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Infective endocarditis in infants and children in the Western Cape, South Africa: a retrospective analysis

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Abstract

Infective endocarditis is a microbial infection of the endothelial surface of the heart, predominantly the heart valves, that is associated with high mortality and morbidity. Few contemporary data exist regarding affected children in our context.

Aims and Objectives: We aimed to describe the profile and treatment outcomes of infant and childhood endocarditis at our facilities. *Methods:* This is a retrospective analysis of infants and children with endocarditis at two public sector hospitals in the Western Cape Province of South Africa over a 5-year period. Patients with "definite" and "possible" endocarditis according to Modified Duke Criteria were included in the review. *Results:* Forty-nine patients were identified for inclusion; 29 had congenital heart disease as a predisposing condition; 64% of patients met "definite" and 36% "possible" criteria. The in-hospital mortality rate was 20%; 53% of patients underwent surgery with a post-operative mortality rate of 7.7%. The median interval from diagnosis to surgery was 20 days (interquartile range, 9–47 days). Valve replacement occurred in 28% and valve repair in 58%. There was a significant reduction in valvular dysfunction in patients undergoing surgery and only a marginal improvement in patients treated medically. Overall, 43% of patients had some degree of residual valvular dysfunction. *Conclusion:* Endocarditis is a serious disease with a high in-hospital mortality and presents challenges in making an accurate diagnosis. Despite a significant reduction in valvular dysfunction, a portion of patients had residual valvular dysfunction. Early surgery is associated with a lower mortality rate, but a higher rate of valve replacement compared with delayed surgery.

Infective endocarditis is a microbial infection of the endothelial surface of the heart, predominantly the heart valves, that is associated with high mortality and morbidity.[1] It typically occurs when bacteria, or other microorganisms, enter the bloodstream in patients with abnormal or denuded endothelium.

Congenital heart disease (CHD) and rheumatic heart disease (RHD) are the main predisposing cardiac conditions in children with endocarditis in low- and middle-income countries.[2] Central indwelling catheters, through their ability to introduce bacteria into the blood stream and potential to cause endocardial erosion, is also a risk factor.[3] Endocarditis has also been identified in patients with no predisposing cardiac conditions, particularly in association with *Staphylococcus aureus* bacteraemia.[4]

The diagnosis of endocarditis is approached as a syndrome using the Modified Duke Criteria that classifies it as "definite", "possible" and "rejected" according to major and minor clinical criteria.[3] In an analysis of 100 consecutive patients in the Duke University database with "definite" endocarditis according to pathological criteria, 76 had clinical criteria for "definite" endocarditis and 24 had clinical criteria for "possible" endocarditis, while none had criteria for "rejected" endocarditis.[5]

Surgery is an important part of the management of these patients. Achieving a low mortality rate, a low embolic rate and no residual valvular dysfunction is the ideal outcome. There was a significant reduction in mortality and systemic embolisation in adult patients who had early surgery compared with delayed surgery in The Early Surgery versus Conventional Treatment for Infective Endocarditis (EASE) study.[6] Findings from a retrospective review of the surgical management of children at Texas Children's Hospital were that early surgery is associated with a low risk of embolisation, recurrence and operative mortality.[7]

At our facility we follow the 2002 and updated 2015 American Heart Association guidelines for the management of endocarditis in children.[1,3] However, in the absence of clinical trials in

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children, these recommendations are based on case series and expert opinion, with low levels of scientific evidence.[3] In patients who are surgically managed for valvular endocarditis, it is our policy to achieve valve repairs as far as possible. The decision to replace or repair a valve is made at the time of surgery based on the viability of the valve. Outcomes of the management of these children in our settings are not known, making it difficult to assess the treatment strategies used and optimise the management of this complex disorder. We therefore aimed to describe the profile of infants and children with infective endocarditis at our facility and assess their outcomes to assist in optimal decision-making.

Methods

Study population

A retrospective chart review of children, from birth to 14 years of age, diagnosed with endocarditis at Red Cross War Memorial Children's and Tygerberg Hospitals in Cape Town, South Africa, from January 2013 to December 2017 was conducted. These two tertiary-level government hospitals serve the public sector of the Western Cape Province of South Africa.

Patients were identified through a search of the paediatric cardiology unit database using the search terms "Infective Endocarditis, Endocarditis and Vegetation". This was augmented with cross-referencing echocardiograms, ward and surgery record books, and a search of discharge summaries using the relevant ICD-10 code (I33.0). Each case was classified using the Modified Duke Criteria. Patients meeting criteria for "possible" endocarditis (without a suitable alternate diagnosis) and "definite" endocarditis were included for analysis. Patients meeting criteria for "rejected" endocarditis were excluded. Information was entered and stored on the University of Cape Town-supported research electronic data capture (REDCap) database.

Demographic details and basic patient characteristics, including human immunodeficiency virus status, were entered into the database. Echocardiographic findings prior to and after the completion of treatment were recorded. We used the most recent American Heart Association/American College of Cardiology classification to quantify valve regurgitation or stenosis as mild, moderate or severe in standardised echo reports.[8] The causative organism, if identified, was recorded. Complications and embolic phenomena were described. The type of intervention performed (medical and surgical), the time interval from diagnosis until surgery as well as the type of surgical intervention were noted.

Statistical analysis

Data were analysed using Stata 14.2 (StataCorp, Texas, United States of America). Continuous variables have been expressed as medians with interquartile ranges, and categorical variables are expressed as absolute number frequencies and percentages. The change in classification of valvular dysfunction from pre- to post-treatment was analysed using the McNemars-Bowker test of symmetry.[9]

Results

Over a 5-year period from January 2013 to December 2017, 49 new cases of infant and childhood endocarditis were identified, the equivalent of approximately one new case every 5–6 weeks. Patient characteristics are depicted in Table 1. The in-hospital mortality rate was 20% (n = 10). According to the Modified Duke Criteria, 63% (n = 31) were classified as "definite" and 37% (n = 18) were classified as "possible" endocarditis.

In 82% (n = 40) of the reviewed cases, a causative organism was identified, whereas culture-negative endocarditis occurred in 18% (n = 9). Gram-positive organisms were the most common type of causative organism. *Staphylococcus aureus* was the commonest organism cultured (Table 2), occurring in 33% (n = 16) of patients; 44% (n = 7) of those patients had surgery. The case fatality rate was

Table 1. Patient characteristics.

Characteristic	n (%), total n = 49
Hospital	
Tygerberg Hospital	21 (43)
Red Cross Children's Hospital	28 (57)
Area of residence	
Cape Town	17 (35)
Western Cape (excl. CPT)	29 (59)
Other (RSA)	3 (6)
Sex	
Male	22 (45)
Female	27 (55)
Age (months), median (IQR)	81.3 (31.1–21.7)
HIV status, n (%)	
Positive	0
Negative	43 (88)
HIV-exposed but negative	6 (12)

Table 2. Organisms and their frequency of occurrence.

Organisms	n (%), total n = 40
Staph aureus cloxacillin-sensitive	10 (25)
Strep Viridans (tissue diagnosis, n = 1)	5 (12.5)
Streptococcus pneumoniae	5 (12.5)
Methicillin-resistant *Staph aureus*	4 (10)
Coagulase-negative *Staph aureus*	2 (5)
Streptococcus gordoni	2 (5)
Enterococcus species	2 (5)
Group G *streptococcus*	1 (2.5)
Group A *streptococcus*	1 (2.5)
Streptococcus agalactia	1 (2.5)
Abiotrophia defectiva (tissue diagnosis)	1 (2.5)
Corynebacterium species	1 (2.5)
Bacillus cereus (tissue diagnosis)	1 (2.5)
Candida species	1 (2.5)
Moraxella catarrhalis	1 (2.5)
Pseudomonas aeruginosa	1 (2.5)
Mycobacterium tuberculosis (tissue diagnosis)	1 (2.5)

Table 3. Underlying conditions.

Underlying cardiac lesion	n (%), total n = 49
Unrepaired VSD	10 (20)
PDA	2 (4)
Unrepaired ASD	2 (4)
Unrepaired aortic stenosis	2 (4)
Unrepaired congenitally abnormal mitral valve	2 (4)
Unrepaired DORV	1 (2)
Dilated cardiomyopathy	1 (2)
Repaired VSD	3 (6)
Repaired Tetralogy of Fallot	3 (6)
DORV post-palliative procedure (Glenn shunt)	1 (2)
Tricuspid atresia post-surgical shunt (Grotex)	1 (2)
PDA post-percutaneous device occlusion	1 (2)
RHD unoperated	4 (8)
RHD operated (prosthetic valve)	1 (2)
Structurally normal heart	15 (31)

VSD = ventricular septal defect; PDA = patent ductus arteriosus; ASD = atrial septal defect; DORV = double outlet right ventricle.

Table 4. Sites of endocardial infection.

Site	n (%), total n = 53
Native aortic valve	8 (15.0)
Native mitral valve	16 (30.0)
Native tricuspid valve	12 (23.0)
Native pulmonary valve	5 (9)
Repaired mitral valve	1 (2.0)
Surgical graft	3 (6.0)
Surgical shunt	1 (2.0)
No valvular involvement	7 (13.0)

37.5% (n = 6). Out of the 10 in-hospital deaths, 60% (n = 6) were associated with *S. aureus*.

Table 3 indicates the underlying cardiac lesions. Unrepaired CHD occurred in 41% of cases; the most frequently identified lesion, unrepaired ventricular septal defect, was identified in 20% (n = 10) of cases. RHD was the predisposing condition in 10% (n = 5) of cases. In one patient, endocarditis occurred after mitral valve replacement for RHD. Repaired or previously operated CHD occurred in 18% (n = 9), while 31% (n = 15) of patients had structurally normal hearts. Six per cent (n = 3) of patients had a central venous catheter and 6% (n = 3) had dental caries.

There were 53 sites involved, with more than one site occurring in four patients. The list of sites involved is shown in Table 4. Left-sided valvular endocarditis (47%) occurred more frequently than right-sided valvular endocarditis (32%).

Embolic phenomena and complications

Congestive heart failure occurred in 41% (n = 20) of patients with a mortality rate of 14% (n = 3). All patients with multi-organ dysfunction died. Pulmonary embolus occurred in three patients with a mortality rate of 33%, and cerebral embolus occurred in four patients with a mortality rate of 25% (Table 5). Three out of 26 patients (11.5%) who had surgery had embolic phenomena prior to the operation.

Table 5. Complications and associated mortality.

Complications/embolic phenomena, n (%)*	Mortality rate
Heart failure, 20 (40)	3 (14)
Cerebral embolisation, 4 (8)	1 (25)
Pulmonary embolisation, 3 (6)	1 (33)
Mycotic aneurysm, 4 (8)	1 (25)
Acute renal failure, 5 (10)	1 (20)
Arrhythmia, 1 (2)	0
Glomerulonephritis, 4 (8)	0
Osteomyelitis/septic arthritis, 3 (6)	0
Multiple organ dysfunction, 2 (4)	2 (100)

*Data not available on one patient who was transferred to another facility.

Surgery

Surgery was performed in 53% (n = 26) of patients, and medical therapy alone was used in 45% (n = 22). Information on management could not be obtained for one patient who had been transferred to another facility. Time interval from admission to surgery was a median of 20 days (interquartile range, 9–47 days). Twenty-three per cent (n = 6) had tricuspid valve repair, 15% (n = 4) had mitral valve repair, 11.5% (n = 3) had aortic valve repair, one had a removal of infected graft and tricuspid valve repair, and one had both aortic and tricuspid valve repair. Fifteen per cent (n = 4) had mitral valve replacement with a mechanical valve, 8% (n = 2) had aortic valve replacement with a mechanical valve. One patient had aortic valve replaced by pulmonary autograft (Ross procedure).

Treatment outcomes

Valvular regurgitation and valvular stenosis were grouped together as valve pathology resulting from endocarditis and classified as mild, moderate or severe valvular dysfunction. Patients were classified according to the most severe category of valve dysfunction. Table 6 is a description of the number of patients who underwent medical treatment in each classification of valvular dysfunction prior to and at the completion of treatment. The symmetry test was not significant (p = 0.08) and the marginal homogeneity test was borderline significant (p = 0.05), indicating a marginal shift in the classification of valvular dysfunction pre- and post-treatment. Six of 14 patients treated medically for valvular endocarditis died in hospital (mortality rate = 43%).

Table 7 is a description of the number of patients who underwent surgery in each classification of valvular dysfunction prior to surgery and before discharge. Both the symmetry test and the marginal homogeneity test are highly significant, thus indicating a shift in the classification of valvular dysfunction pre- and post-treatment (p = 0.007 and 0.002). Two of 26 patients managed surgically died postoperatively (post-operative mortality rate = 7.7%).

Table 6. Outcomes of valve dysfunction in those who had medical treatment.

Pre-treatment valve dysfunction	Post-treatment valve dysfunction					
	None	Mild	Moderate	Severe	Death	Total
None	2	0	0	0	1	3
Mild	2	0	0	0	2	4
Moderate	0	0	1	0	0	1
Severe	0	0	2	1	3	6
Death	0	0	0	0	0	0
Total	4	0	3	1	6	14

Symmetry test p = 0.08 and marginal homogeneity test p = 0.05.

Table 7. Outcomes of valve dysfunction in those who had surgery.

Pre-surgical valve dysfunction	Post-surgical valve dysfunction					
	None	Mild	Moderate	Severe	Death	Total
None	0	0	1	0	0	1
Mild	0	0	0	0	0	0
Moderate	2	4	3	0	0	9
Severe	3	4	5	2	2	16
Death	0	0	0	0	0	0
Total	6	8	9	2	2	26

Symmetry test p = 0.007 and marginal homogeneity test p = 0.002.

Overall 6% (n = 3) of patients had severe residual valvular dysfunction, 24% (n = 12) had moderate residual valvular dysfunction, and 16% (n = 8) had mild residual valvular dysfunction at the completion of their treatment.

Discussion

Although infective endocarditis is a rare condition in children, challenges remain in the diagnosis and management of these patients. We have shown a high in-hospital mortality rate of 20%, and despite a significant reduction of valvular dysfunction with treatment, >40% of patients were left with some degree of residual valvular dysfunction – the long-term impact of which is not apparent in this review. In total, the need for surgery was high, with more than half of patients undergoing surgical treatment.

The cases of endocarditis in this review were identified at the two government hospitals in the province but did not include Christian Barnard Netcare Hospital (a private facility). Approximately 83% of South Africans use public healthcare facilities, making this a good representation of childhood endocarditis in the province.[10]

A reduction in mortality rate in children with endocarditis from 35% to 20% over the last 40 years at our facility may be accredited to the introduction of echocardiography in 1982, which improved diagnostic capabilities, allowing for prompt treatment.[11] Echocardiography is central to the diagnosis and management of endocarditis with a sensitivity of up to 95% in detecting vegetations in children with "definite" endocarditis.[12] The clinical usefulness of echocardiography is limited however, as not all vegetations are detected and not all patients have criteria for "definite" endocarditis.[13] The use of Modified Duke Criteria in children has limitations as well.[1,14] In our analysis, a third of the patients had criteria for "possible" endocarditis. Refinement of the Duke Criteria and alternate methods of diagnosing endocarditis are necessary.[14] Molecular techniques for the identification of organisms in patients with culture-negative endocarditis have been developed, but are far better suited for detecting organisms on tissue specimens compared with blood samples.[15] Tissue characterisation cardiac MRI, not yet available at our facility, has been shown to be an effective method for detecting endocardial inflammation in patients with endocarditis.[16] Further studies are required to validate the utility of this method.

None of the patients in this review were infected with the human immunodeficiency virus. This finding, supported by the analysis of childhood endocarditis in Leuven, Belgium,[17] suggests that human immunodeficiency virus infection and an immune-compromised state does not increase the risk of developing endocarditis in children. The hypothesis that a damaged or denuded endothelium in the presence of bacteraemia is the dominant risk factor holds true for most cases, but does not account for endocarditis that occurred in patients with structurally normal hearts. It is interesting to note that this occurred twice as many times in our analysis compared with that previously described at our facility (31% versus 14%).[11] Increasing use of central venous catheters in patients in neonatal and paediatric intensive care units may partly explain this.

Our facility follows the South African Heart Association guidelines, which are adapted from the European Society of Cardiology guidelines, for antibiotic prophylaxis for the prevention of endocarditis following dental procedures.[18] They recommend restricting the use of antibiotics to certain high-risk lesions (cyanotic heart disease and patients with prosthetic material).[19] They also emphasised the need for prophylaxis in patients with RHD,[19] an important recommendation given the persistent finding of RHD as a significant predisposing condition at our facility over the last few decades.[11] The large number of patients with underlying unrepaired ventricular septal defects (20%) suggests that these patients would also likely benefit from antibiotic prophylaxis for dental procedures.

Staphylococci and *streptococci* are the most common organisms isolated in children with endocarditis.[7,17] *S. aureus* endocarditis is a severe form of the disease accounting for 60% of the in-hospital deaths. Just over one-third of patients with *S. aureus* endocarditis died, and almost half were managed surgically. Its presence necessitates early surgical intervention.[20]

Residual valvular dysfunction typically results in ventricular dysfunction, which may contribute to mortality outside of the treatment period.[7] Despite the significant pre- to post-treatment reduction in valvular dysfunction, a portion of patients had ongoing valve dysfunction after treatment. Patients who underwent antibiotic therapy exclusively showed only a marginal improvement in valvular dysfunction with a high mortality rate (43%), while patients who had surgery showed a significant improvement in valvular dysfunction and a far lower mortality rate (7.7%). Surgery is an important part of the management of these patients, and one of its life-saving benefits is the ability to decrease the infectious load.[3]

The EASE trial clearly showed better short- and long-term outcomes in terms of embolic phenomena, congestive heart failure, and death in adult patients with large, left-sided vegetations who had surgery within 48 hours of diagnosis.[6] There was a high rate of valve replacements in the early surgery group (75%) compared

with a slightly lower rate in the conventional management group (63%).[6] The median interval from diagnosis to surgery in the review from Texas Children's Hospital was 3 days (interquartile range, 1.0–7.5 days), and half of the patients had valve replacements.[7] The median interval from diagnosis to surgery in our facility was longer (20 days; interquartile range, 9–47 days), and 27% of patients underwent valve replacement surgery, compared with 58% who had valve repair surgery. The post-operative mortality rate was, however, higher in our facility (7.7% versus 2%).[7] A mechanical valve replacement in a child has a life-long risk of thromboembolism and need for anticoagulation and monitoring.[21] In patients in whom a mechanical valve replacement is inevitable and the social/geographical factors preclude ongoing surveillance, decisions are made in the combined cardiothoracic-cardiology meeting at our facility to treat the patient medically.

Limitations of the study

This was a retrospective study of a relatively small number of patients. This study focused on short-term outcomes and did not capture complications or mortality that may have occurred after the treatment period under review. A prospective registry would provide better clinical evidence to guide decision-making with regard to indications for surgery, optimal timing of surgery, and long-term outcomes of these patients.

Conclusion

Infective endocarditis is a rare, heterogeneous disease. However, it is associated with a high morbidity and mortality. Confirming a definite diagnosis was not possible in at least a third of the cases, highlighting the need for novel techniques for detecting endocardial infection. Early surgery has better outcomes than delayed surgery, but with higher rates of valve replacement. In order to attain the lowest overall mortality rate, the lowest post-operative mortality rate and the highest rate of valve repair, the ideal timing for surgical intervention appears to be between 3 and 20 days.

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Human Research Ethics Committee of the University of Cape Town and University of Stellenbosch) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by University of Cape Town (Human Research Ethics Committee reference number 539/2018) and the University of Stellenbosch (Human Research Ethics Committee reference number N19/01/017).

Contributions. M.L.W. devised the study, conducted the study, wrote the first draft and edited all subsequent drafts. W.B. set up the electronic database and provided statistical analysis. S.R.P. assisted with development of protocol, formatting and editing. G.A.M.C. supervised the project and edited all drafts of the manuscript. B.F. assisted with identifying cases, data capturing and editing all drafts of the manuscript. J.B.L. supervised the project from protocol development stage, identified patients, reviewed echocardiograms and revised all drafts of the manuscript. L.J.Z. supervised the project from protocol development to the final editing. All authors revised the drafts and approved the final version of the manuscript.

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