Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study

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Summary

Background: The last 50 years have seen major changes in the epidemiology of infective endocarditis (IE).
Aim: To evaluate local patient characteristics, risk factors, clinical sequelae, microbiology, morbidity and mortality in patients with definite IE.
Design: Prospective observational study.
Methods: Over a three-year period, patients referred with probable IE were prospectively enrolled. All received a standardized diagnostic evaluation. Epidemiological data were documented; underlying risk factors for IE were sought. Initial evaluation and follow-up (to 6 months) included the documentation of vascular or immunological phenomena, morbidity and mortality.
Results: Of 92 patients referred with probable IE, 47 had definite IE. These patients had a mean age of 37.7 years with a male predominance (1.6:1). Rheumatic heart disease was present in 36 (76.6%). Eight had prosthetic valves. Three had congenital heart disease, mitral valve prolapse or multiple central intravascular catheters, respectively. All denied the use of intravenous recreational drugs and only one tested seropositive for HIV. Renal involvement (59.6%) and clubbing (29.8%) were commonly observed. The 6-month mortality rate was 35.6%, while 44.7% needed valvular replacement. An aetiological diagnosis was made in 21, with viridans streptococci the most common isolate.
Discussion: Infective endocarditis in the Western Cape of South Africa is a disease of younger adults, with a male predominance. Rheumatic heart disease is the major predisposing factor. Degenerative heart disease and intravenous drug abuse are not important risk factors. Our data do not support the notion that HIV infection is an independent risk factor for IE. Local mortality rates are much higher than recent international figures, as is the proportion of ‘culture-negative’ IE.

Introduction

The second half of the 20th century has witnessed major changes in the epidemiology, bacteriology and clinical presentation of infective endocarditis,1–9 as well as major advances in the diagnosis and management of this classical disease.6 The changes observed in the patient profile and clinical presentation of infective endocarditis in affluent societies,1,5,6,10–12 as well as a definite decline in ‘culture-negative’ endocarditis3,4,6,9 have been highlighted extensively. What was previously described as a disease of younger adults6,13 with underlying rheumatic heart disease, has shifted towards an affliction of older patients with a different spectrum of risk factors and clinical sequelae.1,4–9 Changes in patient profile have largely been attributed to a declining incidence of rheumatic fever,1,4,5 a greater prevalence of degenerative heart disease accompanying increased longevity,4 intravenous drug abuse,5,6,8,9 the increasing number of patients with prosthetic valves14,15 and
longer survival of patients with congenital heart disease. Other factors include an increased exposure to nosocomial bacteraemia, the refinement of diagnostic methods and possibly an association with HIV infection other than the risk associated with intravenous drug abuse.

Despite the high prevalence of rheumatic heart disease in the Western Cape Province and other parts of South Africa, few recent data have been published on the epidemiological relationship of infective endocarditis and rheumatic heart disease or any other potential risk factors seen in sub-Saharan Africa.

In this prospective study, patients with infective endocarditis (IE) were evaluated with regard to epidemiological characteristics and identifiable risk factors. As a secondary goal, we aimed to give a current overview of the clinical presentation, microbiology, morbidity and mortality attributable to this condition.

Methods

All patients referred to the Department of Internal Medicine at Tygerberg Academic Hospital with the presumptive diagnosis of infective endocarditis were enrolled prospectively over a period of almost 3 years between 1997 and 2000. Infective endocarditis was diagnosed according to the Duke criteria. Patients in whom the diagnosis of IE was ultimately rejected were retained as controls. Tygerberg Academic Hospital is a 1200-bed university hospital in Cape Town, South Africa. It is one of only two referral centres rendering a tertiary service to a population of approximately 2.5 million people, most of whom are of mixed ethnicity or African descent, and live under poor socio-economic conditions.

Diagnostic evaluation

All subjects were clinically evaluated on the day of referral and daily while in hospital thereafter. Demographic data and base-line characteristics were collected and a structured history was taken. Specific attention was paid to potential risk factors, which included a history of previous rheumatic fever or valvular heart disease, previous infective endocarditis, congenital heart disease, mitral valve prolapse (with mitral regurgitation), cardiac surgery (valve replacement or repair), intravenous drug use, degenerative heart disease (e.g. calcified aortic stenosis), indwelling intravenous catheters or other potential risk factors such as HIV infection.

During the physical examination, the presence or absence of any vascular or immunological phenomena (as defined by the Duke criteria) were actively sought and documented.

A two-step diagnostic protocol was used in the evaluation of all study patients. The ‘primary’ evaluation was only followed by a ‘secondary’ evaluation if the diagnosis of IE was not confirmed or rejected within 72 h. During the primary evaluation, three blood cultures were taken from three different sites, approximately half an hour apart. Any exposure to oral or intravenous antibiotics during the two days prior to the attainment of blood cultures was documented. In affected cases, Bactec Aerobic Plus, a standard culture medium with resin for the neutralization of antibiotics, was used, rather than the standard Bactec Aerobic media used in all other cases.

All patients were examined by transthoracic echocardiography using a Hewlett Packard S 2000. Parasternal long- and short-axis windows, as well as apical four- and two-chamber views, were used to obtain two-dimensional evaluations, M-mode dimensions and duplex Doppler studies. Vegetations were defined according to the Duke criteria. Transoesophageal echocardiography (TOE) was performed whenever transthoracic visualization was suboptimal or when paravalvular extension of the disease was suspected (e.g. valve-ring abscess), as well as in all cases of suspected prosthetic valve endocarditis. The valvular apparatus was specifically scrutinized for any evidence, and if present, the nature, of preceding valvular heart disease. Nodular thickening and/or fusion of the valve leaflets, and calcification, fibrosis or thickening of the subvalvular apparatus were regarded as suggestive of previous rheumatic heart disease.

Twelve-lead electrocardiograms were performed on all patients. Further investigations included in the primary diagnostic evaluation as a full blood count and ESR, routine biochemistry, serology (C-reactive protein (CRP), Complement fractions 3 and 4 (C₃ and C₄), circulating immune complexes (CIC), Rheumatoid factor (RF), Antinuclear factor (ANF) and syphilis serology) and urinalysis (urine dipsticks and microscopy).

Only patients who gave informed consent were tested for infection with HIV-1 and HIV-2. The University of Stellenbosch Medical Virology laboratory performed these tests. A diagnosis of HIV was made by a combination of three different positive ELISAs confirmed by a second specimen tested by a separate ELISA. CD4 and CD8 lymphocyte counts were obtained for all HIV-positive patients.

The Microbiology Department of Tygerberg Academic Hospital performed all microbiological
investigations. An automated BACTEC fluorescent blood culture system (BACTEC 9240) was used for blood culturing. Specimens were incubated for 14 days to ensure detection of possible fungal infections and slow metabolizing bacteria. Organisms were identified by standard laboratory practices. Antimicrobial susceptibility testing, using the disc diffusion method, was performed according to the National Committee for Clinical Laboratory Standards (NCCLS). Where indicated, penicillin MICs were determined using the E-test method (AB Biodisc). For *Staphylococcus epidermidis* to be accepted as the infectious agent, it had to be repetitively cultured or occur in the setting of artificial valves (as required by the Duke criteria). The same applied to other possible contaminants, such as *Micrococcus* species.

Nephelometry was used to quantify the C-reactive protein (CRP), complement fractions (C3 and C4) and rheumatoid factor (RF), whereas circulating immune complexes were quantified by ELISA testing. The rapid plasma reagin (RPR) agglutination test was used to screen for syphilis, followed by a fluorescent treponemal antibody absorption test (FTA-Abs) for confirmation. Antinuclear factors (ANF) and RF were screened for by Hep-2 immunofluorescence and by latex testing, respectively.

The secondary evaluation included two further blood cultures, using Bactec Lytic/10 Anaerobic/F. These media are suitable for anaerobic organisms, as well as for intracellular aerobic organisms.

Serosal tests to screen for the so-called atypical bacteria, not all of which are readily amenable to culturing, were also included in the secondary evaluation. Table 1 summarizes the investigations performed. These tests were only considered positive if a rising antibody titre could clearly be demonstrated, and thus required that a follow-up specimen be taken when initial studies were insignificantly positive (specimens taken at day 14).

Finally, the Duke criteria (as published in 1994) were strictly applied to classify all patients as either ‘definite’, ‘possible’ or ‘rejected’ infective endocarditis.

**Patient management**

All patients were managed according to published guidelines. Cultures and antimicrobial susceptibility testing (according to penicillin MIC for viridans streptococci and resistant pneumococci) guided the choice of antibiotics, whereas empirical therapy was given to culture-negative cases. Patients presenting with the subacute form of the disease (native valves) generally received intravenous penicillin G (20 MU/day intravenously for 6 weeks) and gentamicin (1 mg/kg q8h intravenously for 2 weeks), whereas cloxacillin (2 g q4h intravenously) was added to the treatment in those presenting with more acute disease. The β-lactam antibiotics were substituted by vancomycin if methicillin-resistant *staphylococci* were suspected, or in patients with a convincing history of penicillin allergy. Prosthetic valve endocarditis was treated with a combination of intravenous vancomycin and oral rifampicin for 6 weeks in combination with 8-hourly intravenous gentamicin for the first 2 weeks of the therapy. Antibiotics were administered intravenously for the appropriate duration, which in the case of culture-negative IE was considered to be 6 weeks. No patients received out-patient parenteral antibiotic therapy (OPAT). Whenever aetiological diagnoses and MICs allowed shorter intravenous courses (2 weeks), patients were discharged on high doses of an appropriate oral antibiotic, usually amoxycillin.

A team of cardiologists, infectious diseases specialists, microbiologists, cardio-thoracic surgeons and social workers was involved in the care of patients with complicated IE, such as those with cardiac failure and other complications potentially requiring valvular replacement or other forms of cardiac surgery as indicated by internationally excepted guidelines.

**Table 1** Serological screening for atypical organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Technique</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chlamydia species</em></td>
<td>ELISA</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Latex agglutination</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Rickettsia conorii</em></td>
<td>Immunofluorescent testing</td>
<td>IgM and IgG titres &lt; 1:20</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>Immunofluorescent testing</td>
<td>Negative</td>
</tr>
<tr>
<td><em>Brucella species</em></td>
<td>ELISA</td>
<td>0–20 ELISA units</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Immunofluorescent testing</td>
<td>Negative*</td>
</tr>
</tbody>
</table>

*A single titre of > 1:128 is considered positive (otherwise a rising titre needs to be shown).*
In-patient monitoring and follow-up after discharge

All patients (including those with rejected IE) were seen daily while hospitalized and at 3 and 6 months after discharge. Embolic and immunological sequelae were actively sought and further diagnostic evaluations, for example computerized tomography (CT) of the brain, were performed when indicated. The following clinical outcomes were specifically documented: death, worsening left ventricular function (including worsening dyspnoea according to the New York Heart Association Classification\textsuperscript{24}), intensive care unit (ICU) admissions, valvular surgery or replacement, duration of hospitalization and vascular/embolic and immunological phenomena as defined by the Duke Criteria.\textsuperscript{20}

Statistical analysis

Collected data were stored in a Microsoft Access database. The baseline characteristics of all enrolled patients were evaluated to identify known underlying risk factors, and to calculate the mean age and gender distribution. Morbidity parameters (especially embolic and immunological phenomena) were documented to attain their relative frequency in definite, possible and rejected IE. Patients lost to follow-up were excluded from the analysis of the 6-month crude mortality rate.

Table 2 General epidemiological data and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Definite IE</th>
<th>Possible IE</th>
<th>Rejected IE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td>47</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>37.7</td>
<td>37.8</td>
<td>31.3</td>
</tr>
<tr>
<td>SD</td>
<td>13.4</td>
<td>15.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Range</td>
<td>57</td>
<td>51</td>
<td>71</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td><strong>Rheumatic heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>25 (53.2%)</td>
<td>4 (30.8%)</td>
<td>16 (50.0%)</td>
</tr>
<tr>
<td>Echocardiographic evidence</td>
<td>36 (76.6%)</td>
<td>8 (61.5%)</td>
<td>26 (81.3%)</td>
</tr>
<tr>
<td><strong>Previous IE</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1 (VSD)</td>
<td>1 (VSD)</td>
<td>1 (ASD)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Previous cardiac surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td>8</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Other cardiac surgery</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Positive HIV serology</strong></td>
<td>1/34 (2.9%)</td>
<td>0/10 (0%)</td>
<td>1/20 (5.0%)</td>
</tr>
</tbody>
</table>

IE, infective endocarditis; VSD, ventricular septal defect; ASD, atrial septal defect.

Ethical aspects

This study was approved by the Ethical Committee of the University of Stellenbosch (Project number 97/089) and the Research Committee of the Department of Internal Medicine, Tygerberg Hospital and was performed in accordance with the Helsinki Declaration of 1975 (as revised in 1983).

Results

Ninety-two patients with suspected infective endocarditis were evaluated during the study period. Of these, 47 were ultimately classified as having ‘definite’ IE, and 32 eventually assigned alternative diagnoses (‘rejected’ IE). Thirteen patients were classified as ‘possible’ IE and fully treated as ‘culture negative’ IE. Only six patients were lost to follow-up during the duration of this study. Two belonged to the ‘definite’ IE group, three to the ‘possible’ IE group, and one to the ‘rejected’ IE group.

Epidemiological and general baseline characteristics are summarized in Table 2. Patients with definite endocarditis had a mean age of 37.7 years (SD 13.4 years). Twenty-nine of the 47 with definite IE (61.7\%) were males, constituting a male-to-female predominance of 1.6:1.

Thirty-six of the 47 (76.6\%) patients with definite IE (including one patient with previous IE) and eight of 13 patients with possible IE either had a
history of rheumatic heart disease (RHD) or definite echocardiographic features thereof. All the cases of prosthetic valve endocarditis occurred in patients who were known to have had previous RHD (one had been previously treated for definite IE). Thus, looking purely at native valve endocarditis, 28/39 (71.8%) of definite IE occurred in the setting of underlying chronic RHD. Three other known risk factors were identified (for definite IE): ventricular septal defect, mitral valve prolapse (with significant mitral valve regurgitation) and multiple intravascular catheters. All of the 92 patients enrolled in this study denied the use of intravenous recreational drugs. Only in 8/39 cases (20.5%) with definite native valve IE could no identifiable underlying predisposing condition be identified.

Seventy-four patients consented to have HIV status tested (Table 2). One of 34 tested with definite IE (2.9%) and one of 20 with rejected IE (5.0%) tested seropositive. Both of these were incidental diagnoses of stage I HIV infection (WHO staging25), with one being completely asymptomatic and the other having only generalized lymphadenopathy (without HIV-associated systemic complaints). The patients were both females of childbearing age and had CD4 counts of 413/mm3 and 462/mm3, respectively.

Alternative diagnoses that supported the exclusion of infective endocarditis are summarized in Table 3. The eight cases where ‘chronic rheumatic heart disease’ was given as a diagnosis were all patients previously known to our institution with this diagnosis. Without exception, they were all admitted via the Cardiac unit’s out-patient department specifically to actively exclude IE, and were found to have cardiac decompensation compatible with the natural progression of their valvular lesions. Underlying rheumatic heart disease was present in 18 of the 24 other patients (75%) with rejected IE, but alternative firm diagnoses were made to explain their presentation. Five of the six patients with an acute exacerbation of rheumatic fever were known to have rheumatic heart disease.

The mortality, morbidity and clinical signs attributed to infective endocarditis are summarized in Table 4. Rejected IE cases are given for comparison. Physical examination revealed an audible cardiac murmur in every patient evaluated, including those with rejected IE. Renal involvement was observed in 59.6% of patients with definite IE. Microscopic haematuria with active urinary sediment with or without low complements (C3 and C4) or proteinuria were used to establish a diagnosis of ‘renal involvement’ in these patients. Renal biopsies were not performed as part of this observational study. Three cases of rejected IE (9.4%) were found to have ‘renal involvement’. The final diagnoses in these patients were systemic lupus erythematosus, post-streptococcal glomerulonephritis and acute rheumatic fever respectively. Clubbing (29.8%) and splinter haemorrhages (19.1%) were other commonly observed features known to be sequelae of IE. Only 2.1% presented with classical Osler nodes. Stroke (12.8%) and other major artery emboli (21.3%) were the commonest observed vascular phenomena in patients with definite IE.

Sixteen of the 45 patients followed up for 6 months (excluding the two patients lost to follow-up) died, including six who had undergone valvular replacement or surgery after their enrolment. All of these deaths were ascribed to their primary medical condition and no patient died a traumatic or unrelated death. The six-month crude mortality rate of patients with definite IE (inclusive of those who died after cardiac surgery) was thus 35.6%.

Twenty-one of the 47 patients (44.7%) needed valvular replacement. Six of them died, giving a mortality rate of 28.6% in this subgroup (none of these patients were lost to follow-up).

Four of the 31 patients with ‘rejected IE’, who were followed for 6 months, died. Two deaths were due to end-stage inoperable valvular disease; the other two died from advanced anaplastic lymphoma and complicated systemic lupus erythematosus, respectively.

An aetiological diagnosis was reached in 21 of the 47 patients with definite IE (Table 5). The positive blood cultures (n=21) yielded the following organisms: viridans streptococci (n=6, 28.6%), pneumococci (n=2, 9.5%), group D streptococcus (n=1, 4.8%), other streptococci (n=2, 9.5%), staphylococci (n=3, 14.3%), HACEK organism
other Gram-negative bacilli \( (n=3, 14.3\%) \), and other micro-organisms \( (n=3, 14.3\%) \). Three of these cultures were positive in patients with late prosthetic valve endocarditis, including two cultures that were positive for Gram-negative bacilli and one for \textit{Staphylococcus epidermidis}. One case of \textit{Staphylococcus aureus} native valve endocarditis was found in an ICU patient who was subjected to multiple central lines. Of the remaining 26 patients (i.e. ‘true’ culture negative IE), 23 had received oral or intravenous antibiotics during the 48 hours preceding the collection of blood cultures, whereas only eight of the 21 patients with positive blood cultures had received antimicrobial agents prior to the collection of cultures.

The serological markers for the ‘atypical’ organisms did not show a significantly positive result with a rising titre in any patient. One case of an insignificantly raised Brucella IgM titre was however never clarified, as the patient unfortunately died before a follow up specimen could be obtained. The cause of death was complicated acute rheumatic fever (rejected IE), and the raised IgM titre was thus considered to be an incidental and insignificant finding.

Laboratory data gathered for the definite IE group showed that 96.9\% of cases had a raised ESR and that 97.9\% had a raised CRP, while only 36.2\% of patients was found to have an abnormally high white cell count. Circulating immune complexes tested positive in 31.8\% of patients with definite IE, with 53.3\% and 32.6\% having abnormally low C3 and C4 complement fractions, respectively. Forty-four percent of definite IE cases tested positive for rheumatoid factor, and none of these patients was known or suspected to have rheumatoid arthritis. With few exceptions, the investigations described were done on all patients. Unfortunately the circulating immune complex assays were unavailable to our laboratory for a period, which limited the collection of study data in this regard (22/47 definite IE and 16/32 possible IE were tested).

**Discussion**

**Epidemiology and risk factors**

Patients with definite IE had a mean age of 37.7 years (SD 13.4 years). Almost 72\% of those with native valve endocarditis had underlying rheumatic heart disease. When comparing our observations to the epidemiology described in the literature, some important similarities and differences become apparent. Between the 1920s and 1940s, the mean age of patients with IE (USA and Western Europe) was between 30 and 39 years and up to three-quarters of the patients had underlying rheumatic heart disease. Today, more than half of all new cases of infective endocarditis are reported in patients older than 50 years and rheumatic heart disease is implicated in less than 25\%. In fact, mitral valve prolapse is currently the most common underlying cardiovascular abnormality observed in patients with IE in the US.
We found that the epidemiology of IE in the Western Cape was similar to that experienced in the developed countries in the pre-antibiotic era.1,13 The high background of rheumatic heart disease, coupled with a poor socio-economic conditions and poor dental health, could provide explanations for this observation.

Intravenous drug abuse and degenerative heart disease (e.g. calcified aortic stenosis) are two relatively commonly encountered risk factors for infective endocarditis in the US.6,27,28 We could not identify a single patient with these predispositions, suggesting that they do not play a significant role in the patient population attending our public health facilities.

HIV disease has many potential cardiac manifestations,31 and it has been suggested that HIV infection may independently increase the risk of infective endocarditis.6,17 Our observations do not support this idea, as only one (2.9%) of the 34 patients with definite IE who were tested actually had positive serology for HIV (asymptomatic infection/incidental diagnosis). This is less than the background prevalence of HIV infection in our study population, estimated as 5% or more32 at the time of this study. HIV infection in our study population is for practical purposes a heterosexual disease with very little association with intravenous drug abuse.33–35 This seems to suggest that concomitant intravenous recreational drug abuse6,17 in the US is confounding the apparent association with HIV.

A number of large series6,9,23 has reported that IE occurs more commonly in men, with a male:female ratio of 1.7:1 (range 1.0–3.0:1) and that the change in epidemiology did not alter this ratio. The ratio of 1.6:1 found in our study confirms this discrepancy in gender-associated risk.

**Microbiology**

Forty-seven of the 92 patients enrolled satisfied the Duke criteria for ‘definite’ IE, but an aetiological diagnosis could be established in only 44.7% of these definite cases and none of ‘possible’ cases of IE. The figure is low when compared to published data and international standards.4–6,9,14 In the US, ‘culture negative’ endocarditis constitutes only 2.5–30% of all IE diagnosed,6,26,30,36–39 while in The Netherlands this figure is even as low as 1.1%.9 We found that 33/36 ‘culture negative’ patients had been exposed to antibiotics within 48 h prior to blood culture sampling. No other reason could be identified.

Group D streptococci and staphylococci have emerged as the commonest causative agents in IE patients in the Western world.4–8 The 21 aetiological diagnoses made in our study are compatible with the results of earlier studies,2,3,30,36,40–43 but differ substantially from more recent figures.4–8 Contrary to the trends observed in industrialized countries, viridans streptococci were still the most common isolate in our study. Although dental pathology was not specifically evaluated in this study, the assumption that this phenomenon was related to poor dental health is probably justified. Our study population has very limited access to dental services.

We also isolated a relatively high percentage (18.2%) of Gram-negative bacilli. Two of the four patients with Gram-negative bacilli had prosthetic valve endocarditis. The relatively high frequency of these organisms may be due to their greater antibiotic resistance, and these cultures may have been less affected by use of antimicrobials prior to blood culture sampling. In our study, the screening for ‘atypical’ bacteria played an important role to exclude these organisms, but did not contribute to establishing a definite aetiological diagnosis, as all the serological tests were negative.

<table>
<thead>
<tr>
<th>Infectious agents</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viridans streptococci</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus mutans</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus sanguis</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus salivarius</td>
<td>1</td>
</tr>
<tr>
<td>Unspecified viridans streptococcus</td>
<td>1</td>
</tr>
<tr>
<td>Group D streptococci</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1</td>
</tr>
<tr>
<td>Abiotrophia adjacens*</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>1</td>
</tr>
<tr>
<td>Micrococci</td>
<td>1</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>1</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>1</td>
</tr>
<tr>
<td>HACEK group</td>
<td>1</td>
</tr>
<tr>
<td>Eikenella corrodens</td>
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</tr>
<tr>
<td>Gram-positive bacilli</td>
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<td>Bacillus species</td>
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<td>Fungi</td>
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<tr>
<td>Candida albicans</td>
<td>1</td>
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</tbody>
</table>

*Previously known as ‘Streptococcus adjacens’ or nutritionally variant streptococci. **Prosthetic valves.
Clinical presentation, morbidity and mortality

According to published data, 10% or more of patients with definite IE do not have an audible cardiac murmur, whereas all 92 patients (including 32 cases of rejected IE) enrolled in this study presented with a cardiac murmur on auscultation. The reasons for this discrepancy may reflect the differences in epidemiology and risk factor profile of our patients; alternatively, the South African emphasis on clinical examination may have missed the diagnosis in patients without cardiac murmurs.

The traditional classification of systemic phenomena as immunological, embolic or vascular, stems from the clinical features associated with the pathogenesis of IE, although in practice this division is not always clear-cut. We found immunological phenomena (Table 4) to be common and in keeping with the subacute presentation of IE seen in the majority of our patients. With the exception of renal involvement, our clinical data are remarkably similar to those previously published. However, almost 60% of the patients had significant renal involvement, defined as the presence of proteinuria or microscopic haematuria with active urinary sediment, with or without low levels of complement C3 and C4. We excluded nephrototoxic renal failure and other incidental renal involvement.

In our study population, renal involvement occurred significantly more frequently than documented in previous clinical studies, in which only 10–25% of patients were found to have renal disease, but it is entirely in keeping with autopsy data demonstrating renal disease in 56% of patients. The relatively common occurrence of renal abnormalities probably reflects the late presentation of our patients with subacute endocarditis. It may to some degree be a biased observation, brought about by the relative few positive cultures and thus a greater reliance on minor criteria to make a ‘definite’ diagnosis.

The all cause 6-month mortality rate of 35.6% found in our patients with definite IE was significantly higher than the mortality rate of 10% recorded in the patients with ‘possible endocarditis’. More importantly, this figure was, despite the frequent use of valvular surgery, also significantly higher than published rates (range 16–27%) . Many factors complicate the comparison of mortality data, including variables such as stage of presentation, degree of underlying cardiac decompensation, number of affected valves in patients with chronic rheumatic heart disease, age of the patient, prosthetic or native valve involvement, and many other factors. The relatively high proportion of ‘culture negative’ endocarditis observed locally might at least provide a partial explanation for the high mortality rate, a low percentage of positive blood cultures being associated with a worse prognosis, though the majority of our negative cultures were associated with exposure to antibiotics prior to proper collection of blood cultures. Another possibility for the observed mortality rate could have been the late referral of patients from primary and secondary health care providers. That 76.6% of patients developed cardiac failure or worsening of cardiac failure, and 59.6% renal complications, may point to late referral and other inefficiencies in the local primary and secondary health care services.

To conclude, IE as seen in the Western Cape of South Africa has distinct epidemiological features. It is still a disease of younger adults with a male predominance. Chronic rheumatic heart disease is the major predisposing factor (in contrast to trends described in the developed world), whereas degenerative heart disease and intravenous drug abuse are not. Our data do not support the notion that HIV infection is an independent risk factor for IE. Local mortality rates (35.6%) are higher than international figures, despite the fact that valvular replacements are commonly performed. ‘Culture-negative’ IE still represents a large proportion of our patients with definite IE.

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References

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