OUTCOMES OF CHILDREN WITH ACUTE MYOCARDITIS AND DILATED CARDIOMYOPATHY ADMITTED TO A TERTIARY HOSPITAL IN THE WESTERN CAPE SOUTH AFRICA: AN 8 YEAR STUDY

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Thesis presented in fulfilment of the requirements for the degree of Master of Medicine in the Faculty of Medicine and Health Sciences at Stellenbosch University

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Dr KJ Carkeek

December 2017

Dedication

Family and friends

I am indebted to my wonderful and supportive family and friends for their constant support over the last few years. I am grateful for their encouragement and belief in me each step of the way.

Children at Tygerberg Hospital

The children at Tygerberg Hospital have been my mascots, cheerleaders and have not only brought immense joy into my life but have taught me things no textbook could have. I have been honored to have cared for so many children and salute them for their bravery, at often exceptionally trying and tough times, in their little lives.

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Contents

Abbreviations

ACE-inhibitors: Angiotensin- converting enzyme inhibitors

ARBs: Angiotensin II receptor blockers

AFM: Acute fulminant myocarditis

BP: Blood pressure

Mean BP: Mean blood pressure

CCF: Congestive cardiac failure

CHIP: Child healthcare problem identification programme

CI: Confidence interval

CK: Creatinine kinase

CMV: Cytomegalovirus

CMV VL: Cytomegalovirus viral load

CMP: Calcium, magnesium and phosphate

CPAP: Continuous positive airway pressure

CPR: Cardiopulmonary resuscitation

CRP: C-reactive protein

CTR: Cardiothoracic ratio

CXR: Chest X-ray/chest radiograph

DCMO: Dilated cardiomyopathy

DISA: Distributed Information System Architecture

DOB: Date of birth

ECG: Electrocardiogram

ECM: Enterprise Content Management

ECHO: Echocardiography

ECMO: Extracorporeal membrane oxygenation

EEG: Electroencephalogram

EF: Ejection fraction

EMB: Endomyocardial biopsy

ESBL: Extended-spectrum-beta-lactamases

ESR: Erythrocyte sedimentation rate

GCS: Glasgow coma scale

GFR: Glomerular filtration rate

HIV: Human immunodeficiency virus

HHV-6: Human Herpes Virus-6

HR: Heart rate

ICU: Intensive care unit

IDCM: Idiopathic dilated cardiomyopathy

IgM: Immunoglobulin M

IPPV: Intermittent positive pressure ventilation

IQR: Interquartile range

ISFC: International Society and Federation of Cardiology

IVIG: Intravenous immunoglobulin

JVP: Jugular venous pressure

LFTs: Liver function tests

LV: Left ventricular

MC: Myocarditis

MRI: Magnetic resonance imaging

NEC: Necrotizing enterocolitis

NHLS: National Health Laboratory System

NPA: Nasopharyngeal aspirates

PALS: Paediatric advanced life support

PCR: Polymerase chain reaction

PICU: Paediatric intensive care unit

PM: Postmortem

RCWMCH: Red Cross War Memorial Children's Hospital

RR: Respiratory rate

SF: Shortening fraction

TA: Tracheal aspirates

TB: Tuberculosis

TBH: Tygerberg Hospital

UK: United Kingdom

US: United States

VAD: Ventricular assist device

WHO: World Health Organization

Study definitions and reference values

Myocarditis/ Dilated cardiomyopathy: For the purposes of this study these diagnoses were reviewed as a single entity. For this study a case was included if they had:

- structurally normal heart with normal coronary arteries.

As well as both A and B below:

- **A:** On ECHO: systolic dysfunction with a left ventricular shortening fraction of less than 25% and/or an ejection fraction of less than 55%.
  AND/OR: Histopathological finding of myocarditis.
  AND
- **B:** The cardiac dysfunction was not primarily due to septicemia or septic shock.

Any abnormality on CXR: increased cardiothoracic ratio for age, signs of cardiac failure, plethora, pleural effusions, atelectasis/collapse or airway narrowing. Signs of cardiac failure on CXR included: increased cardiothoracic ratio, pulmonary plethora/pulmonary oedema and pleural effusions.

Cardiovascular instability: combination of 1 or more of the following clinical entities: shock, poor perfusion, any hypotension recorded, raised lactate >3 or metabolic acidosis with a pH <7.35, thought to be due to poor perfusion or shock.

Cardiac failure: clinicians' assessment and documentation in the medical notes of "cardiac failure" or "congestive cardiac failure" OR mention of combination of clinical signs including a gallop rhythm, tachycardia, basal crackles and hepatomegaly.

Clinical diagnosis of MC/DCMO: where children were admitted to TBH and the attending doctor made the clinical diagnosis of MC/DCMO, however the child died prior to an ECHO being done and to which no postmortem was consented. These cases were excluded from this study.

Delay in diagnosis: markers of delay in presentation and diagnosis were whether children had longer duration of symptoms before presenting (>7 days), two or more healthcare visits prior to the diagnosis being made or were admitted for more than 24 hours to an alternate hospital with a different diagnosis (e.g. pneumonia) prior to referral.

Depressed level of consciousness/coma: GCS: <8/15 not due to sedation.

ECG abnormal: tachycardia for age, abnormal QTc, abnormal rhythm, abnormal axis, any chamber enlargement, any features of ischaemia.

2 or more abnormalities on ECG: >2 of above signs.

Further admissions: any further admissions to Tygerberg Hospital, having been discharged alive, and after the initial admission during which the diagnosis of acute myocarditis or DCMO was made.

Idiopathic: for the purposes of this study; a case was categorized as "idiopathic" if they had a full workup that included a negative viral screen, a negative basic metabolic screen and a negative autoimmune screen and they had no clinical signs of nephritis nor signs of an arrhythmia; they were also not on chemotherapeutic agents.

Increased cardiothoracic ratio (on CXR): increased cardiothoracic ratio for age:

- Younger than 12 months of age > 60%
- 12 months and older >55%

Inside Metro: immediate TBH drainage area including Khayelitsha.

Most recent clinical encounter: most recent date recorded of patient seen in any clinical area at Tygerberg Hospital.

Not determined or incompletely investigated: cases were assigned to this cause category if they were not investigated fully i.e. did not have ALL of the following: a viral screen, a metabolic screen, an autoimmune screen and an ECG.

Other respiratory support: nasal prongs, facemask oxygen of any form, CPAP, Bi-Pap.

Outside Metro: outside the direct TBH drainage area e.g. Worcester, Paarl, Hermanus etc.

Plethora on CXR: enlargement/increased pulmonary perfusion by opinion of paediatric pulmonologist on review of CXR.

Poor perfusion: documentation in medical notes of "poor perfusion" or clinical entity where child had cool peripheries but did not qualify as "shock".

Prolonged QTc: QTc>470ms.

Presumed viral myocarditis: for the purposes of this study: cases where there was a significant virus known to be associated with myocarditis, isolated on either PCR of TA/NPA, urine or on blood. The metabolic and autoimmune screens in these cases were negative and the ECG excluded an arrhythmia.

QTc: QTc was calculated using the Fridericia's formula (using the QT divided by the cube-root of RR interval).

Respiratory Viral Panel: tracheal aspirate and/or nasopharyngeal aspirate for multiplex PCR.

Shock: documentation in the medical notes of "shock", being hypotensive for age or a combination of absent/poor peripheral pulses, a capillary refill time of more than 3 seconds, and cool peripheries.

Systolic Hypotension: Systolic blood pressures below the lower limit of systolic blood pressure for age.

Suggestive of CCF (CXR): cardiomegaly with signs of plethora.

Tachypnoea for age: respiratory rate above the upper limit of respiratory rate for age. See table below.

Tachycardia for age: heart rate above the upper limit of heart rate for age. See table below.

Tachycardia on ECG: heart rate on ECG above the maximum heart rate for age. See table below

Time to death: number of days from date of diagnosis of acute myocarditis or DCMO to date of death.

Time to follow up: number of days from date of diagnosis of acute myocarditis or DCMO to the date of the most recent clinical encounter or death.

Viral myocarditis: for the purposes of this study: a case where there was a significant virus known to be associated with myocarditis, isolated on either PCR of TA/NPA, urine or on blood. The metabolic and autoimmune screens in these cases were negative and the ECG excluded an arrhythmia.

Age linked normal values for this study*

	Tachycardia	**Tachypnoea**	**Systolic Hypotention**
Birth	Above 200	Above 60	Below 40
Birth-28 days	Above 200	Above 60	Below 60
1 month-1 year	Above 190	Above 53	Below 70
1- 2 years	Above 140	Above 37	70 + (age in years x2)
3-5 years	Above 120	Above 28	70 + (age in years
6- 11 years	Above 118	Above 25	Below 90
12-13 years	Above 100	Above 20	Below 90

*Adapted from the Paediatric Vital Sign Reference Chart -Pedscses.com PALS 2015 (1)

Abstract

Introduction: Approximately 27% of new cases of paediatric cardiac failure in well-resourced settings are due to abnormalities of the myocardium. Acute myocarditis and dilated cardiomyopathy (DCMO) may be clinically indistinguishable at presentation but are distinct diseases. The clinical presentations of myocarditis and DCMO can range from asymptomatic, to fulminant cardiac failure or sudden death. The diagnoses are dependent upon early clinical suspicion as cardiac failure is present in 90%-100% of cases and this is commonly misdiagnosed as respiratory disease.

Viral infections (in the case of myocarditis) and the sequelae of viral myocarditis (in the case of DCMO) are the most important causes of myocardial failure, but there are a number of other infections and conditions as well as toxins that are implicated in both these diseases. The cause of myocardial failure may remain obscure, particularly if cases are not rigorously investigated. Entero- and adenoviruses remain important viral pathogens associated with viral myocarditis although there seems to be a viral shift with parvovirus B19 and herpes virus now being commonly implicated. Increasing sophistication of genetic and metabolic evaluations is reducing the number of idiopathic cases.

Diagnostic tests are directed at confirming the diagnosis of myocardial dysfunction and identifying the cause. Chest radiographs (CXR) and electrocardiograms (ECG) are widely used initial investigations and are abnormal in above 90% of cases. Echocardiographic (ECHO) examination is used to confirm the diagnosis, exclude structural and other causes of cardiac failure and establish a baseline for follow-up. Polymerase chain reaction (PCR) can detect viral genomes in many tissues and PCR identification of viruses on respiratory specimens correlates well with those obtained from the myocardium. Supportive therapy focusing on treatment of fluid overload and under perfusion is the mainstay of care. Access to ventilatory support, extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VAD) and cardiac transplantation has dramatically changed the outcomes in well-resourced settings where children who survive an initial hospitalization have survival at 1 year of 94% and 89% at 5 years. The predictors and risk factors for death are age (neonatal period and older age at presentation), congestive cardiac failure, lower shortening fraction (SF<15%) and ejection fraction (EF <30%) and in the case of DCMO the aetiology. Nearly all data on the outcome of children presenting with and treated for acute myocarditis and DCMO are reported from developed countries with sophisticated medical services and interventions. There is little data on the clinical presentation, course, outcomes and causes of myocarditis and DCMO in children in middle and low resourced settings, where high burdens of complicating infectious diseases including tuberculosis and HIV exist. A single study from South Africa reports only on children who required paediatric intensive care (PICU) and shows an initial hospital survival of 47% of children. There are no data on the longer-term outcomes.

Aims and Objectives: The aim of this study is to investigate the clinical presentation, course and outcome; including morbidity and mortality of children with myocarditis and DCMO, and to attempt to determine factors that predict for outcome. The results hope to guide local clinicians in developing guidelines for children, assist prognostication and potentially identify areas where management and the utilization of scarce resources can be improved.

Methods: We conducted a retrospective descriptive review of children from birth to 13 years, diagnosed with acute myocarditis and DCMO from 1 January 2008 to 31 December 2015 at Tygerberg Hospital, a tertiary hospital in the Western Cape, South Africa. For the purposes of this study myocarditis and DCMO were studied as a single entity due to various complexities in separating these entities clearly and the continutuum/overlap that often pursues. Inclusion criteria for this study were all patients with the diagnosis of myocarditis or DCMO, based on ECHO findings of an EF <55% and/or a SF <25%, or antemortem or postmortem histology. Children were excluded if there were structural or vascular abnormalities of the heart, or where the myocardial dysfunction was thought to be due to septicemia with septic shock. We identified cases through the admission/discharge diagnoses using the International Statistical Classification of Diseases codes (ICD10 codes), reviewing ECHO request records and manually reviewing the “Causes of deaths register”. Data were collected from the paper and electronic notes made by doctors, cardiology outpatient records and autopsy reports. Demographic, clinical, laboratory, ECHO, ECG and CXR data were collected on case report forms. Viral myocarditis, for the purposes of this study was a case where a significant virus, known to be associated with myocarditis, was isolated on either PCR of tracheal aspirate (TA)/nasopharyngeal aspirate (NPA), urine or on blood test. In children where cytomegalovirus was found on any specimens we considered it a significant infection only if the blood viral load was shown to be more than 1000 copies/ml (Log 3). The metabolic, autoimmune screens and ECGs in these cases were normal. Statistical analysis was performed with StataCorp. 2015. *Stata Statistical Software: Release 14*. Standard descriptive analysis, including measures of central tendency and dispersion, was performed for measured variables while frequencies and proportions were described for categorical variables. For comparisons based on mortality, chi-squared test (or exact tests for sparse data) and t-and rank sums for parametric and non-parametric data were used. Analysis of survival/mortality used time to event methods including Kaplan-Meier graphs. For patients lost to follow up, survival was censored at the last known date to be alive. For all hypothesis tests a significance level of 0.05 was used while the 95% confidence intervals (CI) were reported were necessary.

Results: We identified 227 potential cases within the broad diagnoses groups of myocarditis, dilated cardiomyopathy, myocardial dysfunction etc. Based on the inclusion and exclusion criteria stated in the methods 117 cases were included. Nineteen children were diagnosed at postmortem only. The median overall age at presentation was 18.9 months (Interquartile range (IQR) 8.9-52.2), with the children diagnosed at post mortem only slightly younger with a median of 10.6 months (IQR 2.2-28.8). Ninety-five percent (n=94/99) were in cardiac failure at presentation and 85.7% (n=90/105) were noted to have cardiovascular instability. Admission left ventricular ejection fraction was less than 30% in 68.2% (n=60/88). Eighty out of 117 (68.4%) children survived the first admission till hospital discharge and 65/117 (55.6%) children where noted to be alive at the end of the review period. On multivariate analysis the only factors that predicted death where renal dysfunction and cardiac failure at presentation. Thirty-three of 117 (28.2%) children had a short history of symptoms of less than 3 days. CXR at presentation was always abnormal and of the 97 CXR reviewed 90 (92.8%) had an increase in the cardiothoracic ratio. Seventy of 108 cases (64.8%) for which data was clear required pediatric intensive care admission; with the median length of ICU being 7 days (IQR 4-11 days). Forty-six of 107 (43%) children required ventilation for a median of 4 days (IQR 1-5) and 70/101 (69.3%) required inotropic support with 59/94 (62.8%) receiving dopamine and/ or dobutamine, 23/89 (25.8%) adrenaline infusions and 22/88 (25.0%) received milrinone. The overall duration of initial admission was 10 days (IQR 3-18), 5 days (IQR 1-15) for children who died and 12 days (8-20) for those who survived. Complications during hospitalization included acute kidney injury in 82/108 (75.9%) (3 needed dialysis), liver enzyme derangement in 69/81 (85.2%). Fourteen of the 91 children who had blood cultures taken (15.4%) at the time of admission had positive cultures, with 7/14 (50.0%) only diagnosed at postmortem. Aetiology was presumed to be viral myocarditis in 54/117 (36.7%) of the children. In 34/117 (29.1%) of cases, either their investigations/work-up was not complete hence classified as “not determined” or their full screen (excluding genetic testing) was negative hence “idiopathic” classification. Viral studies were positive in 73 (76.8%) of the 95 children where specimens were sent however not all cases with positive viruses where classified as having viral myocarditis, it depended on the virus isolated and other factors. Parvovirus PCR was positive in 17/41 (41.5%), significant CMV viral load in 16/40 (40%), Adenovirus in 5/69 (7.2%) and enteroviruses in 6/69 (8.7%). Two or more viruses where found in 37/95 (38.9%) patients. Twenty-four of the 117 (20.5%) children were known to be HIV exposed and of these 7 (29.2%) were HIV infected. 4 of the HIV infected children died, 5 (71.4%) dying within 7 days of diagnosis. The median duration of follow up time from first diagnosis was 474 days (IQR 147-820). 62 of the 80 first admission survivors attended cardiac OPD. Fourteen of the 62 children (22.6%) recovered fully and were discharged from the service, and in total 38 of the 62 clinic attenders (61.3%) were noted at a point with a normalized EF. Twenty-four of the 80 initial survivors (30%) were lost to follow-up. The median EF at the latest ECHO was 53% (IQR 35%-59%). The change in EF from diagnosis to latest ECHO was a median increase of 22.5% (IQR 9%-34%).

Conclusions

This study confirms that myocarditis and DCMO are an important cause of cardiac morbidity and mortality in South African. This study emphasises the need for a high index of suspicion of myocarditis and rapid PICU access to improve mortality. Bacterial infections are important contributors to death in this cohort and must be considered. Although we may be underestimating the total deaths in this cohort the survival after the first admission was good and supports the current recommendation to provide a full set of interventions to these patients.

Abstrak

Inleiding: Ongeveer 27% van nuwe gevalle van hartversaking in kinders van hulpbron-ryke lande is die gevolg van siektes van die miokardium. Dit is dikwels nie moontlik om akute miokarditis en gedilateerde kardiomiopatie (DCMO) klinies van mekaar te onderskei nie, tog is dit unieke siekte entiteite. Miokarditis en DCMO het verskeie oorsake, maar virale infeksie is die algeenste oorsaak van miokarditis, en virale miokarditis is die algemeenste oorsaak van DCMO
Die oorsaak mag onbekend bly, veral wanneer gevalle nie deeglik ondersoek word nie. Entero-en adenoviruse is steeds belangrike oorsake van miokarditis maar mettertyd het die rol van parovirus B19 en herpes virusses al hoe duideliker geword.
Toenemende ontwikkeling van genetiese en metaboliese evaluering het ook tot ‘n vermindering van die getal idiopatiese gevalle gelei. Die kliniese simptome van miokarditis en DCMO sluit die volle spektrum van asimptomaties, tot skielike hartversaking of dood in. Pasiente word dikwels inisieel foutiewelik met respiratoriese siekte gediagnoseer. Kinders met DCMO is gewoonlik uiters siek by diagnose, met hartversaking wat in 90%-100% van gevalle teenwoordig is.

Diagnostiese toetse word gebruik om die diagnose van miokardiale disfunksie te maak en om die oorsaak te indentifiseer. Borskas radiografie (CXR) en elektrokardiogramme (EKG) word dikwels gebruik as voorlopige ondersoeke en is in meer as 90% van gevalle abnormaal. ECHO-ondersoeke word gebruik om die diagnose te maak, om strukturele en ander oorsake van hartversaking uit te skakel en ‘n basislyn te bepaal. Polimerase kettingreaksie (PCR) kan virale genome in verskeie weefsels identifiseer – PCR identifikasie van viruse op respiratoriese monsters korreleer sterk met virale infeksie in die miokardium. Terapie is gefokus op die behandeling van volume oorlading and swak perfusie. Toegang tot ventilatoriese ondersteuning, ekstrakorporeale membraan-oksigenasie (ECMO), ventrikulêre ondersteunings toestelle (VAD) en hartoorplantings het drastiese gevolge gehad vir die uitkomstes en resultate in hulpbronryke lande. Kinders wat in hulpbronryke lande gehospitaliseer word het ‘n oorlewingsyfer van 94% teen 1 jaar en 89% teen 5 jaar. Die risikofaktore en voorspellers vir dood is ouderdom (neonatale periode en ouer kinders), hartversaking, laer verkortingsfraksie (SF<15%) en uitwerpfraksie (EF <30%), en etiologie van DCMO. Byna alle data van die uitkomstes van kinders met – of wat behandeling ontvang vir – akute miokarditis en DCMO word kom van ontwikkelde lande met gesofistikeerde mediese dienste en intervensies. Daar is min data wat die kliniese uitbeelding, uitkomstes en oorsake van miokarditis en DCMO in kinders in middel- tot lae hulpbron instellings beskryf. Die enigste studie vanuit Suid-Afrika rapporteer die aanvanklike hospitaal-oorlewing as 47% van kinders in die pediatriese intensiewe sorgeenheid (PICU), met geen data oor langtermyn uitkomstes nie.

Doelstellings en Doelwitte: Die doel van hierdie studie is om die kliniese uitbeelding, koers en uitkomste – insluitend siektekoers en sterftekoers van kinders met miokarditis en DCMO – te ondersoek en te probeer om vas te stel watter faktore n swak uitkoms voorspel. Die resultate hoop om plaaslike klinici te lei in die ontwikkeling van riglyne vir kinders, hulp met voorspelling van siektes, en potensieel te help om areas te identifiseer waar die bestuur en die gebruik van skaarse hulpbronne verbeter kan word.

Metodes: Ons het gebruik gemaak van ‘n retrospektiewe, beskrywende studie in kinders vanaf geboorte tot 13 jaar, gediagnoseer met akute miokarditis en DCMO, vanaf 1 Januarie 2008 tot 31 Desember 2015 by Tygerberg Hospitaal – ‘n tersiêre sorg hospitaal in die Wes Kaap, Suid-Afrika. Insluitings-kriteria was die diagnose van miokarditis of DCMO, gebasseer op ECHO bevindinge of ‘n EF <55% en/of ‘n SF <25%, of antemortem of postmortem histologie. Kinders was uitgesluit indien daar strukturele of vaskulêre abnormaliteite van die hart was, of waar die miokardiale disfunksie toegeskryf was aan septisemie met kompliserende septiese skok. Ons het gevalle geïdentifiseer deur die opneem/ontslag diagnoses, die “International Statistical Classification of Diseases” kodes (ICD10), en deur handmatig die doodsoorsaak-register) te ondersoek. Die kardiologie-buitepasiënt rekords en nadoodse-ondersoek verslae was ook nagegaan en papier en digitale doktersnotas. Demografiese, kliniese, laboratorium, ECHO, EKG en CXR data was ingesamel op verslagvorms. Virale miokarditis was, vir die doel van hierdie studie, ‘n geval waar ‘n betekenisvolle virus, geassosieer met miokarditis, geïsoleer was op of PCR of trageale aspirasie/nasofaryngeale aspiraat, urine of bloed toetse. In kinders met sitomegalovirus op ‘n respiratoriese of urine monster het ons dit slegs as ‘n ernstige infeksie klassifiseer indien die virale vlak in die bloed bewys was om meer as 1 000 kopieë/ml (Log 3) te wees. Die metaboliese, outoimmuunsiftings en EKGs was in hierdie gevalle normaal. Statistiese analise was uitgevoer met StataCorp. 2015. *Stata Statistical Software: Release 14.* Standaard beskrywende analise, insluitend mates van sentrale neiging en verspreiding, was uitgevoer op gemete veranderlikes, terwyl herhalings en verhoudings beskryf was vir kategoriese veranderlikes. In gevalle van vergelykings gebasseer op mortaliteit, was chi-squared toetsing (of presiese toetse vir skaars data), en T- en rang berekeninge vir parametriese en nie-parametriese data gebruik. Vir die analise van oorlewing/sterflikheid was gebruik gemaak van verskeie metodes, insluitend Kaplan-Meier beramings. In die gevalle waar pasiënte verlore gegaan het vir opvolg-ondersoeke, was oorlewing gesensuur teen die laaste bekende datum van oorlewing. Vir alle hipotetiewse toetse was ‘n betekenispeil van 0.05 gebruik, terwyl die 95% CI soos nodig gerapporteer was.

Resultate: Ons het 227 potensiële gevalle identifiseer, waarvan 117 ingesluit was. Negentien kinders was slegs met postmortem gediagnoseer. Die mediaan-ouderdom teen die tyd van presentering was 18.9 maande (IQR 8.9-55.2), met die kinders gediagnoseer tydens postmortem slegs effens jonger, met ‘n mediaan van 10.6 maande (IQR 2.2-28.8). Vyf en negentig present (n=94/99) was in hartversaking tydens presentering en 85.7% (n=90/105) gediagnoseer met

kardiovaskulêre onstabiliteit. Toelating ventrikulêre ejeksie was minder as 30% in 68.2% (n=60/88). Tagtig uit 117 (68.4%) kinders het hospitaal ontslaning oorleef op diagnosis toelating en die totale oorlewingssyfer was 65/117 (55.6%). Volgens meerveranderlike studie is nier- en hartversaking tydens presentasie die enigste voorspellers vir dood. Drie en dertig uit 117 (28.2%) kinders het ‘n kort geskiedenis van simptome gehad, oor ‘n tydperk van minder as drie dae. CXR by presentasie was altyd abnormaal en, van die 97 CXR wat bestudeer is, het 90 (92.8%) ‘n toename in kardiotorakale ratio getoon. Seventig van 108 (64.8%) van die pasiënte het pediatriese intensiewe sorg toelating benodig, met die mediaan PICU verblyf op 7 dae (IQR 4-11 dae). Ses en veertig van 107 (43%) kinders het ventilasie benodig vir ‘n mediaan van 4 dae (IQR 1-5) en 70/101 (69.3%) het inotropiese ondersteuning benodig, terwyl 59/94 (62.8%) dopamien en/of dobutamien ontvang, 23/89 (25.8%) ontvang adrenalien infusie, en 22/88 (25.0%) ontvang milrinone. Die algehele voortduring van aanvanklike toelating was 10 dae (IQR 3-18), 5 dae (IQR 1-15) vir dié kinders wat gesterf het en 12 dae (8-20) vir dié wat oorleef het.

Komplikasies gedurende hospitalisering sluit in akute nierbesering in 82/108 (75.9%) kinders waarvan 3 pasiënte dialise benodig, lewer-ensiem versteuring in 69/81 (85.2%) en bakteriële sepsis. Veertien van die 91 kinders (15.4%) wat bloed kulture geneem het, het positiewe bloed kulture tydens opname, met sewe uit viertien (50.0%) hiervan wat eers tydens postmortem gediagnoseer word. Etiologie was aanvaar as virale miokarditis in 54/117 (36.7%) van die kinders. In 34/117 (29.4%) van gevalle was die ondersoeke of onvoltooid en dus geklassifiseer as “nie-vasgestel”, óf die volle toetse (uitsluitend genetiese toetsing) was negatief, dus die “idiopatiese” klassifisering. Virale studies was positief in 73 (76.8%) van die 95 kinders wie se monsters gestuur en ondersoek was. Parovirus PCR was positief in 17/41 (41.5%), beduidende CMV virale las in 16/40 (40%), Adenovirus in 5/69 (7.2%) en enteroviruse in 6/69 (8.7%). Twee of meer viruse is by 37/95 (38.9%) van die pasiënte gevind. Vier en twintig van 117 (20.5%) van die kinders was blootgestel aan MIV en, van die, was 7 (29.2%) geïnfekteer met MIV. Vier van die MIV-geïnfekteerde kinders het gesterf, 5 (71.4%) binne die eerste sewe dae na diagnose.

Die mediaan-duur van opvolg-tyd vanaf die eerste diagnose was 474 dae (IQR 147-820). Twee en sestig van 80 eerste opname oorlewendes her hartpatiente bygewoon. Veertien van die twee en sestig kinders (20.3%) het herstel en was onstlaan vanuit die harteenheid, in 38/62 kinders (61.3%) het EF genormaliseer. Vier en twintig van die tagtig aanvanklike oorlewendes (34.7%) was verlore vir opvolgondersoeke. Die mediaan EF tydens die mees onlangse ECHO was 53% (IQR 35%-59%). Die verandering in EF vanaf diagnose tot die laaste ECHO was ‘n mediaan toename van 22.5% (IQR 9%-34%).

Gevolgtrekkinge: Binne ons raamwerk en instellings is akute miokarditis en DCMO geassosieer met opmerklike morbiditeit en mortaliteit. Hierdie studie benadruk die behoefte na ‘n hoër indeks van agterdog van miokarditis en versnelde toelating tot PICU om sodoende oorlewing te verbeter. Bakteriële infeksies is belangrike bydraers tot dood in hierdie kohort en moet dus oorweeg word. Alhoewel ons moontlik die totale dodetal binne die kohort onderskat, was die oorlewing na eerste toelating goed en ondersteun dus die voorstel om ‘n volle stel intervensies daar te stel vir hierdie pasiënte.

Introduction/Literature review

Apart from congenital structural heart disease, cardiac failure in children has many causes. Approximately 27% of new cases of paediatric cardiac failure in the United States are due to abnormalities of the myocardium. Acute myocarditis and dilated cardiomyopathy (DCMO) may be clinically indistinguishable at presentation but are distinct diseases. Acute myocarditis results in DCMO in 21-30% of cases and is an important cause of DCMO in children. (2,3)

In 1995 the World Health Organization (WHO) and International Society and Federation of Cardiology (ISFC) established a histopathological case definition for myocarditis, the Dallas criteria. For the diagnosis to be made, an endomyocardial biopsy (EMB) must be performed and specific immunological and immunohistochemical criteria should be met. (4,5,6,7,8) EMB remains the gold standard for the diagnosis of myocarditis, but in many high and low resource settings, the diagnosis is made by a combination of clinical findings, echocardiography (ECHO) and increasingly magnetic resonance imaging (MRI), where it is available. (3,4,5,6,7,8)

Cardiomyopathies are broadly defined as "diseases of the myocardium associated with cardiac dysfunction". (9) The cardiomyopathies are then subdivided by the anatomical and physiological anomalies. The causes of DCMO include myocarditis and a broad range of genetic and acquired disorders that manifest as a spectrum of electrical and functional abnormalities. The clinical phenotype is that of ventricular dysfunction with chamber enlargement.

For the purposes of this study, myocarditis and DCMO were studied as a single entity due to various complexities in separating these entities clearly and the continutuum/overlap that often pursues.

Incidence of myocarditis and dilated cardiomyopathies

The initial diagnosis of myocarditis is highly dependent upon clinical suspicion. Early acute myocardial dysfunction may be missed, and the diagnosis of myocarditis may only be obvious when fulminant disease is present, or when considered in retrospect, when the child presents with DCMO. (10) Using screening electrocardiograms (ECG), the approximate incidence of myocarditis is estimated to be 7 per 60 000 (0.012%) in asymptomatic Japanese children. (8) This incidence increases to between 0.15% and 0.6% of the population when using postmortem data. (8) The prevalence in a Canadian paediatric emergency department was estimated to be 0.5 cases per 10 000 emergency department visits. (11) There are no data on the incidence or prevalence in South African children.

The incidence of DCMO in developed countries is between 0.57 and 1.3 cases per 100 000 children aged 1-18 years. (12) Infants have the highest incidence in the paediatric age group, ranging between 4.1 and 8.34 per 100 000. (13,14) The incidence is higher in boys than in girls, and higher in Africans than in Caucasians. Similar to myocarditis there are no data on the DCMO incidence in South African children.

Causes of myocarditis and dilated cardiomyopathies

Although there are a number of infections and conditions that can cause myocarditis, the cause often remains obscure, particularly if cases are not rigorously investigated. Viral infections are the most important cause. (5,6,8,15,16,17) In viral myocarditis the initial viral infection is often accompanied by a prodrome of respiratory and gastrointestinal symptoms and during this phase direct myocyte injury can occur. This is followed by injury caused by the T cell and

cytokine activation of the host immune response. In a subset of survivors, long-term dysfunction results in DCMO, and it is not clear why this happens in some but not all cases. Current suggestions include specific immunogenetics allowing for long-term autoimmune and inflammatory damage. (6,15) Enteroviruses including Coxsackie group B, adenovirus, parvovirus B19, and human herpes 6 (HHV-6) have been noted to be important aetiological agents. (8,17,18,19,20,21) A shift in causes has been noted over time, and although entero- and adenoviruses remain important, parvovirus B19 and herpes virus are increasingly recognized as common causes. (21,22,23) Studies of the causes of viral myocarditis are summarized in Appendix 1: A table summarizing studies from 1999-2016 in which viruses were isolated in cases of myocarditis.

There are few local data sources; in a recent report of children presenting in heart failure to the Paediatric Intensive Care Unit (PICU) of Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, the aetiology was presumed viral myocarditis in (83/95) 87% and idiopathic DCMO in (13/95) 13%. (24) Adenovirus PCR was positive in 28/95, Parvovirus in 19 with multiple positive viral studies in 32/95. (24) Myocarditis can also be caused by non-viral infections, medication, toxins and hypersensitivity (eosinophilic myocarditis). (4) Other causes include arrhythmias, metabolic diseases, autoimmune and inflammatory conditions.

Forty-eight to 60% of DCMO cases in children are idiopathic; the remaining cases are secondary to viral myocarditis (22.3%), familial disease (14.7%), metabolic disease (4-11%), neuromuscular disease and cardiotoxic drugs. (22,25) As genetic screening and metabolic evaluations are becoming increasingly sophisticated, the numbers of idiopathic cases is becoming smaller. Myocardial dysfunction due to myocarditis and DCMO, with or without cardiac failure is a well-known complication of human immune deficiency virus infection. (4,26,27) Pulmonary disease and infections and HIV itself, can trigger the cardiac failure in these children, with both systolic and diastolic dysfunction being well described. (28)

Clinical Presentation

The clinical presentations of myocarditis can range from asymptomatic to fulminant cardiac failure, life threatening arrhythmias or sudden death. (4,5,7,8,10,15,17,29) Between these extremes, patients have non-specific systemic symptoms of fever, upper respiratory symptoms, cough, fatigue and gastrointestinal symptoms such as nausea, poor feeding and vomiting. (6) There is a large variability in the presentations of different age groups, with infants presenting with tachypnoea, poor feeding and failure to thrive and older children with chest pain, palpitations, effort intolerance and syncope. (5,15) In a study of 90 patients younger than 16 years who died suddenly and unexpectedly, myocarditis was found to be a major cause of death in 17%, and of these, 60% had prodromal symptoms. (10) Symptoms may not be recognized initially as myocarditis, and 57%- 84% of patients required more than one visit to a physician within 14 days before the diagnosis was made. (8,10) Children are often initially diagnosed with respiratory illness. (8,10)

Children with DCMO are usually very ill at the time of initial assessment, with cardiac failure being present in 90%-100% of patients. (22,24,25) A population-based cohort study of all children in Australia who presented with cardiomyopathy at age 0 to 10 years over a 10-year period showed hospitalization on initial presentation is common (88%) and of the children that require hospitalization, 45.1% needed intensive care admission on initial presentation. (30) The majority of patients with DCMO require inotropic medication and nearly half endotracheal intubation and assisted ventilation. (30)

Diagnosis

Diagnostic tests are directed towards confirming the diagnosis of myocardial dysfunction and identifying the cause. Chest radiograph (CXR) is abnormal in 90% of cases (10) with findings consistent with cardiac failure in the form of cardiomegaly (60%) and increased pulmonary markings suggestive of pulmonary oedema. (10,15) Cardiomegaly on paediatric CXR is highly predictive of ventricular dilatation on ECHO. (12)

Electrocardiogram (ECG), despite its low sensitivity and specificity, is widely used as a screening tool and is frequently abnormal in between 93% and 100% of cases with myocardial dysfunction. (4,5,8,10,12) The typical ECG has sinus tachycardia with low-voltage QRS complexes, but beyond this, there are a variety of abnormalities including ST and T wave abnormalities, widened QRS complexes, axis deviation, and arrhythmias. (4,6,8,12,15)

ECHO examination is used to confirm the diagnosis, exclude structural and other causes of cardiac failure and to establish a baseline for monitoring and follow-up. (4,5,12,23) The examination looks at the measurement of ejection fraction (EF) and shortening fraction (SF), the presence or absence of atrioventricular valve regurgitation, as well as the presence of pericardial or pleural effusion and intraventricular thrombi. (12,15) An EF of less than 55% and/or a SF of less than 25% are commonly used as criteria to diagnose left ventricular systolic dysfunction. (12,22)

Non-specific laboratory studies include general markers of inflammation and infection, such as a full blood count, a differential count, a serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). (4,15) These markers may be elevated in cases of acute myocarditis but normal values do not exclude an acute myocardial inflammatory process. (4) Lactate, acid base, hepatic enzymes tests and creatinine are useful to assess perfusion. (15)

Cardiac troponins T and I and creatine kinase (CK), which are markers of cardiac injury, may assist with the diagnosis of myocarditis, but there are limited data on their use in children. (4,5,6,8) In patients with clinically suspected myocarditis, troponins are more sensitive than CK levels as markers of cardiomyocyte injury, but normal serum levels do not exclude myocarditis. (5) Cardiac troponin T may provide better sensitivity for detecting micro-necrosis because of a proportionally higher and longer lasting elevation of serum levels. (8) Troponin I has high specificity but limited sensitivity in the diagnosis of myocarditis, whereas cardiac troponin T has been reported to have a sensitivity of 71%. (15)

In the absence of EMB, the diagnosis of viral myocarditis relies on the identification of virus by molecular techniques, culture for peripheral specimens, and serial serology. (19) A 4-fold rise in acute antibody titers is necessary to assign causality to a specific virus. (6) Polymerase chain reaction (PCR) can detect viral genomes in many tissues including nasal pharyngeal aspirates (NPA), tracheal aspirates (TA), stool, urine and myocardial biopsy samples. (6,26) The identification of viruses on respiratory specimens with PCR correlates well with those obtained from the myocardium, hence the widespread use of this method to identify potential viral causes. (30,31) Detection of a viral genome does not necessarily indicate causality however, as for instance, cytomegalovirus may shed due to disease, and the presence of respiratory viruses in the upper airways may occur in asymptomatic children. (32)

EMB however, remains the gold standard of diagnosis, with histology complemented by sensitive histochemical and molecular methods. (23) Histology provides crucial information regarding the type of inflammatory infiltrates such as lymphocytes, neutrophils, eosinophils, granulomas or giant cells. (23) EMB is not routine in South Africa and even in high-income settings it is thought that the risks may outweigh the benefit. If EMB should be performed, the Dallas

"histopathologic" criteria, developed to improve diagnostic capabilities and decrease the high rate of diagnostic disagreement by establishing uniform criteria, should be used. (19)

Cardiac MRI provides detailed functional and morphological assessment of the heart, as well as reliable visualization of tissue markers of myocarditis, including oedema, inflammation and fibrosis. (8) To standardize cardiac MRI in diagnosing myocarditis, the International Consensus Group on Cardiovascular Magnetic Resonance created the "Lake Louise Criteria". (8) Two out of the following three criteria are required to fulfill the diagnosis of myocarditis:

1. On T2 scan a myocardium to skeletal muscle ratio > 1.9
2. Delayed enhancement in subepicardial and or mid-myocardium in nonischemic distribution
3. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1weighted images.

Not only is MRI a non-invasive adjunct in diagnosing myocarditis, but it is also useful in the monitoring of disease progression. More data are needed in children. (2,5,8,12,15) Nuclear imaging with gallium-67, Tl-201 and indium-111-labeled anti- myosin antibodies (5,6) can also be used in the myocarditis diagnosis. Cardiac catheterisation is part of the pre-transplant work-up, diagnostic biopsy or of left atrial decompression after extracorporeal membrane oxygenation (ECMO) cannulation. (25)

Management

The approach to therapy for patients with myocarditis and DCMO remains supportive care. (4) Medical therapy in children with myocarditis and DCMO is less effective than in adults. Whilst mortality and the requirement for eventual cardiac transplantation may be reduced by aggressive use of medical therapies, such as ACE-inhibitors in children, their impact in the youngest of patients has yet to be defined. (30) The long-term limitations of transplantation, and the lack of sufficient young donors justify the continuing search for better medical therapy. (30)

Initial management is focused on fluid overload, under perfusion or both. (12) Stabilization includes access to ventilatory support and intravenous inotropic support, extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VAD) and cardiac transplantation. In children with decompensated cardiac failure who have evidence of low cardiac output, poor perfusion and shock; inotropes, including dopamine, dobutamine and milrinone are used to improve the end organ perfusion. (12) There are no clinical studies to guide inotropic use, however milrinone is currently the preferred inotrope because of its afterload reduction. (8)

Loop diuretics, such as furosemide, play a key role in the active management of patients with symptomatic cardiac failure. (12) In advanced cardiac failure, angiotensin-converting enzyme inhibitor (ACE-I) therapy is usually introduced after the stabilization of heart failure symptoms with a diuretic, and simultaneous to withdrawal of inotropic support. Captopril is typically first choice for most children. (12) ACE- inhibitors may also help to prevent the remodeling that evolves in DCMO. (8) Data regarding the role of aldosterone antagonist therapy such as spironolactone in the treatment of children with cardiac failure are very limited. (12) Spirinolactone is typically initiated in children in whom therapy with an ACE-inhibitor has not resulted in improved ventricular function or reversal of ventricular remodeling. (8,12)

Preventative anticoagulation may be considered if the EF is severely decreased, in atrial arrhythmias and as therapy in patients with intraventricular thrombi. (8) Systemic anticoagulation was administered in 24/175 (13.7%) of Daubeney et al's patients. (30)

An area of significant controversy involves the use of immune modulators in the context of myocarditis. (8,15) More than 20 treatment trials performed in adults have been reported using immunosuppressive, immune modulating or anti-inflammatory drugs. (4) It is difficult however to extrapolate the findings of adult studies to the paediatric population. Paediatric studies of agents such as prednisone, azathioprine and cyclosporine are rare and inconclusive. (6,8) A small randomized controlled trial, comparing 3 different immunosuppressive treatment strategies, failed to show any haemodynamic or clinical improvement with steroid use. A recent Cochrane review does not support the use of corticosteroids in the treatment of myocarditis. (12) Intravenous immunoglobulin (IVIG) is the most commonly used immune modulator in myocarditis. (30) Despite several reports that suggest improved outcome in children who received IVIG, a review of a large number of registry patients from Canada showed no improvement in outcome. Many patients with myocarditis have spontaneous improvement. It is therefore difficult to know if the observed improvement after treatment with immunosuppression or IVIG is attributable to treatment or the natural course of the disease. (8)

The rationale for the use of antiviral drugs results from the knowledge that most common causes of myocarditis are induced by viral infections. (4) Acyclovir and ganciclovir may be considered in patients with herpes virus or cytomegalovirus infections and as newer agents become available these will need to be considered as therapeutic agents. (4,5,33)

Mechanical support devices and ECMO are other treatment or management modalities. Mechanical support devices have been said to be life saving in 67% of patients, especially those with acute fulminant myocarditis (AFM). (6) For patients with cardiogenic shock due to AFM who deteriorate despite optimal medical therapy, VAD or ECMO might be required for the aggressive short-term treatment of refractory cardiogenic shock, to bridge the patient to recovery or heart transplantation. (4)

Early data suggest that a third of children die or undergo transplantation within 1 year of presentation. (34) The improvement in survival with paediatric cardiac failure in the United Kingdom (UK), Ireland and the United States (US) does appear to be related to an earlier and more aggressive recourse to transplantation. (34)

Short and long-term outcomes

Myocarditis and DCMO, with or without cardiac failure, have substantial morbidity and mortality. (35,36) Overall survival rates in children with myocarditis or DCMO have varied in the literature and depend on the aetiology, clinical presentation, disease stage, access to care and management. (4,5) Survival should be distinguished from full recovery. There is an ongoing debate about the extent to which outcomes of heart failure from heart muscle disease in children have improved over the years. (37) An entire generation of paediatric cardiologists in the UK and internationally was taught that in children with myocardial disease, a third (33%) die, a third develop chronic impairment, and a third get better. (6,36) This originated from Greenwood's 1976 study of 161 children. (38) Kantor reports that 66% of patients recover, 10% show incomplete recovery and 24% progress to death or transplantation. (12) A large, multi-centered study including all age groups showed that there was a significant mortality in neonates (33-45% survival) (8) with older infants and young children having better outcomes (78-80% survival). AFM may have a better prognosis. (39)

Patients are more likely to experience complete recovery of left ventricular function, if aggressive pharmacological, mechanical and ventilatory supports are initiated early. (4,7,25) Therefore, despite an increased likelihood of death early in their illness trajectory, patients with an acute fulminant presentation should be managed aggressively. (39)

Apart from age at initial presentation, poor outcome from acute myocarditis has been shown to be more likely in patients with elevated CRP, elevated CK, EF <30%, and intraventricular conduction disturbances. (6) There is no difference in the outcomes of children with biopsy confirmed versus probable myocarditis. (26) Myocarditis may account for nearly half of all children with DCMO and 1-8% of patients with acute myocarditis eventually go on to transplant. (8)

It is essential to try and establish the aetiology of DCMO in order to determine the subsequent optimal management and gauge accurate prognosis. The overall prognosis of idiopathic forms of DCMO tends to be poor with a reported 5-year mortality rate in the literature of 14-50%. (22) DCMO secondary to viral myocarditis has substantially better outcomes. (2,6) The Australian Childhood Cardiomyopathy Study and the American Pediatric Cardiomyopathy Registry provided valuable data about longer-term outcomes for specific diagnostic groups. (40,41) The most recent overall survival rates in North America, from a large population cohort, are a 1-year survival of 87% and 5-year survival of 77%. (13)

Similarly Andrews has recently shown that children who survive an initial hospitalization with heart failure from heart muscle disease have a good medium-term survival (82% overall 1-year survival but 77% at 5 years and 73% at 10 years, with survival conditional on 1-year survival 94% & 89% at 5 and 10 years respectively). (36) This cohort differs from the US and Australian cohorts in that it was selected to look at outcomes of symptomatic new-onset clinically significant heart failure in children, rather than cardiomyopathy *per se*. The predictors of outcome were similar. (36) These predictors and risk factors for death of DCMO are age (neonatal period and older age at presentation, sparing the group of infants and toddlers), congestive cardiac failure, lower SF (<15%) and EF (<30%) as well as idiopathic DCMO. (8,13,17,22,25,37,40,42,43,44) Patients with cardiac failure at presentation were 4 times more likely to experience death or transplantation within 1 year of diagnosis. (25)

The only study from South Africa reports an initial hospital survival of 47% for children admitted to PICU. (24) There are no data on the long-term outcomes for this cohort.

Research justification

Although there is a large body of evidence on the outcomes of infants and children presenting with and treated for acute myocarditis and DCMO, nearly all of this data are reported from developed countries with sophisticated medical services and interventions, such as ventricular assist pumps and cardiac transplantation. These reports may have limited applicability to children who live in countries where predominantly the population income is middle to low, or where the causes of myocardial failure may differ, or where access to health care is a challenge and often delayed. Middle and low-income countries, as well, are burdened by complicating infectious diseases including tuberculosis and HIV infection and disease.

At Tygerberg Hospital, children have access to a specialized cardiology service, and limited access to paediatric intensive care and high care. Children are diagnosed with myocarditis and DCMO through history, clinical assessment and ECHO. This study creates the opportunity to investigate these infants and children collectively in order to determine which factors predict a poor outcome. The results of such a study would support clinicians to develop guidelines for infants with acute myocarditis and DCMO.

Local data on the outcomes of the children will assist with prognostication and potentially identify areas where management and the utilization of scarce resources can be improved.

Aims and Objectives

The aim of this study is to investigate the clinical presentation, course and outcome; including morbidity and mortality of children with myocarditis and DCMO presenting to Tygerberg Hospital, and to attempt to determine the factors that predict for outcome.

Study Methods

Setting

This study was performed in Tygerberg Hospital, a tertiary care hospital in the Western Cape, South Africa; which is a referral hospital for parts of the Cape Town Metropolitan and two health regions of the Western Cape. The reference population is approximately 2 million persons of which 35% are children. The region has a high prevalence of tuberculosis and HIV, with the Western Cape currently having the fourth highest TB incidence rate in South Africa (739.1 per 100 000 population). (45) A 2011 estimate of TB prevalence in Cape Town is 511/100 000 in children under 5 years of age. (46) The HIV prevalence in 2012 was reported as 2.4% in children aged between 0-14 years. (47) The paediatric cardiology service has qualified paediatric cardiologists with access to ECHO and other highly technical investigations. There are a limited number of PICU and high care beds resulting in competition for access to these beds.

Study design

Period of study, study population and eligibility criteria

A retrospective descriptive study of all children from birth to 13 years (age limit due to paediatric admission criteria) diagnosed with acute myocarditis or DCMO presenting to TBH from 1 January 2008- 31 December 2015, was performed.

We identified potential cases through an extensive search of the admission and discharge diagnoses of patients admitted to all paediatric services. The patients with myocarditis and DCMO were identified using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems codes (ICD10 codes) (Appendix 2), to search through the hospital electronic systems. The "Causes of deaths register" kept as part of the National CHIP programme was also manually reviewed. The laboratory, ECHO and cardiology service records as well as cardiology outpatient records and autopsy reports were also reviewed.

A case of myocarditis or DCMO (for study purposes included as as a single entity due to the difficulty in clinically distinguishing these entities) was defined as a child younger than 13 years of age at diagnosis, with myocardial dysfunction as determined by an ECHO with an EF of less than 55% and/or a SF of less than 25%. Children in whom the diagnosis was made at postmortem, through histology, were also included. Children were excluded if there were structural or vascular abnormalities of the heart, or where the myocardial dysfunction was thought to be due to septicemia with complicating septic shock.

Data Collection

Paper and electronic notes made by doctors were reviewed for both the inpatient and outpatient services. A registered paediatric cardiologist reviewed all ECHOs and ECGs. CXRs were reviewed by a paediatric pulmonologist. Demographic, clinical, laboratory, ECHO, ECG and CXR data were collected on case report forms (Appendix 3) and transcribed to an Excel spread sheet (®Microsoft).

NHLS (National Health Laboratory System) was reviewed for all investigation results, based on the available departmental guidelines. These guidelines exist to assist clinicians in the investigations to be performed at baseline, in attempting to establish a possible cause in a new patient with acute myocarditis or DCMO. (Appendix 4)

Data Management

All patient identifiers were removed prior to electronic capturing of the data. The data was stored on a password-protected computer and only the principle investigator had access to this data. Copies of the database were regularly made and copies were kept in a locked cupboard at a site outside the hospital. The data were transformed by members of the statistics department, to be compatible with the Stata 14 software for statistical analysis.

Statistical analysis

Statistical analysis was performed with Stata14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Standard descriptive analysis, including measures of central tendency (mean, median,

proportions) and dispersion (standard deviations [SD], interquartile ranges [IQR] and 95% confidence intervals [CI]) were performed for measured variables (depending on whether the variables were normally distributed or not) while frequencies and proportions were described for categorical variables. For comparisons based on mortality, chi-squared tests (or exact tests for sparse data) and t and rank sums for parametric and non-parametric data were used. Analysis of survival and mortality used time to event methods including Kaplan-Meier graphs. For patients lost to follow up, survival was censored at the last known date to be alive. For all hypothesis tests a significance level of 0.05 was used while the 95% CI were reported were necessary. The p values reported include analysis of all data including data 'missing'.

Ethical considerations

Approval from the Health Research Ethics Committee of Stellenbosch University and the hospital management of Tygerberg Hospital was obtained prior to the collection of data. (Appendix 5) There was a waiver of individual informed consent due to the retrospective nature of the study, as it had no interventions and minimal risk. Children were already cared for by the treating clinicians.

Study clinicians created anonymity by giving each case a case number linked to their hospital number on a separate data sheet. This was stored separately from the case report forms. Case report forms and statistical spreadsheets contained case numbers only and all computerized data files were password protected.

Results

We identified 227 possible cases of acute myocarditis/DCMO. Sixteen children with a clinical diagnosis of myocarditis were excluded because they died soon after admission, prior to ECHO and without an autopsy being performed. Ninety-four (94) further children were excluded because they did not meet the diagnostic criteria for the study, had inadequate records to determine whether they met the inclusion criteria, or were diagnosed outside of the study period, or at another hospital. (Figure 1)

Of the remaining 117 children, 92 (78.6%) were included due to ECHO findings only, 19 (16.2%) on histology only and 6 (5.1%) met both ECHO and histology criteria with antemortem biopsy performed in 4 of these children.

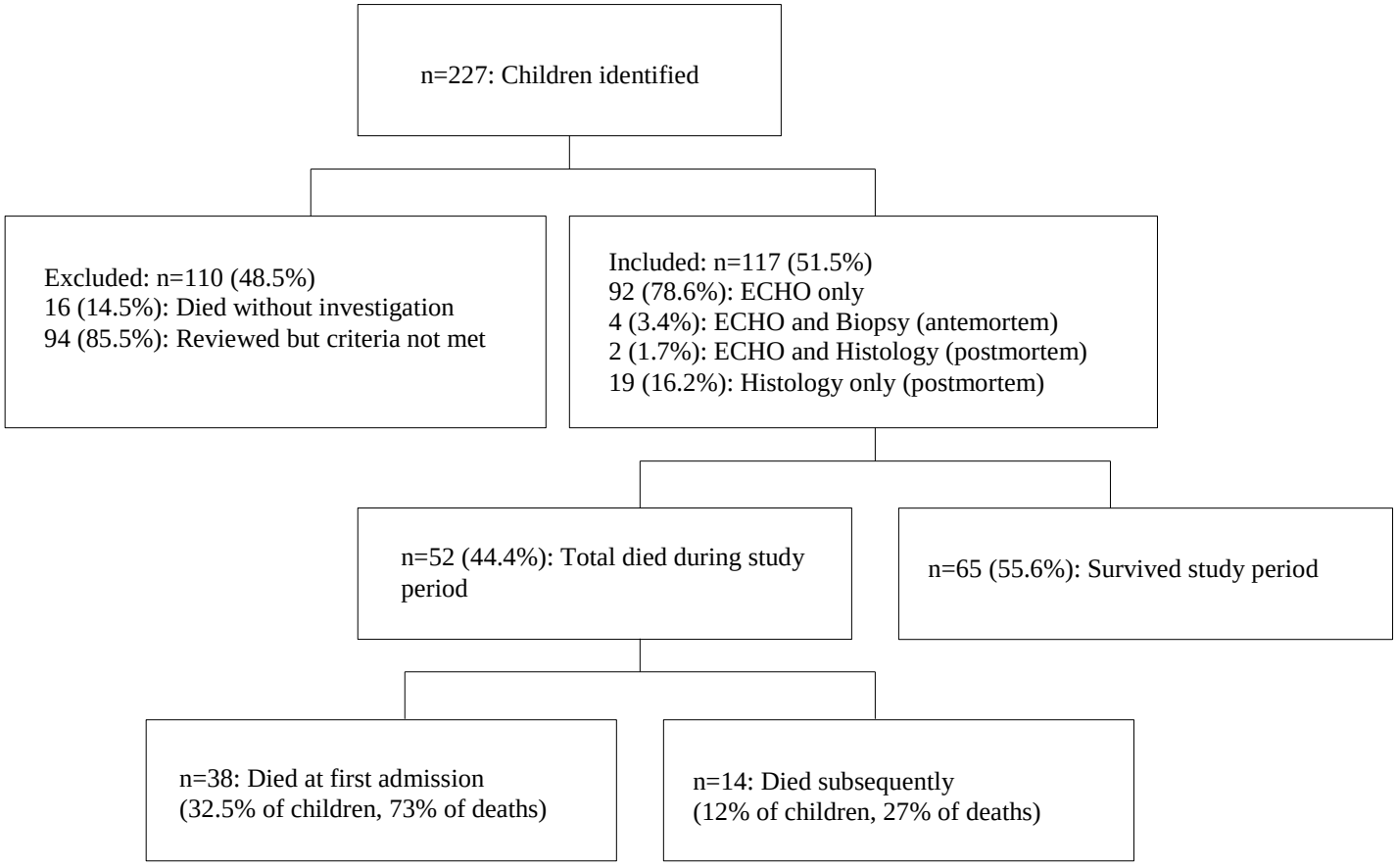


Figure 1: Screening, inclusion and outcomes of children in study

Demographics and description of cohort

The median age of the 117 cases at diagnosis was 18.9 months (IQR 8.9-52.2), with 90 (76.9%) under 5 years of age and 42 (35.9%) less than 12 months of age at diagnosis. There were 65 (55.6%) females. The median weight-for-age z-score at diagnosis was -1.13 (IQR -2.6 - 0.3). There was no difference in the age, male: female ratio or weight for age z- score between those children that died and to those that survived. (Table 1)

Sixty-four children (54.7%) were from inside the Cape Town metropolitan area and 28 (23.9%) were from outside the metropolitan region. In 25 children we could not determine the residential area from the record.

The HIV status was known in 80 children, in the remaining 37 (31.6%) no record of a laboratory or point of care test could be found. Twenty-four of 117 (20.5%) children were known to be HIV exposed and of these 7 (29.2%) were HIV-infected. Four of the 7 HIV-infected children (57.1%) were receiving antiretroviral therapy. Other conditions included current therapy for tuberculosis (10.2%), current or previous therapy for childhood malignancies (4.3%) and being born prematurely (11.1%). (Table 1)

The Paediatric Emergency Centre at Tygerberg Hospital was the first contact point at Tygerberg Hospital for 52 (44.4%) of the cases and the PICU for 25 (21.4%). Twenty-nine patients (24.8%) were initially diagnosed directly in one of the paediatric wards and not in the PICU or Emergency centre. PICU as the initial contact area was predictive of death in univariate analysis (p=0.001).

Table 1: Demographic and description of cohort

	Total	Survived Study	Died	P value
Number (%)	117 (100%)	65 (55%)	52 (45%)	
Age: Median months (IQR[1])	18.9 (8.9-52.2)	21.6 (9.1-46.0)	15.9 (7.3-55.0)	0.270
Less than 12 months	42 (35.9)	20 (47.6)	22 (52.4)	0.530
1 year-5 years	48 (41.0)	30 (62.5)	18 (37.5)	
5-10 years	17 (14.5)	10 (58.8)	7 (41.2)	
Older than 10 years	10 (8.6)	5 (50.0)	5 (50.0)	
Sex: Female	65 (55.6)	37 (56.9)	28 (43.1)	0.739
Weight z score Median (IQR[1])	-1.1 (-2.6- 0.3)	-1.3 (-2.8-0.1)	-0.9 (-2.2-0.4)	0.475
HIV[2] infected	7 (5.9)	3 (42.9)	4 (57.1)	0.450
On TB[3] Treatment	12 (10.3)	8 (66.7)	4 (33.3)	0.184
Childhood cancer	5 (4.3)	3 (60.0)	2 (40.0)	0.295
Prematurity	13 (11.1)	6 (46.2)	7 (53.8)	0.663
Residential Area				
Inside Metro	64 (54.7)	42 (65.7)	22 (34.4)	0.120
Outside Metro	28 (23.9)	12 (42.9)	16 (57.1)	
First Contact at TBH[4]				
PICU[5]	25 (21.4)	8 (32.0)	17 (68.0)	0.001
Emergency centre	52 (44.4)	33 (63.5)	19 (36.5)	
Paediatric ward	29 (24.8)	22 (75.9)	7 (24.1)	
COPD[6]	2 (1.71)	1 (50.0)	1 (50.0)	
Not Known	9 (7.7)	1 (11.1)	8 (88.9)	

Abbreviations: IQR[1]: Interquartile range, HIV[2]: Human Immunodeficiency virus, TB[3]: Tuberculosis, TBH[4]: Tygerberg Hospital, PICU[5]: Paediatric Intensive Care unit, COPD[6]: Cardiac outpatient department

Presenting complaints and initial clinical findings

Non-specific symptoms were common including fast breathing (94.2%), cough (83.1%), lethargy (68.5%) and poor feeding (66.1%). (Table 2) Over a quarter of children (28.2%) had a short duration of symptoms and presented for care within 3 days of the onset of symptoms, of these 10 (8.6%) presented on day 1. (Table 3) Forty (34%) of children however had symptoms for more than one week and in 13 (11.1%) symptoms were present for more than a month prior to diagnosis. This shows the range in timing of presentation although duration of symptoms was not predictive of outcome (p=0.444). Few (16%) children had two or more health care contacts prior to the diagnosis and the time between the onset of symptoms and diagnosis was not greater for children who were referred from outside the Cape Town Metro (p=0.444). Twenty-five of the 38 children (65.8%) who died at TBH during their first admission died within the first 24 hours of admission.

Table 2: Most common presenting symptoms

Symptom	Number of cases presence/absence of symptom was documented n (% of 117)	Number of cases symptom present in n (% of those documented)	Survived Study n (%)	Died n (%)	P Value
Fast breathing	86 (73.5)	81 (94.2)	45 (55.6)	36 (44.4)	0.133
Cough	83 (71.0)	69 (83.1)	44 (63.8)	25 (36.2)	0.152
Lethargy/fatigue	51 (43.6)	35 (68.6)	23 (65.7)	12 (34.3)	0.276
Poor feeding	62 (53.0)	41 (66.1)	25 (61.0)	16 (39.0)	0.721
Oedema	49 (41.9)	27 (55.1)	17 (63.0)	10 (37.0)	0.275
Fever	73 (62.4)	34 (46.6)	21 (61.8)	13 (38.2)	0.339
Loss of weight	42 (35.9)	17 (40.5)	11 (64.7)	6 (35.3)	0.264
Vomiting	68 (58.1)	27 (39.7)	18 (66.7)	9 (33.3)	0.420
Flu like symptoms	42 (35.9)	16 (38.1)	11 (68.8)	5 (31.2)	0.150
Sweating	43 (36.8)	16 (37.2)	10 (62.5)	6 (37.5)	0.199
Abdominal pain	40 (34.2)	12 (30.0)	8 (66.7)	4 (33.3)	0.256
Irritability	35 (29.9)	10 (28.6)	7 (70.0)	3 (30.0)	0.247
Diarrhoea	62 (53.0)	14 (22.6)	12 (85.7)	2 (14.3)	0.059
Coryza	43 (36.8)	11 (25.6)	8 (72.7)	3 (37.3)	0.316
Tight chest	35 (29.9)	8 (22.9)	5 (62.5)	3 (37.5)	0.439
Rash	41 (35.0)	9 (22.0)	8 (88.9)	1 (11.1)	0.083
Cyanosis	32 (27.4)	6 (18.8)	2 (33.3)	4 (66.7)	0.100
Seizure	34 (29.1)	5 (14.7)	3 (60.0)	2 (40.0)	0.303
Palpitations	33 (28.2)	4 (12.1)	3 (75.0)	1 (25.0)	0.210
Chest pain	31 (26.5)	3 (9.7)	2 (66.7)	1 (33.3)	1.000
Hemiplegia	30 (25.6)	2 (6.7)	2 (100.0)	0 (0.0)	0.159
Conjunctivitis	31 (26.5)	2 (6.5)	0 (0.0)	2 (100.0)	0.089
Arthralgia	29 (24.8)	1 (3.4)	1 (100.0)	0 (0.0)	0.207
Haemoptysis	30 (25.6)	1 (3.3)	0 (0.0)	1 (100.0)	0.130

Table 3: Duration of symptoms and health care contact prior to diagnosis and time to clinical suspicion at TBH

		Total n (% of 117)	Inside Metro n (%)	Outside Metro n (%)	Unknown area n (%)	P value
Duration of Symptoms	1-3 days	33 (28.2)	21 (63.6)	5 (15.2)	7 (21.2)	0.444
	4-6 days	14 (11.9)	8 (57.1)	5 (35.7)	1 (7.2)	
	7-14 days	18 (15.4)	10 (55.6)	5 (27.8)	3 (16.7)	
	14-28 days	9 (7.7)	6 (66.7)	3 (33.3)	0 (0.0)	
	> 1 month	13 (11.1)	7 (53.9)	1 (7.7)	5 (38.5)	
2 or more healthcare contacts prior to presentation		16 (13.7)	13 (81.2)	3 (18.8)	0 (0.0)	0.219
Admission to peripheral hospital > 24 hours with incorrect diagnosis		10 (8.6)	3 (30.0)	7 (70.0)	0 (0.0)	0.049

The common clinical signs (Table 4) suggestive of possible cardiac disorder included displaced apex beat (92.1%) cardiovascular instability (85.7%) and clinical signs of cardiac failure (95%). Blood pressure was poorly documented in the doctors' notes and only noted in 69 (59%) of case files (nursing notes were not reviewed). Of these children 18.3% (n=15) were hypotensive for their age. Signs of central nervous system dysfunction were common and included a GCS <8/15 (17.4%), seizures on admission (19.5%) and hemiplegia (15.2%). Tachycardia for age (p=0.015), cardiovascular instability (p= 0.005), cardiac failure (p=0.023), a displaced apex beat (p= 0.002) were predictive of death on univariate analysis. (Table 4)

Table 4: Clinical signs at initial presentation to Tygerberg Hospital

Clinical Sign	Presence or absence recorded in notes n (%)	Sign noted n (%)	Survived Study n (%)	Died n (%)	P Value
Tachypnoea for age	63 (53.9)	62 (98.4)	42 (67.7)	20 (32.3)	0.333
Tachycardia for age	83 (70.9)	75 (90.4)	47 (62.7)	28 (37.3)	0.015
Systolic Hypotension	69 (59.0)	15 (18.3)	8 (53.3)	7 (46.7)	0.154
Cardiovascular Instability	105 (89.7)	90 (85.7)	49 (54.4)	41 (45.6)	0.005
Cardiac Failure	99 (84.6)	94 (95.0)	58 (58.6)	36 (38.4)	0.023
Displaced Apex	89 (76.1)	82 (92.1)	51 (62.2)	31 (37.8)	0.002
Hepatomegaly	90 (76.9)	83 (92.2)	53 (63.9)	30 (36.1)	0.105
Raised JVP[1]	20 (17.1)	17 (85.0)	13 (76.5)	4 (23.5)	0.150
Crackles	75 (64.1)	57 (76.0)	34 (59.7)	23 (40.3)	0.076
Oedema	67 (57.3)	49 (73.1)	28 (57.1)	21 (42.9)	0.199
Wheeze	63 (53.9)	24 (38.1)	14 (58.3)	10(41.7)	0.297
CNS Disease					
Depressed LOC[2]	69 (59.0)	12 (17.4)	8 (66.7)	4 (33.3)	0.112
Seizures	36 (30.8)	7 (19.5)	3 (42.9)	4 (57.1)	0.221
Hemiplegia	33 (28.2)	5 (15.2)	4 (80.0)	1 (20.0)	0.137

Abbreviations: JVP[1]: Jugular venous pressure, LOC[2]: Level of consciousness.

Imaging and special investigations

CXR on admission

All the 97 CXRs available for review were abnormal. (Table 5) Six (6.2%) had isolated cardiomegaly with no other abnormalities. Ninety (91.8%) displayed cardiomegaly, whilst plethora was seen in 75 (77.3%), pleural effusion in 59 (60.9%) atelectasis/collapse 28 (28.9%) and/or airway narrowing in 42 (43.3%) CXRs. The median cardiothoracic ratio was 69.9% (IQR 63.7%-74.6%) and the abnormal radiological signs were not different between those that died or those that survived. (Table 5)

Table 5: Description of first chest radiograph at Tygerberg Hospital

	Total n=97	Survived Study n=56	Died n=41	P Value
Cardiothoracic Ratio % Median (IQR[2])	69.9 (63.7-74.6)	69.9 (62.4-74.9)	70.3 (63.7-74.6)	0.217
CXR[1] isolated cardiomegaly n (%)	6 (6.2)	4 (66.7)	2 (33.3)	0.647
Increased cardiothoracic ratio for age n (%)	90 (91.8)	46 (51.7)	44 (48.3)	0.560
Plethora n (%)	75 (77.3)	37 (49.3)	38 (50.7)	0.178
Pleural effusions n (%)	59 (60.9)	30 (50.9)	29 (49.1)	0.329
Atelectasis/collapse n (%)	28 (28.9)	15 (53.6)	13 (46.4)	0.358
Airway narrowing n (%)	42 (43.3)	26 (61.9)	16 (38.1)	0.098

Abbreviations: CXR[1]: Chest x-ray/radiograph, IQR[2]: Interquartile range

ECG on admission

Fifty-five admission ECGs were available and were reviewed. (Table 6) Only three (5.5%) ECGs were normal. The median heart rate was 144 (IQR 130-166) with 50 (90.91%) showing a sinus rhythm. Five children (9.1%) had an arrhythmia, 53 (96.4%) had chamber enlargement and 30 (54.5%) had features suggestive of ischaemia.

Table 6: Description of first electrocardiograph at Tygerberg Hospital

	Description of abnormality	Number n (% of 55)
ECG[1] abnormal	Any ECG abnormality	52 (94.6)
2 or more abnormalities	>2 ECG abnormalities	39 (70.9)
Tachycardia for age	Heart rate >max HR[2] for age	31 (56.4)
Prolonged QTc[3]	Prolonged QTc >470ms	2 (3.6)
Any rhythm abnormality apart from sinus tachycardia n=5 (9.1%)	Ventricular Tachycardia	2 (3.6)
	Supraventricular Tachycardia	1 (1.8)
	Other arrhythmia	2 (3.6)
Abnormal axis n=7 (12.7%)	Left	1 (1.8)
	Right	5 (9.1)
	Extreme left	1 (1.8)
Any chamber enlargement n=53 (96.4%)	RVH[4]	9 (16.4)
	LVH[5]	31 (56.4)

	RA[6] enlargement	12 (21.8)
	LA[7] enlargement	1 (1.8)
Any features of ischemia n=30 (54.5%)	Q wave	4 (7.3)
	ST abnormality	7 (12.7)
	Upright T in V1	2 (3.6)
	Upright T in V2	17 (30.9)

*Abbreviations: ECG[1]: Echocardiogram, HR[2]: Heart rate, QTc[3]: Calculated using Fredericia method, RVH[4]: Right ventricular hypertrophy, LVH[5]: Left ventricular hypertrophy, RA[6]: Right atrial, LA[7]: Left atrial.

Echocardiography findings at diagnosis

Ninety-eight cases (83.8%) had an echocardiogram as part of their diagnostic work-up. (Table 7) Due to the study inclusion criteria, there were no patients who had a normal initial ECHO, and where chemotherapy (in the context of childhood cancer) was the cause of the DCMO, I have reported their first abnormal ECHO as their diagnostic ECHO.

Ejection fraction was the most readily available measurement. Eighty-eight diagnostic EFs and 49 diagnostic SFs were documented. The median EF was 24% (IQR 15%-32.5%) with 68.2% of the cases having a diagnostic EF of less than 30%. The median SF was 12% (IQR 10%-18%) and was not different in the survivors compared to those that died (p=0.099 and p=0.477). (Table 7)

An intracardiac thrombus was noted in 5 (5.1%) children and small pericardial effusions in 13 (13.3%).

Table 7: Echocardiography findings at diagnosis

		Total	Survived Study	Died	P Value
EF[1] at diagnosis Median (IQR[2]) n=88		24(15-32.5)	26.5 (18-35)	22 (15-26)	0.099
SF[3] at diagnosis Median (IQR[2]) n=49		12 (10-18)	15 (11-18)	11 (10-15)	0.477
EF[1] at diagnosis n=88 (%)	Less than 20%	35 (39.8)	23 (65.7)	12 (34.3)	0.040
	21-30%	25 (28.4)	19 (76.0)	6 (24.0)	
	31-55%	28 (31.8)	23 (82.1)	5 (17.9)	
SF[2] at diagnosis n=49 (%)	Less than 10%	12 (24.5)	7 (58.3)	5 (41.7)	<0.001
	11-20%	29 (59.2)	19 (65.5)	10 (34.5)	
	21-25%	8 (16.3)	4 (50.0)	4 (50.0)	

Abbreviations: EF[1]: Ejection fraction, IQR[2]: Interquartile range, SF[3]: Shortening fraction

Follow- up echocardiography of survivors

Improvements in the EF and SF values were noted when comparing the diagnostic percentages to the latest ECHO percentages. (Table 8) The median EF at the latest ECHO was 53% (IQR 35%-59%) with the latest SF median being 25% (IQR 17.5%-33%). The change in EF from diagnosis to latest ECHO was a median increase of 22.5% (IQR 9%-34%) and SF increase a median of 10% (IQR 2%-16%). Children that survived had a significantly higher latest EF than those that died (p=<0.001) in univariate analysis. The time between the first and latest ECHO was a median of 372 days (IQR 125-789).

Table 8: Echocardiography findings of 65 study survivors

		ECHO[1] at diagnosis n=65 (%)	Last available ECHO[1] n=65 (%)
EF[2] Category	<20%	23 (35.4)	11 (16.9)
	21-30%	19 (29.2)	10 (15.4)
	31-55%	23 (35.4)	27 (41.5)
	>55%		17 (26.2)

Abbreviations: ECHO[1]: Echocardiography EF[2]: Ejection fraction, IQR[3]: Interquartile range, SF[4]: Shortening fraction

Other investigations at time of diagnosis

In 48 children with a documented pH (arterial), a median pH of 7.35 (IQR 7.25-7.43) was demonstrated. Overall there was no significance in initial pH between those who died and those that survived the study, however seventy-five percent of the cases with a pH of less than 7.15 on admission died (p=0.035). (Table 9) The median serum lactate level (n=51) was 3 (IQR 2.7-6.0) with 83% of those with a serum lactate great than 10mmol/l dying, although this was not statistically significant (p=0.068). (Table 9) There were 30 children who had both a lactate greater than 3 and a pH less than 7.35 but this also did not predict poor outcome (p=0.139).

The children's length was not collected and therefore the glomerular filtration rate was not calculated, but serum creatinine and creatinine kinase were more likely to be raised in children who died (p= 0.002 and p= 0.007). Three children required peritoneal dialysis during their ICU stay. Fourteen children 14/91 (15.4%) had positive bacterial blood cultures at the time of admission and 9/14 (64.3%) died during the study. (Table 9)

Table 9: Other investigations at time of diagnosis

	Tests performed n (%)	Total abnormal n (%)	Survived Study n (%)	Died n (%)	P Value
pH >7.35	48 (41.0%)	27 (56.3)	17 (63.0)	10 (37.0)	0.035
pH 7.15-7.34		13 (27.1)	9 (69.2)	4 (30.8)	
pH <7.15		8 (16.7)	2 (25.0)	6 (75.0)	
Lactate 3-5	51 (43.6%)	20 (39.2)	12 (60.0)	8 (40.0)	0.068
Lactate 5.1-10		10 (19.6)	6 (66.0)	4 (40.0)	
Lactate >10		6 (11.8)	1 (16.7)	5 (83.3)	
CRP[1]	91 (77.8)	56 (61.5)	26 (46.4)	30 (53.6)	0.098
Serum creatinine	108 (92.3)	82 (75.9)	37 (45.1)	45 (54.9)	0.002
CK[2]	85 (72.7)	46 (54.1)	21 (45.7)	25 (54.3)	0.007
Troponins	54 (46.2)	27 (50.0)	17 (63.0)	10 (37.0)	0.611
AST[3]	81 (69.2)	69 (85.2)	35 (50.7)	34 (49.3)	0.450
Blood cultures	91 (77.8)	14 (15.4)	4 (28.6)	10 (71.4)	0.089
Basic metabolic screen	64 (54.7)	2 (3.1)	1 (50.0)	1 (50.0)	0.598
Autoimmune Screen	34 (29.1)	3 (8.8)	2 (66.7)	1 (33.3)	0.969

Abbreviations: CRP[1]: C-reactive protein, CK[2]: Creatinine kinase, AST[3]: Aspartate transaminase

Investigations to determine possible viral cause

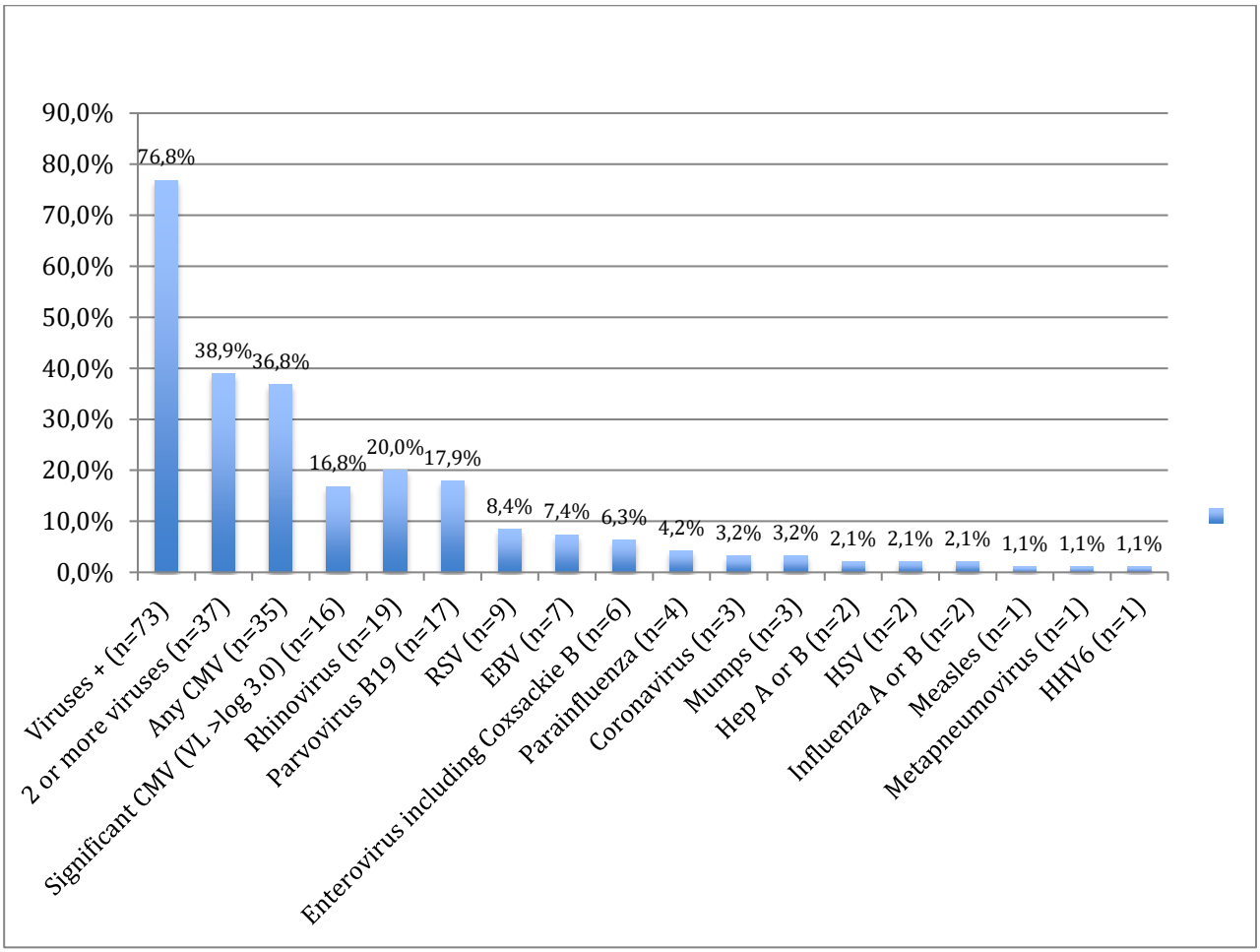
Investigations for viral pathogens were not performed on all children. Of the viral studies done on 95 cases, 73 (76.8%) were positive for one or more viruses and 37 (38.9%) positive for multiple viruses. (Table 10) The most common viruses found were cytomegalovirus (CMV), rhinovirus, respiratory syncytial virus and parvovirus. Of all the viral investigations performed there was not a single virus that was more common than others in those children who died. (Table 10) In children with CMV on a respiratory or urine specimen, it was considered to be a significant infection only if the viral load in the blood was shown to be more than 1000 copies/mL (Log 3).

Table 10: Viral studies performed

Organism	Test	Performed n (% of 117)	Positive n (% of performed)		Survived Study n (%)	Died n (%)	P Value
CMV[1]	Resp Panel PCR[2]*	69 (59.0)	20 (29.0)		9 (45.0)	11 (55.0)	0.556
	Urine	7 (6.0)	2 (28.6)		1 (50.0)	1 (50.0)	0.762
	Blood IgM	49 (41.9)	4 (8.2)		1 (25.0)	3 (75.0)	0.002
	Blood Viral Load	40 (34.2)	Log <3	19 (47.5)	13 (68.4)	6 (31.6)	0.432
			Log3.0-4.0	9 (22.5)	6 (66.7)	3 (33.3)	
			Log4.1-5	5 (12.5)	1 (20.0)	4 (80.0)	
			Log >5	2 (5.0)	1 (50.0)	1 (50.0)	
Rhinovirus	Resp Panel PCR[2]	69 (59.0)	19 (27.5)		11 (57.9)	8 (42.1)	0.874
RSV[3]	Resp Panel PCR[2]	69 (59.0)	9 (13.0)		4 (44.4)	5 (55.6)	0.783
Adenovirus	Resp Panel PCR[2]	69 (59.0)	5 (7.2)		5 (100.0)	0 (0.0)	0.175
Influenza	Resp Panel PCR[2]	69 (59.0)	2 (2.9)		1 (50.0)	1 (50.0)	0.655
Parainfluenza	Resp Panel PCR[2]	69 (59.0)	4 (5.8)		1 (25.0)	3 (75.0)	0.929
Coronavirus	Resp Panel PCR[2]	69 (59.0)	3 (4.3)		2 (66.7)	1 (33.3)	0.981
Enterovirus	Resp Panel PCR[2]	69 (59.0)	3 (4.4)		2 (66.7)	1 (33.3)	0.624
Stool Viral Screen		31 (26.1)	0 (0.0)		0 (0.0)	0 (0.0)	1.000
Coxsackie	Serology	50 (42.7)	3 (6.0)		3 (100.0)	0 (0.0)	0.137
Mumps	IgM	50 (42.7)	3 (6.0)		3 (100.0)	0 (0.0)	0.031
	PCR[2]	18 (15.4)	1 (5.6)		1 (100.0)	0 (0.0)	0.807
Measles	IgM	10 (8.5)	1 (10)		1 (100.0)	0 (0.0)	1.000
Rubella	IgM	54 (46.2)	1 (1.9)		1 (100.0)	0 (0.0)	0.424
Parvo B19	IgM	44 (37.6)	11 (25.0)		8 (72.7)	3 (27.3)	0.131
	PCR[2]	41 (35.0)	17 (41.5)		14 (82.3)	3 (17.6)	0.436
EBV[4]	IgM	58 (49.6)	7 (12.1)		4 (57.1)	3 (42.9)	0.025
Herpes (HHV6[5])	PCR[2]	8 (6.8)	1 (12.5)		1(100.0)	0 (0.0)	0.282
Hep A	IgM	9 (7.7)	2 (22.2)		0 (0.0)	2 (100.0)	0.027
Multiple Viruses isolated		37 (31.6)			23	14	0.926

*Resp Panel PCR: Respiratory viral panel PCR

Abbreviations: CMV[1]: Cytomegalovirus, PCR[2]: Polymerase chain reaction, RSV[3]: Respiratory syncytial virus, EBV[4]: Epstein Barr virus, HHV6[5]: Human herpes virus



Abbreviations: CMV: Cytomegalovirus, RSV: Respiratory syncytial virus, EBV: Epstein-barr virus, HSV: Herpes simplex virus, Other: HHV-6: Human herpes virus-6/measles and metapneumovirus

Figure 2: Bar chart of viruses in the 95 tested patients

Children with viral myocarditis/DCMO associated with viral myocarditis, were not younger than the general cohort, with a median age at diagnosis of 16.1 months (IQR 8-28.1). The 6 children with CMV as the only virus found and who had a viral load of more than Log >3 copies per mL, were younger than the general cohort median age 5.6 months (IQR 2.4-11.9). There were 2 patients with equivocal EBV IgMs and 1 with equivocal Rubella IgM.

Proposed causes of acute myocarditis/DCMO

With reviewing both the "given" proposed causes in the case files and on creating case definitions for the purpose of this study, on retrospective classification it was found that 54/117 (36.7%) of children had probable viral myocarditis. 4/7 (57.1%) of the HIV-infected children also had presumed viral causes not HIV related. In 34/117 (29.1%) of cases, either their investigations/work up was not complete hence the true cause could not be determined, or their full screen (except genetic testing) was negative hence the "idiopathic" classification. (Table 11) Death from viral myocarditis was not more common than death from the other causes. Chemotherapy (in the context of childhood cancer) was causal in 5 (4.3%) and arrhythmias and nephritis in 4.3% and 3.4% respectively. Other presumed causes (n=8) (6.8%) included autoimmune disease, metabolic disease and in two cases proximity to early childhood vaccination was noted. (Table 11)

Table 11: Proposed Cause of Myocarditis/DCMO in 117 children

	Total n=117 (%)	Survived Study n (%)	Died n (%)	P Value
Presumed Viral myocarditis	54 (36.7%)	33 (61.1)	21 (38.9)	0.503
Not determined	31 (26.5%)	12 (38.7)	19 (61.3)	
Idiopathic	3 (2.6%)	2 (66.7)	1 (33.3)	
HIV[1] Disease/ARVs[2]	3 (2.6%)	2 (66.7)	1 (33.3)	
HIV[1]+ with a virus	4 (3.4%)	1 (25.0)	3 (75.0)	
Cancer/Chemotherapeutic Drugs	5 (4.3%)	3 (60.0)	2 (40.0)	
Arrythmia	5 (4.3%)	4 (80.0)	1 (20.0)	
Nephritis	4 (3.4%)	3 (75.0)	1 (25.0)	
Autoimmune	3 (2.6%)	2 (66.7)	1 (33.3)	
Metabolic Disease	2 (1.7%)	1 (50.0)	1 (50.0)	
Presumed Vaccine related	2 (1.7%)	2 (100.0)	0 (0.0)	
Congenital/Perinatal	1 (0.9%)	1 (100.0)	0 (0.0)	

Abbreviations: HIV[1]: Human immunodeficiency virus, ARVs[2]: Antiretrovirals

Management/interventions and outcomes of cohort

Thirty-seven children 37/117 (31.6%) died during the first admission to hospital. Of the 52/117 (44.4%) children who died during the study period, 6/52 (11.5%) died in the emergency centre and 34/52 (65.4%) in the PICU. The median length of hospital stay for the first admission was 12 days (IQR 8-20 days). Children who died stayed 5 days (IQR 1-15 days) and 25/52 deaths (48.1%) occurred in the first 24 hours. (Tables 12 and 13)

Seventy of 108 (64.8%) children were admitted to PICU on their first admission with the median duration of PICU stay being 7 days (IQR 4-11 days). In 9 children the PICU admission status was unclear. The mortality of those admitted to the PICU was 51.4% (36/70). This was significantly different from those that survived PICU 34/70 (48.6%) (p=0.002). In PICU 46/107 (43%) cases were ventilated with a median duration of ventilation being 4 days (IQR 1-5 days).

Seventy of 101 children (69.3%) required inotropic support during their hospitalization with 59/94 (62.7%) receiving dopamine and/or dobutamine and 23/89 (25.8%) also requiring adrenalin infusions. Milrinone was used in 22/88 (25.0%) cases. Thirty-three 33/101 (32.7%) required 2 or more inotropes during their first admission. Generally inotropes were given in PICU but the above represents all inotropic support even if started in the emergency unit and/or in the wards. PICU admission (p=0.002), being ventilated (p=<0.001) and receiving inotropic support (p=<0.001) (including more than one inotropic drug and adrenaline infusion) were all associated with increased mortality in the univariate analysis. Adrenalin infusion was associated with 87% mortality (p=<0.001). Thirty (25.6%) children required cardio-pulmonary resuscitation (CPR) during their first admission. Of those requiring CPR 73.3% died. (Table 12)

Diuretics were used in 89 (94.6%) of cases, captopril in 67 (79.7%) and digoxin and b-blockers in 9 (15.0%) and 2 (3.3%) respectively. Steroids were used in 11 (9.4%) cases either for blood pressure support or immune modulation and intravenous immune globulin in 2 (1.7%) cases. The use of diuretics, (p=<0.001) captopril, (p=<0.001) and digoxin (p=0.015) reflected initial survival. (Table 12)

Aspirin was given to 36 (40.9%) cases whereas warfarin to only 5 (4.3%) of the cases. Thirty-one (49.2%) received B vitamins and/or carnitine orally. Twenty-one (33.9%) received transfusion of blood products. (Table 12)

Table 12: Outcomes and management of cases of myocarditis/DCMO during first admission

Interventions (n refers to the number of patients in which interventions were provided/indicated in medical records)	Total	Survived Study	Died	P Value
Duration of 1st admission Median days (IQR[1])	10 (3-18)	12 (8-20)	5 (1-15)	0.0007
Duration of PICU[2] Median days (IQR[1])	7 (4-11)	7 (4-11)	6 (2-10)	
	Total n (%)	Survived Study n (%)	Died n (%)	P Value
Survived 1st admission		80 (68.4)		
Died first admission			37 (31.6)	
PICU[2] admission n=108 (92.3)	70 (64.8)	34 (48.6)	36 (51.4)	0.002
Ventilated n=107 (91.5)	46 (43.0)	17 (37.0)	29 (63.0)	<0.001
Duration of ventilation (days) Median (IQR[1])	4 (1-5)	5 (4-9)	2 (1-4)	0.0018
Inotropic support n=101 (86.3)	70 (69.3)	33 (47.1)	37 (52.9)	<0.001
Dopamine and/or Dobutamine n=94 (80.3)	59 (62.8)	31 (52.5)	28 (47.5)	<0.001
Adrenalin n=89 (76.1)	23 (25.8)	3 (13.0)	20 (87.0)	<0.001
Milrinone n=88 (75.2)	22 (25.0)	10 (45.5)	12 (54.5)	0.020
>2 Inotropes n=101 (86.3)	33 (32.7)	11 (33.3)	22 (66.7)	0.002
Non-invasive oxygen support n=92 (78.6)	73 (79.4)	45 (61.6)	28 (38.34)	0.082
Cardiac arrest/CPR[3] n=117 (100.0)	30 (25.6)	8 (26.7	22 (73.3)	<0.001
Diuretics n=94 (80.3)	89 (94.7)	61 (68.5)	28 (31.5)	<0.001
Captopril n=84 (71.8)	67 (79.8)	49 (73.1)	18 (26.9)	<0.001
Beta-Blockers n=60 (51.3)	2 (3.3)	2 (100.0)	0 (0.0)	0.313
Digoxin n=60 (51.3)	9 (15.0)	9 (100.0)	0 (0.0)	0.015
Steroids n=56 (47.9)	11 (19.9)	6 (54.5)	5 (45.5)	0.929
Polygam n=51 (43.6)	2 (3.9)	1 (50.0)	1 (50.0)	0.950
B-Vitamins/Carnitine n=63 (53)	31 (49.2)	18 (58.1)	13 (41.9)	0.502
Clexane/Warfarin n=90 (76.9)	5 (5.6)	3 (60.0)	2 (40.0)	0.645
Aspirin n=88 (75.2)	36 (40.9)	23 (63.9)	13 (36.1)	0.317
Transfused any Blood Products n=62 (53.0)	21 (33.9)	11 (52.5)	10 (45.5)	0.880

Abbreviations: IQR[1]: Interquartile range, PICU[2]: Paediatric intensive care unit, CPR[3]: Cardiopulmonary resuscitation

Table 13: Comparisons of risk factors for death at various time periods

		Total Cohort	Total Deaths	Died <24 Hours	Died 24 Hours- Day 7	Died Day 8- 30	Died Day 31- 6 Months	Died 6 Months to 1 year	Died after 1 year	P Value
Number of cases n=(%)		117 (100.0)	52 (44.4)	25 (48.1)	7 (13.5)	5 (9.6)	10 (19.2)	3 (5.8)	2 (3.9)	
Age at diagnosis in months Median (IQR[1])		18.9 (8.9- 52.2)		10.6 (2.6- 19.3)	79.1 (16.3- 134.6)	56.2 (43.2- 91)	20.3 (11- 49.2)	2.4 (1.8- 175.2)	10.6 (9.3- 11.9)	0.0604*
Age at death in months Median (IQR[1])				10.8 (2.6- 19.6)	80.4 (16.6- 136.7)	58.0 (44.5- 92.8)	22.2 (14.7- 52.0)	6.8 (6.4- 183.8)	43.7 (26.1- 61.2)	0.0375**
Weight z score Median (IQR[1])		-1.1 (-2.6- 0.3)		-0.4 (-2.2- 0.4)	-1.5 (-2.2- 0.8)	-0.5 (0.9- -0.3)	-2.2 (-4.0- -1.4)	-1.3 (-3.2- 1.2)	1.7 (1.7- 1.7)	0.2457
Sex Female n=(%)		65 (55.6)	26 (40.0)	8 (30.8)	6 (23.1)	3 (11.5)	6 (23.1)	2 (7.7)	1 (3.9)	0.322
HIV[2] exposed n=(%)		24 (20.2)	12 (50.0)	8 (66.6)	0 (0.0)	0 (0.0)	2 (16.6)	1 (8.3)	1 (8.3)	0.057
HIV infected n=(%)		7 (5.9)	4 (57.1)	1 (25.0)	0 (0.0)	1 (25.0)	2 (50.0)	0 (0.0)	0 (0.0)	0.721
Place of presentation n=(%)	PICU[3]	25 (21.0)	17 (68.0)	10 (58.8)	1 (5.9)	2 (11.8)	1 (5.9)	2 (11.8)	1 (5.9)	0.001
	Emergency centre	52 (43.7)	19 (36.5)	8 (42.1)	3 (15.8)	2 (10.5)	5 (26.3)	1 (5.3)	0 (0.00)	
	Ward	29 (24.4)	6 (20.7)	0 (0.0)	2 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	1 (16.7)	
EF[4] at diagnosis n=(%)	Less than 20%	35 (29.9)	12 (34.3)	3 (25.0)	2 (16.7)	2 (16.7)	3 (25.0)	1 (8.3)	1 (8.3)	<0.001
	21-30%	25 (21.4)	6 (24.0)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	
	31-55%	28 (23.9)	5 (17.9)	1 (20.0)	1 (20.0)	1 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	
	No EF available	10 (8.6)	5 (50.0)	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	No Echo done	19 (16.2)	19 (100.0)	16 (84.2)	3 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.016
CCF[5] at diagnosis n=(%)		94 (80.3)	35 (37.2)	13 (37.1)	4 (11.4)	4 (11.4)	10 (28.6)	3 (8.6)	1 (2.9)	0.005
CVS[6]: instability at diagnosis n=(%)		90 (76.9)	40 (44.4)	17 (42.5)	4 (10.0)	5 (12.5)	9 (22.5)	3 (7.5)	2 (5.0)	0.057
Shock n= (%)		28 (23.9)	20 (71.4)	12 (60.0)	3 (15.0)	2 (10.0)	1 (5.0)	2 (10.0)	0 (0.0)	<0.000
Decreased LOC[7] n=(%)		12 (10.3)	4 (33.3)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0.016
Seizures n=(%)		7 (5.9)	3 (42.9)	3 (100.0)	0 (0.0)	0 (0.0)	0 0(0.0)	0 (0.0)	0 (0.0)	0.362
Hemiplegia n=(%)		5 (4.2)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0.476
PICU admission		70	36	14	5	5	6	3	1	0.157

n=(%)	(58.8)	(51.4)	(38.9)	(13.8)	(13.8)	(16.7)	(8.3)	(2.8)	
Ventilated n=(%)	46 (38.7)	28 (60.9)	17 (60.7)	4 (14.3)	4 (14.3)	1 (3.6)	2 (7.1)	0 (0.0)	<0.001
Inotropes n=(%)	70 (58.8)	37 (52.9)	16 (43.2)	4 (10.8)	4 (10.8)	7 (18.9)	3 (8.1)	1 (2.7)	0.011
CPR[8] during admission n= (%)	30 (25.6)	22 (73.3)	14 (46.7)	1 (3.3)	2 (6.7)	3 (10.0)	1 (3.3)	0 (0.0)	0.001

Abbreviations: IQR: Interquartile range, HIV[2]: Human immunodeficiency virus, PICU[3]: Paediatric intensive care unit, EF[4]: Ejection fraction, CCF[5]: Congestive Cardiac failure, CVS[6]: Cardiovascular system, LOC[7]: Level of consciousness, CPR[8]: Cardiopulmonary resuscitation

*post hoc analysis using Dunn test with Bonferroni adjustment for multiple comparisons, showed no significant differences between the groups

**post hoc analysis using Dunn test with Bonferroni adjustment for multiple comparisons, showed no significant differences between the group

Children diagnosed on postmortem alone

There were 19 children diagnosed only at postmortem with no diagnostic ECHO prior to this. (Table 14) Twelve of these infants died on day one of admission which may support the rapidity in their disease progression, hence little time for a confirmative ECHO, or that they presented late or were misdiagnosed. Five of the 19 children (26%) were under 3 months of age. Three of these 5 infants had admissions between 29 and 58 days, yet despite extensive investigations, the diagnosis of myocarditis was only made at postmortem. (Table 15)

Table 14: Subset of children diagnosed on postmortem alone

	Total Deaths n=52 (45%)	Postmortem Cases n=19 (36.5%)
Age in months Median (IQR[1])	15.9 (7.3-55.0)	10.6 (2.2-28.8)
Less than 12 months	22 (42.3)	10 (52.6)
1 year-5 years	18 (34.6)	5 (26.3)
5-10 years	5 (9.6)	1 (5.3)
Older than 10 years	5 (9.6)	3 (15.8)
Sex: Female	28 (53.8)	8 (42.1)
HIV[2] infected	4 (7.7)	2 (22.2)
Place of arrival at TBH[4]		
PICU[5]	17 (32.7)	5 (26.3)
Emergency centre	19 (36.5)	6 (31.6)
Paediatric ward	7 (13.5)	1 (5.3)
Not Known	8 (15.4)	7 (36.8)
Duration of symptoms		
<3 days	16 (31.0)	6 (31.6)
4-6 days	7 (13.5)	1 (5.3)
7-14 days	5 (9.6)	2 (10.5)
15-30	2 (3.8)	0 (0.0)
> 1 month	4 (7.7)	1 (5.3)
Unclear	18 (34.6)	9 (47.4)
On arrival		
Intubated on arrival	12 (23.1)	5/11 (45.5)
Cardiovascular instability	41 (78.8)	11/12 (91.7)
CCF[7]	36 (69.2)	8/9 (88.9)
Delay in diagnosis	20 (38.5)	4/8 (50.0)
Management		
Admitted to PICU[5]	36 (69.2)	9/13 (69.2)
Intubated/Ventilated	29 (55.8)	10/11 (91.0)
Inotropes	37 (71.2)	9/10 (90.0)
Adrenalin	20 (38.5)	8/10 (80.0)
2 or more inotropes	22 (42.3)	6/8 (75.0)
Died day 1	25 (48.1)	12 (63.2)
Died days 2-7	7 (13.5)	4 (21.1)
Died > day 7	20 (38.5)	3 (15.8)
Investigations		
Positive Blood cultures	10 (19.2)	7/14 (50.0)
Staphylococcus aureus	2 (20.0)	2 (28.6)
Streptococcus pneumoniae	2 (20.0)	1 (14.3)
MRSA[10]	1 (10.0)	1 (14.3)

ESBL[11] klebsiella	2 (20.0)	1 (14.3)
Haemophilus influenza and streptococcus pneumoniae	1 (10.0)	1 (14.3)
Candida and klebsiella	2 (20.0)	1 (14.3)
Viral screen positive	26 (50.0)	7/10 (70.0)
Parainfluenza	3 (11.5)	3 (42.9)
CMV[12]	13 (50.0)	3 (42.9)
CMV[12] (significant)	8 (30.8)	2 (28.6)
Parvovirus B19	3 (11.5)	1 (14.3)
Rhinovirus	7 (26.9)	1 (14.3)
Hepatitis A	1 (3.8)	1 (14.3)
Metabolic screen positive	1 (1.9)	0 (0.0)
Autoimmune screen positive	1 (1.9)	0 (0.0)
CXR[13] abnormal	41 (33.8)	12/12 (100.0)
ECGs[14] done	16 (30.7)	0 (0.0)
Cause category		
Viral	21 (40.4)	4 (21.1)
HIV[2] +virus	4 (7.7)	2 (10.5)
Not determined	19 (36.5)	13
Days of 1st admission median (IQR[1])	5 (1-15)	1 (0-5)
Place of death		
PICU[5]	34 (65.4)	10 (52.6)
Emergency centre	6 (11.5)	4 (21.1)
Wards	3 (5.8)	1 (5.3)
Other	9 (17.3)	4 (21.1)

Abbreviations: IQR[1]: Interquartile range, HIV[2]: Human Immunodeficiency virus, TB[3]: Tuberculosis, TBH[4]: Tygerberg Hospital, PICU[5]: Paediatric Intensive Care unit, COPD[6]: Cardiac outpatient department, CCF[7]: Congestive cardiac failure CK[8]: Creatine kinase, CRP[9]: C-reactive protein, MRSA[10] : Methicillin resistant staphylococcus aureus, ESBL[11]: Extended-spectrum-beta-lactamases, CMV[12]: Cytomegalovirus, CXR[13]: Chest x-ray/radiograph, ECG[14]: Electrocardiograph

Table 15: Summary of five children under the age of three months: diagnosed on postmortem

Case	Service	Duration in hospital (days)	Age at death (days)	ECHO[1] previously	Clinical information
1	NICU[2]	6	6	No	27 week gestation neonate HIV[3] exposed but uninfected/tuberculosis exposed/syphilis but uninfected HMD[4] Congenital pneumonia Confirmed blood streak infection (ESBL Klebsiella)
2	Neonatal Ward	28	28	Yes	33 week gestation neonate HIV[3] exposed but uninfected Apnoeas with presumed sepsis Encephalopathy on EEG Deranged liver function
3	Neonatal Ward	58	58	Yes	27 week gestation infant HIV-infected Jaundice Treated for necrotizing enterocolitis
4	NICU[2]	56	77	No	Term infant Hirschprung disease on biopsy Confirmed blood stream infection (MRSA) PM[6] showed pancarditis with macroscopic cardiac abscesses.
5	PICU[5]	1	66	No	Premature infant (unknown gestation)/low birth weight Tuberculosis exposed Apnoea Septic shock Confirmed blood stream infection (Staphylococcus aureus)

Abbreviations: ECHO[1]: Echocardiography, NICU[2]: Neonatal intensive care unit, HIV[3]: Human immunodeficiency virus, HMD[4]: Hyaline membrane disease, PICU[5]: Paediatric intensive care unit, PM[6]: Postmortem

The Kaplan-Meier plot (Figure 3) illustrates that a large number of deaths occur early. This is seen by the steep decrease in the total number at risk. A relative plateau follows this, especially after a year from diagnosis.

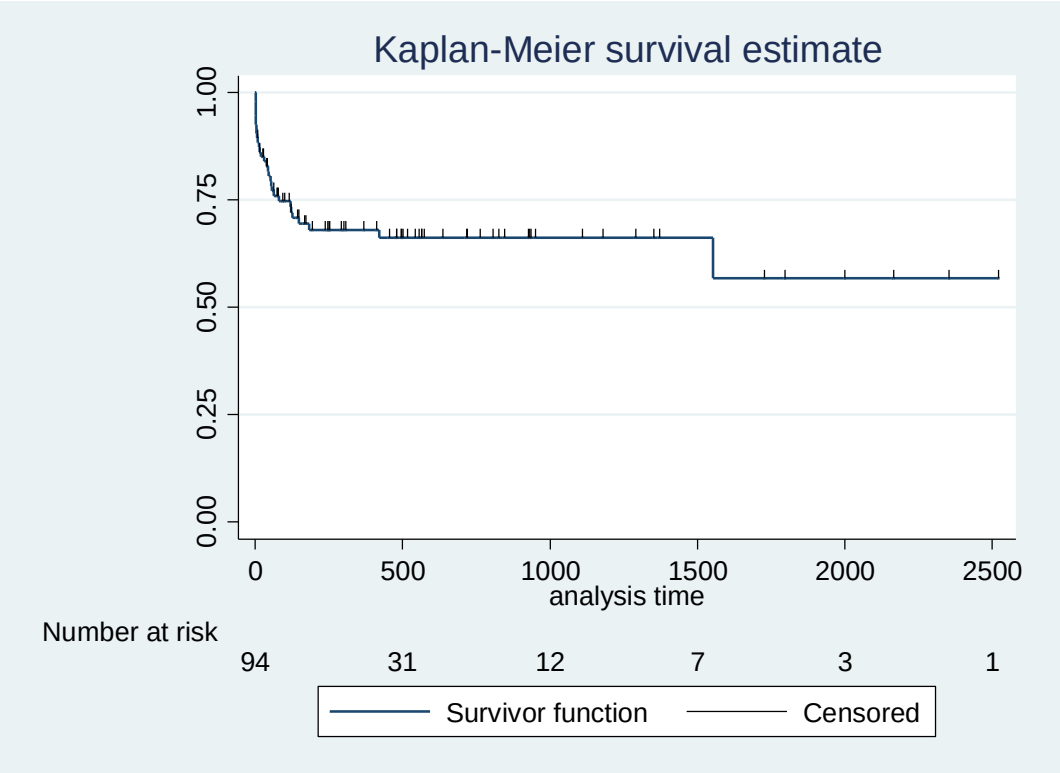


Figure 3: The relationship between time of admission to death is illustrated on the Kaplan-Meier plot.

Most recent cardiac outpatients follow up

Of the 80 children who survived the first admission, 62 children attended outpatients at least once. (Table 16) The median duration of follow up time from first diagnosis was 474 days (IQR 147-820). (Table 16) Fourteen (20.3%) recovered and were discharged from cardiac outpatient services, 24 (34.7%) had normalized EF and 24 (34.7%) were lost to follow-up. Five children died during or subsequent to follow up, however it was not noted whether these deaths were directly related to myocarditis/DCMO or not.

Table 16: Most recent cardiac outpatients follow up for survivors

Number of patients followed up at COPD[1]	62
Number of COPD follow up visits Median (IQR[2])	3 (2-7)
Length of follow up since 1st admission median (days) (IQR[2])	474 days (147-820)
Age of follow up median in months (IQR[2])	37 (23-66)
Symptomatic	18 (29.0)
Clinical signs of cardiomegaly	34 (54.8)
Clinical signs of cardiac failure	16 (25.8)
Medications at follow up	38 (61.3)
>2 medications on follow up	38 (61.2)
Furosemide	38 (61.3)
Spirinolactone	34 (54.8)
Captopril	36 (58.1)
Digoxin	10 (16.1)
Aspirin	17 (27.4)
Warfarin	3 (4.8)
Other	11 (17.7)
Outcome of children who attended COPD[1]	
Recovered and were discharged from COPD[1]	14 (22.6)
Still attend COPD[1] with normal EF[3]	21 (33.9)
Still attend COPD[1] with impaired EF[3]	5 (8.1)
Lost to follow up impaired EF[3]	21 (33.9)
Lost to follow up normal EF[3]	3 (4.8)
Died	5 (8.1)

Abbreviations: COPD[1]: Cardiac outpatients department, IQR[2]: Interquartile range, EF[3]: Ejection fraction

Younger age, admission from outside the metropolitan area (p=0.001), lower EF at diagnosis (p=0.000), CCF at diagnosis (p=0.005), CVS instability (p=0.057), inotrope use and shock (p=0.000) was associated with death on the univariate analysis. On the multivariate analysis renal dysfunction and cardiac failure remained significant. (Table 17)

Table 17: Multivariate analysis using death versus survival as outcome

	Univariate Analysis		**Multivariate Analysis**	
Variable	OR[2] (95%CI)	P Value	OR[2] (95%CI)	P Value
Place of arrival	0.8 (0.1-29.4)	0.001	0.8 (0.5-1.0)	0.089
Age at diagnosis	1.0 (1.0-1.0)	0.649		
Weight z score at diagnosis	0.9 (0.9-1.1)	0.461		
HIV[1] positive	0.9 (0.5-1.8)	0.824		
Admitted to another hospital prior	0.9 (0.3-2.9)	0.899		
Delay in diagnosis	1.0 (0.4-2.7)	0.924		
Intubated on arrival	2.8 (1.0-7.8)	0.042	0.7 (0.1-5.8)	0.768
Tachycardia for age	1.8 (0.3-9.5)	0.495		
Depressed level of consciousness	1.4 (0.3-5.5)	0.675		
Cardiovascular instability	5.4 (1.2-25.5)	0.032		
Cardiac failure	2.4 (0.4-15.2)	0.023	85.1 (1.4-5225.9)	0.034
Displaced apex	3.6 (0.4-31.7)	0.241		
EF[3] on diagnosis	3.1 (1.0-9.2)	0.045	3.6 (0.7-18.2)	0.122
Thrombus ever	1.0 (0.1-12.0)	0.976		
Effusion ever	0.6 (0.1-2.2)	0.415		
Acidosis	1.5 (0.5-4.9)	0.462		
Raised lactate	0.8 (0.4-1.6)	0.535		
Renal dysfunction	3.7 (2.1-21.1)	0.001	8.2 (1.8-38.0)	0.007
Raised CK[4]	3.8 (1.5-9.9)	0.005	1.7 (0.6-4.7)	0.274
ICU[5] admission	3.4 (1.4-8.2)	0.006	0.5 (0.0-8.1)	0.640
Ventilated	5.7 (2.5-13.3)	<0.001	0.7 (0.1-4.5)	0.691
Inotropes	7.6 (2.4-23.9)	0.001	10.1 (0.4-271.9)	0.170
Dopamine and or Dobutamine	3.6 (1.4-9.6)	0.010		
Adrenalin	24.8 (6.4-95.4)	<0.001	6.3 (0.8-52.2)	0.087
Milrinone	2.4 (0.9-6.4)	0.081		
2 or more inotropes	3.6 (1.5-8.4)	0.003	0.6 (0.1-3.6)	0.561
CPR[6]	5.2 (2.1-13.1)	<0.001	4.1 (0.9-21.1)	0.061

Abbreviations: HIV[1]: Human Immunodeficiency virus, OR[2]: Odds ratio, EF[3]: Ejection fraction, CK[4]: Creatine kinase, ICU[5]: Intensive care unit, CPR[6]: Cardiopulmonary resuscitation

Discussion

This study highlights, for the first time in our setting, the significant burden of disease, as well as mortality and morbidity of children with myocarditis and DCMO. We describe a cohort of 117 children with myocarditis/DCMO, where the majority of cases were due to probable viral myocarditis or viral myocarditis transitioning/transitioned to DCMO. Children were young with a median age at diagnosis of 18.9 months (IQR 8.87-52.2) with 36% younger than 12 months of age. These children were younger than the RCWMCH PICU cohort where the median age was 27 months. (24) In both the TBH and RCWMCH cohorts, infants were much younger than the 9.2 years reported in a large American cohort. (48) We did not observe the bimodal peak seen in other paediatric cohorts, but as in the US cohort, a large number of children were between 6 months and 12 months of age. (48) This age difference may be due to a higher burden of common infections with potentially severe outcomes in our community; without the additional data on the incidence of these infections, in all the age cohorts, we are unable to explore this further.

At TBH, like in other resource-deplete settings, there is no access to cardiac transplantation, ECMO or ventricular assist devices and there is limited access to PICU beds. One of the most striking results found was an overall 44% mortality, with the majority, 73%, of these children dying during the initial admission and 48% dying within 24 hours of the initial admission. Although we appreciate that myocarditis and DCMO with or without cardiac failure have substantial morbidity and mortality (35,36) this high mortality is in stark contrast to the outcomes reported in cohorts from the US where survival has improved and is now up to 90% in cohorts of acute myocarditis. (8,49) Locally at the RCWMCH PICU, 47% survived PICU admission in a cohort where 55% of patients were ventilated and 100% required inotropic support. (24)

Poor perfusion with cardiovascular instability, cardiac failure, low EF, receiving inotropic support, and intubation on arrival and required PICU admission were identified as predictors of mortality in univariate analysis. In the multivariate analysis renal dysfunction and cardiac failure were the only features that remained significant. Age at presentation, cardiac failure and lower EF and SF have consistently been identified as prognostic factors and are predictive of death and need for transplantation. (6,13,22,25) Patients with cardiac failure were 4 times more likely to succumb or would require transplantation within 1 year of diagnosis. (25) Neonatal presentation (8,22,42) and children of older age (13,30,34) have the highest mortality. Our cohort had 6 infants diagnosed under a month old (of whom 3 died) and 10 children more than 10 years of age (of whom 5 died), and there was no statistical significance between the age overall of those who survived and died in our study. Though the 95% CIs are wide, cardiac failure at presentation (OR 85.1 95% CI 1.4-5225.9) (p=0.03) and renal dysfunction (OR 8.2 95% CI 1.8-38.0) (p=0.007) were predictive of death.

Finding an EF of less than 30% and/or SF of less than 15%, left ventricular dilatation, and mitral valve regurgitation on ECHO are known to be predictive of negative outcomes in other cohorts, but we were not able to show this on multivariate analysis. (8) Mortality is also associated with the use of ECMO, VAD, and vasoactive intravenous medication, which reflects the most severely ill children. The lower number of children who accessed PICU in this study compared to international data does not suggest that these children suffered from less complex disease. The result suggested by the higher mortality in our settings, may be due to the local pressures of fewer PICU and high care beds as well as understaffing. The high mortality, though not necessarily due to delay in diagnosis, may rather reflect a delay in rapid access to intensive care and no access to sophisticated cardiac interventions at the first admission. Six

(11.5%) children died in the emergency centre.

Nineteen children were diagnosed on postmortem alone. These children were slightly younger than the general cohort (10 months vs. 18 months) and were critically ill, with 92% showing signs of cardiovascular instability and 89% in cardiac failure. Forty-five percent arrived intubated with a further 5 needing intubation on arrival/before dying. Many of these children were poorly investigated as to the potential causes of cardiac dysfunction prior to death, due to their short duration of admission. In those who were investigated prior to death, high percentages of children showed complications in the form of renal dysfunction, a raised CK and a raised CRP. Seven of the 14 who had blood cultures taken before death had positive cultures where pathogenic organisms were isolated. The secondary bacterial infections may play a role in the disease progression and death in these children, with bacterial infections possibly causing additional inflammatory changes and cardiovascular dysfunction. This phenomenon has not been described before in myocarditis/DCMO per se, however may have played a role in the rapid deterioration and death of these children. In respiratory tract infections, it is well described that frequently viruses and bacteria can co-infect the same host, resulting in heightened pathology and severity of illness compared to single infections. (50) This possibly supports the use of broad-spectrum antibiotics in children with suspected myocarditis or DCMO, until bacterial infections are excluded. There are also children in this cohort who had prior ECHOs that were not suggestive of myocardial failure, highlighting the evolution of disease over time and the potential need to repeat ECHO in some cases. These children also highlight the important role of the postmortem in diagnosis of cases where the cause of death is uncertain, even in the face of confirmed bacteremia. A postmortem study from Sweden reported the incidence of myocarditis to be 1.06 % in 12 747 consecutive autopsies (51) and in the UK histologically proven myocarditis was seen in 1.8%, of cases younger than 18 years. In the latter study 54% of the deaths occurred in infants less than 1 year of age, accounting for 2% of infant deaths referred for autopsy, compared with around 5% of childhood deaths over the age of 5 years. In almost 40% of cases there were no macroscopic cardiac abnormalities, the diagnosis being entirely dependent on histological examination of the heart. (52) Our study only reports on postmortems requested by medical teams since we do not have access to data from medico legal postmortems. Myocarditis may well however be implicated in cases of sudden unexpected death in infancy (SUDI) that are referred to the medical examiners. For a full appreciation of the prevalence and incidence of mortality these cases will need to be included in studies in the future.

Despite the high rate of early mortality, the outlook for children who survive the initial admission, is cautiously hopeful. Twenty percent of children who attended COPD (12% of total cohort) recovered fully and were discharged from cardiology care. The EF normalized in a further 30.4% of children still in care. Despite these good outcomes, the long-term mortality may be underestimated due to the high levels of children lost to follow-up (34.7%). Andrews et al recently showed that children who survive an initial hospitalization with heart failure from heart muscle disease, have a good medium - term survival (82% overall 1 - year survival but 77% at 5 years and 73% at 10 years, with survival conditional on 1 - year survival 94% & 89% at 5 and 10 years respectively). (36) Therefore, despite an increased likelihood of death early in their illness trajectory, patients with an acute fulminant presentation should be managed aggressively. (39) These data support ongoing access to high care and intensive care for these children since they may recover or stabilize, as reported in international data. (36) We did not explore markers of long-term outcome.

Retrospectively assigning causality in this study was in certain cases complicated by the incomplete evaluation, especially for metabolic and autoimmune diseases as well as the lack of access to genetic testing. It is clear that clinicians should be further educated on the guidelines to investigate children, as well as the importance of correct and

timeous specimen collection necessary as soon as possible after admission. Though 48-60% of DCMO cases in children are idiopathic, (22,25) cases need to be extensively investigated prior to making this diagnosis. After case reviews we concluded that presumed viral myocarditis occurred in 54 (36.7%) and a cause could not be determined in 31 (26.5%). Due to incomplete evaluation we were however not able to classify them as idiopathic. In the study from RCWMCH 87% of children had presumed viral myocarditis and idiopathic DCMO occurred in 13%. (24) Despite the known correlation of respiratory PCR with viral myocarditis, finding viruses in the respiratory tract does not necessarily indicate they are causal. A positive PCR may be related either to shedding, or due to a respiratory infection that may trigger admission in a child with established myocardial dysfunction. Multiple viruses were found in a large number of children, and where viral pathogens were identified, 38.9% had 2 or more viruses. Like other studies we found that adenovirus, parvovirus, enteroviruses and CMV virus were common. The role of CMV and rhinovirus is not clear in the cause of myocarditis. In the case of CMV, it was considered the potential cause in this study if there was no other cause found and there was a confirmed viraemia of more than Log 3. Locally we have used a VL of >60 000 to suggest significant pulmonary infections in children with HIV, and Log 3 (VL 1000 copies per ml) is widely reported as a significant level of viraemia in children undergoing transplantation. There are no cut-offs for myocarditis and interpreting CMV viral load is complicated. Where CMV was considered in the cohort as the potential cause, the median age of children was younger than 6 months, which indicated acute infection.

Myocardial dysfunction is a well-known complication of human immune deficiency virus infection. (4, 26, 27) Of the 80 children tested in the cohort, twenty-four (20.5%) of the children were HIV exposed and of these 7 (29.2%) were HIV-infected. Four of the 7 HIV-infected children (57.1%) were on ARVs. A large proportion (31.6%) of children were not tested for HIV and in a setting of high HIV prevalence this needs to be addressed. Four of the HIV-infected children included in this study died.

Ten percent of the children were being treated for TB disease and were on therapy at the time of diagnosis. Unfortunately more detailed information was not available and collected on these children, but this may indicate that these children had chronic symptoms causing them to seek health care. One could postulate that in some of these children, symptoms may have been due to cardiac disease rather than TB. Of interest is also the number of children with compressed airways on the CXR. We did not confirm whether this finding was in children with TB diagnosis at the time of presentation. Cardiac enlargement may cause airway compression (53) and in settings with a high TB prevalence, TB may be the incorrect diagnosis.

As in all retrospective studies there are a number of limitations. Despite an extensive initial case search through Clinicom, the ICU and ward databases, and all COPD files, there may have been sampling errors and missed cases. Children were occasionally coded with the incorrect ICD 10 codes as well. Retrospective data extraction from clinical records occasionally did not allow for complete data sets, as there was information missing, illegible handwriting and incomplete documentation in the doctors' notes. Assessing the given causes and re-assigning the causes for the study definitions was also complex.

The strengths of this study include that it is the first at TBH in Cape Town, and provides information of an interesting cohort of South African children. In addition, we feel that apart from rheumatic heart disease, acquired disorders and other diseases of the heart muscle are under appreciated in the current climate. There is a focus on the rapid and effective management of correctable structural lesions of the heart. This study is the first to confirm our suspicions.

We are now collaborating in a registry that will prospectively evaluate and enrol these children, and the data will form part of the backdrop for prospective work in this field.

Conclusions

This study strikingly shows the high mortality in our local cohort, and this emphasises the need for a high index of suspicion of myocarditis in the emergency room setting. Similarly rapid PICU access and specialist intervention is needed to improve mortality. Secondary bacterial infections are important contributors to death in this cohort and must always be considered. Although we may be underestimating the total deaths in this cohort, the survival after the first admission was fair and supports the current recommendation to provide a full set of interventions to these patients. Adherence to the myocarditis/DCMO investigation protocol needs to be improved to allow for improved diagnosis and prognostication. Future studies in local and under resourced settings are needed to allow for prevalence and incidence to be calculated and these should include data from medical and medico legal postmortems.

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Appendix 1: Summary of studies 1999-2016 reporting the viruses isolated in myocarditis cases

Study	Martin et al (51)	Bowles et al (20)	Bowles et al (19)	Amabile et al (7)	Marholdt et al (18)	Durani et al (10)	Kim et al (17)	Foerster et al (2)	Saji et al (6)	Miranda et al (22)	Lin et al (21)	Rossouw et al (24)
Year	1994	1999	2003	2006	2006	2009	2010	2010	2012	2014	2014	2016
TOTAL N=	34	32	773	11	128	62	33	94	169	61	45	95
Viruses + (%)	76%	34%	35%	45%	68%	68%	64%	33%	22%	18%	64%	87%
Adenovirus	44%	19%	21%			3%	3%	3%	0.6%		2%	29%
Enterovirus including Coxsackie B	24%		13%	9%		6%	24%	11%	9%		7%	
CMV[1]	3%	9%	2%					11%	0.6%	3%		
EBV[2]			0.4%	9%				2%				
Echovirus							6%		2%			
Hepatitis B								1%				
Herpes Zoster				9%					0.6%			
HHV6[3]					13%							
HSV[4]	6%		0.6%					2%			2%	
Influenza A or B			0.6%			3%	6%		6%	2%	2%	
Measles									0.6%			
Metapneumovirus							3%					
Mumps							3%		0.6%			
Parainfluenza						13%						
Parvovirus B19			0.8%	18%	38%	2%		1%	1%	13%	18%	20%
Rhinovirus							3%				2%	
RSV[5]			0.1%				15%	1%				
Multiple Viruses		6%	3%		12%	4%					4%	34%

CMV[1]: cytomegalovirus, EBV[2]: Epstein-Barr virus, HHV6[3]: Human Herpes Virus 6, HSV[4]: Herpes simplex virus, RSV[5]: respiratory syncytial virus

Appendix 2: List of ICD 10 codes used in the electronic data base searches

I40 Myocarditis

- I40.0 Infective myocarditis
- I40.1 Isolated myocarditis
- I40.8 Other acute myocarditis
- I40 9 Acute myocarditis, unspecified
- I41.0 Myocarditis in bacterial diseases classified elsewhere
- I41.1 Myocarditis in viral diseases classified elsewhere
- I41.2 Myocarditis in other infectious and parasitic diseases classified elsewhere
- I41.8 Myocarditis in other diseases classified elsewhere

Cardiomyopathy

- I42.0 Dilated cardiomyopathy
- I42.1 Obstructive hypertrophic cardiomyopathy
- I42.2 Other hypertrophic cardiomyopathy
- I42.3 Endomyocardial (eosinophilic) disease
- I42.4 Endocardial fibroelastosis
- I42.5 Other restrictive cardiomyopathy
- I42.7 Cardiomyopathy due to drugs and other external agents
- I42.8 Other cardiomyopathies

I42.9 Cardiomyopathy, unspecified

Cardiomyopathy in diseases classified elsewhere

- I43.0 Cardiomyopathy in infectious and parasitic diseases classified elsewhere
- I43.1 Cardiomyopathy in metabolic diseases
- I43.2 Cardiomyopathy in nutritional diseases
- I43.8 Cardiomyopathy in other diseases classified elsewhere

Appendix 3: Case report form

DATA COLLECTED	CODE
PATIENT NUMBER	1/2/3 ETC
DOB	YEAR/MONTH/DATE
AGE AT DIAGNOSIS (DAYS)	1/2/3/4
MONTHS AT DIAGNOSIS	1/2/3/4
YEARS AT DIAGNOSIS	1/2/3/4
SEX	MALE (1) FEMALE (2)
WEIGHT AT DIAGNOSIS	(IN KG)
Z SCORE WEIGHT FOR AGE	
METRO AREA	INSIDE TBH (1) KHAYELITSHA (2) OUTSIDE TBH (3) NOT AVAILABLE (4)
DATE OF DIAGNOSIS OF MYOCARDITIS/DCMO	YEAR/MONTH/DATE
DIAGNOSIS BASED ON	CLINICAL ALONE (1) CLINICAL AND ECHO (2) ECHO, CLINICAL AND POST MORTEM (3) POST MORTEM ALONE (4) CLINICAL AND PM (5) CLINICAL, ECHO, BIOPSY (6)
CONFIRMED DIAGNOSIS (WITH ECHO/HISTO)	YES (1) NO (2)
DIAGNOSIS ADMISSION DATE	YEAR/MONTH/DATE (DON'T KNOW =1999/01/01)
DIAGNOSIS DISCHARGE/DEATH DATE	YEAR/MONTH/DATE
NUMBER OF DAYS 1ST ADMISSION	1/2/3/4/5 ETC
DIED ON 1ST ADMISSION	NO (1) YES (2)
DIED ON SUBSEQUENT ADMISSION	NO (1) YES (2)
DIED DURING STUDY IN HOSPITAL	NO (1) YES DIED IN HOSPITAL (2)
SURVIVED	NO (1) YES (2)
NEW SURVIVAL COLUMN	0=SURVIVED 1=DIED 1ST ADMISSION 2=DIED SUBSEQUENT ADMISSION
IF DEAD: DATE OF DEATH	YEAR/MONTH/DATE
AGE AT DEATH (DAYS OLD)	1/2/3/4
AGE AT DEATH (MONTHS)	1/2/3/4
PLACE OF DEATH	COPD (1) GGR (2) G10 (3) G9 (4) G7 (5) G3 (6) PICU (7) OTHER (8) NOT DOCUMENTED (9) RXH (10) DID NOT DIE (11)
TIME TO DEATH (FROM DIAGNOSIS) (DAYS)	0/1/2/3 (DAYS)
FURTHER ADMISSIONS	YES (1) NO (2) INFO NOT CLEAR (3)
FURTHER ICU ADMISSIONS	YES (1) NO (2) INFO NOT CLEAR (3)
ADMISSIONS REQUIRING INOTROPES	YES (1) NO (2) INFO NOT CLEAR (3)
ADMISSIONS REQUIRING VENTILATION	YES (1) NO (2) INFO NOT CLEAR (3)
MOST RECENT CLINICAL ENCOUNTER	YEAR/MONTH/DATE
TIME OF FOLLOW UP (DAYS)	1/2/3/4 (DAYS)
TIME OF FOLLOW UP (MONTHS)	1/2/3/4 (MONTHS)
EF ON ECHO AT DIAGNOSIS	LESS THAN 5% (1) 6-10%(2) 11-20% (3) LESS THAN 20% (11) 21-30% (4)

	31-40% (5) 41-50% (6) 51-55% (7) MORE THAN 55% (8) NO ECHO DONE (9) INFO NOT AVAILABLE (10)
THROMBUS EVER ON ECHO EFFUSION EVER ON ECHO MOST RECENT ECHO	YES (1) NO (2) NO ECHO DONE (3) NOT DOC(4) YES (1) NO (2) NO ECHO DONE (3) NOT DOC(4) YEAR/MONTH/DATE
EF ON **MOST RECENT ECHO**	LESS THAN 5% (1) 6-10%(2) 11-20% (3) LESS THAN 20% (11) 21-30% (4) 31-40% (5) 41-50% (6) MORE THAN 51-55% (7) MORE THAN 55% (8) NOT AVAILABLE (9) NO ECHO DONE (10)
NUMBER OF ADMISSION TO TBH AFTER DIAGNOSIS 2008-2015	1/2/3 ETC
NUMBER OF ICU ADMISSION TO TBH AFTER DIAGNOSIS 2008-2015	1/2/3 ETC
NUMBER OF COPD VISITS AT TBH 2007-2015 TOTAL NUMBER OF ECHOS ON ECHO SYSTEM	0/1/2/3 ETC 0/1/2/3 ETC
CAUSE OF MYOCARDITIS/DCMO	ACUTE VIRAL INFECTION (1) HIV DISEASE (2) DRUG ARV (3) DRUG CHEMO (4) IMMUNIZATIONS (5) METABOLIC (6) ARRHYTHMIA (7) UNIDENTIFIED (7) OTHER (8) HPT (WITH NEPHRITIS) (9) VACCINE (10) AUTOIMMUNE (11) BACTERIAL (12) PERINATAL (13)
HIV EXPOSED	YES (1) NO (2) NOT DOCUMENTED (3)
HIV POSITIVE	YES (1) NO (2) TEST NOT DONE (3)
ON ARVS AT TIME OF DIAGNOSIS ADMISSION	YES (1) NO (2) N/A (3) NOT SURE (4)
TIME OF SYMPTOMS PRIOR TO PRESENTATION	1 DAY (1) 2 DAYS(2) 3 DAYS(3) 4-6 DAYS (4) 7-10 DAYS (5) 10-14 DAYS (6) 2-4 WEEKS (7) MORE THAN A MONTH (8) NOT DOCUMENTED (9)

DELAY IN DIAGNOSIS PRESENTATION IF YES: REASON MORE THAN 2 HEALTHCAREVISITS ADMITTED TO ANOTHER HOSPITAL FIRST MORE THAN 4 DAYS SYMPTOMS DIFFERENT DIAGNOSIS IN NOTES PRIOR TO MYOCARDITIS/DCMO	YES (1) NO (2) NOT CLEAR (3) MULTIPLE CLINIC/GP VISITS PRIOR (1) ADMITTED AT ANOTHER HOSPITAL PRIOR (2) NOT APPLICABLE (3) DIFFERENT DIAGNOSIS SUSPECTED (4) MORE THAN 5 DAYS SX (5) YES (1) NO (2) NOT CLEAR (3) YES (1) NO (2) NOT CLEAR (3) YES (1) NO (2) NOT CLEAR (3) YES (1) NO (2) NOT CLEAR (3)
PLACE OF ARRIVAL IN TBH	COPD (1) GGR (2) G10 (3) G9 (4) G7 (5) G3 (6) PICU (7) OTHER (8) NOT DOCUMENTED (9)
AFTER ARRIVAL AT TBH TIME TO DIAGNOSIS SUGGESTED IN NOTES	IMMEDIATE (1) HOURS (2) DAYS (3) WEEKS (4) MONTHS (5) UNKNOWN (6)
SEIZURE HEMIPLEGIA NEUROLOGY NOTED	YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3)
HIV DISEASE	YES (1) NO (2) NOT DOCUMENTED (3)
TB CURRENTLY PREMATURITY/LBW CHILDHOOD CANCER	YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3)
INTUBATED ON ARRIVAL	YES (1) NO (2) NOT DOCUMENTED (3)
ANY OXYGEN SUPPORT ON ARRIVAL	YES (1) NO (2) NOT DOCUMENTED (3)
SYSTOLIC HYPOTENSION ON ARRIVAL MEAN BP HYPOTENSION ANY HYPOTENSION	YES (1) NO (2) NOT DOCUMENTED (9) YES (1) NO (2) NOT DOCUMENTED (9) YES (1) NO (2) NOT DOCUMENTED (9)
GCS ON ARRIVAL	15/15 (1) 11-14 (2) 9-10 (3) 8 OR LESS (4) NOT DOCUMENTED (5) INTUBATED (6)
HR TACHYCARDIA FOR AGE	MORE THAN 160 (1) 140-159 (2) 120-139 (3) 100-119 (4) 80-99 (5) 60-79 (6) LESS THAN 60 (7) NOT DONE (8) YES (1) NO (2) NOT DOCUMENTED (8)
RR	0-12 (1) 13-18 (2) 19-25 (3) 26-35 (4) 36-50 (5) 51-60 (6) MORE THAN 60 (7) VENTILATED (8) NOT DOCUMENTED (9)

SHOCK POOR PERFUSION ANY HYPOTENSION ACTUAL LACTATE RESULTS RAISED LACTATE (>3) PH ACIDOSIS PH <7.35 CARDIOVASCULAR INSTABILITY (1 OR MORE OF ABOVE +)	YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (9) 1/2/3/4 ETC YES (1) NO (2) TEST NOT DONE (7) ACTUAL PH YES (1) NO (2) TEST NOT DONE (7) NOT DOCUMENTED (8) YES (1) NO (2) TOO LITTLE INFORMATION (3)
SIGNS OF CARDIAC FAILURE DISPLACED APEX HEPATOMEGALY RAISED JVP CREPS WHEEZE PALLOR OEDEMA	YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3) YES (1) NO (2) NOT DOCUMENTED (3)
RENAL FUNCTION DONE RENAL DYSFUNCTION (RAISED CREATININE)	YES (1) NO (2) YES (1) NO (2) TEST NOT DONE (3)
ELECTROLYTES DONE ELECTROLYTE DYSFUNCTION	YES (1) NO (2) YES (1) NO (2) TEST NOT DONE (3)
LFTS DONE	YES (1) NO (2)
LFT ABNORMALITIES (RAISED AST)	YES (1) NO (2) TEST NOT DONE (3)
LACTATE DONE	YES (1) NO (2)
LACTATE RESULT	LESS THAN 1 (1) 1.1-3 (2) 3.1-5 (3) 5.1-7 (4) 7.1-10 (5) MORE THAN 10 (6) TEST NOT DONE (7) REJECTED (8)
CK DONE	YES (1) NO (2)
CK RAISED	YES (1) NO (2) TEST NOT DONE (3)
TROPONINS DONE	YES (1) NO (2)
TROPONINS RAISED MORE THAN 0.1UG/LITRE	YES (1) NO (2) TEST NOT DONE (3) REJECTED (4)
BLOOD GAS DONE pH	YES (1) NO (2) MORE THAN 7.45 (1) 7.35-7.44 (2) 7.25-7.34 (3) 7.15-7.24 (4) 7.0-7.14 (5) LESS THAN 7 (6) TEST NOT DONE (7) NOT DOCUMENTED (8)
BLOOD CULTURE DONE	YES (1) NO (2)
BLOOD CULTURE +	YES (1) NO (2) TEST NOT DONE (3)
ENTEROVIRUS SCREEN + (URINE, STOOL, BLOOD)	YES (1) NO (2) TEST NOT DONE (3) TEST DONE/NO RESULT (4)
COXSACKIE + (2 SPECIMENS IGM/IGG)	YES (1) NO (2) TEST NOT DONE (3) REJECTED (4)
MUMPS DONE	YES (1) NO (2)
MUMPS IGM+ MUMPS PCR + MUMPS EITHER +	YES (1) NO (2) TEST NOT DONE (3) REJECTED (4) YES (1) NO (2) TEST NOT DONE (3) REJECTED (4) YES (1) NO (2) TEST NOT DONE (3) REJECTED (4)
RUBELLA DONE	YES (1) NO (2)
RUBELLA IGM +	YES (1) NO (2) TEST NOT DONE (3)
PARVO B19 TESTED	YES (1) NO (2)
PARVO B PCR + PARVO B IGM+ PARVO EITHER +	YES (1) NO (2) TEST NOT DONE (3) REJECTED (4) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3)

CMV SEROLOGY DONE CMV IGM + CMV VL DONE	YES (1) NO (2) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2)
CMV VL RESULT	LDL (1) LOG LESS THAN 2 (2) LOG 2.1-3 (3) LOG 3.1-4 (4) LOG 4.1-5 (5) LOG MORE THAN 5 (6) TEST NOT DONE (7)
CMV PCR ON URINE DONE	YES (1) NO (2)
CMV URINE PCR +	YES (1) NO (2) TEST NOT DONE (3)
EBV IGM DONE	YES (1) NO (2)
EBV IGM +	YES (1) NO (2) TEST NOT DONE (3)
HERPES SCREEN DONE	YES (1) NO (2)
HERPES SCREEN (IGM OR PCR +)	YES (1) NO (2) TEST NOT DONE (3)
NPA/TA DONE	YES (1) NO (2)
NPA/TA + CMV+ RHINOVIRUS + INFLUENZA VIRUS A + INFLUENZA VIRUS B + INFLUENZA VIRUS C + ADENOVIRUS RSV+ CORONA VIRUS + ENTEROVIRUS + OTHER VIRUS +	YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3) YES (1) NO (2) TEST NOT DONE (3)
CTR AT DIAGNOSIS CARDIOTHORACIC RATIO ACTUAL PLETHORA PLEURAL EFFUSION(S) ATELECTASIS/COLLAPSE AIRWAY NARROWING	LESS THAN 40% (1) 41-50% (2) 51-55% (3) 56-60% (4) MORE THAN 60% (5) NO CXR AT DIAGNOSIS (6) YES (1) NO (2) YES (1) NO (2) YES (1) NO (2) YES (1) NO (2)
WARD INITIALLY ADMITTED TO	GGR (1) G3 (2) G7 (3) G9 (4) G10 (5) PICU (6) HIGH CARE (7) OTHER (8) NOT ADMITTED (10)
ICU ADMISSION NUMBER OF DAYS IN ICU	YES (1) NO (2) UNKNOWN (3) 1/2/2/4 ETC
VENTILATED IF YES: NO OF DAYS	YES (1) NO (2) 1/2/3/4 ETC
NONINVASIVE OXYGEN SUPPORT	YES (1) NO (2) NOT DOC/NO INFO (3)
INOTROPES	YES (1) NO (2)
DOPAMINE/DOBUTAMINE	YES (1) NO (2)
ADRENALIN/NOR-ADRENALIN	YES (1) NO (2)
MILRINONE	YES (1) NO (2)
TOTAL NUMBER OF DAYS OF INOTROPES >>2 INOTROPES	1/2/3/4/5/6/7/8/9/10 ETC YES (1) NO (2)
DIURETICS USED (LASIX +-SPIRO)	YES (1) NO (2)
ACE-INHIBITOR USED	YES (1) NO (2)
B-BLOCKER USED	YES (1) NO (2)
DIGOXIN	YES (1) NO (2)
ANY STEROIDS	YES (1) NO (2)
POLYGAM RECEIVED	YES (1) NO (2)
B VITAMINS/CARNITINE GIVEN	YES (1) NO (2)
ASPIRIN USED	YES (1) NO (2)
CLEXANE/WARFARIN USED TRANSFUSED ANY BLOOD PRODUCTS	YES (1) NO (2) YES (1) NO (2)

MOST RECENT COPD VISIT DATE	YEAR/MONTH/DATE
AGE AT FOLLOW UP (DAYS)	1/2/3/4/5
AGE AT FOLLOW UP (MONTHS)	1/2/3/4/5
WEIGHT AT FOLLOW UP	IN KG
WEIGHT Z-SCORE AT FOLLOW UP	
ANY SYMPTOMS REPORTED	YES (1) NO (2) NOT DOCUMENTED (3) N/A (DIED(4) NEVER FOLLOWED UP (5)
DISPLACED APEX (CARDIOMEGALY)	YES (1) NO (2)
SIGNS OF CCF	YES (1) NO (2)
MEDICATIONS	YES (1) NO (2)
2 OR MORE MEDICATIONS	YES (1) NO (2)
DIURETICS	YES (1) NO (2)
ASPIRIN	YES (1) NO (2)
WARFARIN	YES (1) NO (2)

Appendix 4: Tygerberg Hospital DCMO workup guideline

Dilated Cardiomyopathy Workup

Sample type	Test	Lab	Tube	Special conditions	Expected time until result	Date sent	Results
Blood	Lactate	TBH Chem	Grey 1-2ml	Deliver on ice within 30 minutes	<24 hours		
	Glucose	TBH Chem	Grey		<24 hours		
	Calcium	TBH Chem	Green		<24 hours		
	Phosphate	TBH Chem	Green		<24 hours		
	Thyroid function	TBH Chem	Yellow 1-2ml		<24 hours		
	*Carnitine profile	RXH Chem (sent to UK)	Green or gold	Deliver to lab immediately	2-3 weeks		
	CK (incl CKMB%)	TBH Chem	Green or Yellow	CKMB sent to GSH Chem	<24 hours		
	Troponin T	TBH Chem	Green	Do not spin	<24 hours		
	CRP	TBH Chem	Green		<24 hours		
	*Autoimmune screen	TBH Immunology	Gold		1-2 weeks		
	ESR	TBH Haem	Purple	At least 1ml	<24 hours		
	Coxsackie B	TBH Virol.	Yellow		1-2 weeks		
	Mumps	TBH Virol.	Yellow		1-2 weeks		
	Rubella	TBH Virol.	Yellow		1-2 weeks		
	Parvovirus B19	TBH Virol.	Purple	Sent to Johannesburg	2 weeks		
	CMV	TBH Virol.	Yellow		<1 week		
	EBV	TBH Virol.	Yellow		<1 week		
	Blood culture	TBH Micro	BC Bottle		Up to 5 days		
	Amino Acids	RXH Chem	Yellow		1-2weeks		
Urine	Ketones	TBH Chem	Urine tube		<24 hours		
	Reducing substances	RXH Chem	Urine tube		2 weeks		
	Organic acids	RXH Chem	Urine tube		1 week		
Stool	Enterovirus including coxsackie A and echovirus	TBH Virol.	Specimen container		10 days		
NPA	Respiratory virus screen	TBH Micro	Viral medium in specimen container		2-3 days		
Echo	Date:	Findings:					
ECG	Date:	Findings:					
Muscle biopsy*	Date:	Findings:					

- * D/W **consultant**
- **'Gold' tube = yellow 'adult' clotted tube.**

TBH Haem:
TBH Micro/serology results:
TBH Immunology:
TBH Virology : Ext 9557
RXH Chem: 0216585226/5224

Appendix 5: Ethics approval

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot • your knowledge partner

20-Oct-2014 Carkeek, Katherine Janita KJ

Ethics Reference #: S14/07/154

Title:

Outcomes of children admitted to Tygerberg Children's Hospital with Myocarditis and Dilated Cardiomyopathy between 1 January 2008 and 30 May 2014.

Approval Notice New Application

Dear Dr Katherine Janita Carkeek,

The **New Application** received on **14-Jul-2014**, was reviewed by Health Research Ethics Committee 2 via Committee Review procedures on **06-Aug-2014** and has been approved. Please note the following information about your approved research protocol:

Protocol Approval Period: **06-Aug-2014 -06-Aug-2015**

Present Committee Members:

Davids, Mertrude MA Fernandez, Pedro P Blaauw, Renee R Botha, Philip PR Barsdorf, Nicola N

De Roubaix, John JAM Engelbrecht, Susan S Edwards, C E Holgate, Sandi SL Hansoti, Bhakti B Weber, Franklin CFS

Please remember to use your **protocol number** (**S14/07/154**) on any documents or correspondence with the HREC concerning your research protocol. Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or

monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372 Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel:+27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389207.

Included Documents:

Investigator CV (Carkeek)HREC New application form Investigator declaration (Carkeek) ProtocolInvestigator declaration (Rabie) Cover letterHREC general checklist Investigator CV (Rabie)Protocol Synopsis

Sincerely,

Mertrude Davids HREC CoordinatorHealth Research Ethics Committee 2

Investigator Responsibilities

Protection of Human Research Participants

Some of the responsibilities investigators have when conducting research involving human participants are listed below:

1.Conducting the Research. You are responsible for making sure that the research is conducted according to the HREC approved research protocol. You are also responsible for the actions of all your co-investigators and research staff involved with this research.

2.Participant Enrolment. You may not recruit or enrol participants prior to the HREC approval date or after the expiration date of HREC approval. All recruitment materials for any form of media must be approved by the HREC prior to their use. If you need to recruit more participants than was noted in your HREC approval letter, you must submit an amendment requesting an increase in the number of participants.

3.Informed Consent. You are responsible for obtaining and documenting effective informed consent using **only** the HREC-approved consent documents, and for ensuring that no human participants are involved in research prior to obtaining their informed consent. Please give all participants copies of the signed informed consent documents. Keep the originals in your secured research files for at least fifteen (15) years.

4.Continuing Review. The HREC must review and approve all HREC-approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is **no grace period.** Prior to the date on which the HREC approval of the research expires, **it is your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in HREC approval does not occur.** If HREC approval of your research lapses, you must stop new participant enrolment, and contact the HREC office immediately.

5.Amendments and Changes. If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of participants, participant population, informed consent document, instruments, surveys or recruiting material), you must submit the amendment to the HREC for

review using the current Amendment Form. You **may not initiate** any amendments or changes to your research without first obtaining written HREC review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to participants and the HREC should be immediately informed of this necessity.

6.Adverse or Unanticipated Events. Any serious adverse events, participant complaints, and all unanticipated problems that involve risks to participants or others, as well as any research-related injuries, occurring at this institution or at other performance sites must be reported to the HREC within **five (5) days** of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the HRECs requirements for protecting human research participants. The only exception to this policy is that the death of a research participant must be reported in accordance with the Stellenbosch University Health Research Ethics Committee Standard Operating Procedures www.sun025.sun.ac.za/portal /page/portal/Health_Sciences/English/Centres%20and%20Institutions/Research_Development_Support/Ethics/Application_package All reportable events should be submitted to the HREC using the Serious Adverse Event Report Form.

7.Research Record Keeping. You must keep the following research-related records, at a minimum, in a secure location for a minimum of fifteen years: the HREC approved research protocol and all amendments; all informed consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence from the HREC

8.Reports to the MCC and Sponsor. When you submit the required annual report to the MCC or you submit required reports to your sponsor, you must provide a copy of that report to the HREC. You may submit the report at the time of continuing HREC review.

9.Provision of Emergency Medical Care. When a physician provides emergency medical care to a participant without prior HREC review and approval, to the extent permitted by law, such activities will not be recognised as research nor will the data obtained by any such activities should it be used in support of research.

10.Final reports. When you have completed (no further participant enrolment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the HREC.

11.On-Site Evaluations, MCC Inspections, or Audits. If you are notified that your research will be reviewed or audited by the MCC, the sponsor, any other external agency or any internal group, you must inform the HREC immediately of the impending audit/evaluation.