage of 8Gy, was given in 10 fractions at 0,8Gy per fraction. Treatment was given anteriorly and posteriorly, with all fields treated per session. Two fractions were given per week with at least two days between fractions. (27)

Prior to each treatment, haematological indices in the form of a full blood count and differential count were monitored. Treatment was interrupted if the total white cell count was less than 1,2 x 10^9/l, the neutrophil count less than 0,8 x10^9/l or the platelet count less than 50 x 10^9/l. A treatment delay was also instituted with any evidence of infection.

Patients receiving cyclophosphamide were given an initial intravenous bolus of 500 - 750mg/m², and then an 8 week course of oral therapy at 2 - 3 mg/kg, starting two weeks after the intravenous cyclophosphamide. Some patients were not given the initial intravenous bolus, instead the course consisted of an 8 week oral course of cyclophosphamide at 3mg/kg/day. Dosage was adjusted to maintain the white cell count above 3 x 10^9/l.

Surgical intervention was instituted to improve organ perfusion in patients showing features of ischemia to vascular stenosis or occlusion.

STATISTICS

Where appropriate:

1. The student-t test (two tailed) to assess comparative data in matched groups.
2. Two-tailed Fisher exact to compare results showing absolute end points, eg. mortality.

CASE REPORTS

Patient 1

A young black girl was admitted to our unit aged 12 years and 9 months. Prior to this, she had been hospitalised in the Transkei, where she had presented with coughing, shortness of breath and swelling. Upon admission, she was found to be hypertensive with a blood pressure of 145/105mm Hg, and in congestive cardiac failure. All her pulses were palpable. Initial investigations included a PPD, which ulcerated. An ESR was raised at 65mm/hr. A chest X-ray revealed a cardio-thoracic ratio of 75% and a left pleural effusion. Her renal function was normal with a calculated clearance of 107ml/min/1.73m^2. All her serological investigations were negative. An echocardiogram showed poor myocardial function, with dilatation of the descending aorta and narrowing of both renal arteries.
At angiography there was 80% narrowing of the abdominal aorta. The left renal artery showed 80% stenosis, with large lumbar collateral supply. No right renal artery was visualised. DMSA scan revealed cortical function of 11% on the right and 89% on the left. On gallium spect scan there was uptake in the abdominal aorta.

She was managed with antifailure therapy, antihypertensives and corticosteroids. She also received 10 cycles of TLI and experienced no complication during this therapy. Subsequently she had bilateral renal autotransplants, which were uncomplicated.

Post therapy her ESR was 15mm/hr and her Gallium scan was negative. Her blood pressure was 118/72mm Hg and her renal function was normal. At 5 year follow up, she is clinically well and off all medication.

Patient 2

A young Caucasian girl was referred to our unit for management at approximately 11 years of age. She had presented a year previously in Bloemfontein with episodes of abdominal pain, seizures and loss of consciousness.

Of relevance in her past medical history was that she had been cared for in Bloemfontein since about 3 years of age. She had recurrent chest infections and bronchospasm. Tuberculosis was initially suspected and she was treated for this. A final diagnosis of Hyper IgE syndrome was then made. Clinically at this presentation she was pale, and had palpable lymphnodes in the neck and inguinal region. She had an eczematous rash and bilateral serous otitis media. Cardiovascular examination revealed that all her pulses were present and she was hypertensive with a blood pressure of 200/135mmHg.

Investigations revealed an ESR of 45mm/hr, and normal renal function and full blood count. A PPD was negative.
A renin level was markedly raised.
A CT scan of the brain and renal ultrasound was normal.
DTPA scan revealed decreased perfusion of the left kidney.

At angiography, she was found to have extensive disease, with irregularity of the aorta and iliac vessels. The left renal artery showed severe narrowing and a percutaneous balloon angioplasty was performed. The superior mesenteric artery was also stenosed. Subsequent to this procedure there was improvement in the control of her blood pressure.

Approximately one year later she complained of headaches, abdominal pain and orthopnea. She was again severely hypertensive and in congestive cardiac failure. At this stage she was transferred to our unit, at Johannesburg Hospital.

Clinically, she was an ill child, with generalised oedema. She had a tachycardia and her blood pressure was 220/110mmHg. Her apex beat was displaced and on auscultation of her heart sounds, a gallop rhythm was evident. Her liver was palpated at 7cm below the right costal margin.
She was managed with anti-failure therapy and intravenous antihypertensives. Her blood pressure remained extremely difficult to control and a hypertensive crisis precipitated acute pulmonary oedema for which she was ventilated.

Subsequently, emergency surgery was performed whereby she had an interposition of a vein graft (saphenous vein) to the left renal artery. Histological examination of the end of the renal artery and small section of the aorta was compatible with Takayasu's arteritis.

Her blood pressure showed improvement and some antihypertensives were weaned. Further management consisted of Aspirin, corticosteroids, a bolus of intravenous cyclophosphamide and then an 8 week oral course. (A possible trigger in this patient for Takayasu's arteritis may have been repeated BCG's, as her PPD was repeatedly negative.)

Patient 3

A 4 year old Coloured girl presented to Coronation Hospital with shortness of breath and swelling. She was clinically hypertensive and in cardiac failure. She was referred to our unit at Johannesburg General for further management.

Upon admission, the pulses of the left arm and right leg were decreased. She was hypertensive with a blood pressure of 170/110mmHg.

Investigations included a Mantoux test which ulcerated. (She had a positive family history of tuberculosis).
Her renal function was reduced at a calculated clearance of 70ml/min/1.73m^2.
Angiography revealed narrowing of the abdominal and thoracic aorta, with bilateral renal artery stenosis. (The left more affected than the right.)
The superior mesenteric artery was also narrowed.

Management consisted of antituberculous therapy, antihypertensives, corticosteroids and oral cyclophosphamide.
A right renal autotransplant was attempted, but failed with vessel occlusion in the peri-operative period.
Her renal function deteriorated and continuous ambulatory peritoneal dialysis was commenced. She unfortunately developed a fungal peritonitis and therefore cyclophosphamide was discontinued, as was the peritoneal dialysis. Haemodialysis was commenced, though her blood pressure remained extremely labile and she died suddenly. (Approximately 6 months after initial presentation).

Patient 4

A 10 year old black girl presented to Tshepong Hospital with a history of headaches and nosebleeds for a prolonged period of time. She was found to be hypertensive and was referred to Baragwanath Hospital for investigation. A preliminary diagnosis of neurofibromatosis (she had small café au lait lesions on the right hypochondrium) with a renal artery stenosis was made and she was transferred to Johannesburg General for an autotransplant.

Clinically at admission, all her pulses were palpable. She was hypertensive with a blood pressure of 230/200mmHg. Heart sounds were normal.
Abdominal examination revealed no palpable masses, but a right renal artery bruit was heard. At fundoscopy arterial narrowing was noted.

Investigations revealed normal renal function and a full blood count. An ESR was elevated at 115mm/ hr. A random renin level was elevated. A Mantoux test was done and ulcerated. A TB elisa was positive. At DMSA scan both kidneys were normal. A DTPA scan revealed delayed filling of the right kidney. Angiography revealed a normal aortic arch and neck vessels. Coronary vessels and pulmonary arteries were normal. The aorta showed tapering below the level of the renal arteries, and the right renal artery was occluded.
A gallium scan revealed positive uptake. As a result of her clinical findings and subsequent positive investigations, she was diagnosed as having Takayasu's arteritis.

She was managed with antihypertensives, corticosteroids, antituberculous therapy and Aspirin. She also received 10 cycles of TLI, during which time she experienced no complications. A right renal autotransplant was subsequently performed successfully. Her blood pressure settled and antihypertensives were stopped.

She was well at follow up, off all treatment, with normal blood pressure and renal function.

Patient 5

An 8 year old black male presented to Baragwanath Hospital complaining of swollen joints and painful eyes. Clinically, he was found to have phlyctenular conjunctivitis. He also had swollen lower limb joints but normal range of motion. His left carotid pulse as well as the left brachial and radial pulses were not palpable. His blood pressure was elevated, with a reading of 170/120mmHg recorded.

Investigations revealed normal renal function with a calculated clearance of 119ml/min/1.73m^2.
His initial ESR was not recorded, but a C-reactive protein was 4mg/l. A Mantoux test was strongly positive.
Initial gallium scan was negative.
Angiography demonstrated narrowing of the aortic arch with stenosis of the left common carotid and left subclavian arteries. The right renal artery was also stenosed.
DMSA scan revealed 58% function on the left and 42% function on the right.

He was commenced on antituberculous therapy, corticosteroids and antihpertensives. A right renal artery stent was attempted and failed. He subsequently had a right nephrectomy.

At last follow up, he was well, off all medication with a normal blood pressure and renal function.

Patient 6

A 10 year old black male presented to Baragwanath Hospital with coughing and fever.

Clinically, upon admission, his height was below the third percentile. He had cervical and significant axillary lymphadenopathy. The left brachial and radial pulses were absent. He had a prominent pulsation in the neck. A left carotid bruit was heard. His blood pressure measured at 180/130mmHg. The JVP was elevated. The apex beat was laterally displaced. At auscultation, the heart sounds were normal with no gallop. A soft ejection systolic murmur was heard. The abdomen was soft and there were bilateral renal artery bruits. Central nervous system was intact. Fundoscopy was normal (no features of Takayasu's arteritis).

Investigations included a Mantoux test which was strongly positive (24 x 28mm). He was mildly anemic with a haemoglobin of 9,3g/dl. Renal function was deranged with a calculated clearance of 63ml/min/1.73m^2. Initial ESR was elevated at 60mm/hr.
Echocardiography and sonography revealed a normal ascending aorta. Coronary and pulmonary arteries were normal. A fusiform dilation of the descending aorta, with aneurysmal dilatation of the left common carotid artery was noted. There was bilateral renal artery stenosis (left kidney measured 7,5cm; right kidney 9,5cm).
DMSA scan – the left kidney barely visualised. Morphology on the right was normal.
Gallium scan revealed abnormal uptake in the anterior chest.
Angiography revealed stenosis of the left subclavian, stenosis and aneurysmal dilatation of the left common carotid, dilatation of the descending aorta and bilateral renal artery stenosis (left more severe than right).

He was commenced on antituberculous therapy, corticosteroids, antihypertensives, aspirin, and received 3 intravenous monthly boluses of cyclophosphamide.

He was transferred to Johannesburg General for a left nephrectomy and right autotransplant. A left autotransplant was attempted but abandoned. A right autotransplant was performed and post operative DTPA revealed good perfusion. Antihypertensives and steroids were weaned. Subsequently, at follow up, a pelvi-ureteric junction obstruction of the transplant kidney was diagnosed. A pyeloplasty was performed. His last blood pressure was 120/80mmHg on antihypertensives and calculated clearance was 105ml/min/1.73m^2.

Patient 7

An 8 year old black girl presented to Baragwanath Hospital. Upon admission she was found to be in cardiac failure and hypertensive. Her upper limb pulses could not be palpated. Her lower limb pulses recorded with Doppler, measured 170 mmHg systolic. Examination of the heart, showed the apex beat to be displaced and a gallop rhythm was heard on auscultation.

Investigations revealed normal renal function and an initial C-reactive protein of 7mg/l.
A Mantoux test was strongly positive.
A Gallium scan demonstrated no uptake.
Angiography demonstrated stenosis of the right and left subclavian arteries, and the right common carotid. The abdominal aorta was dilated, with bilateral renal artery stenosis, the right more severe than the left.
DMSA scan revealed 67% function on the left and 33% on the right.

She was managed with antihypertensives, corticosteroids, aspirin and antituberculous therapy. She also received 4 intravenous bolus doses of cyclophosphamide at monthly intervals.
A right nephrectomy was performed.

At last follow up, 1½ years after initial presentation, she was clinically stable, with a blood pressure controlled on antihypertensives, with normal renal function.

Patient 8

A 2½ year old black girl presented to Baragwanath Hospital. Clinically she was hypertensive and in congestive cardiac failure. Her blood pressure was recorded as 140/80mmHg. Examination of the heart revealed a displaced apex beat and on auscultation, a gallop rhythm was heard.

Initial investigations revealed normal renal function of 109ml/min/1.73m² (calculated clearance).
The ESR was 4 mm/hr.
A Mantoux test was strongly positive.
Angiography demonstrated narrowing of the ascending aorta and arch, resembling a coarctation
The renal arteries were normal.
The external iliac arteries showed narrowing.

She was treated with antituberculous, antifailure therapy and antihypertensives.
Repair of the coarctation was performed. Histological examination of this section of the aorta was in keeping with Takayasu's arteritis.

Post-operatively she remained well, of antihypertensives, with normal renal function and blood pressure.

Patient 9

An 8 year old black girl presented to Baragwanath Hospital with shortness of breath and swelling. Clinically, upon examination, she was oedematous and distressed. The right radial and brachial pulses were absent. Her blood pressure was measured as 110/80mmHg. Examination of her heart revealed left ventricular hypertrophy and a gallop rhythm on auscultation Abdominal examination revealed a palpable hepatomegaly.

On initial investigations, the C-reactive protein was elevated and renal function was deranged with a calculated clearance of 80ml/min/1.73m^2.
A Mantoux test was positive.
A DTPA scan demonstrated diminished perfusion of the right kidney suggesting a renal artery stenosis on this side.
Angiography showed narrowing of the aortic arch, with stenosis of the right subclavian and common carotid arteries.

Her treatment included antifailure therapy as well as corticosteroids and antituberculous therapy. She was also given an intravenous bolus of cyclophosphamide and an 8 week oral course.

Her blood pressure remained stable and renal function improved. Her cardiac failure remained difficult to control. She was unfortunately lost to follow up.

Patient 10

An 8 year old black girl presented to Baragwanath hospital with convulsions. Clinically, she was found to be hypertensive with a blood pressure of 180/150mmHg, and encephalopathic. All her pulses were palpable.

Investigations included a Mantoux test which was strongly (4+) positive. An initial ESR was 93mm/hr and calculated clearance was 118ml/min/1.73m².
Angiography revealed an abdominal aortic aneurysm with bilateral renal artery stenosis. A DTPA scan showed hypoperfusion of the right kidney and delayed accumulation and excretion in the left kidney.
She was treated with antihypertensives, antituberculous therapy and corticosteroids were commenced.
Surgery was performed at Baragwanath Hospital, whereby she had bilateral renal bypass gore-tex grafts. (It is not sure if she was given subsequent anticoagulation therapy).

Approximately one year later she was admitted again with a hypertensive encephalopathy.
She had been seen at Clinic two weeks previousiy and was well with normal renal function. Her blood pressure was difficult to control; her renal function deteriorated progressively and peritoneal dialysis was commenced.
A repeat arteriogram showed poor perfusion to the left kidney. The gore-tex graft on the right was occluded.
She was transferred to the Johannesburg General for further management and a left renal autotransplant.

Clinically, upon admission to our unit, she was extremely ill, with a markedly elevated blood pressure of 204/132 mmHg. She was also in congestive cardiac failure. She was placed on intravenous therapy to control her blood pressure. She was taken to theatre for an emergency left autotransplant. At surgery, the left gore-tex graft was completely thrombosed and the kidney was supplied by collaterals. The graft was excised, and the stump of the left renal artery was anastomosed to the left internal iliac artery. Her blood pressure improved and antihypertensives were weaned. Peritoneal dialysis was discontinued, and she was transferred back to Baragwanath Hospital.

She, however, died a few months subsequently, when the remaining Gore-Tex graft on the right renal artery eroded into the duodenum and she exsanguinated.

Patient 11

An 11 year old black girl presented to Baragwanath Hospital with swelling, coughing and shortness of breath. At examination, she was distressed and had pedal oedema. All her pulses were equally palpable. Her blood pressure measured 110/70mmHg. Cardiac examination revealed the apex beat to be displaced. At auscultation, a gallop rhythm was heard, as well as a loud pulmonary second sound. At abdominal examination, a hepatomegaly was detected.

Initial investigation revealed a strongly positive Mantoux test. Her renal function was normal and ESR was elevated at 75mm/hr.
At angiography, narrowing of the ascending arch was noted. The iliac vessels were also involved. Pulmonary hypertension with pulmonary involvement was also demonstrated.

She received antifailure and antituberculous therapy as well as corticosteroids. In addition, she was given an intravenous bolus of cyclophosphamide, followed by an 8 week oral course.

Her congestive cardiac failure remained intractable and she was unfortunately lost to follow up.

Patient 12

An 8 year old black male was admitted to Baragwanath Hospital. At clinical examination, he was noted to be hypertensive with a blood pressure of 135/90mmHg and in congestive cardiac failure.

His investigations revealed normal renal function, with a calculated clearance of 109mm/min/1.73m^2. His ESR was elevated at 60mm/hr. A Mantoux test was strongly positive. Angiography demonstrated abdominal aortic involvement and bilateral renal artery stenosis; the left more severe than the right.
A DMSA scan revealed 17% function on the left and 83% function on the right.

His treatment included antihypertensives, corticosteroids and antituberculous therapy.
Post therapy, his ESR decreased to 14mm/hr. His renal function remained normal and his blood measure was normal. He was last well at follow up, 3 years after presentation.

Patient 13

A 4 year old black male was admitted to Baragwanath Hospital with swelling and shortness of breath. Clinically he was in cardiac failure with oedema, a gallop rhythm on auscultation and a palpable hepatomegaly. All his pulses were palpable. His blood pressure was recorded at 95/86mmHg.

His initial investigations revealed deranged renal function with a calculated clearance of 35ml/min/1.73m^2. His ESR was elevated at 80mm/hr. Angiography demonstrated an ascending aortic aneurysm and no arterial supply was noted to the right kidney.

He was treated with antihypertensives, corticosteroids and antituberculous therapy. He also received an eight week course of cyclophosphamide. Surgery was recommended, but this was refused by the parents. On follow up investigations, post cyclophosphamide treatment, his ESR had settled to 20mm/hr and renal function had improved. His blood pressure was controlled with antihypertensives. He was unfortunately lost to follow up, subsequent to the refusal of surgery.

Patient 14

A 4 year old Caucasian girl was referred to our unit at Johannesburg Hospital via the cardiologists. She had presented to them a few months previously and coarctation of the aorta was suspected.

Clinically, upon admission, the lower limb pulses were absent, with radio-femoral delay evident. She was hypertensive with a blood pressure of 140/70mmHg. Bruits were heard along the carotids, the vertebral, the abdominal aorta and renal arteries.

Investigations revealed a strongly positive Mantoux test. The initial ESR was elevated, the full blood count and renal function were normal.
DTPA scan revealed a non-functioning right kidney.
At angiography there was marked narrowing of the abdominal aorta, with bilateral renal artery stenosis (the right more severe than the left).
Management consisted of antihypertensives, corticosteroids, antituberculous therapy, an initial intravenous bolus of cyclophosphamide and then an 8 week oral course.
Surgery consisting of a right axillo-femoral bypass graft was attempted, but the gradient between the upper and lower limbs remained. (Blood pressure upper limbs 130/86mmHg; lower limbs - Doppler 80mmHg).

Her blood pressure remained difficult to control. Enalapril was commenced with initial good effect but renal function then deteriorated and it was discontinued. She died suddenly related to a hypertensive episode.

Patient 15

A 6 year old black boy was referred to our unit at Johannesburg General Hospital for management of uncontrolled hypertension. He had presented to Garankuwa Hospital with a history of tiredness, pain in his legs and seizures. He had no known tuberculosis contacts.

Clinically, upon admission to our unit, he was found to be an ill little boy. He had significant generalised lymphadenopathy. His pulses were all palpable and he had a heart rate of 52/minute. Four limb blood pressures were recorded as follows: Right arm 180/120mmHg; left arm 190/130mmHg; right leg 162mmHg systolic; left leg 150mmHg systolic. He showed features of cardiac failure with a JVP elevated to the angle of his jaw. His apex beat was displaced and on auscultation, a gallop rhythm was heard. The abdomen was distended, with a 10cm hepar palpable. His central nervous system was intact, but fundoscopy revealed narrowing of the arteries and exudates were noted.

Investigations included a Mantoux test which was strongly positive. Initial full blood count was normal. His ESR was elevated. He had renal dysfunction, with an initial clearance calculated at 40ml/min/1.73m^2. All serological investigations were negative. On chest X-ray, the cardio-thoracic ratio measured 85% and four-chamber enlargement and a small pericardial effusion was noted at echocardiography. Angiography revealed narrowing of the mid-abdominal aorta. The renal arteries were not visualised bilaterally.

He was managed with antifailure therapy and numerous antihypertensives in an attempt to alleviate his hypertension. He unfortunately developed intractable pulmonary oedema, then adult respiratory distress syndrome, and died despite active intervention.

At post mortem he was found to have a 5cm stenosis of the abdominal aorta adjacent to the renal arteries. Both renal arteries were occluded. There was biventricular cardiomegaly. Examination of the brain revealed numerous cortical infarcts and a single granuloma.

Patient 16

A four year old black girl was referred to our unit at Johannesburg General Hospital, from Baragwanath Hospital for further management. She had initially presented at Tshepong Hospital with a history of dyspnoea and palpitations.

Of note on the family history was that the mother had received treatment for tuberculosis a year previously.

Clinically, at admission she was an ill little girl. She had generalised lymphadenopathy. Her pulses were all palpable and equal with a rate of 104/min. Her 4 limb blood pressures measured as follows: right arm 172/118mmHg; left arm 172/100mmHg; right leg 188mmHg systolic, left leg 190mmHg systolic. Features of cardiac failure included a gallop rhythm on auscultation of the heart, bilateral crepitations of the chest and a 5cm palpable hepatomegaly. Central nervous system was normal with normal fundi.

Investigations included a Mantoux test which was strongly positive. At chest X-ray, her cardio-thoracic ratio measured 62% and she had hilar and mediastinal lymph nodes. Her ESR was elevated at 45mm/hr and initial renal function was normal with a calculated clearance of 111ml/min/1.73m^2. All serological tests were negative. Angiography revealed narrowing of the left subclavian artery. The aorta showed narrowing from the coeliac axis to the renal arteries. There was bilateral renal artery stenosis, the left more severe than the right. A gallium scan showed positive uptake in the aorta.

She was managed with antituberculous therapy, corticosteroids, antifailure therapy and antihypertensives. Her blood pressure remained difficult to control and an ACE inhibitor was added, but this was withdrawn subsequent to a deterioration in her renal function.
A left autotransplant was attempted, but was unsuccessful. In view of ongoing disease activity, TLI was commenced. She received 10 cycles and her lowest white cell count was 1,3 x10^9 /l. Her blood pressure remained labile. She was then taken for a right autotransplant, which unfortunately failed due to a vascular thrombus in the peri-operative period. She was initially haemodialysed and then commenced on peritoneal dialysis.

Six months later she received a successful cadaver transplant.
Her renal function returned to normal (calculated clearance 94ml/min1.73m^2) and she was discharged on immunosuppressives.

Two years later she suffered a rejection episode, probably related to poor compliance. This was aggressively managed with some improvement of her renal function. This, however, deteriorated steadily and she was recommenced on dialysis.

At this stage she was noted to have a left neck swelling which on biopsy and histological examination proved to be a papillary carcinoma of the thyroid. She had a radical thyroidectomy and received radio-ablative iodine. She was further managed on peritoneal dialysis but became repeatedly hypertensive and overloaded. We received notification from Schweizer Reynecke Hospital that she had died.

Patient 17

A 7 year old black boy was referred to our unit at Johannesburg General Hospital for further management. He initially presented to Kalafong Hospital and was then transferred to H F Verwoerd Hospital for investigation of hypertension and cardiac failure.

Initial investigations there included a full blood count which was normal. An ESR was 4mm/hr. Renal function was normal with a calculated clearance of 97 ml/min/1.73m^2. A Mantoux test was negative. All serological tests were negative. A random renin assay was markedly elevated. A renal sonar showed a small right kidney but normal left kidney. At angiography, stenosis of the left renal artery was found, with a non-functioning right kidney. A left renal angioplasty was performed but the artery went into 'spasm'. The patient was heparinised but blood pressure became more difficult to control and his urine output decreased markedly. A DTPA scan revealed a non-functioning right kidney with no perfusion on the left. As a result of deteriorating renal function he was commenced on peritoneal dialysis and referred to Johannesburg General Hospital.

On admission, his blood pressure was normal on therapy. All his pulses were palpable. Examination of the heart revealed a laterally displaced apex beat and a gallop rhythm was heard at auscultation. A tender 3cm hepar was palpable. Bruits were also heard over the carotid, temporal and femoral arteries, as well as over the chest and abdomen.
At repeat angiography, the arch and descending aorta were normal. Coronary arteries were normal. The descending aorta showed narrowing with irregularity at the inferior mesenteric artery. The renal arteries were not outlined. The main pulmonary artery was normal but there were multiple peripheral pulmonary arterial stenoses.
He was managed with antituberculous therapy, corticosteroids, antihypertensives, aspirin and peritoneal dialysis. He also received 10 cycles of TLI, which were uncomplicated.

He subsequently received a cadaver transplant, but died 2 days later as a result of persistent anastomotic ooze, as well as generalized oozing from the diseased aorta.

Patient 18

A young black male was transferred to our unit at Johannesburg General Hospital at 9½ years of age. He had presented at Garankuwa Hospital with repeated episodes of epistaxis and seizures. Clinically, at Garankuwa Hospital, he was found to have diplopia and to be hypertensive. A Mantoux test was done which ulcerated. He has no history of tuberculosis contacts.

Clinically, upon admission to our unit, he was an alert, co-operative boy. A scar from the Mantoux test was noted on his right forearm. Cardiovascular examination revealed the right radial and brachial pulses to be absent. Four limb blood pressures were recorded as follows: left arm 154/106mmHg; left leg 148mmHg systolic, right leg 144mmHg systolic. Examination of the heart was normal. Bruits were heard over the carotid vessels and the abdomen. Fundoscopy revealed silver wiring and AV nipping.

Investigations revealed normal renal function, and initial C-reactive protein was raised at 41 mg/l. A chest X-ray and electrocardiogram were normal. At angiography stenosis of the right subclavian and right common carotid arteries was noted. The aorta was narrowed at the mid-portion.The right kidney was supplied by two vessels. There was bilateral renal artery narrowing; the left was more severe. He was treated with antituberculous therapy, corticosteroids, antihypertentives and aspirin. He was also given an initial intravenous bolus of cyclophosphamide and then an eight week oral course. Subsequent activity markers were normal and a Gallium scan was negative. A successful left renal autotransplant was then performed.

Approximately 3 months later he was readmitted. His ESR had increased to 41mm/hr. Renal function and full blood count were normal. His blood pressure was well controlled.
Repeat angiography revealed stenosis of the right common carotid and brachiocephalic artery. There was mid-abdominal aortic narrowing. The right renal artery was normal and the left kidney attached to the left internal iliac artery had normal supply.

He was treated with a 10 cycle course of TLI. There was a short interruption between cycle 3 and 4. The WCC decreased to 2,2 x 10^9/l and the platelets to 97x10^9/l - this settled spontaneously. He is presently off all hypertensives. At his most recent visit his blood pressure was normal. Renal function was normal and ESR 4mm/hr.

Patient 19

An 11 year old coloured girl was transferred to our unit at Johannesburg General Hospital for further management. She had initially presented to Coronation Hospital with a history of fever, weight loss and ulcerating lesions of her legs. Subsequently, she developed cardiac failure secondary to hypertension. She was also noted to have absent pulses.

Past medical history of relevance, a Garré's tumour of the left mandible was excised and curetted 3 years previously at Red Cross Hospital. Six months later she returned with symptoms and signs of pulmonary tuberculosis. This was confirmed on chest X-ray and Mantoux testing. She received appropriate therapy. At this stage she was also noted to have bilateral sensorineural deafness.

Angiography prior to transfer from Coronation Hospital revealed bilateral carotid artery involvement, occluded subclavian arteries and bilaterally narrowed renal arteries. There was an aneurysm of the descending abdominal aorta. The inferior mesenteric artery was absent and the external iliac arteries were partially occluded. Her blood pressure was controlled with antihypertensives but acute renal failure was precipitated with the addition of a potent loop diuretic.

Clinically upon transfer, she was an extremely ill girl. She was distressed, pale and oedematous. No upper limb pulses could be detected. A Doppler measurement of the left leg revealed a systolic pressure of 170mmHg. The JVP was elevated to the angle of the jaw and on auscultation of the heart, a gallop rhythm was heard. Her abdomen was distended with an 8cm palpable hepatomegaly. Central nervous system was intact, except for a partial left LMN 7^{th} cranial nerve lesion. Fundoscopy revealed arteriolar narrowing with no haemorrhages or exudates. There were granulating lesions on both thighs. Investigations revealed an elevated C-reactive protein, with renal dysfunction
(a calculated clearance of 26ml/min/1.73m^2).
She was managed with antihypertensives and peritoneal dialysis. Two days after admission, an emergency right renal autotransplant was performed. Her cardiac failure and hypertension continued, but renal function returned to normal and peritoneal dialysis was discontinued.

Five days later, a left autotransplant was performed. At DTPA, good perfusion and excretion of both autotransplanted kidneys was noted. Her cardiac failure improved and antifailure therapy was stopped. Her antihypertensives were weaned.

Further management consisted of corticosteroids, aspirin and TLI. She received 10 cycles of TLI and had no complications. Her subsequent ESR was 10mm/hr and renal function was normal with a calculated clearance of 150ml/min/1.73m^2.

Approximately 10 months later she was again noted to have skin lesions on her legs. She also had impetigo. Her activity markers had increased with an ESR of 100mm/hr and a CRP of 108 mg/l. Her blood pressure and renal function remained normal once her infection was controlled. She was then given and intravenous bolus dose of cyclophosphamide and then an 8 week oral course. She responded very well. At present, after 9 years follow up - she is clinically well off all antihypertensives and has normal renal function.

Patient 20

A young black girl was referred to our unit at 9 years of age. She had presented to her paediatrician complaining of headaches and shortness of breath. She was previously well. Clinically, she was hypertensive and had congestive cardiac failure. She was treated with antihypertensives.

Angiography revealed mid-abdominal narrowing with bilateral renal artery stenosis.

Upon admission she was a co-operative little girl. Induration from a Mantoux test on her left forearm was strongly positive. She was undistressed. She had no oedema. Examination of the cardiovascular system revealed all pulses to be palpable. Four limb blood pressures were as follows : Right arm 150/100mmHg; left arm 140/98mmHg; left leg 140mmHg systolic, right leg 130mmHg systolic. The apex beat was displaced, but no gallop was heard. Abdominal examination was normal except for soft renal bruits heard on auscultation. At fundoscopy, silver wiring was noted.

Investigations revealed a normal full blood count and renal function. The ESR was elevated at 58mm/hr. At echocardiography the inferior vena cava was dilated, there was abdominal aortic narrowing from the coeliac trunk. There was bilateral renal artery narrowing. Ejection fraction was 30% and a puff of aortic incompetence was seen.

Management consisted of antituberculous therapy, corticosteroids, antihypertensives and aspirin. She was given an intravenous bolus of cyclophosphamide and then an 8 week oral course. Her activity markers settled.

A successful left renal autotransplant was done, with a gore-tex patch to the aorta to improve distal run off. (Histology revealed no activity in the section of renal artery). Her blood pressure improved transiently, then increased again. Antihypertensives were continued. Two months later a right renal autotransplant was performed. DTPA scan showed good perfusion, accumulation and excretion in both autotransplanted kidneys. Her blood pressure improved and antihypertensives were weaned.

At repeat echocardiography, the IVC was undilated. There was left ventricular hypertrophy. The ejection fraction was 50%. (the aortic incompetence had settled.)
At subsequent follow up she has been clinically well with normal renal function and activity markers. Her blood pressure is well controlled with low dose antihypertensives.

Patient 21

A 12 year old black girl was referred to Johannesburg General Hospital for further management. She had presented to Baragwanath Hospital with vomiting, diarrhea and confusion. She had previously had convulsions. She had no history of tuberculosis contacts.

Clinically at admission, she had a large ulceration on her right forearm from a Mantoux test. Her popliteal pulses and dorsalis pedis pulses could not be palpated. Her four limb blood pressures (with Doppler) were recorded as follows: right arm 132/82mmHg, left arm 128/84mmHg, right leg 128mmHg systolic, left leg 138mmHg systolic. Examination of the heart was normal. A bruit was heard over the abdomen.

Investigations revealed an initial ESR of 24mm/hr and full blood count and renal function were normal. At ultrasonography, the left kidney measured 8cm and the right 9cm. Angiography revealed a normal aortic arch. The aorta was ectactic at the level of the renal vessels. The left renal artery was not visualised and the right renal artery was 50% stenosed.

She was managed with antihypertensives, steroids, aspirin and antituberculous therapy. She also received an intravenous bolus of cyclophosphamide and then an 8 week oral course.

A left renal autotransplant was performed, but at subsequent DTPA no perfusion of the left kidney was noted.

Subsequent to her immunosuppressive therapy, her antihypertensives were weaned, her renal function is normal and her ESR was 7mm/hr.

Follow up angiography revealed the aorta to be similar. The right renal artery was patent and there was double supply to the kidney. The left kidney attached to the left internal iliac artery was patent for the first 2cm and then there was abrupt cut off.

At last follow up, she was well with normal renal function and blood pressure. She was on no antihypertensives or medication. She delivered a well baby, with no complications, 5 years after initial presentation.
Activity markers and blood pressure were normal.

Patient 22

A 14 year old black male was transferred to our unit for further management from an adult unit at Baragwanath Hospital. He had presented initially to a hospital in Potchefstroom complaining of pain radiating down from both his axillae to the subcostal region. This was aggravated by exercise. He had no cough, orthopnea, paroxsymal nocturnal dyspnoea or oedema. His effort tolerance was decreased. There was no family history of tuberculosis.

Clinically upon referral, he was an alert young boy. All his pulses were present and bounding. Four limb blood pressures were measured as follows: right arm 170/30mmHg; left arm 120/50 mm Hg, right leg 130mmHg; left leg 130mmHg systolic. A right carotid bruit was heard. Examination of the heart showed the apex beat to be normal. A soft ejection systolic murmur was heard at the 2nd right intercostal space and a 2/4 early diastolic murmur at the aortic area. A bruit was heard over the abdomen. His central nervous system was intact but fundoscopy revealed pulsatile vessels, more so on the left.

Investigations included a Mantoux test, which ulcerated. His renal function was normal. Initial activity markers were increased with an ESR of 65mm/hr and a CRP of 60 mg/l. All serological investigations were negative. An electrocardiogram was normal. A chest X-ray showed a prominent aortic arch and unfolding of the aorta. Echocardiography revealed an aneurysm of the aorta with aortic regurgitation . At angiography the aortic annulus was dilated with a moderate aortic incompetence. The ascending aorta, the arch and thoracic aorta were dilated and aneurysmal. The renal vessels were normal. The right pulmonary artery showed a small fusiform dilatation. There was possibly mild proximal narrowing of the right coronary artery.

MRI revealed marked aortic dilatation from the aortic valve to the upper abdomen. There was obstruction of the innominate artery and the left carotid and subclavian origins. There was no aortic dissection.
A Gallium scan revealed increased activity in the aortic arch. A DTPA scan was normal.

He was managed with antihypertensives, corticosteroids, aspirin and antituberculous therapy. He also received an intravenous bolus dose of cyclophosphamide and then an 8 week oral course.

His subsequent activity markers were normal, with an ESR 2mm/hr and a repeat Gallium scan was negative.After 4 years of follow up he is clinically stable. His blood pressure is controlled with minimal antihypertensives and his renal function is normal.

Patient 23

A 6 year old black boy presented to our unit at Johannesburg General Hospital complaining of an 8 month history of coughing and associated chest pain. He also experienced facial weakness, painful, swollen ankles and abdominal pain. He had lost weight but had a good appetite. He was seen at Baragwanath Hospital a few months previously complaining of sore eyes. A test for tuberculosis was done, which was negative.

Clinically he was not acutely ill. All his pulses were equally palpable. His blood pressure was 80/56mmHg. He had shotty cervical lymphadenopathy. Examination of the chest and heart, revealed the trachea to be deviated to the right and the heart was normal. An epigastric pulsation was seen. Examination of the central nervous system revealed a right 7th UMN cranial nerve lesion. He had ptosis of the left eye. His ankles were swollen but he had a normal range of motion.

Investigations revealed normal renal function and an elevated ESR of 108mm/hr. A Mantoux test was negative, as were all serological tests.
Chest X-ray showed a cardio-thoracic ratio of 43% with a widened mediastinum.
Echocardiography demonstrated a massive aneurysm of the descending aorta.
The aorta valve and heart was normal.
At CAT scan, the aneurysm was shown to start at the level of the left subclavian artery and extend the entire thoracic course. A thrombus was detected in the wall. There was no calcification.
Cardiac catheterisation confirmed the aortic aneurysm. Pulmonary vessels and renal arteries were normal.
Gallium scan revealed 2 areas of uptake, at the level of the heart and origin of the renal vessels.

At ophthalmology consultation, he was reported as having deep corneal scarring with neovascularisation. (possibly herpes related.)

He was managed with corticosteroids, aspirin and antituberculous therapy. He also received 10 cycles of TLI, during which time he had no complications. His activity markers settled and a follow up Gallium scan was negative.

Approximately one year ago, (5 years after initial presentation and treatment), he showed features of a uveitis. His activity markers again increased (ESR 100mm/hr. and C-reactive protein 80 mg/l). A gallium scan was negative. He was given 3 monthly intravenous boluses of cyclophosphamide, but showed little response. He was therefore recently commenced on a weekly dose of oral Methotrexate and recommenced on antituberculous therapy. His uveitis has resolved and ESR has settled to 14mm/hr.

Patient 24

A 10 year old black girl was referred from Garankuwa Hospital where she had presented with hypertension and in congestive cardiac failure. One year previously she was diagnosed as having rheumatic fever with mild left ventricular hypertrophy and mixed mitral valve disease. Approximately 6 months later she was diagnosed as having pulmonary tuberculosis, as evidenced by positive chest x-ray changes and an ulcerating Mantoux test.

Clinically at admission to our unit she was alert and co-operative. A scar was noted from the Mantoux test.
Bruits were heard over the left carotid artery, the abdominal aorta and femoral vessels.

Investigations revealed normal renal function. Her ESR was raised >106mm/hr.
Gallium scan showed increased activity in the heart.
Cardiac catheterisation demonstrated a dilated left ventricle with mitral incompetence and stenotic leaflets. The right subclavian artery was stenosed. The coronary vessels were normal. The aorta was stenosed from the descending thoracic to mid-abdominal level. Collaterals supplied the kidneys. The left renal artery was stenosed at it's origin.
She was commenced on aspirin, antihypertensives, corticosteroids and antituberculous therapy.
She received 10 cycles of uninterrupted TLI.
She subsequently had bilateral renal autotransplants. DTPA scan demonstrated good perfusion and excretion of both kidneys.
(Histological examination of the renal arteries revealed intimal profileration.) Her blood pressure showed improved control, but she still required antihypertensives. (This was thought to be as a result of intrarenal arterial narrowing of the left kidney).

She is subsequently stable on antihypertensives and has normal renal function.

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Clinically at admission to our unit she was alert and co-operative. A scar was noted from the Mantoux test.
Bruits were heard over the left carotid artery, the abdominal aorta and femoral vessels.

Investigations revealed normal renal function. Her ESR was raised >106mm/hr.
Gallium scan showed increased activity in the heart.
Cardiac catheterisation demonstrated a dilated left ventricle with mitral incompetence and stenotic leaflets. The right subclavian artery was stenosed. The coronary vessels were normal. The aorta was stenosed from the descending thoracic to mid-abdominal level. Collaterals supplied the kidneys. The left renal artery was stenosed at it's origin.
She was commenced on aspirin, antihypertensives, corticosteroids and antituberculous therapy. She received 10 cycles of uninterrupted TLI.
She subsequently had bilateral renal autotransplants. DTPA scan demonstrated good perfusion and excretion of both kidneys.
(Histological examination of the renal arteries revealed intimal profileration.) Her blood pressure showed improved control, but she still required antihypertensives. (This was thought to be as a result of intrarenal arterial narrowing of the left kidney).

She is subsequently stable on antihypertensives and has normal renal function.

Patient 25

A 9 year old black girl was transferred from Leratong Hospital to Baragwanath Hospital with convulsions and severe hypertension. Initially it was thought this was related to a head injury secondary to involvement in a recent motor vehicle accident. At examination, she was hypertensive with a blood pressure recorded at 200/140mm/Hg. All her pulses were equally palpable. She also had features of cardiac failure with a gallop rhythm audible on auscultation of the heart.

Investigations revealed a strongly positive Mantoux test. Her renal function was normal. All other serological investigations were negative.
At angiography the abdominal aorta showed narrowing and bilateral renal artery stenosis was present.
Surgery was performed with bilateral bypass gore-tex grafts placed between the right renal artery and aorta and left renal artery and aorta. Post operatively the left graft was suspected to be obstructed and an embolectomy was performed. Renal function was maintained with peritoneal dialysis, which was discontinued once function settled. A later DTPA scan revealed poor perfusion of the right, but perfusion on the left had improved. She was managed with steroids and antituberculous therapy.

Unfortunately she was lost to follow up for 6 months and was then readmitted with convulsions. She was markedly hypertensive and in established renal failure with a creatinine of 575mmol/l. Angiography revealed a patent graft on the left only. DMSA scan demonstrated non-functioning of the right kidney and lower pole of the left kidney. Peritoneal dialysis was recommenced as her renal function deteriorated further. She was transferred to Johannesburg General Hospital for further management.

During her stay in the unit, she coped well with CAPD and her blood pressure was well controlled. She received 10 cycles of TLI but because of a prolonged gap between these cycles because of neutropenia, an eleventh dose was given . She then had a successful cadaver transplant, and regained normal renal function. She is now 10 years post transplant (13 years post diagnosis) with a well-controlled blood pressure and normal renal function.

Patient 26

An 11½ year old black male was referred to our unit at Johannesburg General Hospital from an adult unit at Baragwanath hospital. He had presented with seizures. He was found to be markedly hypertensive and encephalopathic. Upon referral he was a happy, well nourished child. There were no peripheral signs of vasculitis. His 4 limb blood pressures were recorded as follows: right arm 148/90mmHg; left arm 148/114mmHg; right leg 148mmHg systolic, left leg 146mmHg systolic. All his pulses were palpable. No bruits were heard. At fundoscopy, flame shaped haemorrhages were noted.

Investigations revealed a Mantoux test, which was ulcerated. Renal function and full blood count were normal. Initial ESR was 16mm/hr. All serological tests were negative. Renin was raised. A Gallium scan showed extensive uptake. Angiography demonstrated a saccular aortic aneurysm distal to the superior mesenteric artery, involving right renal artery take off.
He was managed with antihypertensive, corticosteroids, aspirin and antituberculous therapy.
He also received an intravenous bolus of cyclophosphamide and then an 8 week oral course.
Post therapy, his ESR was 4mm/hr, but Gallium scan revealed a hot spot in the aortic arch. A right nephrectomy was performed.

Approximately 6 months later he presented with sudden onset hypertension recorded at 168/100mmHg). All pulses were equally palpable. A soft bruit was heard over the abdomen and left renal artery. His blood pressure was difficult to control and required numerous antihypertensives.

At cardiac catheterisation, the aortic arch was normal. The coronary vessels were normal. At the level of the left renal artery, there was constriction of the abdominal aorta with proximal and distal dilatation. The left renal artery was proximally stenosed. Iliac arteries and pulmonary arteries were normal.

He then received 10 cycles of TLI with no complication. A left renal autotransplant was performed, and the procedure was uneventful. Renal function was normal post operatively.

Three years later, he was well off all antihypertensives, with normal renal function and activity markers.

Patient 27

This 4 year old Caucasian boy presented to our unit. His problems started approximately one year previously. He complained of pain in his ankles, which extended to the knees. He also developed nodules on his shins and gangrene of his toes.

At examination he was apyrexial. The left radial pulse was not palpable and the dorsalis pedis pulses were not heard on Doppler. The femoral pulses were also less well felt. His blood pressures were recorded as follows: right arm 148/118mmHg; left arm 142mmHg (Doppler); right leg 140mmHg (Doppler); left leg 140mmHg (Doppler). No bruits were heard. Examination of the heart was normal. A 4 cm hepatomegaly was palpated on abdominal examination.

Investigations revealed a normal full blood count and renal function. His activity markers were elevated. CRP 75 mg/l and ESR 32mm/hr. All serological tests were negative. A TB elisa was positive. Chest x-ray and electrocardiogram were normal.
Angiography demonstrated a thoracic aortic arch aneurysm. The left popliteal artery was occluded.
He was treated with aspirin, antihypertensives, corticosteroids and antituberculous therapy. He was also anticoagulated with heparin then warfarin. He was commenced on a course of 10 cycles of TLI. He experienced no complications. During this time the lower limb pulses improved, the posterior tibials were palpable and dorsalis pedis pulses detected on Doppler. The gangrene demarcated and the affected portions of the toes dropped off. A repeat Gallium scan was cold. A CAT scan revealed no progression of the aneurysm with no thrombi and warfarin was discontinued.

He was well until one year later when he was suddenly noted to have hypertension. Bruits were audible over the renal arteries and a gallop rhythm was heard on auscultation of the heart. His activity markers were also elevated. Electrocardiogram showed a normal axis with left ventricular hypertrophy.
Chest x-ray showed a normal cardio-thoracic ratio, but a massively dilated aortic arch. At echocardiography, a poorly functioning myopathic heart was detected. Repeat angiography revealed a grossly dilated ascending aorta with mild aortic incompetence. There was narrowing of the aorta just distal to the renal arteries. The right renal artery was severely stenosed. The pulmonary arteries were normal and the inferior mesenteric artery was stenosed.

He was treated with antihypertensives. Corticosteroids were restarted. Aspirin was continued. He received an intravenous bolus of cyclophosphamide and then an 8 week oral course. His blood pressure was stable and aortic incompetence settled.
A successful right renal autotransplant was performed. A DTPA scan showed delayed excretion. Repeat echocardiography demonstrated normal left ventricular function. Shortening fraction 33% and ejection fraction 62%. The aneurysms of the aorta remained static.

At his last follow up, 9 years after initial diagnosis, his blood pressures were normal. There was no thyromegaly. His ESR was 1mm/hr. and renal function was normal. He is only on aspirin.

Patient 28

A 14 year old Caucasian male was admitted to Johannesburg Hospital with a 3 month history of fever, malaise and loss of weight. He also complained of pain in his legs which was aggravated by exercise. His left knee and ankle were also painful and swollen. He also had a non-healing ulcer on his left thigh.
Serological tests were negative. Skin biopsy revealed a granulomatous dermatitis in keeping with tuberculosis or Takayasu's arteritis. A short saphenous vein biopsy revealed a granulomatous vasculitis. He was assessed as having Takayasu's arteritis and he received a full course of antituberculous therapy, corticosteroids and 10 cycles of TLI.

Of relevance in his past medical history, he had presented at 8 years of age with back and joint pains. A diagnosis of juvenile rheumatoid arthritis was made by exclusion. He had presented with similar problems 2 years subsequently.

At 15 years of age he presented with a 3 month history of decreased effort tolerance, paroxysmal nocturnal dyspnoea, abdominal pain and cellulitis.
Clinically at this time he was a wasted, growth retarded child. His lower limb pulses could not be palpated. Four limb Doppler blood pressures were measured as follows: right arm 96mmHg; left arm 114mmHg; right posterior tibial 94mmHg systolic. Left pedal pulses were not detectable. A left subclavian bruit was heard. Examination of the heart revealed a loud P_2 on auscultation. A 4cm hepatomegaly was palpable. His central nervous system was intact and fundi were normal. The capillary filling time of both feet was markedly decreased. Papulonecrotic lesions were present on the left foot and ankle and behind the knees.
Investigations revealed a normal full blood count and renal function. His C-reactive protein was raised at 59 mg/l. His chest x-ray showed a cardio-thoracic ratio of 59%, with interstitial oedema. Electrocardiogram revealed a normal axis, with a sinus rhythm of 90 beats/min. There was right ventricular hypertrophy and ST-segment depression.

Cardiac catheterisation demonstrated a large main pulmonary artery, and mild pulmonary incompetence. The right pulmonary artery tapered off abruptly. There was moderate pulmonary hypertension with a dyskinetic left ventricular segment.

He was managed with antibiotics and dressing for the ulcers. He also received high dose corticosteroids, which were tapered; an intravenous bolus of cyclophosphamide and an 8 week oral course.

His blood pressure and renal function were normal. His ESR had decreased to 2mm/hr.

He was admitted with repeat episodes of cardiac failure, secondary to his pulmonary hypertension. He was not accepted onto the cardiac transplant programme in Cape Town.

He passed away 2 years later (5 years after his initial presentation) secondary to his cor pulmonale.

Patient 29

A 3 year old black boy was referred from Baragwanath Hospital. He had presented with coughing, shortness of breath, night sweats and swelling of his face. He was diagnosed as having congestive cardiac failure. He had a significant family history of tuberculosis, 2 of his siblings and his father were receiving antituberculous therapy.

Clinically upon admission he was a pleasant co-operative little boy. He was not distressed. He had no lymphadenopathy. At cardiovascular examination his left brachial pulses were poorly felt. Bruits were heard over the subclavian and femoral arteries. His blood pressure was measured at 130/90mmHg. His heart sounds were normal on auscultation. The abdomen was soft with a 4cm hepatomegaly. The central nervous system was intact with normal fundi
Investigations revealed a normal full blood count and renal function. A Mantoux test was strongly positive. An initial ESR was 3m/hr.
Echocardiography revealed a dilated inferior vena cava. Ejection fraction 36%.
Angiography revealed narrowing of the subclavian arteries and stenosis of the left renal artery.
His treatment included steroids, aspirin, antituberculous and antihypertensives.
He received 10 cycles of TLI and experienced no complication.

At repeat angiography a stent was placed in the left renal artery.He was heparinised. His blood pressure settled initially.
Six months later the left renal artery had narrowed because of intimal proliferation and he was admitted with hypertension.
A left renal autotranplant was then done. His blood prossure settled and all antihypertensives were discontinued. His ESR was 9mm/hr; his renal function was normal.

Patient 30

A 2½ year old black girl was admitted at Baragwanath Hospital with a hypertensive encephalopathy and congestive cardiac failure.
Clinically her pulses were all equally palpable. Her blood pressure was recorded at 160/110mmHg. She was assessed as having right and left ventricular hypertrophy. On auscultation of the heart, a gallop rhythm was heard, as well as a $^{2}/_{6}$ ejection systolic murmur. Palpation of her abdomen revealed hepatosplenomegaly.

Investigations included a Mantoux test, which was strongly positive. Chest x-ray demonstrated cardiomegaly and hilar adenopathy. Echocardiography revealed poor left ventricular function and mild aortic incompetence on Doppler.
Her renal function and full blood count were normal.
At angiography, narrowing of the abdominal aorta was noted. The right renal artery was thrombosed and the left renal artery was stenosed.
She was treated with antihypertensives, antifailure and antituberculous therapy.
She was then referred to Johannesburg General Hospital for a left autotransplant.

Upon referral she was clinically still hypertensive. All her pulses were palpable. A one centimeter hepatomegaly and tip spleen were palpated.
A DMSA scan revealed 12% function on the right, 88% on the left.

A right nephrectomy was then performed, as well as a left autotransplant. Post operatively, she was however anuric. A DTPA scan revealed no perfusion to the left kidney. She was taken back to theatre, and at surgery a clot was found in both the artery and the vein. She remained anuric and dialysis was commenced.
Antituberculous therapy was continued, with corticosteroids and a course of 10 cycles of TLI added to control disease activity. She remained on antihypertensives and aspirin.
Her TLI was uninterrupted with no complications.

Four months later she received a successful cadaver transplant. She did well post operatively and renal function returned to normal.

She remained very well but a year after her transplant she presented acutely with pallor. Investigations revealed a panycytopenia secondary to a haemophagocytic syndrome caused by Ebstein-Barr virus.

She died despite aggressive therapeutic intervention.

At post mortem, the thoracic and abdominal aorta revealed no evidence of Takayasu's arteritis. The intima was smooth with no stenosis of the major vessels. Lymphoid tissue showed effacement of the lymph nodes and proliferation of immunoblasts. Erythrophagocytosis was prominent consistent with an Ebstein-Barr virus trigger.

Patient 31

A 13 year old girl was referred to us from JG Strydom Hospital for further management. She had presented there approximately one month previously with shortness of breath. She was found to be hypertensive and in cardiac failure. She was commenced on antifailure therapy and antihypertensives. Angiography demonstrated an ectatic ascending aorta, arch and thoracic aorta. The left common carotid, subclavian as well as renal arteries were occluded.

Clinically upon referral, the left carotid, brachial and radial pulses were absent. The four limb blood pressures were recorded as follows with Doppler; right arm 182/100mmHg, right leg 148mmHg systolic, left arm not heard, left leg 152mmHg systolic. Bruits were heard over the left carotid and renal arteries. Her JVP was elevated to 3cm. Her apex beat was laterally displaced. Clinically there was right and left ventricular hypertrophy. At auscultation a gallop rhythm was heard. On abdominal examination a 6cm hepatomegaly was palpated.

Investigations revealed a normal full blood count and renal function. Her ESR was 38 mm/hr. A Mantoux test ulcerated. A gallium scan revealed no uptake. A DMSA scan revealed 8% function on the left with 92% function on the right. MRI revealed LV hypertrophy and a fusiform aneurysm of the ascending aorta.

She continued on her antihypertensives. Corticosteroids, antituberculous therapy and aspirin were added. A left autotransplant was attempted but was unsuccessful. She received 10 cycles of TLI with no complications. Subsequently her blood pressure was easier to control and bruits were less evident. Previously an ACE inhibitor was introduced, but was withdrawn when renal function deteriorated.

At follow up angiography 6 months later, there was dilatation of the ascending aorta. There was a small stump in the region of the left innominate. No flow was noted into the left vertebral or subclavian arteries. There was retrograde filling of the left common carotid. The right renal artery showed some proximal narrowing but distal dilatation, with a prompt nephrogram. The left kidney was attached to the external iliac artery and had a delayed nephrogram.

A few weeks later the blood pressure increased again. There was a 25mmHg gradient between the right arm and right leg.
A right autotransplant was performed. Post operatively a DTPA scan showed good perfusion, adequate accumulation but prolonged excretion.

Her blood pressure remained difficult to control and an ACE inhibitor was re-introduced with good effect and no complications.

She remained stable on antihypertensives with normal renal function. Four and a half years after her initial presentation she was found to be 25 weeks pregnant at one of her follow up visits. The ACE inhibitor was withdrawn. She delivered a well, term baby. At her last visit, she was stable on antihypertensives.

RESULTS

A total of 31 patients, who fulfilled the diagnosis of Takayasu's arteritis, over approximately a 15 year period, were retrospectively evaluated. The clinical and treatment profiles of these patients are delineated in Figure 1, table 1 and detailed in each case synopsis.

The mean age of our patients was 8,42 ± 3,59 years (Range 2,4 - 14,5 years, with a median of 8 years.) There were 13 males and 18 females. The racial origins of the group were black in twenty five cases, with the rest made up of 4 Caucasians and 2 of mixed race. There were no Asian children.

The majority of our patients presented with signs and symptoms related to the cardiovascular system. Hypertension was the predominant finding occurring in 26 patients. Twenty patients exhibited signs of congestive cardiac failure, usually secondary to the hypertension. Aortic incompetence was present in 4 patients. One patient displayed definite clinical features in the form of bounding pulses and typical auscultatory findings. In the remaining three patients aortic incompetence was detected echocardiographically and it settled with treatment of the hypertension and the disease itself.

Vascular bruits and/or reduced or absent pulses denoting vascular stenoses was also a common physical finding. Multiple bruits were found in 12 patients, and these were most commonly renal artery bruits. Eleven patients had absent pulses, mostly the radial and brachial arteries. Four patients had symptoms of limb claudication, with only one of these expressing upper limb vascular insufficiency.

Seven patients had clinical features of encephalopathy. All presented with seizures, and in all it was secondary to the hypertension.
Only two patients had constitutional features related to loss of weight or fever. Two patients presented with skin lesions, one patient showed features of erythema nodosum and one patient had papulonecrotic lesions.
Two patients had arthralgia; one patient had been diagnosed as having juvenile rheumatoid arthritis years previously. Conjunctivitis was present in 2 patients; in one patient interstitial keratitis was diagnosed, and he was recently diagnosed as having a uveitis.

In twenty-seven of our patients, the Mantoux test was positive. In the majority of the patients it was strongly positive, that is, > 15mm induration; or ulcerated. This strongly positive reaction occurs in 5% of the control population. Three patients were receiving therapy for pulmonary tuberculosis at the time of diagnosis, one had prior treatment of tuberculosis and three had a family history of tuberculosis.
The ESR or CRP was elevated in 23 patients. Gallium spect scintigraphy, also to assess activity was performed in 16 patients. In 12 patients positive uptake was shown and in 4 it was negative.

All 31 patients demonstrated angiographic findings compatible with Takayasu's arteritis; with arterial lesions reflecting either occlusion, stenosis or aneurysm formation. We classified our patients into five types according to the extent or anatomical level of vascular involvement depicted angiographically. Sedation for the procedure consisted of intravenous midazolam plus local anaesthetic (or ketamine in younger patients). Types I - III as proposed originally by Ueno (35) and IV modified by Lupi Herrera et al (36) with type V added in 1988 by Pantanowitz et al. (Figure 2).

The patients were divided as follows:

Eleven had Type II alone;
Eleven had Type III;
Four had Type IV;
Five had Type V.

The renal arteries with resultant renovascular hypertension were most frequently involved in our patient series. Eleven patients had unilateral artery involvement and 15 had bilateral vessel involvement.

All our patients received antituberculous therapy. All except two received corticosteroids. Aspirin was also given for its antithromboxane effect. More aggressive immunosuppressive therapy to halt disease progression consisted of TLI or cyclophosphamide. Twenty-six patients were included, with 13 in each group. The parameters assessing pre- and post therapy included blood pressure, creatinine clearance, relapses and outcome were comparable in the two groups as reflected in Table 2. In three of the patients receiving TLI, treatment had to be interrupted due to leukopenia, whereas in the patients receiving cyclophosphamide, therapy was not interrupted. Two patients within each of these treatment groups relapsed, but responded upon treatment with the opposite immunosuppressive. In all 4 of these patients an accelerated ESR was a good marker of reactivation, since it had decreased with the previous immunosuppressive therapy, and again upon re-institution of further immunosuppressive treatment.

Repeat Gallium scanning, subsequent to therapy was negative in eleven of the 12 patients, who initially demonstrated positive uptake. One patient, in whom positive uptake was still shown, had a reactivation 8 months later.

Vascular procedures or surgery, to halt further vascular compromise was performed on 23 patients. Peri-operatively, heparin was used to prevent occlusion, and low dose aspirin was used long term for its antithromboxane effect. In total 35 procedures were performed (see Table 3). In our series, autotransplants (11 out of 15) were the most successful, with less success in the other procedures, though these had mostly been performed at other centres. In 2 patients, PTRA (percutaneous transluminal renal angioplasty) was performed. In one patient, this area later re-stenosed and in the other a thrombus occurred post procedure.

Renal artery stenting was also performed in 2 patients; in one patient this failed and in the other patient it re-stenosed. It proved to be a good temporary 'holding' procedure, with the patient subsequently having a successful autotransplant.(Fig.3 + Fig.4) Two patients had bilateral bypass gore-tex grafting, and in both these patients these grafts occluded.

Of our 31 patients, eight have died. Two of these patients had received no immunosuppressive therapy. In one patient, bilateral aortorenal gore-tex bypass grafts had been performed prior to transfer to our unit. Both these grafts subsequently occluded, though renal function was salvaged with an autotransplant. The patient, however, succumbed as a result of a delayed aortoduodenal fistula related to the remaining gore-tex graft. The other patient died with severe hypertension, pulmonary oedema and an intracranial bleed prior to surgical intervention.

Two patients who received cyclophosphamide died (one had only received a three week course). One patient who had bilateral renal artery stenosis, a right axillofemoral graft was performed which occluded. The other patient also had bilateral renal artery stenosis, in whom a unilateral autotransplant occluded.

Of the patients who had received TLI, four have died. One patient had severe pulmonary hypertension. (A cardiac and lung transplant at Cape Town was refused.) One patient who had no salvageable renal function; (a thrombus developed post PTRA of his only functioning kidney) died two days after a cadaver transplant; secondary to a persistent aortic anastomotic bleed, as well as generalised oozing from the diseased aorta. A third patient, who had had a nephrectomy and a failed autotransplant, also received a cadaver transplant, but died 20 months after the latter with an EBV induced haemophagocytic syndrome. At post-mortem, her aorta, which had been severely affected by Takayasu's arteritis prior to treatment, was found to be normal macroscopically as well as microscopically. The reversal of significant pathology is remarkable and stresses the potential of adequate immunosuppression. The fourth patient had bilateral autotransplants, which occluded, then received a cadaver transplant. Seven years after her TLI therapy, she presented with a papillary carcinoma of the thyroid. Treatment consisted of a radical thyroidectomy and radio-ablative iodine. She, however, died recently secondary to failure of her graft, with hypertension and poor compliance on peritoneal dialysis.

In a further 14 patients who received TLI or cyclophosphamide, surgical intervention has been successful. Patients have been followed up for a mean of 3½ years (range 1 year to 15 years). Three patients have been lost to follow up. (They had been seen for 1 year, 3 years and 3 years respectively). One patient who had bilateral autotransplants, had a normal term pregnancy, with a well baby delivered by Caesarean section.(Fig.5) Another patient who had a unilateral autotransplant has also delivered a normal baby. A further patient received a cadaver transplant. She had bilateral prosthetic grafts prior to transplantation, but these grafts occluded. She is well 10 years post transplant.

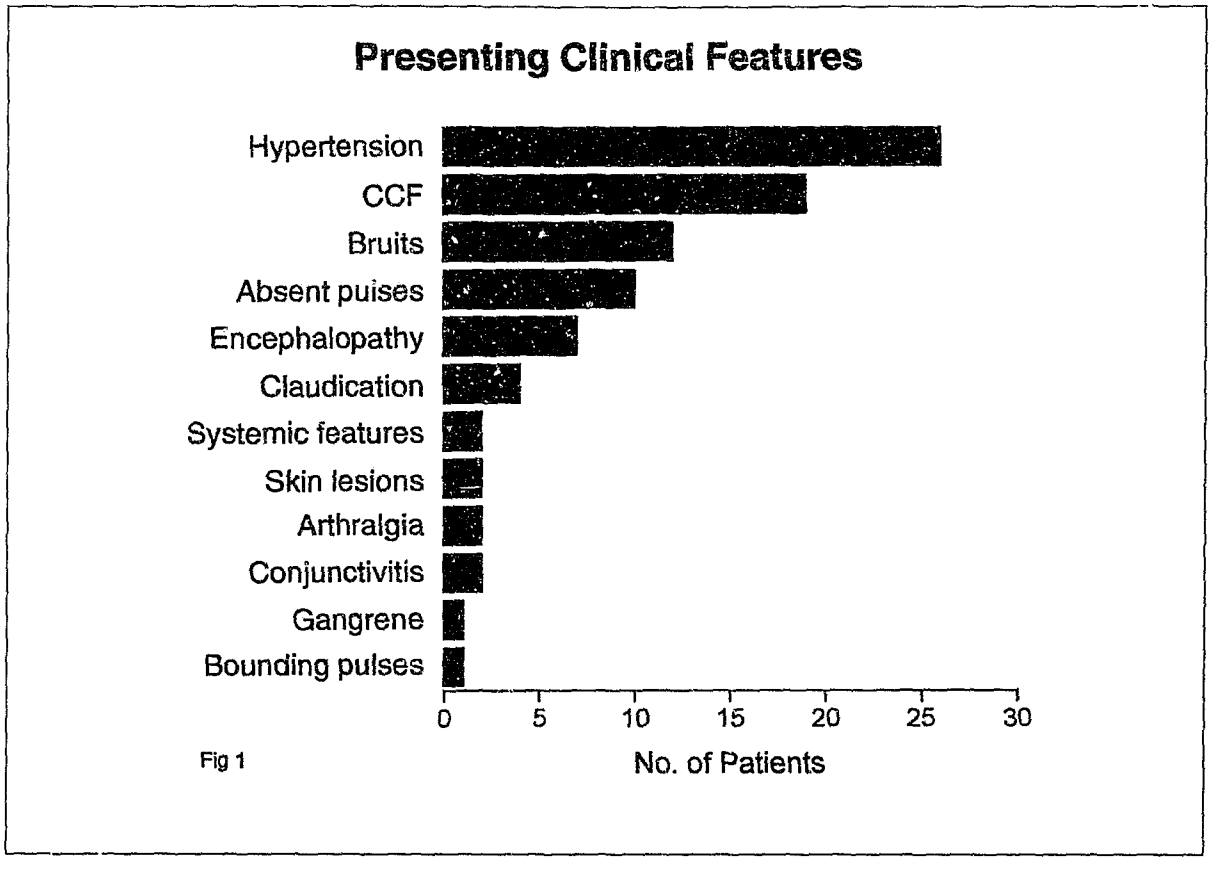

Presenting Clinical Features
Hypertension
CCF
Bruits
Absent puises
Encephalopathy
Claudication
Systemic features
Skin lesions
Arthralgia
Conjunctivitis
Gangrene
Bounding pulses
0
5
10
15
20
25
30
No. of Patients

Fig 1

Table 1 *Angiographic ..igs,Treatment and Outcome*

Patients	Vascular Involvement	Immunosuppression	Surgery	Outcome
1	Stenosis abdominal aorta,left renal artery stenosis	TLI	Bilat.autotranplants	Alive
2	Stenosis abdominal aorta,Left RAS; iliacs	Cyclophosphamide	Saphenous interposition L.renal artery	Alive
3	Stenosis abdominal aorta; Bilat.RAS	Cyclophosphamide	R.autotransplant clotted	Died (hypertension)
4	Stenosis abdominal aorta; right RAS	TLI	R.autotranplant	Alive
5	Left common carotid; right RAS	Nil	Failed ren.art stent Nephrectomy	Alive
6	Left common carotid; Bilat.RAS	Cyclophosphamide	R.autot/plant; L. nephrect.	Alive
7	R.+ L. subclavian; Bilat.RAS	Cyclophosphamide	R. nephrectomy	Alive
8	Coarct.arch + asc.aorta; ext. iliacs	Nil	Repair coarctation	Alive (histology-Takayasu's)
9	Aneurysm arch; R.subclavian + carotid	Cyclophosphamide	Nil	Alive
10	Aneurysm abdominal aorta;Bilat.RAS	Nil	Bilat.Gore-tex grafts-blocked L.autotransplant	Died (graft erosion)
11	Asc.Aorta; bilat.iliacs;pulm.art.	Cyclophosphamide	Nil	Alive
12	Stenosis abdominal aorta;Bilat.RAS	Nil	Nil	Alive
13	Aneurysm asc.aorta;Right RAS	Cyclophosphamide	Nil (refused)	Alive
14	Stenosis abdominal aorta;Bilat.RAS	Cyclophosphamide	R.axillo-femoral bypass-occluded	Died (hypertension)
15	Stenosis abdominal aorta;Bilat.RAS	Nil	Nil	Died (before Rx.could be given)
16	Stenosis L.subclavian;Bilat.RAS	TLI	Bilat.autotransplants-failed	Cadaver transplant. Papillary ca.thyroid.Died

17	Stenosis abdominal aorta;right RAS,pulm.arteries Hypoplastic right kidney	TLI	Angioplasty L.renal artery-failed	Died-post cadaver transplant
18	Stenosis R.carotid+brachioceph.; left RAS	Cyclophosphamide	Left autotransplant	Alive.Relapse- TLI
19	Stenosis bilat carotids;Bilat.RAS;partial ext.iliacs	TLI	Emergency- bilateral autotransplants	Alive
20	Stenosis abdominal aorta; Bilat.RAS	Cyclophosphamide	Bilat.autotransplants Gore-tex patch aorta	Alive
21	Aneurysm abdominal aorta;Right RAS,no L.ren.art.	Cyclophosphamide	Left autotransplant- failed	Alive-delivered a term well baby
22	Aneurysm asc.+ desc.arch;AI; pulm.arteries	Cyclophosphamide	Nil	Alive
23	Aneurysm arch,thoracic+ abdominal aorta	TLI	Nil	Alive
24	Aneurysm arch+ abdominal aorta;Bilat. RAS	TLI	Bilat.Autotransplants	Alive
25	Stenosis abdominal aorta; Bilat.RAS	TLI	Bilat gore-tex grafts- blocked	Alive- cadaver transplant
26	Aneurysm abdominal aorta involving R.renal artery	Cyclophosphamide	R. nephrectomy Later L.autotransplant	Alive.Relapse- TLI.(L.autot/p)
27	Aneurysm arch+ desc aorta;fem-pop.occlusion	TLI	Later R.autotransplant	Alive.Relapse-cyclo.(R.autot/p)
28	Bilat.pulmonary arteries.Pulmonary hypertension	TLI	Nil	Died
29	Bilat.subclavian stenosis, left RAS	TLI	L.renal artery stent- failed L.autotransplant	Alive
30	Left RAS;right renal artery thrombus	TLI	R.nephrectomy L.autotransplant-failed	Died.Cadaver transplant.EBV Haemophagocytic syndrome
31	Aneurysm arch; left RAS	TLI	L.autotransplant-failed R.autotransplant	Alive-Delivered term well baby

RAS= renal artery stenosis
AI = aortic incompetence

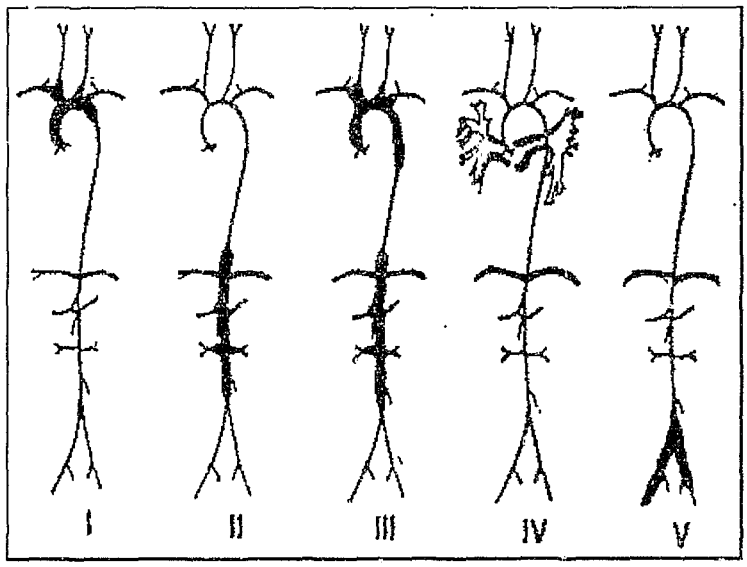


Figure 2. Classification of Takayasu's arteritis. Thicker areas denote regions involved. Type IV indicates pulmonary arterial involvement. Type V disease includes iliac involvement alone or in combination with one of the other types. (Reproduced with permission from Pantanowitz D. Modern Surgery in Africa. Johannesburg : Southern, 1988)

Table 2: Additional Immunosuppressive Therapy (Total Lymphoid Irradiation and Cyclophosphamide) Patient Profiles

	TLI ($n = 13$)	CYCLOPHOS ($n = 13$)
Systolic BP (mm Hg)		
Pre treatment	158 ± 10	144 ± 9
Post treatment	119 ± 8	126 ± 8
Creat.cl. (ml/min/ 1.73m^2)		
Pre treatment	104 ± 35	94 ± 30
Post treatment	108 ± 38	100 ± 33
Relapses	2	2
Alive	10	11
Deaths	4	2

Creat.clearance calculated by Schwartz formula. Ref.37

(There were no significant differences between the two groups)

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Deaths	4	2

Creat.clearance calculated by Schwartz formula. Ref.37

(There were no significant differences between the two groups)

Table 3 : Surgical treatment of patients

Type of procedure	Number of procedures (n = 34)
Unilateral autotranplant	9 (3 failed)
Bilateral autotranplants	6 (1 failed)
Nephrectomy	5
Coarctation repair	1
By – pass grafts (gore – tex)	4 (Bilaterally in 2 patients. All occluded)
Saphenous interposition	1
Axillofemoral bypass	1 (failed)
Renal artery stent	2 (i. Failed, ii restenosed,then successful autotransplant)
Angioplasty renal artery	2 (failed)
Cadaver transplants	4

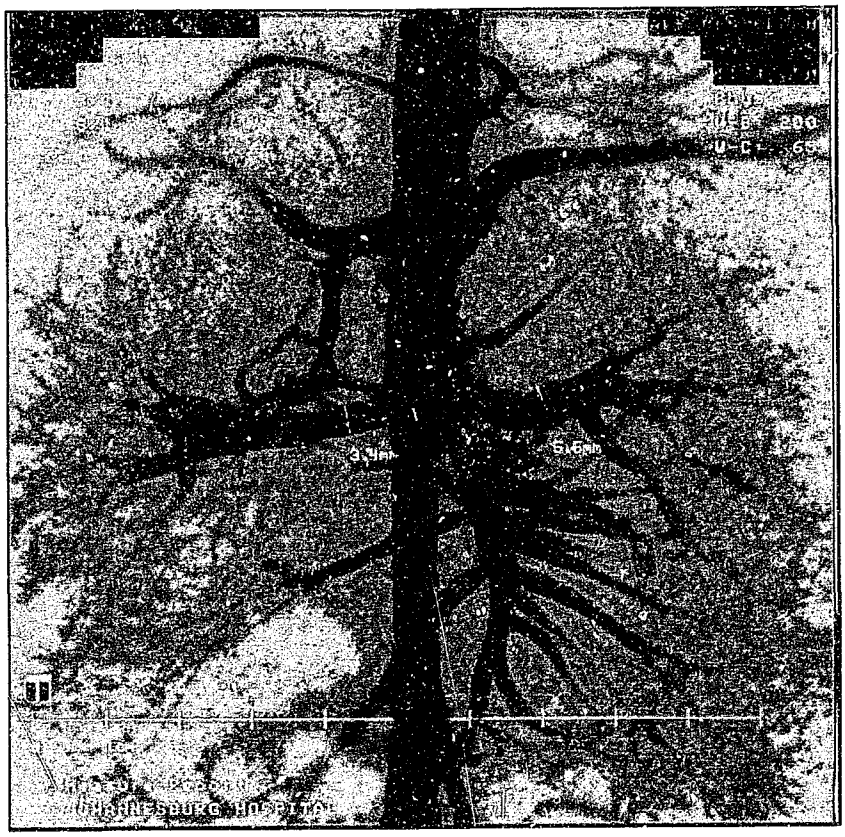


Fig.3 Angiogram of the abdominal aorta demonstrating left renal artery stenosis.

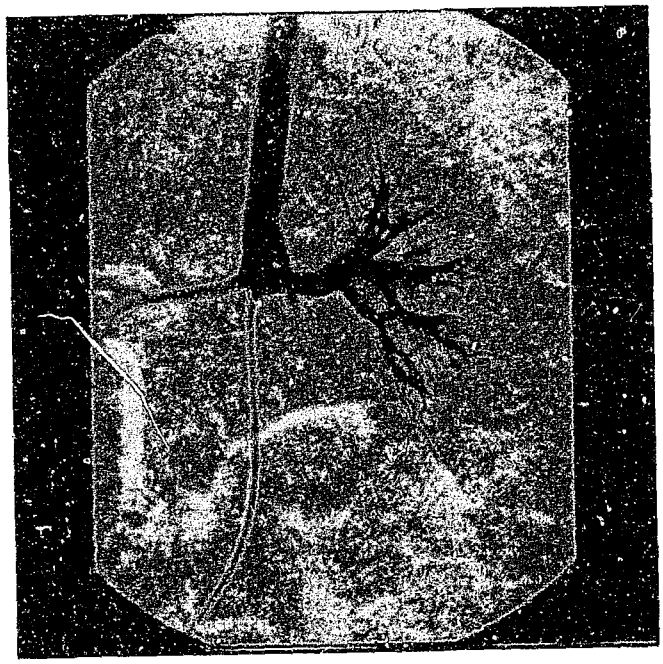


Fig 4. Angiogram of the same patient depicted in Fig.3 subsequent to placement of a stent in the left renal artery.



Fig.5 Angiogram of abdominal aorta showing bilateral autotransplantation

DISCUSSION

EPIDEMIOLOGY

Takayasu's arteritis is documented most commonly in the Eastern countries, but increasing reports from Europe, Africa, the Middle East and America have established it as a worldwide entity. (6,7,20, 36,38,39,40).

The mean age of our patients is 8, 2 years, which appears similar to other childhood reports, with the youngest reported case aged 7 months (11, 41, 42, 43). Eighteen were female and 13 were male, with a male: female ratio of 1:1,3. The disease classically has a greater female preponderance, though some authors have reported similar incidence in the sexes. (20,26,40) Our findings possibly reflect a pre-pubertal ratio, which is more even, as is seen with other auto-immune diseases pre-pubertally.(Table 4)

Takayasu's arteritis also shows racial predilections, with the highest incidences in the Orient, South America and black populations in South Africa. (5,40,44). Japan has an estimated incidence of 150 cases per year. A report in Sweden in a white population revealed an incidence of 1,2 per million per year, and a Minnesota population study documented 2,6 cases per million per year. (44,45).

This is reflected in our patient population, which shows the majority to be black, with few Caucasians or patients of mixed race. There are however, more black Africans in South Africa and tuberculosis is more common.

TABLE 4 COMPARISON OF CHILDHOOD STUDIES

	Mean age (Yrs)	N	Male	Female	M : F
Wiggelinkhuizen (1976)	9,25	8	3	5	0,6
Golding (1977)		18	8	10	1,25
Isaacson (1961)	9,57	7	2	5	0,4
Morales (1991)	11,7	26	6	20	0,3
Sharma (1991)	10,8	32	11	21	1,9
Present Study (1998)	8,2	31	13	18	1,38

AETIOPATHOGENESIS

The aetiology of Takayasu's arteritis, despite its initial description nearly a century ago is still elusive. An auto-immune basis is strongly suspected, but genetic and environmental factors are probably involved in disease susceptibility. (12,13,14).

With the predilection of this disease for young females, earlier reports suggested hormonal imbalances as a relative factor. (46) The strongest support for a genetic predisposition heralded from Japan where several familial cases as well as monozygotic twin sisters have been reported (47). With HLA-analysis, 50% of Japanese Takayasu's arteritis patients had Bw52 or Dw12 antigens compared to healthy controls. DQw1 and DR2 also show increased frequency in a similar population (48). A co-operative study between Japan, Korea and India confirmed the presence of HLA-Bw52 or B5 was closely associated with Takayasu's arteritis in all three countries (49, 50). More recently, DNA analysis is facilitated by the use of PCR (polymerase chain reaction) or SSOP (sequence specific oligonucleotide probe). This reveals how two alleles differ, allowing for precise identification of individual alleles or polymorphic residues that are critical for disease susceptibility and resistance. Kimura observed positive associations of Takayasu's arteritis with HLA-B52 and B-39. The DNA typing of the HLA-B gene and class II genes (DRB, DQA, DPBI) showed positive associations of the disease with HLA-B52, B39.2, DRBI*1502 and DPBI*0901. Comparison of the odds ratio for disease risk revealed that HLA-B52 and B39.2 were predominantly involved in susceptibility, while associations with DRBI*1502 and DRBI*0901 reflect a strong linkage disequilibrium of the class II alleles with HLA-B52 in the Japanese population (51). Data suggests that a Takayasu's arteritis susceptibility gene is located between HLA-B locus and HLA-DR and DQ loci, and HLA-B52 and B39.2 are in linkage disequilibrium with it (52).

Similar HLA and Takayasu's arteritis correlations are less evident in Western countries. Earlier reports suggest DR4 and Dw3 (MB3) were more common in Takayasu's arteritis patients in North America, though in a subsequent investigation a similar association is not found (53). In contrast to an HLA predisposition to Takayasu's arteritis, this Canadian report reveals a reduced frequency of HLA-DRI in their patients. This negative association between Takayasu's arteritis and the DR-1 antigen suggests that this antigen may be protective against the development of the disease (54).

In our group of patients, the HLA-typing was unfortunately not assessed. There is also no South African report giving an indication of possible genetic predisposition.

Among possible infective factors, evidence implicating *Mycobacterium tuberculosis* has been provided by reports of :

i) increased response to purified protein derivative of the bacteria (8, 11, 12, 42);
ii) presence of granulomatous inflammation in the arterial wall (10);
iii) demonstration of tuberculous lymph nodes in the proximity of arterial lesions (55);
iv) increased levels of agalactosyl 1gG (56).

Twenty-seven of our patients had a strongly positive Mantoux test, usually without active tuberculosis, suggesting an auto-immune trigger. It is important to emphasize that the black population without Takayasu's arteritis only has a 5% prevalence of strongly reactive Mantoux tests. The incidence of tuberculosis presently in South Africa ranges from 200/100 000 to a community in the Cape with 700/100 000 (57). In our patients, 22% either had a history of being treated for tuberculosis or a strong family history. Toma shows a 70% positive tuberculin reaction in his review but fails to comment on this (5).

Morrison and Franklin, intrigued by the possible association between tuberculosis and Takayasu's arteritis, pursued further investigation (58). Firstly, they confirmed that the aortic tissue was not directly invaded by mycobacterial organisms, nor were immune complexes or antibodies detected on immunoflourescence. Postulating the presence of an antigen in the aortic wall, an anti-BCG antibody was directed against this mycobacterial antigen, to stain the aortic tissue. In all the patients with Takayasu's arteritis that were examined, there was a staining of spindle-shaped cells in the aortic media. In control groups, (including patients with tuberculosis, but not Takayasu's arteritis, or individuals with syphilitic aortitis), this staining was negative. Furthermore, in some sections these spindle-shaped cells expressed class II antigens, making these cells have the capacity to present antigen to lymphocytes in the aorta. The antigens on the spindle cells may be autologous, but may cross react with the mycobacterial protein and may therefore stimulate the lymphocytes, which are hypersensitive to mycobacterial protein. The concept that Takayasu's arteritis is an organ specific, auto-immune disease of the aorta, occurring in individuals who may be sensitive to an external antigen (possibly mycobacterial in origin), was favored. Incorporation of this antigen directly onto the cells of the aorta, or the presence of cross-reacting antigen on the cells, results in a marked inflammatory response.

Further evidence implicating cell-mediated auto-immunity as an important role in the immunogenesis of Takayasu's arteritis was suggested by histological studies demonstrating the presence of an inflammatory cell infiltrate and necrosis of the arterial vascular walls. These infiltrating cells were shown to be CD 8 positive lymphocytes by Scott and colleagues (14).

Cytotoxic T-lymphocytes (CTL's) and natural killer cells (NKC), play a major role in cell-mediated cytotoxicity. They are thought to kill virus-infected cells or tumour cells through effector molecules in their cytoplasmic granules. One of these effector molecules is known as pore-forming protein or perforin. In their study, Seko et al, demonstrated that the infiltrating cells in the aortic tissue with Takayasu's arteritis were perforin-expressing killer cells, which directly injure the vascular wall by secreting perforin. Hence, providing evidence that cell-mediated cytotoxicity plays a central role in the vascular cell injury involved in Takayasu's arteritis (59).

Phenotypic analysis of the infiltrating cells revealed that 30% were γδ-lymphocytes in Takayasu's arteritis; while there was virtually no infiltration of these lymphocytes in the aortic tissue of patients with atherosclerosis. This may indicate that different immunological mechanisms are involved in the pathogenesis of Takayasu's arteritis compared with atherosclerosis.

At the inflammatory site, particularly the vasa vasorum; (as demonstrated by Morrison,) enhanced expression of class II antigens as well as ICAM 1 was confirmed. The increased expression of these cells may establish the vascular cells as target cells for natural killer cells and T-lymphocytes, and may facilitate the cytotxicity of these killer cells. Activated T-cells and NK cells also synthesize cytokines including IFN-γ or TNF-α in high concentration at the inflammatory site. It is therefore suspected that cytokines released by the infiltrating cells may play a role in inducing the expression of HLA's and ICAM – I in the aortic tissue.

It was also found that HSP-65 (heat shock protein), to which γδT-lymphocytes are shown to respond, was strongly induced in the media and vasa vasorum, thereby supporting the role of γδT-lymphocytes in Takayasu's arteritis. In contrast, there is only weak expression of HSP-65 in atherosclerosis. The γδT-cells have been implicated in the defence against Mycobacterium tuberculosis and they are the dominant cellular response to Mycobacterial HSP (60)

Recent data points to a further link between auto-immune disease and mycobacteria, through mycobacterial heat shock proteins. Molecular cross-reactivity between mycobacterial HSP's and host HSP's or other proteins as an initiating factor for auto-immunity has been suggested (61). The 65kDa family of HSP's has also been implicated in rheumatic disease (62). In their study, Aggarwal et al demonstrated that their patients with Takayasu's arteritis had a heightened humoral response to mycobacterial antigens, in particular its 65kDa HSP (61). Is a cause and effect relationship possible, suggesting an association between Takayasu's arteritis and the presence of antibodies to mycobacterial antigens? Advances in auto-immune disease understanding suggest this may be so. HSP's are a group of phyllogenetically conserved proteins found from bacteria to humans.

Their expression is induced by numerous stimuli including heat, from which the name 'heat shock proteins' is derived. Mycobacterial infection could therefore induce an immune response to mycobacterial HSP. These antibodies could then aberrantly cross-react with human HSP's or with other human proteins.

Cross-reactivity of immune response between HSP's of infective agents and host proteins is currently thought to be responsible for rheumatic diseases (62). A similar mechanism may occur in patients with Takayasu's arteritis, where the antibodies to mycobacterial HSP's may be cross-reacting with proteoglycans of the arterial adventitia. The host HSP's themselves, however, may also be the target of attack by antibodies to mycobacterial HSP's.

The primary cause triggering the auto-immune process in Takayasu's arteritis remains to be clarified. It is thought that the infiltrating T-cells may recognise some antigen, either in the form of a small, processed protein fragment or as a superantigen, in association with HLA's. It is also unclear whether or not the antigen recognised by infiltrating $\gamma\delta$T-lymphocytes is the same as that recognised by $\gamma\beta$T-lymphocytes. (59)

We have thought that mycobacterial tuberculosis would be a common trigger of Takayasu's arteritis in South Africa, particularly because of the strong reaction to tuberculin in most of our patients. Atypical mycobacterial diseases would be less likely to give such a marked reaction, as would BCG itself. However, in Japan, a strongly immunogenic BCG is given repetitively if no reaction to Mantoux testing is obtained. (63) Different BCG 'strains' are employed worldwide, and though these vaccines are considered equally efficacious in promoting immunity to tuberculosis, some have different reactogenicity. (64) This could prime the patient to reacting abnormally, particularly if there was already an underlying immune disorder albeit not severe. One of our Caucasian patients had Hyper IgE syndrome and had been given BCG on five separate occasions because of non-response to Mantoux testing. She had no history or evidence of previous tuberculosis, but responded at 11 years of age with diffuse Takayasu's arteritis; (the Hyper IgE syndrome having presented many years before,) but only after the BCG had been given repeatedly. She was still negative to tuberculin testing. Hence, it would seem that a mycobacterial stimulus need not give a positive Mantoux in all patients, but could still be a prime trigger for Takayasu's arteritis. Persistence of lymphocyte response to tubercular antigens even in the presence of a negative tuberculin test in previously vaccinated children is well described. (65, 66)

CLINICAL FEATURES

Takayasu's arteritis may present with a heterogeneity of features, with a clinical picture that may differ considerably in various countries. Patients may be initially asymptomatic with signs such as pulselessness or hypertension detected as an incidental finding. Conversely, presentation may be dramatic with a stroke or congestive cardiac failure as the heralding event. (44,45,67,68)

Original descriptions emphasized two stages of the disease process. The first a 'pre-pulseless' or inflammatory phase characterized by protean constitutional features including fever, malaise, loss of weight, night sweats and chest or abdominal pain. (21) The late or 'pulseless phase' is related to vascular occlusion, with clinical features dependant on the level of arterial involvement. (5, 21,26)

The initial inflammatory features are said to precede the signs and symptoms related to vascular insufficiency. These features rarely last for more than a few weeks, but may recur after intervals of months to years. (36) The dominance of these inflammatory features and the lack of specificity of initial symptoms often result in a delay in the diagnosis of Takayasu's arteritis. Patients may be investigated and treated for other disease processes such as juvenile rheumatoid arthritis, pyrexia of unknown origin or endocarditis. (45, 69) In a report by Kerr, the delay in diagnosis is longer in children, with a period of 19 months between onset of symptoms and diagnosis of Takayasu's arteritis. (44)

The acute phase may pass unrecognised and only later in the chronic phase with features of arterial occlusion, is the diagnosis made. The clinical presentation then depends on the location of arterial involvement, the efficacy of collateral vessels and the tempo of the disease. (5, 11, 26)

Comparative findings of different childhood series, including this study are reflected in Table 5. In our series of patients only 2 presented with typical constitutional features of loss of weight and fever. With the inclusion of arthralgia and skin lesions, there are 6 patients (19%). One of our patients had previously been diagnosed with juvenile rheumatoid arthritis. Herrera has indicated that in children, up to 50%, usually present acutely. (36) In a report by Morales, 65% of patients presented with constitutional features. (42) In other South African reports including Schrire and Wiggelinkhuizen, constitutional features are also less prominent at presentation. (10, 11) This may reflect ethnic variation or genetic factors. In other centres, patients may present and be diagnosed earlier, whereas in South Africa, with many patients stemming from rural areas, the early phase may pass unrecognised.

The clinical picture in the chronic or pulseless phase in different countries or ethnic groups varies to a considerable extent. (52, 55) Most of our patients presented in this phase. Hypertension occurs in 33 - 76% of Takayasu's arteritis patients. It was the most common presenting sign among our patients as well as many other childhood reports. (41, 42) In our series 87% of patients presented with hypertension; Sharma (41) and Morales (42) showed similar figures, with 75% and 86% respectively. It occurs most commonly secondary to renal artery stenosis and it is a predominant cause of renovascular hypertension in our black childhood population. (70) Hypertension may also occur as a result of coarctation of the aorta, loss of elasticity in the affected vessels, direct inflammatory impairment of the baroreceptors and aortic incompetence. (11, 26, 71)

Other vascular manifestations included diminished or absent pulses in up to 96% of patients or bruits in 94% of patients. (45) Approximately, one third of our patients presented with these features. All of the patients in Morales' series presented with absent pulses.(42) In the other South African series, the figures were similar to ours; with 50% in Schrire's group(10), and approximately 25% in Wiggelinkhuizen's (11) and Isaacson's(9) patients. Cardiac failure is a frequent (up to 67%);and often an acute manifestation in Takayasu's arteritis, especially in children. (9, 38, 72) In our series and that of Morales (42); 65% of the patients presented in cardiac failure. This feature was less common in the series by Sharma (41), where 37% presented with cardiac failure. Reasons postulated for cardiac failure include:

1) Systemic hypertension; (30)
2) Pulmonary artery involvement (73, 74): Pulmonary vessels are involved in as many as 50% of cases. Most are asymptomatic, but pulmonary hypertension and right-sided heart failure may occur. Clinical pulmonary symptoms are usually rare or absent, and severe symptoms are infrequent. The pulmonary vessels should therefore be routinely studied at angiography. In our series, 4 patients had pulmonary artery involvement. Two of them had pulmonary hypertension; one patient died and one was lost to follow up.
3) Coronary artery or coronary ostial involvement: this is a rare manifestation, with patients presenting with angina or myocardial infarction. It is usually documented angiographically or at necropsy. (10, 75)
4) Valvular heart disease: aortic or mitral valve regurgitation caused by non-rheumatic retraction of the valve leaflets is recorded. Aortic incompetence is the most common and occurs as a result of aneursymal dilatation of the ascending aorta.
   Aortic incompetence was only evident in one of our patients (3 patients had transient features only). It is more common in Japan as a consequence of higher frequency of involvement of the aortic arch and its branches. (67)

5) Myocarditis: in reports by Schamroth et al and Talwar et al, definite myocardial involvement contributing to myocardial dysfunction was found, particularly in the acute phase of the disease. Hypertension, coronary artery involvement and valvular disease had been excluded indicating a primary myocardial factor; that was proven on endomyocardial biopsy. (72, 76)

Neurological symptoms reflect the extent of involvement of the 4 cerebral branches of the aortic arch. Symptomatology includes dizziness, syncopes, strokes or TIA's and are the most common mode of presentation in Japan. (67) Hypertensive encephalopathy was a predominant presentation in South African reports (10, 11) including this study, but is rarer in other childhood studies. (42)

Skin manifestations occur in 8 - 81% of a pooled series and show geographic variation. (44, 77). The various lesions described include papulonecrotic eruptions, erythema induratum, ulcerated subacute nodular lesions, erythema nodosum, erythema multiforme, facial lupus rash. The absence of other etiological agents and a chronological sequence favour a relationship between skin lesions and Takayasu's arteritis. (26)

Recently, it has been postulated that Takayasu's arteritis may be more of a generalised systemic disorder than was previously thought, with primary parenchymal changes in addition to vascular involvement. (78)
It has been documented to occur with systemic lupus erythematosus (79), glomerulonephritis (80), interstitial lung disease and inflammatory bowel disease. (78)

TABLE 5 COMPARATIVE CLINICAL FEATURES

	Wiggelinkhuizen	Isaacson	Schrire + Asherson	Morales	Sharma	Present Study
	1976	1961	1963	1991	1991	1998
	n=8	n=7	n=12	n=26	n=32	n=31
Constit. Features						
Fever, Low	1		2	17	6	2
Cardiovascular						
Absent pulses	3	2	6	26	23	10
Bruits			3		23	12
Hypertension	5	7	7	22	24	27
CCF	3	5	5	17	12	20
Aortic Incomp.						4 (3 transient)
Claudication			5	8	4	3
Neurologic						
Encephalopathy	5	7				7
Headache				13		
Rheumatologic						
Arthralgia/ Arthritis			2	17		2
Dermatologic						
Skin eruptions			1	5		2
Gangrene			2			1
GIT						
Abd. pain			2	13		1

DIAGNOSIS AND INVESTIGATIONS

The diagnosis of Takayasu's arteritis, specifically in the acute phase remains difficult and is often delayed because of the heterogeneous clinical findings, with no pathognomonic features (44, 81). No specific or diagnostic laboratory investigation is available, and non-specific investigations may only give an indication of inflammation.

Angiography is traditionally considered to be the investigation of choice in establishing the diagnosis and determining the level and extent of vascular involvement. Total aortography is usually mandatory in the initial evaluation of the disease. (5, 40, 44) However, this technique is invasive and cumulative radiation toxicity with repeated studies to further assess disease progression is a major risk. It also inadequately assesses wall architecture, the presence of calcification and intravascular thrombi. The major change in the diagnosis of the disease is the availability of newer non-invasive imaging techniques such as Doppler ultrasonography, CT scanning and MRI which circumvent radiation
risks. (22)

Reliable, non-invasive means of detecting and diagnosing active vasculitic lesions is still unavailable. Chen et al hoped to demonstrate uptake with Indium-III labeled leucocytes in active vasculitic lesions, but this proved to be insensitive. (82)

Gallium 67-citrate scintigraphy, which demonstrates sites of inflammation is shown to be a useful diagnostic tool in assessing vasculitic activity in Takayasu's arteritis. (27, 83, 84) It should be used in conjunction with angiography or MRI angiography in elucidating the diagnosis of the disease. (83) In our series, 12 out of 16 patients were shown to have abnormal uptake in affected areas, with Gallium scintigraphy.

With real time ultrasonography concentric mural thickening of vessels, particularly the common carotids are demonstrated. Using pulsed Doppler, stenotic or occlusive lesions are identified. High resistance flow patterns were detected in diseased vessels; though subtle mural irregularities and stenotic lesions were missed by duplex evaluation. The thoracic aorta and major arterial branches of the abdominal aorta are impossible to evaluate accurately ultrasonographically. Duplex ultrasound, though is a useful tool in monitoring disease progression and effect of therapy. (85, 86)

CT scanning has also been shown to be helpful in the active phase of the disease in demonstrating high densities in affected areas; increased thickness and attenuation of the aortic walls and thrombi are delineated more clearly. In a study by Sharma et al, he reveals that angiography often reveals skip areas of involvement of the aorta. These areas, between those segments of luminal abnormality appear normal at angiography. In his study, he observes that these apparently normal segments show abnormal wall morphology. This suggests that Takayasu's arteritis involves contiguous segments of the aorta, producing wall and luminal diameter changes in some areas and only wall abnormalities in the intervening segments. (83, 87)

Data regarding the performance of MRI in the diagnosis of Takayasu's arteritis remains controversial. Yamada et al compared MRI images with those of conventional angiography in 77 patients and described its usefulness. (88.) In a further study, on a lesion by lesion basis, MRI was found to be inferior to angiography in evaluating Takayasu's arteritis. (89) MRI may be useful in the follow up of specific lesions, or when radiation is contra-indicated. However, it is expensive, requires expertise, and its unavailability is most relevant to areas where the disease is most prevalent.

TREATMENT

Medical Management

Management of the patient with Takayasu's arteritis remains complex, with no specific therapy as yet. We recommend a multifaceted approach involving both medical and surgical therapy. Initial medical therapy consists of management of hypertension, cardiac failure, antiplatelet aggregation therapy and control of the inflammatory process related to the arteritis. Hypertension related to renal artery lesions is an important cause of morbidity in Takayasu's arteritis and is also an indicator of a poor prognosis. (19, 20) Hypertension should therefore be vigorously controlled according to accepted therapeutic regimens. In their report, Grossman et al describes three patients in whom hypertension and cardiac failure was alleviated with the introduction of an angiotensin-converting enzyme (ACE) inhibitor. (90) One patient had bilateral renal artery stenosis and renal function remained stable. (90) ACE inhibitors should rather be used cautiously with careful monitoring of renal function, particularly with bilateral renal artery stenosis or a single functioning kidney with renal artery stenosis. (30) Antiplatelet agents have been used in treatment protocols, especially in patients with neurological symptoms.(91) We used aspirin for its antithromboxane effect.

All our patients received antituberculous therapy and this is advised in a few studies (11, 27, 92) though the issue remains controversial. (18) The use of glucocorticoids as the mainstay of therapy for active, inflammatory Takayasu's arteritis is widely accepted. (44, 93) An elevated ESR usually defines this, though the ESR as a sole determinant of disease activity is inaccurate and clinical, laboratory and angiographic criteria should be utilised together. (44) Dosage, duration and efficacy of therapy are variable, with success ranging between 20 - 100%. (22, 23) Results are generally disappointing, unless treatment is started promptly and irreversible vascular lesions have not already developed. Most of our patients presented in this latter phase.

Gardner documents the return of pulses in a young woman who received high dose corticosteroids. The patient, though, was diagnosed early and therapy was promptly instituted. (94) In their report, Fraga et al describe symptomatic relief in their patient's receiving corticosteroids, with improvement or return of pulses in seven instances. (95) This may occur with reappearance of the arterial lumen as inflammation settles, recanalisation of old thrombi or development of collateral circulation. (95) Hall et al (45) also describes the return of pulses in eight of sixteen patients on steroid therapy.They suggest higher steroid dosages before the ESR returned to normal. Symptoms improved as long as the elevation in ESR was controlled. To prevent frequent relapse of the disease Ishikawa advised gradual weaning of the steroid dosage.

When the ESR is persistently < 10mm/hr for 3-6 months on maintenance dose of prednisone, a small reduction in dose is usually feasible. (96) Moriwaki and Numano suggested that HLA Bw52 positive patients need a higher dosage of steroids for a longer peroid, and one needs to be watchful for relapse of the disease. (97)

In up to 40% of cases, additional cytotoxic therapy, traditionally in the form of cyclophosphamide, is required since the disease cannot be controlled by glucocorticoids alone or requires higher toxic dosages. (22, 23) In the series by Kerr et al (22); 60 patients were prospectively studied. Patients with active disease were treated with corticosteroids administered orally at a dose of 1 mg/kg daily for 3 months. If the dosage could then not be weaned to an alternate day regimen without disease exacerbation, a cytotoxic agent was added. Cyclophosphamide or Azathioprine was administered as a daily oral dose of 1-2 mg/kg, in conjunction with daily corticosteroids. Methotrexate was given once weekly, ranging from 0,15- 0,35 mg/kg orally. The usual dose was 15 mg/week, with 0,25mg increments every 2-3 weeks, to a maximum tolerated weekly dose of 25mg. Daily corticosteroids were weaned to an alternate day regimen if disease activity settled; and further weaned and stopped if the disease remained inactive. Cytotoxics were continued alone for a year after remission; then gradually weaned and stopped. Twenty five patients received cytotoxic agents because of an inability to induce remission with corticosteroids alone or failure to wean corticosteroids once the disease was controlled.Ten patients received more than one cytotoxic agent at different periods of disease activity, though no patient received combination cytotoxic therapy. The response to corticosteroids with a cytotoxic agent was similar for pediatric and adult onset patients. Twenty three percent of all treated patients, more than 50% of whom were followed for 3 or more years, never achieved remission.
Shelhamer et al (33) report on 7 of 16 patients who received cytotoxic therapy because of poor response to corticosteroids; as there was no clinical improvement during a 3 month period of daily prednisone. All their patients received a dose of 1 mg/kg. All these patients received cyclophosphamide in addition to previous steroid therapy. In all the patients with the addition of cyclophosphamide, the prednisone could be adjusted to an alternate day regimen, and in one patient it was stopped altogether. Cyclophosphamide was associated with a decrease in the progression of vascular lesions in four of six patients who had shown progression on prednisone therapy only.
As a result of poorer outcomes in our region, patients were more aggressively managed with added immunosuppressives including TLI or cyclophosphamide as mentioned. Twenty-six of our patients received further immunosuppression in one of these two forms. Our data suggest comparable profiles in the two groups (Table 2) and the beneficial effects of the two treatment modalities.

With both treatment modalities the activity of the disease settled, (as evidenced by a decrease in the ESR, or a negative gallium scan) However, the increased number of complications experienced in our transplant patients prepared with TLI, (98) would make cyclophosphamide a wiser first choice. (These complications are discussed in the following section.)

Long term use of cyclophosphamide may have significant risks including haemorraghic cystitis, infertility, herpes zoster, bladder cancer and other malignancies. Kerr et al (22) reports on continuing a cytotoxic agent for a further year after remission; (the estimated median time to remission was 20 months); though in their prolonged follow up, no malignancies occurred. In the series by Shelhamer et al (23) patients received cyclophosphamide for a mean of 27,3 months per patient. Our patients received a maximum course of eight weeks, and one intravenous bolus; and perhaps for this reason we have not encountered the complications described.
Because of the longterm risks of cyclophosphamide, and since the disease may progress despite combination therapy including corticosteroids and cyclophosphamide; alternative protocols of lesser toxicity are been investigated. Hoffman et al (25,100) with the use of methotrexate, describes the induction and facilitation of remission in 81% of 18 patients in whom corticosteroids, and in some cases cytotoxic therapy had previously failed. The most significant toxic effects included nausea and vomiting, which required a dosage reduction in 4 patients. In 5 patients, dosages were reduced since liver function values, particularly enzymes had increased to twice the upper limits of normal. The patients have been followed up for a mean of 2,8 years. Seven patients (44%) experienced relapses as glucocorticoids were tapered. Retreatment again led to remission, and 3 of these 7 patients have successfully stopped glucocorticoid therapy. Of the patients who achieved remission, 50% have sustained remissions, 4 - 34 months, (mean 18 months) and 4 in this group have not required glucocorticoid or methotrexate therapy for 7 - 18 months (mean 11, 3 months).

Mevorach et al (101) also describe a patient who failed to achieve remission after 4 months of cyclophosphamide therapy, but who responded to weekly pulse methotrexate therapy.

To date only one of our patients in this series has been commenced on methotrexate (10mg/m^2 given orally once a week), with a good clinical response and reduction of his activity markers.

SURGICAL AND INTERVENTIONAL TREATMENT

Surgery plays an important complimentary role in the management of Takayasu's arteritis. Corticosteroids and cytotoxic agents usually alleviate systemic symptoms and suppress inflammation but fail to reverse stenotic lesions. Should these lesions become fixed or approach 70% or more of the vessel wall involved, a surgical procedure of some form or another to relieve ischemic symptoms is indicated. Regardless of which technique is chosen, the outcome is more favourable when the disease is in its quiescent phase. Many strategies are recommended ranging from PTCA (percutaneous transluminal angioplasty) to bypass grafting and autotransplantation.

Balloon angioplasty, a less invasive method, has offered a new approach for the relief of stenotic lesions in patients with Takayasu's arteritis. Surgery, is traditionally used during the chronic phase of the disease to deal with the late complications, though, significant mortality rates, a high frequency of multiple vessel involvement, anastomotic site aneurysms, graft occlusion and the frequently progressive inflammatory nature of the disease has precluded it's widespread use. (102) PTCA, first used since 1980 in Takayasu's arteritis, is primarily a palliative procedure, is indicated in renal artery stenosis and stenosis of the aorta. (40, 102)
Recently, two large series of patients undergoing PTRA (percutaneous renal angioplasty) were reported.

Sharma et al reviewed the results of renal angioplasty in 20 patients with 33 stenoses (41) In 3 patients, the procedure could not be performed as a result of extreme proximal narrowing of the renal artery. One patient suffered a renal vein lesion requiring surgery. In 4 patients, re-stenosis requiring repeat angioplasty occurred within 12 months. Including this second procedure, control of hypertension was achieved in 17 of the 20 patients, followed up for a mean of 6 months.

In a more recent, long- term study, Tyagi et al (102) have reviewed 35 children with severe hypertension having ≥75% renal artery stenosis. Thirty one of the patients had Takayasu's arteritis, the remaining 4 had fibromuscular dysplasia. In 27 patients there was bilateral renal artery stenosis. PTRA was immediately successful in 54 of 59 stenotic lesions; 31 of 35 patients (86%). In 5 lesions angioplasty was unsuccessful due to an inability to cross the lesion, or the lesion could not be dilated. One patient who experienced flank pain, was shown to have an acute re-occlusion, but with re-angioplasty at low pressure, the vessel was successfully opened. In the successfully treated cases the degree of stenosis decreased from 89,3± 9,1% to 18,5± 11,4% ($p<0,01$). The blood pressure decreased within 24 - 48 hours and was maintained thereafter. In some patients a further decrease was noted a week after angioplasty.

There was a re-stenosis rate of 25,8%, higher than an adult population. Disease activity may be associated with increased development of re-stenosis. Location and length of the renal artery stenosis is an important determinant in the success of PTRA. The best results are achieved when there are discrete, non-ostial lesions. Juxta-aortic narrowing and ostial involvement makes catheter engagement and crossing of the stenotic area difficult. Availability of appropriate catheters is also a limitation. High pressure balloons (burst pressure of 17 atm) on a 5 - 8F shaft have also improved results.

In patients having stenoses of the renal artery as well as the aorta, renal angioplasty also does not provide complete relief from hypertension. Dilatation of the associated stenosis of the aorta is required to improve results. Once again, Tyagi et al (102) have shown that balloon dilatation is highly effective in relieving stenosis of the aorta, more particularly in patients with discrete lesions. There was an immediate decrease of PSG (peak systolic gradient) of 67% (75,1 ± 29,1mmHg to 24,8 ± 19 mmHg); with an increase of 113,3% in diameter (4,5 ± 2,2 to 9,6 ± 3,8mm) of the constricted segment.

These findings indicate that balloon angioplasty of aortic and renal artery stenosis is effective in relieving hypertension in patients with Takayasu's arteritis. A further factor, which may be beneficial in an improved outcome, is the use of anticoagulation measures and antiplatelet therapy. In the series by Tyagi et al (102) the patients all received intra-arterial heparin 100u/kg, during the procedure, then intravenously 6 hourly for two days. They also received aspirin 50 - 100 mg/day, which was continued for 6 months.

Complications related to the procedure included dissection, pseudo-aneurysm or the creation of intimal flaps. Despite the technical difficulties, PTRA can be safely performed, resulting in excellent angiographic and clinical results, with sustained improvement on follow up. It is also less invasive, less expensive and requires a shorter hospital stay.

Of the patients in our series, 2 patients underwent PTRA, both at other centers. In one patient, re-stenoses of the vessel occurred. In the other patient, a thrombus occurred, (in the remaining viable kidney) and renal failure followed. Two patients received renal artery stents. In one patient, performed at another center, the process failed and he subsequently had a nephrectomy. In the second patient, a stent was placed at our centre. Although this subsequently re-stenosed, it proved to be an excellent holding procedure till an autotransplant could be performed. The re-stenosis was related to intimal proliferation.

With the recent rapid advances in Interventional Radiology and Cardiology, angioplasty and stenting may be avenues that need to be more actively explored; even as a temporary procedure; should one have severe difficulty controlling blood pressure secondary to renovascular hypertension. Tyagi (102) suggests that angioplasty should be performed early, before stenotic lesions of the vessel occur. Most of our patients unfortunately present with well established stenotic lesions already. We have also advocated that control of disease activity should be achieved prior to any vascular intervention.

Where patients have occlusive arterial disease not amenable to balloon angioplasty or previous attempts have failed, the definitive treatment is operative. Surgery is performed to ameliorate those complications of Takayasu's arteritis that are known to adversely affect life expectancy, including renovascular hypertension, cerebrovascular insufficiency, aortic incompetence and aneurysmal disease. Operative procedures are avoided in the active phase of the disease, since an increased incidence of anastomotic aneurysms, graft occlusions and post operative haemorrhage are reported in this time period.

Recently, favourable results with the use of bypass and interposition grafts using prosthetic or autogenous conduits tailored to the existing arterial anatomy have been reported. (24, 68) Weaver et al have experienced excellent patency of such reconstructions regardless of the arterial substitute.(104) Of 16 arterial reconstructions at risk only 2 late graft occlusions were recognised. Lagneau et al emphasize that in Takayasu's arteritis the correct placement of the proximal and distal graft anastomoses in relatively disease free artery is an important factor in long term graft patency. Preferably, the proximal anastomoses should be placed in the aorta proximal to gross disease. He favours bypass grafting, mentioning that revascularisation by direct implantation of the renal artery into the aorta is rarely possible because of associated abdominal aortic lesions. He, however, does not discuss iliac vessel involvement and the potential use of autotransplantation.(105)

We have had some reservation in the use of bypass grafting, since in two of our patients, bilateral renal vessel gore-tex grafts occluded, and earlier patients treated at Baragwanath hospital had very poor results. (31) In contemplating autotransplantation, the aorto-iliac vessels require evaluation and therefore we recommend the classification of Takayasu's arteritis as described in Figure 2. Iliac vessel involvement is not used in the new classification of angiographic findings in Takayasu's arteritis, based on the Conference in 1994, though Gupta et al (106) have also mentioned aorto-iliac disease in their report in 1981.The technique of autotransplantation is well described in the article by Beale et al (28) on managing hypertension in Takayasu's arteritis using autografting or allograft transplantation. In our series, failed autotransplants occurred in children 5 years old and younger. A single surgeon performed the majority of our surgery and improved outcome in subsequent cases may be due to accumulated experience. (28) Surgical mortality in Takayasu's arteritis, both early and late is 10 - 20%.

OUTCOME AND COMPLICATIONS

Data reflecting the morbidity and survival of patients with Takayasu's arteritis, are best reflected in Ishikawa's series of 81 patients whom he analysed prospectively. (19) He clearly demonstrated that patients with a more severe clinical picture had a poorer prognosis. The 81 patients involved were divided into categories according to clinical findings and complications which included Takayasu's retinopathy, aortic incompetence, hypertension and aneurysmal lesions.

Forty six patients were included in the Uncomplicated/Mild group (Groups I + IIa). This included patients with no complications or one mild complication Two patients in this group were treated surgically. The more Moderate/Severe group (II b + III) included 35 patients with one severe; or two or more complications. Five patients in this group were managed surgically.
Seventy four patients (excluding the seven patients who were managed surgically) were then analysed. The overall survival for the 74 patients was 89,7% at 5 and at 10 years respectively. When comparing the two groups; the combined group I + IIa had a 10 year survival of 100%. The survival rates of the 30 patients in the combined group IIb + III was 74,2% at 5 and 10 years respectively. This is significantly lower than the patients in the first group ($p < 0,005$).

A severe event was defined as a life threatening or disabling condition attributed to Takayasu' s arteritis, occurring during follow up. Such events included cerebrovascular accidents, acute pulmonary oedema,dissecting aortic aneurysm, unilateral or bilateral permanent blindness and massive hemoptysis or hematemesis.The overall eventless survival decreased from 86,8% in the 5 th year to 80,3% in the tenth year. In comparing the two groups, Group I + IIa had an eventless survival of 97% at 10 years. In Group IIb + III this rate decreased considerably during the first five years (71,7%) and the decrease continued through the 10 year period. (58,6%) A significant difference between the 5 and 10 year eventless survival rates for the patients in groups I + IIa and those in Groups IIb + III is shown. (respectively , $p < 0,01$ and $p < 0,002$). The occurrence of a severe event during follow up was usually an ominous sign of later death or resulted in marked restriction of physical activity, or both.
Subramanyan et al (20) who analysed 88 patients according to similar categories showed a cumulative survival at 5 and at 10 years after onset, of 91% and 84% respectively; while the event free survival rates at the same intervals was 74,9% and 64%. The event free survival of Groups I+ IIa was 97% at 10 years (and 87,3% at 11 years); while in Groups IIb+ III this decreased sharply in the first 5 years to 57,7% and 38,8% at 10 years. ($p < 0,001$)

In a univariate analysis of factors that could affect event free survival the following factors showed significance:
Severity (Groups I+IIa vs IIb+III) $p < 0,002$
Hypertension (severe vs mild to moderate) $p < 0,01$
Cardiac involvement- CCF vs cardiomegaly on ECG (presence vs absence) $p < 0,05$
Age at onset, or age at diagnosis; gender; ESR; anatomic or pathologic type (obstructive vs aneurysmal lesions) showed no significance.

Ishikawa (19) suggests that extrapolation of his data to populations from other institutions, except for surgical departments (since surgically managed cases were not analysed), may be feasible if patients are similarly grouped. The majority of our patients presenting with severe hypertension and associated congestive cardiac failure; would be grouped in the more severe group.

Long term follow up studies in children are scanty, with mortality rates ranging from 21 – 40% in the short term.(10,11,31). The major causes of death in our patients included uncontrolled hypertension or complications related to surgery. In the series by Morales(42) two deaths were related to surgery; with the other deaths occurring during the early phase of the illness. With follow up of up to 15 years our mortality rate has been 25%. In comparison to the use of Gore-tex grafting our morbidity has decreased with the use of autotransplantation.

Thus far no untoward effects of immunosuppression or the disease itself, regarding fertility has been noted in our patients. One patient who received TLI and had bilateral autotransplants, recently delivered a full term normal baby. Angiotensin-converting enzyme inhibitors (ACE) with teratogenic effects such as scalp defects and renal failure in the fetus are contraindicated in pregnancy. (107) This patient was unfortunately exposed to ACE inhibitors, having returned for a follow up visit when she was already 24 weeks pregnant. The baby fortunately suffered no complications. We postulated whether the vasodilatory properties of the Calcium channel blocker she had also been on, had a protective effect. Another patient has also delivered a normal baby. She had received cyclophosphamide and had an autotransplant, but was on no antihypertensive therapy. The inflammatory activity of the disease is not usually exacerbated by pregnancy. Markers of poor maternal and fetal outcome include hypertension, extensive or aneurysmal disease and cardiac failure. A multidisciplinary approach including obstetricians and physicians is required. (108,109)

One of our patients was recently diagnosed with a papillary carcinoma of the thyroid. She had received TLI seven years previously and subsequently had a cadaver transplant. It is very likely that her malignancy was related to her low dose irradiation. (110) This is supported by the observation of a second papillary carcinoma of the thyroid in another patient, eleven years after she underwent TLI prior to renal transplantation. This gives a prevalence of 1 in 25, compared to a maximal described prevalence of 1 in 10 000; but in this age group the prevalence would be unlikely to be more than 1 in 100 000. (111) In the series of Strober et al (34); of the patients receiving TLI for intractable lupus nephritis, the follow up period is relatively short (3- 5 years). The main complications were noted during the administration of therapy and included neutropenia, thrombocytopenia and skin lesions. He notes that long- term side effects of TLI in comparison to other cytotoxic drugs in the treatment of lupus nephritis will need to be ascertained.

Kuruvila et al in a series of 12 patients advocate the use of pretransplant TLI. (112) They believe TLI provides effective immunosuppression and has the potential for reducing and possibly eliminating other immunosuppression. Their short term complications appear rather marked with two deaths related to viral infections. Other complications included fungal infections, hypothyroidism, radiation pneumonits and pericarditis. With longer term follow up for this group of patients one may see more sinister complications.
As a result of our experience we no longer advocate the use of TLI in Takayasu's arteritis or in renal transplantation.(TLI was also shown to have no benefit in pre-transplant immunosuppression, compared to other immunosuppressive medication.98)

CONCLUSION

In conclusion, Takayasu's arteritis remains an ongoing challenge, diagnostically and therapeutically. The etiology remains obscure, with an auto-immune pathogenesis postulated. Tuberculosis seems to be a common trigger in our experience. Early diagnosis and therapy, possibly aided by newer imaging techniques, is essential for a good prognosis. The chronicity and relapsing nature of this disease require treatment regimens of low toxicity. A combination of these modalities and surgical intervention may improve the outcome.

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