Infant and Childhood Infective Endocarditis in the Western Cape, South Africa: A Retrospective Review

M Willoughby, DCH (SA), FCPaed (SA), MMed (UKZN).
Student number: wllmar048
wllmar048@uct.ac.za

Supervisor
Prof Liesl Zuhlke
Co-Supervisors
Dr George Comitis, Dr Barend Fourie, A/Prof John Lawrenson, Susan Perkins, Wisdom Basera

This study was conducted as a dissertation in the part-fulfilment of the MPhil degree (Paediatric Cardiology) for Dr M Willoughby

Contents

Declaration page

DECLARATION

I, Mark Willoughby, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 4/2/2020

Abstract

Introduction

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 review 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; 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 when compared to delayed surgery.

Acknowledgments

The Red Cross Children's Heart Disease Research Unit provided assistance with this study, and Dr Paul Human assisted in acquiring data from the surgical database. Dr Mark Willoughby was first author and therefore devised the study, conducted the study, wrote the first draft and edited all subsequent drafts. Wisdom Basera set up the RedCap electronic database and provided statistical analysis. Susan Perkins assisted with development of protocol, formatting and editing. Dr George Comittis supervised the project and edited all drafts of the manuscript. Dr Barend Fourie assisted with identifying cases, data capturing and editing all drafts of the manuscript. Professor John Lawrenson supervised the project from protocol development stage, identified patients, reviewed echocardiograms and revised all drafts of the manuscript. Professor Liezle Zulhke supervised the project from protocol development to the final editing. All authors revised the drafts and approved the final version of the manuscript. The department of Cardiothoracic Surgery at Red Cross Children's Hospital (Dr Andre Brooks, Professor Johan Brink and Professor John Hewitson) have been an integral part of the surgical management of patients with Infective Endocarditis at Red Cross Children's Hospital and although did not contribute to this manuscript, their contribution to the care of these patients is acknowledged.

Abbreviations

IE	Infective Endocarditis
CHD	Congenital Heart Disease
HACEK	Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella
HIV	Human Immunodeficiency Virus
MRSA	Methicillin resistant Staphylococcus Aureus
RHD	Rheumatic Heart Disease
TTE	Transthoracic Echocardiography
SA	South Africa
CoNs	Coagulase negative staphylococci
NICE	National Institute for Health and Clinical Excellence
AHA	The American Heart Association

Chapter 1

1.1 Context

Infective endocarditis (IE), defined as a microbial infection of the endothelial surface of the heart, is relatively rare in children.[1, 2] It is, however, associated with substantial morbidity and mortality. The most frequent sites involved in endocarditis are the heart valves (native or prosthetic), but it may occur elsewhere on the endocardium such as septal defects, mural endocardium or foreign bodies (intracardiac patches and surgically constructed shunts).[1]

Epidemiological studies of infective endocarditis in paediatric populations in developing countries have demonstrated that congenital heart disease (CHD) and rheumatic heart disease (RHD) are the most significant risk factors for developing IE in these patients. Between 39% and 53%[4] of children have RHD as their underlying condition and approximately 45%[3, 4] of children had CHD as their underlying condition. There are numerous bacteria responsible for causing infective endocarditis[5], however Viridans group streptococci and *Staphylococcus aureus* have been identified in studies from both developed countries and developing countries as being the most common organisms responsible in children [3, 4, 6].

In the so-called 'surgical era', there are increasing numbers of hospital-acquired organisms such as coagulase negative staphylococci (CoNS), gram-negative bacilli, and yeasts that cause IE.[7] In developing countries with less availability of congenital heart surgery this may not be the case, and it is expected that community-acquired IE is the predominant type of IE in those countries.

Catheter-related IE in children and neonates is also a known association. IE may occur in infants and children with no predisposing[8] cardiac conditions, especially in staphylococcus aureus septicemia.[9]

There appears to be conflicting evidence with regards to the effect that Human Immunodeficiency Virus (HIV) infection has on the risk of developing IE. In a prospective study of IE in SA, HIV was not associated with an increased risk for IE in adult patients.[10] However in a multi –centre autopsy study of patients with HIV, it was found that the prevalence of HIV in IE was similar to that in other high-risk groups such as intravenous drug users[11]. It has also been found that patients with advanced HIV disease have a 30% higher mortality with IE than asymptomatic HIV infected patients[12].The high prevalence of HIV infection and RHD in South Africa however, may result in a significant number of patients with IE to be coincidentally HIV infected.[13] To our knowledge no work has been published on relationship between HIV and IE in children.

Bacteria originating from the mouth account for a significant proportion of cases of IE and poor oral hygiene is an important risk factor for IE in patients with predisposing conditions[14]. A transient bacteremia may occur in patients following dental procedures as well as during routine oral activities such as tooth brushing, flushing and chewing, especially in patients with poor oral hygiene placing these patients at an

increased risk of developing IE.[14] It has therefore been a long standing practice to give antibiotic prophylaxis to patients with CHD undergoing dental procedures. However in 2008 in the United Kingdom the National Institute for Health and Clinical Excellence (NICE) guidelines were published stating that antibiotic prophylaxis before any invasive procedure should cease and should only be given at the patient's request[15] The American Heart Association (AHA) stated in their guidelines that it is reasonable to shift a disproportionately large focus on antibiotics prophylaxis to an emphasis on oral hygiene and prevention of oral disease[5] Because of the high prevalence of RHD and poor oral hygiene in SA and other developing countries, the SA Heart association has not adopted the UK guidelines or the AHA guidelines but recommends the use of antibiotic prophylaxis in patients undergoing dental procedures who have cardiac lesions that are considered a high risk for the development of IE[14]. The Western Cape Paediatric Cardiology Service in conjunction with the Dental Departments at Red Cross Children's Hospital and Tygerberg Hospital adhere to the guidelines established by the SA Heart association for the prevention of IE in children undergoing dental procedures.

The diagnosis of IE is based on modified Duke's criteria which classifies IE into 3 groups: definite, possible and those in whom the diagnosis is rejected according to major and minor criteria.[16]

Transthoracic echocardiography (TTE) has a sensitivity of up to 97% in the detection of IE in children and thus plays a central role in its diagnosis and management.[17] The site and size of the lesion, valvular and cardiac function as well as periannular extension of the vegetation can be detected by echocardiography.[18]

Guidelines, based predominantly on expert opinion and case series, exist for the indications and timing of surgery in the management of IE in adults.[19] Recommendations regarding the management of IE in infants and children are extrapolated from the adult guidelines along with a limited number of case series and expert consensus.[5] These indications for surgery are determined by: the size and location of the vegetations (> 10mm, left sided lesions), presence of systemic emboli, progression of heart failure and the presence of abscesses and fistula within the heart.[5, 18]

Early surgical intervention in the management of childhood and infant IE, defined as surgery within 7 days of diagnosis, has been shown to be beneficial and safe when indicated. In a retrospective review of the surgical management of children with IE over a 15-year period at Texas Children's Hospital, 61% of patients underwent surgery within 7 days of diagnosis (25% within the first 3 days after diagnosis). The authors concluded that early surgical therapy had a low risk of septic embolisation, recurrence and operative mortality with high rates of successful valve repair.[20]

Medical management of IE consists of a prolonged course of intravenous antibiotics.[21] The choice of antibiotics and duration of treatment is determined by microbiological cultures of the patient's blood or directly from samples of the vegetation in patients who undergo surgery.[5] The use of central venous catheters in the care of newborns has led to an increase in the incidence of IE in neonates with structurally

normal hearts[5], and the prevention of sepsis is therefore an important tool for the prevention of IE in these patients. Strict adherence to aseptic techniques when inserting and using central venous catheters reduces the frequency of catheter-related infections[22]

A systematic review of the global and regional burden of IE over a 20-year period (1990 – 2010) for all age groups found that 15.8% of patients with IE had strokes, 32.4% underwent valvular surgery and the overall case fatality rate was 21%. In this review, however no studies were identified that reported on the incidence and burden of the disease in Sub-Saharan Africa.[23] A 3-year prospective epidemiological study of IE in the Western Cape looking at patient characteristics, sequelae, morbidity and mortality was conducted at Tygerberg Hospital between 1997 and 2000. The study focused on adult IE, with the mean age of participants being 37.7 years. The 6-month mortality rate was 35% and the predominant underlying condition was RHD, occurring in approximately 76.6% of patients with IE. [10]

The outcomes of infants and children with IE managed in the Western Cape Paediatric Cardiology Service, as well as the impact of this disease in terms of long- term morbidity and mortality in affected children is less well described. The paucity of data pertaining to IE in children in the developing world makes decision-making regarding the optimal treatment of IE in children challenging. There is also a lack of evidence guiding the optimal timing of surgical intervention.

References

1. Ferrieri P, Gewitz MH, Gerber MA, Newburger JW, Dajani AS, Shulman ST, Wilson W, Bolger AF, Bayer A, Levison ME, Pallasch TJ, Gage TW and Taubert KA. Unique features of infective endocarditis in childhood. *Pediatrics*. 2002;109:931-43.

2. Kothari SS, Ramakrishnan S and Bahl VK. Infective endocarditis--an Indian perspective. *Indian Heart J*. 2005;57:289-94.

3. Bitar F, Jawdi R, Dbaibo G, Yunis K, Gharzeddine W and Obeid M. Paediatric infective endocarditis: 19-year experience at a tertiary care hospital in a developing country. *Acta paediatrica (Oslo, Norway: 1992)*. 2000;89:427-430.

4. Sadiq M, Nazir M and Sheikh SA. Infective endocarditis in children—incidence, pattern, diagnosis and management in a developing country. *International Journal of cardiology*. 2001;78:175-182.

5. Baltimore RS, Gewitz M, Baddour LM, Beerman LB, Jackson MA, Lockhart PB, Pahl E, Schutze GE, Shulman ST, Willoughby R, Jr., American Heart Association Rheumatic Fever E, Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Y, the Council on C and Stroke N. Infective Endocarditis in Childhood: 2015 Update: A Scientific Statement From the American Heart Association. *Circulation*. 2015;132:1487-515.

6. Niwa K, Nakazawa M, Tateno S, Yoshinaga M and Terai M. Infective endocarditis in congenital heart disease: Japanese national collaboration study. *Heart*. 2005;91:795-800.

7. Rosenthal LB, Feja KN, Levasseur SM, Alba LR, Gersony W and Saiman L. The changing epidemiology of pediatric endocarditis at a children's hospital over seven decades. *Pediatric cardiology*. 2010;31:813-820.
8. Stockheim JA, Chadwick EG, Kessler S, Amer M, Abdel-Haq N, Dajani AS and Shulman ST. Are the Duke criteria superior to the Beth Israel criteria for the diagnosis of infective endocarditis in children? *Clin Infect Dis*. 1998;27:1451-6.
9. Martin JM, Neches WH and Wald ER. Infective endocarditis: 35 years of experience at a children's hospital. *Clin Infect Dis*. 1997;24:669-75.
10. Koegelenberg CF, Doubell AF, Orth H and Reuter H. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. *QJM*. 2003;96:217-25.
11. BARBARO G, DI LORENZO G, GRISORIO B, BARBARINI G and INVESTIGATORS4 GIPLSCDPADA. Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. *AIDS research and human retroviruses*. 1998;14:1071-1077.
12. Nahass RG, Weinstein MP, Bartels J and Gocke DJ. Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type I-negative and-positive patients. *Journal of Infectious Diseases*. 1990;162:967-970.
13. Ntsekhe M and Hakim J. Impact of human immunodeficiency virus infection on cardiovascular disease in Africa. *Circulation*. 2005;112:3602-3607.
14. Jankelow D, Cupido B, Zühlke L, Sliwa K, Ntsekhe M, Manga P, Doubell A, Lawrenson J and Essop MR. Prevention of infective endocarditis associated with dental interventions. *SA Heart*. 2017;14:170-174.
15. NICE CfCPa. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. 2008.
16. Durack DT, Lukes AS and Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med*. 1994;96:200-9.
17. Penk JS, Webb CL, Shulman ST and Anderson EJ. Echocardiography in pediatric infective endocarditis. *Pediatr Infect Dis J*. 2011;30:1109-11.
18. Marwah A SS. Management of infective endocarditis in children. *Journal of Indian College of Cardiology*. 2011;1:1190124.
19. Prendergast BD and Tornos P. Surgery for infective endocarditis: who and when? *Circulation*. 2010;121:1141-52.
20. Shamszad P, Khan MS, Rossano JW and Fraser CD, Jr. Early surgical therapy of infective endocarditis in children: a 15-year experience. *J Thorac Cardiovasc Surg*. 2013;146:506-11.
21. Hitzeroth J, Beckett N and Ntuli P. An approach to a patient with infective endocarditis. *S Afr Med J*. 2016;106:145-50.
22. Baltimore RS, Gewitz M, Baddour LM, Beerman LB, Jackson MA, Lockhart PB, Pahl E, Schutze GE, Shulman ST and Willoughby R. Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. *Circulation*. 2015;132:1487-1515.
23. Bin Abdulhak AA, Baddour LM, Erwin PJ, Hoen B, Chu VH, Mensah GA and Tleyjeh IM. Global and regional burden of infective endocarditis, 1990-2010: a systematic review of the literature. *Glob Heart*. 2014;9:131-43.

24. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ and O'gara PT. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2017;70:252-289.
25. Ross RD, Bollinger RO and Pinsky WW. Grading the severity of congestive heart failure in infants. *Pediatric cardiology*. 1992;13:72-75.
26. Li JS, Sexton DJ, Mick N, Nettles R, Fowler Jr VG, Ryan T, Bashore T and Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clinical infectious diseases*. 2000;30:633-638.

1.2 Ethical Considerations

A Waiver of Consent was obtained from the Ethics Committee as this is a retrospective study; there were no interactions with subjects or their families. Patient confidentiality has been maintained throughout the study and publication of the final manuscript.

Ethical approval to conduct the study was obtained from UCT and from Stellenbosch university.

UCT HREC number: 539/2018

Stellenbosch HREC number: N19/01/017_Recip_UCT_539/2018

CARDIOLOGY IN THE YOUNG

Submission to *Cardiology in the Young* is exclusively via the web-based peer-review system, *CTY* Manuscript Central.
Online submission enables rapid review and allows online manuscript tracking.
Please use the following URL: http://mc.manuscriptcentral.com/cty

Editorial Policies

Cardiology in the Young is devoted to cardiovascular issues affecting the young and the older patient with the sequels of cardiac disease acquired in childhood. Submission of both basic research and clinical papers is encouraged. Articles on fundamental principles will also be considered for publication. Reviews on recent developments are welcome. The Journal serves the interest of all professionals concerned with these topics. By design, the Journal is international and multidisciplinary in its approach, and the members of the Editorial Board take an active role in the Journal's mission. Prospective authors are encouraged to consult with the editors and members of the Editorial Board with any inquiries. The editors encourage the submission of articles from developing countries.

Articles should be concerned with original research not published previously and not being considered for publication elsewhere. Authors must ensure that their studies comply with appropriate institutional and national guidelines for ethical matters. Specifically, by submission of a manuscript, the authors are responsible for compliance with guidelines and regulations of the authors' institution and all appropriate governmental agencies.

Articles including human subjects must include a statement that informed consent was obtained and that the study was reviewed and approved by the institution's committee on human experimentation. Articles including animal experimentation must conform to the principles of the American Physiological Society, and a statement acknowledging conformation to these standards must be included in the *Materials and methods* section of the manuscript. Authors are also requested to identify possible conflicts of interest, especially if they relate to commercial sponsorship or equity holdings.

Copyright

The policy of Cardiology in the Young is that authors (or in some cases their employers) retain copyright and grant Cambridge University Press a licence to publish their work. In the case of gold open access articles this is a non-exclusive licence. Authors must complete and return an author publishing agreement form as soon as their article has been accepted for publication; the journal is unable to publish the article without this. Please download the appropriate publishing agreement here.

For open access articles, the form also sets out the Creative Commons licence under which the article is made available to end users: a fundamental principle of open access is that content should not simply be accessible but should also be freely re-usable. Articles will be published under a Creative Commons Attribution license (CC-BY) by default. This means that the article is freely available to read, copy and redistribute, and can also be adapted (users can "remix, transform, and build upon" the work) for any commercial or non-commercial purpose, as long as proper attribution is given. Authors can, in the publishing agreement form, choose a different

kind of Creative Commons license (including those prohibiting non-commercial and derivative use) if they prefer.

Use of Abbreviations

Abbreviations are **not** allowed in the text except for the following **only**: NYHA, CHD, MRI, CT, ICU and units of measure such as mmHg or kg, are allowed. However, any abbreviations can be used on tables and figures.

Language

The language of the Journal is English, but acceptance of a manuscript will reflect scientific rather than grammatical content. The editors undertake to facilitate the publication of papers from those authors whose native language is not English.

Manuscripts

Manuscripts should be submitted via the web-based peer-review system, *CTY* Manuscript Central and must include a complete set of Figures. Further information regarding Figure formats is outlined below.

Authorship

Authorship should be assumed only by those workers who have contributed materially to the work and its report, and who accept the responsibility for the accuracy of the concepts expressed. Colleagues who have otherwise assisted or collaborated should be recognized in the section for acknowledgements. An excellent guide to authorship is given by the Style Manual Committee of the Council of Biology Editors, and the editors encourage consultation with this source.

Style

The Journal uses the English language and as such does not use Latin terms such as 'superior vena cava'. Anatomic terms should be given in the English language. Headlines and subheadings should be liberally employed in the methods, results, and discussion sections. Use short paragraphs whenever possible. The authors should strive for clarity of expression, avoiding, in particular, the use of jargon. Authors should also avoid conventions such as Group 1, Group 2, and so on, using descriptive titles rather than alphanumeric codes.

Title page

The manuscript should include a title page, and it should follow these rules:

1. Author qualifications (for example MD) must **not** be included on the authors' list on the title page, except in the address for correspondence.

2. Include the first names of the authors, followed by the initials of any middle names, and finally, the family name.

3. Include the affiliation address(es) for the authors, to include the department, institute, city and country.

4. Include an address for correspondence, with the full postal address, telephone and e-mail address of the author in question.

Manuscript types

Allowed manuscript types are Original Article, Brief Report, Review Article, Editorial, Image, Letter and Guidelines. Each is described below in detail.

Original Articles

Divide the manuscript into the following sections:

- Title Page (see instructions on page 2)
- Abstract
- Keywords (3-6),
- Headings: Introduction, Materials and methods, Results, Discussion, Acknowledgements, Financial Support, Conflicts of Interest, Ethical Standards, References, Tables, Figure legends and Figures

Abbreviations

Abbreviations are **not** allowed in the text except for the following **only**: NYHA, CHD, MRI, CT, ICU and units of measure such as mmHg or kg, are allowed. However, any abbreviations can be used on tables and figures.

Abstract

The Abstract should be no more than 250 words and should include statements identifying relevant methods and results justifying publication. Do not use abbreviations or symbols.

Introduction

The Introduction should be brief and set out the purposes for which the study has been performed. It should not include an extensive review of the literature.

Materials and Methods

The Materials and Methods should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used with appropriate reference to previously published methods. Statements confirming conformation to institutional and governmental review of the experimental protocol (see above in the Editorial policies section) should be included here.

Results

The results should be presented precisely. Reference to Tables and Figures, to the extent that they contribute substantively to help the reader understand clearly the relevant positive and negative findings, is encouraged. Keep discussion of their importance to a minimum in this section of the manuscript.

Discussion

The Discussion should relate directly to the study being reported. The Discussion should interpret the results, should describe the relevance of the results, and should include a discussion of the limitations of the study. Do not include a general review of the topic.

Acknowledgements

Acknowledgements should follow the discussion. Here you may acknowledge individuals or organisations that provided advice and/or support (non-financial). Formal financial support and funding should be listed in the following section. The Acknowledgements should be placed after the main body of the text before Financial Support. If there are no Acknowledgements, the title should be inserted followed by "None". Papers that do not include an Acknowledgements section will not be reviewed.

Financial Support

The Financial Support statement should be placed after the Acknowledgements and before the Conflicts of Interest section. Please provide details of the sources of financial support for all authors, including grant numbers. This is particularly important in the case of research that is supported by industry. Support from industry not only includes direct financial support for the study but also support in kind such as provision of medications, equipment, kits or reagents without charge or at reduced cost and provision of services such as statistical analysis. For example, "This work was supported by the Medical research Council (grant number XXXXXXX)". Multiple grant numbers should be separated by a comma and space, and where research was funded by more than one agency the different agencies should be separated by a semi-colon, with "and" before the final funder. Grants held by different authors should be identified as belonging to individual authors by the authors' initials. For example, "This work was supported by the Wellcome Trust (A.B., grant numbers XXXX, YYYY), (C.D., grant number ZZZZ); the Natural Environment Research Council (E.F., grant number FFFF); and the National Institutes of Health (A.B., grant number GGGG), (E.F., grant number HHHH)". Where no specific funding has been provided for research, please provide the following statement: "This research received no specific grant from any funding agency, commercial or not-for-profit sectors." Papers that do not include a Financial Support statement will not be reviewed.

Conflicts of Interest

The Conflicts of Interest section should be placed after Financial Support. Conflict of interest exists when an author has interests that might inappropriately influence his or her judgement, even if that judgement is not influenced. Because of this, authors must disclose potentially conflicting interests so that others can make judgements about such effects. At the time of submission authors should disclose any financial arrangements or connections they may have that are pertinent to the submitted manuscript and that may be perceived as potentially biasing their paper. Non-financial interests that could be relevant in this context should also be disclosed. If no relevant interests exist, this should be stated. This requirement applies to all the authors of a paper and to all categories of papers including letters to the editor. If there are no interests to declare, the title should be inserted followed by "None". Papers that do not include a Conflicts of Interest section will not be reviewed.

Ethical Standards

The Ethical Standards statement, if required, should be placed after the Conflict of Interest section before the References. Where research involves human and/or animal experimentation, the following statements should be included (as applicable): "The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (please name) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional

committees (please name) ." and "The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guides on the care and use of laboratory animals (please name) and has been approved by the institutional committee (please name)." If the research does not involve human and/or animal experimentation, this statement should be omitted. Papers reporting the results of human and/or animal experimentation that do not contain an Ethical Standards statement will not be reviewed. For more information on the ethical standards and procedures of Cambridge Journals, please visit *Cambridge Journals Online*.

Review Articles

Reviews of recent developments are welcome. Authors are encouraged to contact the editor to determine the appropriateness for inclusion. The format is the same as for Original Articles (above). In particular, please see the note on Abbreviations, above.

Case Reports / Brief Reports

Case Reports which add important new information will be published as Brief Reports, and must conform to the following requirements:

- Abbreviations are **not** allowed in the text except for the following **only**: NYHA, CHD, MRI, CT, ICU and units of measure such as mmHg or kg, are allowed. However, any abbreviations can be used on tables and figures.
- Headings before the References: Financial Support, Conflicts of Interest, Ethical Standards (Please see under *Original Article* above for the exact wording).
- A title page (see instructions on page 2)
- A maximum of three authors
- An abstract (of about 60 words)
- A maximum of 1,000 words
- 3-6 key words
- 2 Figures **OR** 2 Tables only
- A maximum of 2 supplementary material files
- A maximum of 10 references.

Editorials and Letters to the Editor

Readers are encouraged to write about any topic that relates to cardiology in the young. Such letters will appear in *Letters to the Editor.* They should be no longer than 500 words. Please include a title page (see instructions on page 2 above).
Editorials are written on invitation but unsolicited articles of approximately 1,500 words which may have particular topical interest will be welcomed for consideration. Please include a title page (see instructions on page 2 above). For Editorials and Letters please also see the note on abbreviations under Images, below.

Images in Congenital Cardiac Disease

Definitive, unique, or extraordinary pictures of any aspect of congenital cardiac disease will be presented and must conform to the following requirements:

- Abbreviations are **not** allowed in the text except for the following **only**: NYHA, CHD, MRI, CT, ICU and units of measure such as mmHg or kg, are allowed. However, any abbreviations can be used on tables and figures.
- Headings before the References: Financial Support, Conflicts of Interest, Ethical Standards (Please see under *Original Article* above for the exact wording).

- A title page (see instructions on page 2)
- A maximum of three authors
- An abstract (of about 30 words)
- A maximum of 250 words
- 3-6 key words
- A maximum of 4 images
- Only 1 reference.

Instructional value and artistic merit will be considered in addition to scientific import and clinical relevance.

Guidelines

CTY welcomes papers that consist of clear, concise guidelines in any technique or methodology that relates to the practice of cardiology and cardiac surgery in the young. Guidelines should be evidence based and should reflect professional consensus of best practice. Generally they will be expected to be endorsed by professional societies and associations. These papers do not follow any specific format, and may include figures and tables. Guidelines may be subject to peer review before acceptance for publication. Please include a title page (see instructions on page 2 above) and please see the note on Abbreviations under Images.

References

References should be numbered consecutively (in superscript) as they appear in the text. Type the reference list with double-spacing on a separate page. References (using Index Medicus abbreviations) should appear in the style as demonstrated below. Please note that if more than six authors, the **first three** authors should be listed and then 'et al.'. Examples:

1. Redington AN, Rigby ML, Oldershaw P, Gibson DG, Shinebourne EA. Right ventricular function 10 years after the Mustard operation for transposition of the great arteries: analysis of size, shape, and wall motion. Br Heart J 1989; 62: 455-461.
2. Smith VR, Jones AL, Miller W et al. Left ventricular myocardial velocities in children. Eur Heart J 2000; 21: 104-112.
3. Zuberbuhler JR. Clinical Diagnosis in Pediatric Cardiology. Churchill Livingstone, New York, 1981.
4. Frantz EG. Adult respiratory distress syndrome in children. In: Harried HS, Jr (ed.) Pediatric Pulmonary Heart Disease. Little, Brown, Boston, 1990, pp 315-324.

Tables

Tables should follow the style as demonstrated in issues to date, and be essential to the understanding of the text. Tables should have short descriptive titles and should be numbered (1, 2, 3 etc.) as they appear sequentially in the text. If only one Table is included, it should be referred to as Table. Submit each Table on a separate sheet of paper. All abbreviations and symbols should be defined in a footnote below the Table.

Figures

Please ensure that all graphs are exclusively submitted as 2-dimensional images.

To ensure that your figures are reproduced to the highest possible standards, Cambridge Journals recommends the following formats and resolutions for supplying electronic figures.

Please ensure that your figures are saved at final publication size and are in our recommended file formats. Following these guidelines will result in high quality images being reproduced.

Line artwork
Format: tif or eps
Colour mode: black and white (also known as 1-bit)
Resolution: 1200 dpi

Combination artwork (line/tone)
Format: tif or eps
Colour mode: grayscale (also known as 8-bit)
Resolution: 800 dpi

Black and white halftone artwork
Format: tif
Colour mode: grayscale (also known as 8-bit)
Resolution: 300 dpi

Colour halftone artwork
Format: tif
Colour mode: CMYK colour
Resolution: 300 dpi

If you require any further guidance on creating suitable electronic figures, please visit http://journals.cambridge.org/artworkguide

Supplementary On-line Material

The online platform gives authors the opportunity to include data that would be impractical to include in the article itself. These data might substantially enhance the importance of the research and might also be of benefit to readers. Authors may include tables and figures as well as data such as videos, 3-D structures/images, and extensive datasets. All supplementary material must be submitted with the original manuscript as separate files. Supplementary data should be referred to in the text with the prefix "S" (e.g. Supplementary Table S1, Supplementary Figure S1). Supplementary files will not be copy-edited or typeset, and will be published as supplied.

Reprints
Article reprints (hard copy and ePrints) are available from special_sales@cambridge.org. A minimum reprint order of 100 copies is required.

Permission
Requests for permission to reproduce any material originally published in *Cardiology in the Young* should be sent to ctyedoffice@cambridge.org

Announcements and Advertising
Meetings and courses will be announced in each Issue. Please email all details to: ctyedoffice@cambridge.org The Journals homepage, www.journals.cambridge.org/cty, offers paying advertisers the opportunity to promote conferences / courses and recruitment vacancies (subject to editorial approval). For rate details please email: ad_sales@cambridge.org

(Revised 5 March 2014)

Cardiology in the Young

cambridge.org/cty

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

Mark L. Willoughby[1], Wisdom Basera[1,2], Susan R. Perkins[1], George A. M. Comitis[1], Barend Fourie[3], John B. Lawrenson[1,3] and Liesl J. Zühlke[1,4]

[1]Paediatric Cardiology Unit, Department of Paediatrics and Child Health, Faculty of Health Sciences, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa; [2]School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; [3]Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa and [4]Division of Cardiology, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

Original Article

Cite this article: Willoughby ML, Basera W, Perkins SR, Comitis GAM, Fourie B, Lawrenson JB, and Zühlke LJ (2019) Infective endocarditis in infants and children in the Western Cape, South Africa: a retrospective analysis. *Cardiology in the Young*, page 1 of 5. doi: 10.1017/S1047951119002154

Received: 22 May 2019
Revised: 1 August 2019
Accepted: 8 August 2019

Keywords:
Infective endocarditis; endocarditis; Modified Duke Criteria; valvular dysfunction; vegetation

Author for correspondence:
Dr M. Willoughby, Department of Paediatrics and Child Health, Faculty of Health Sciences, Red Cross War Memorial Children's Hospital, University of Cape Town, ICH Building, Room 2.17, Klipfontein Road, Rondebosch 7700, Cape Town, South Africa. Tel: +27 21 532 1836.
E-mail: wllmar048@myuct.ac.za

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

CAMBRIDGE UNIVERSITY PRESS

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.

Acknowledgements. Thank you to the Children's Heart Disease Research Unit for assistance with this study, and Dr Paul Human for assistance in acquiring data from the surgical database.

Financial Support. W.B. is funded by the MRC UK; L.J.Z. is funded by the MRCSA, NRFSA and MRCUK.

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.

References

1. Ferrieri P, Gewitz MH, Gerber MA, et al. Unique features of infective endocarditis in childhood. Circulation 2002; 105: 2115–2126.
2. Sadiq M, Nazir M, Sheikh SA. Infective endocarditis in children – incidence, pattern, diagnosis and management in a developing country. Int J Cardiol Heart Vasc 2001; 78: 175–182.
3. Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. Circulation 2015; 132: 1487–1515.
4. Valente AM, Jain R, Scheurer M, et al. Frequency of infective endocarditis among infants and children with Staphylococcus aureus bacteremia. Pediatrics 2005; 115: e15–e19.
5. Durack DT, Lukes AS, Bright DK, Service DE. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med Sci 1994; 96: 200–209.
6. Kang D-H, Kim Y-J, Kim S-H, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012; 366: 2466–2473.
7. Shamszad P, Khan MS, Rossano JW, Fraser CD Jr. Early surgical therapy of infective endocarditis in children: a 15-year experience. J Thorac Cardiovasc Surg 2013; 146: 506–511.
8. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017; 70: 252–289.
9. https://www.stata.com/manuals13/rsymmetry.pdf (accessed 24/08/2019)
10. http://www.statssa.gov.za/publications/P0318/P03182017.pdf (accessed 24/8/2019)
11. Hugo-Hamman C, Moor Md, Human D. Infective endocarditis in South African children. J Trop Pediatr 1989; 35: 154–158.
12. Penk JS, Webb CL, Shulman ST, Anderson EJ. Echocardiography in pediatric infective endocarditis. Pediatr Infect Dis J 2011; 30: 1109–1111.
13. Evangelista A, Gonzalez-Alujas M. Echocardiography in infective endocarditis. Heart 2004; 90: 614–617.
14. Tissieres P, Gervaix A, Beghetti M, Jaeggi ET. Value and limitations of the von Reyn, Duke, and modified Duke criteria for the diagnosis of infective endocarditis in children. Pediatrics 2003; 112: 1404–1404.
15. Fournier P-E, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis 2010; 51: 131–140.
16. Dursun M, Yılmaz S, Yılmaz E, et al. The utility of cardiac MRI in diagnosis of infective endocarditis: preliminary results. Diagn Interv Radiol 2015; 21: 28.
17. Kelchtermans J, Grossar L, Eyskens B, et al. Clinical characteristics of infective endocarditis in children. Pediatr Infect Dis J 2019; 38: 453–458.
18. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC) endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36: 3075–3128.
19. Jankelow D, Cupido B, Zühlke L, et al. Prevention of infective endocarditis associated with dental interventions. SA Heart 2017; 14: 170–174.
20. Chu VH, Cabell CH, Benjamin Jr DK, et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004; 109: 1745–1749.
21. Choudhary SK, Talwar S, Airan B. Choice of prosthetic heart valve in a developing country. Heart Asia 2016; 8: 65–72.

Appendix

Reviewers Comments

First Review

Date: 7-July – 2019

Reviewer: 1

Comments to the Author

Willoughby et al performed a retrospective study of pediatric infective endocarditis cases in the Cape Town region. They describe a high incidence of valve dysfunction and a better outcome of patients receiving early surgery, well having a high need of valve replacement. The study is well written, and the important issues are discussed. As guidelines for IE prophylaxis have changed, data on this topic are of interest to improve endocarditis diagnosis, treatment and prevention.

Major comments:

1) The authors describe underlying CHD in 29 out of 49 patients. Could you give details on the underlying heart diseases in the un-operated and operated group? It is important to know which underlying heart diseases are predisposing for infective endocarditis in your setting.

2) Associated to comment 1, how is the relation between left and right heart endocarditis? Could you give details which heart valves were involved and if there was any prosthetic heart valve endocarditis in the operated group?

3) As you mention in the introduction, rheumatic fever is an important underlying disease predisposing for endocarditis. It would be important to know what role this disease plays in your patient population.

4) As known, S. aureus accounts for severe infections. Has there been any relation of S. aureus endocarditis with need of surgery or death? Was there any relation of the other underlying microorganisms with the course of the disease?

5) The current guidelines have restricted the recommendations for antibiotic prophylaxis. Do children in your setting get antibiotic prophylaxis? Are the guidelines followed? Is there anything known about entry points for endocarditis or risk factors line dental procedure, skin damage etc?

6) As also mentioned in the discussion, valve replacement is associated with anticoagulant therapy which might be not always evident in follow-up in your setting. Could you give information on the sort of valves which were implanted, biological or metal valves and if the potential problems concerning follow-up treatment influence the decision making in valve implantation.

7) Is there any conclusion you take out of this analysis concerning future treatment of these patients in your setting? Any lesson to learn out of the data?

8) I would suggest to keep the introduction short to mention the most important background information / statements from literature and move the exact numbers of patients etc. to the discussion section. By that results can be compared to these of other studies.

9) Data are compared to lit 12 from an older endocarditis cohort. Are there other important differences than

the incidence of mortality?

Minor comments:

10) According to which guidelines have the children been treated for endocarditis?

11) Please mention the proportion of CHD patients in the abstract under the result section.

12) Could you comment on the follow-up time of patients in the M&M section?

13) I suggest to replace the word review by analysis in the title. That is less confusion towards the content of the study.

Reviewer: 2

Comments to the Author

This study retrospectively analyses data of 49 children with infective endocarditis seen at two centres over last 5 years. However the details of site, size of vegetations, total embolisations, specific valves affected, decision to operate and valve repair vs. replacement has not been described. The conclusions are very similar to those of other studies published in the past, including some from developing countries.

Second review:

Date sent: 31-Jul-2019

Reviewer: 1

Comments to the Author

Please use the same abbreviation for S. aureus throughout the paper (line 53, page 7).

Reviewer: 2

Comments to the Author

The criteria used for making the diagnosis of infective endocarditis must be clearly defined as it has been mentioned as AHA criteria at one place and as Duke criteria at another place.

Size of vegetations and its relation to embolization may also be mentioned if details are available.

The method used for blood cultures may be mentioned because most developing countries have reported much lower percentage of culture positive endocarditis.